Improving Perioperative Care and Patient Outcomes in Orthopaedic Surgery of the Lower Limb

Dr. D-Yin Indy Lin
2023

To my family
My parents, Hai Chat and Ngok Bing
My brothers, D-Yee and D-Arn
My husband, Hidde Kroon
Our children, Noah and Hannah

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Flinders University

Improving Perioperative Care and Patient Outcomes in Orthopaedic Surgery of the Lower Limb

Thesis for PhD by prior published work

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千里之行，始於足下

The journey of a thousand li begins with a single step.
Lao Tzu

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In memoriam Dr Peter Lillie

Statement of Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of Flinders University.

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Dr D-Yin Indy Lin

November 2023

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Contextual Statement Part I: Introduction and Outline of Thesis

<u>Improving Perioperative Care and Patient Outcomes in Orthopaedic Surgery of the Lower Limb</u>

This thesis shall aim to answer the following questions:

1. *Is the novel PENG block an effective regional analgesia technique for hip fractures?*
2. *What can we as anaesthetists do to improve outcomes in hip fracture care?*
3. *Is the novel PENG block an effective regional analgesia technique for hip arthroplasty?*
4. *What can we as anaesthetists do to improve outcomes in lower limb arthroplasty?*

Traditionally, patient care in anaesthesia has been to facilitate the comfort of the patient during surgery, with longer term consequences more of an afterthought. Over the years, the field of anaesthesia has evolved to encompass not only the anaesthetic for the patient during the operation itself but the holistic care of the patient during their whole perioperative trajectory. Anaesthesia is increasingly involved in refining patient outcomes, perhaps because of the immediate and measurable consequences that deficits can bring. (1) Anaesthetists have collectively improved many aspects of perioperative care to reduce avoidable harm, especially in the postoperative period. MPW Grocott said, "while harm directly attributable to the conduct of anaesthesia is rare (<1 in 50 000 mortality), there is arguably an epidemic of avoidable harm after major surgery, with dramatic variation in patient outcomes between institutions and nations which highlight the gap between what is achievable and what is actually achieved." (2)

This is perhaps most true in elderly and frail patients undergoing major surgery. This thesis focusses on the perioperative care of orthopaedic patients undergoing surgery of the lower limb, foremost of the hip joint, and improving the patient outcomes in this often vulnerable group.

Arthroplasty of the hip joint is carried out for two separate and distinct reasons. The first is to replace a fractured neck of femur, often referred to as a fragility fracture. (3) This is a result of an acute trauma, such as a fall, and is an emergency operation in the elderly population. The second reason is as a treatment for osteoarthritis in an elective setting, where the patients have longstanding pain and progressive loss of function. These patients are generally-speaking younger than their hip fracture counterparts and in better health. This thesis examines patient outcomes and pain management in both groups. **Section 1** focusses on the hip fracture population. Hip fractures are a common and debilitating injury, occurring almost exclusively in the geriatric population. (4) Worldwide, approximately 1.5 million people experience a hip fracture each year. Due to the growing and also aging population, this is projected to increase to 7 - 21 million by 2050. (4) Seventy percent of the patients with a hip fracture are aged 80 years or older, with an often-frail pre-operative status and extensive comorbidities. (5) The United Kingdom's National Hip Fracture Database has named key performance indicators, to guide patient care in this vulnerable population, including prompt mobilisation after surgery.(6)

Anaesthetists aim to decrease perioperative pain through regional analgesia techniques, as adequate pain management has been shown to decrease complications and facilitate postoperative mobilization (7). In 2018, Giron-Arango et al. described a novel technique for

regional hip analgesia, and named it the pericapsular nerve group (PENG) block. (8) This new block seemed to be motor sparing, allowing patients to mobilise unimpeded postoperatively, as well as possibly being more effective in providing pain relief than traditionally utilised nerve blocks, such as the femoral nerve or the fascia iliaca block.

PENG Block Procedure Description

The PENG block is placed using ultrasound guidance with a curvilinear probe (2.5-5MHz), while
20mL of ropivacaine 0.5% (100mg) is used. The concentration is probably less important than the volume, as this is a fascial block which relies on hydrodissection of the tissue plane to have effect. The area is aseptically prepped and draped. The curvilinear probe is placed transversely, medial to the anterior inferior iliac spine with the medial end of the probe rotated in a caudad direction to align to the superior pubic ramus. A 100mm Sonoplex needle is inserted in-plane under ultrasound guidance and 20mLs of local anaesthetic injected under the psoas tendon, taking care to ensure medial spread and adequate hydrodissection.

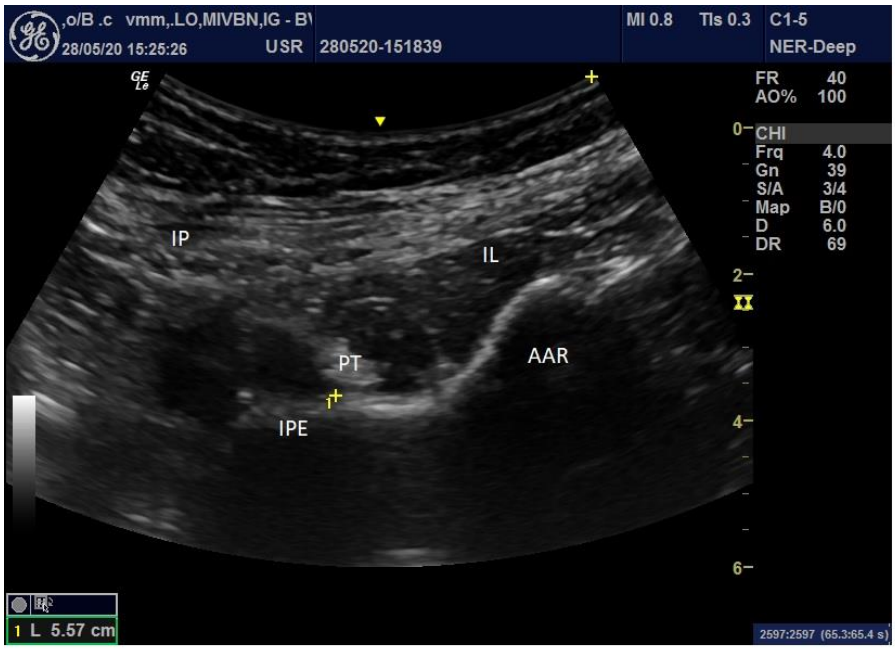

Figure 1: Ultrasound sonoanatomy of PENG block
Ultrasound image obtained for PENG block placement using a curvilinear probe. *Reproduced from Lin et al. Regional Anesthesia and Pain Medicine (9)*

IPE: iliopubic eminence
AAR: anterior acetabular rim
PT: psoas tendon
IL: iliacus muscle

IP: iliopsoas muscle

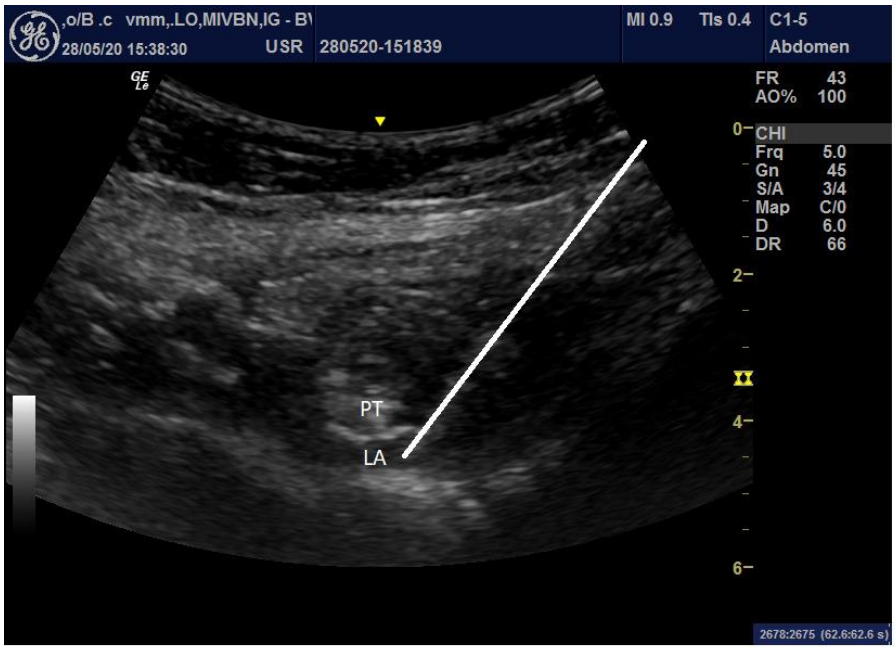

Figure 2: Injection and spread of local anesthetic in PENG block placement
Injection of local anesthetic into the tissue plane under the psoas tendon. Hydrodissection with a white fascial layer above is clearly seen. The path of the needle is demarcated by the white line. *Reproduced from Lin et al. Regional Anesthesia and Pain Medicine (9)*
PT: psoas tendon
LA: local anaesthetic

In **Chapter 1** we examined the literature published to date regarding the PENG block in hip fracture surgery by means of a scoping review. **Chapter 2** is the first randomised controlled trial (RCT) published on the PENG block, evaluating its use in emergency hip fracture cases. **Chapter 3** is a review of the multinational Australian and New Zealand Hip Fracture Registry (ANZHFR), which analyses this large database for anaesthetic type as a risk factor for long term mortality in hip fracture patients.

Section 2 relates to improving pain management in elective hip and knee arthroplasty surgery. **Chapter 4** is our second RCT which looked at the use of the PENG block in elective hip arthroplasty surgery. **Chapter 5** is a review of four years of prospective data collected regarding postoperative opioid use following hip and knee arthroplasty. It includes the protocol used at our institutions to achieve an ultra-low incidence of long-term opioid use following these surgeries.

Section 3 concerns the improvement of patient outcomes in hip and knee arthroplasty surgery. Total hip arthroplasty (THA) is a common operation, with over 32,000 replacements performed per year in Australia (133 per 100,000 in 2017-2018). (10) Learmonth et al. called it “the operation of the century”, (11) citing improvements in quality of life following this

procedure and naming cost-effectiveness as the main factor that would determine future directions in this area. This is often evaluated using health economics tools such as patient-related outcome measures (PROMs).
Chapter 6 describes a validation of the widely utilised health economic measurement, the EQ-5D-5L. This is a PROM not previously validated in the Australian hip arthroplasty population.
Chapter 7 describes a validation of the EQ-5D-5L in knee arthroplasty patients. Once again, this PROM was not previously validated in the Australian knee arthroplasty population. This article also establishes a baseline Minimum Important Difference (MID) for knee arthroplasty patients in Australia, serving as a valuable reference point for future research and patient counselling during the perioperative phase.
Chapter 8 is a prospective database study of the long-term patient outcomes in two different approaches to hip arthroplasty, direct anterior or the posterior approach. The direct anterior approach (DAA) to facilitate total hip arthroplasty was first described by Carl Heuter in 1881. (12) This is a minimally invasive technique that utilises the tissue plane between the tensor fascia lata and rectus femoris. (13) It was later modified into the Smith-Petersen method, (14) and has become increasingly popular in recent years. Some evidence suggests that the DAA results in improved early functional recovery and lower postoperative pain scores, when compared to the more traditional posterior approach (PA), but these results have not been consistently supported (15, 16, 17). We examined the PROM results and patient satisfaction from over 500 patients who underwent a hip arthroplasty at our institutions.

This thesis is concluded with a summary and a future perspectives component, in which new directions for perioperative care in fragility fractures and hip arthroplasty surgery are discussed.

This thesis is significant in that it delves into the intricate realm of patient outcomes in the domain of lower limb orthopaedic surgery. The collective impact is that we aim to scrutinise the current state-of-the-art techniques and protocols and identify areas for enhancement or improvement. As we as health care providers navigate through the published articles featured in this manuscript, a compelling narrative emerges. It showcases the trajectory of clinical practices towards improved patient care in a vulnerable patient population undergoing major surgery. The studies detailed herein shed light on key facets shaping the future of orthopaedic surgery. Specifically, advancements in analgesia are discussed within, a judicious approach to opioid use during surgical recovery, and the validation of evaluation methods employable in health economic analyses. There are a number of firsts in this PhD, from the first RCT on PENG blocks, to the first baseline Minimum Important Difference (MID) for knee arthroplasty patients in Australia, serving as a benchmark for future research and patient counselling during the perioperative phase.

The underlying motivation for this exploration comes from a commitment to improving the standards of care for individuals undergoing orthopaedic interventions of the lower limb. This thesis reflects not only a comprehensive examination of the current landscape but also a vision for the future of patient-centred orthopaedic care. Throughout this academic journey, we have been fortunate to receive unwavering support from our clinical departments, Flinders University and professional organisations. This enabled the successful

conduct of these studies. Additionally, a thoroughly enjoyable and tangible aspect of our publications has been the dissemination of knowledge to fellow clinicians. This has fostered the translation of research findings into improvements in real-world medical practice, as well as multicentre and international collaborative projects.

In expressing our gratitude for the team-based efforts that have facilitated this research, we recognise the significance of the studies contained within this thesis. It is our belief that these publications contribute meaningfully to the collective impact and understanding of effective patient care in orthopaedic surgery of the hip and knee. The synthesis of this thesis underscores the imperative for ongoing advancements and innovations in the realm of perioperative patient care, paving the way for a future characterised by enhanced outcomes and improved quality of life for patients. We hope in this way to be able to repay the trust and time placed in us by them.

ABBREVIATIONS

PENG: Pericapsular nerve group block
RCT: Randomised controlled trial
ANZHFR: Australian and New Zealand Hip Fracture Registry
PROM: Patient related outcome measure
DAA: Direct anterior approach

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Chapter 1

Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review

Chapter 1

Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review

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ABSTRACT

Introduction Pericapsular nerve group (PENG) block is a novel regional analgesia technique to reduce pain after hip surgery and hip fractures. This review was conducted to summarize current literature.

Methods A scoping review was carried out using the Joanna Briggs Institute framework. All articles describing the use of PENG block as a regional analgesia and/
or anesthesia technique for hip pain were considered eligible for inclusion. Ovid Medline, Embase, CINAHL, PubMed and Google Scholar were searched. Adult and pediatric studies were included. Excluded were articles not available in English language, not available in full-text, related to non-orthopedic indications such as soft tissue surgery, and pelvic or femoral shaft fractures.

Results Database searches identified 345 articles, 20 of which could be included in the current review, with a combined patient number of 74. Included articles comprised case reports and case series only, describing 1 to 10 patients. In all studies, PENG block was described to provide sufficient analgesia or anesthesia. Transient motor side effects occurred only when the local anesthetic was deposited in an unintended location (n=2).

Conclusions Current evidence of using PENG block for hip surgery or hip pain is limited to case reports and case series only. PENG block is a promising regional analgesia technique as an alternative to other regional nerve blocks such as femoral nerve block or iliac fascia nerve block. Observational and experimental studies
are required to determine the effectiveness, efficacy and safety of the PENG block.

INTRODUCTION

Effective regional analgesia for pain originating from the hip after a fracture or during surgery can be described as elusive.[1] A variety of regional analgesia techniques, such as femoral nerve block, iliac fascia block and psoas compartment block, are used regularly. The recent Cochrane review on these regional analgesia techniques demonstrated an average pain score reduction of 3.4 points on a 10-point Numerical Rating Scale, 30 min after placement.[1] Although this is a statistically significant reduction in pain exceeding the minimal clinically important difference,[2] international guidelines question whether reductions from currently broadly used nerve blocks are clinically relevant when compared with systemic analgesia in the context of patients with a fractured neck of femur.[3]

One of the difficulties of effective regional analgesia for hip pain is the complex innervation of the joint as it comes from multiple nerves. In an anatomical study, Short *et al*[4] demonstrated that sensory innervation of the anterior capsule of the hip includes articular branches of the femoral, obturator and accessory obturator nerve. They also showed that the 'high' branches of the femoral nerve play a greater role in the sensory innervation of the anterior hip capsule than previously appreciated. In almost all cadavers examined (92%), the femoral nerve had 'high' sensory articular branches cranially to the inguinal ligament, making it difficult to block this nerve with infra-inguinal techniques such as the iliac fascia block or femoral nerve block.[4] Furthermore, it has been demonstrated that techniques, such as the iliac fascia block, often fail to adequately block the obturator nerve, which also provides sensory innervation to the anterior hip capsule.[4] Triggered by these findings, in 2018 Giron-Arango *et al*[5] described the pericapsular nerve group (PENG) block for the first time using a low-frequency curvilinear ultrasound probe to deposit local anesthetic in the musculofascial plane between the psoas tendon anteriorly and the pubic ramus posteriorly. In their hands, PENG block in patients with hip fractures reduced pain scores by a median of 7 points on a 10-point Numerical Rating Scale, without causing motor block.[5]

Given the recent introduction of PENG block, literature describing its safety and efficacy is limited with no review articles available yet. Therefore, we conducted the current scoping review with the goal to map current literature for PENG block as a regional analgesia or anesthesia technique in patients with hip pain encompassing both patients with hip fractures and those undergoing hip surgery.

METHODS

Search strategies and terms

A comprehensive systematic review of literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the framework recom- mended by the Joanna Briggs Institute.[6] The study methods were established prior to conducting the review.

The key search terms were 'pericapsular nerve group block', 'autonomic nerve block', 'nerve block', 'plane block', 'PENG', 'supra-inguinal iliac fascia.' A complete list of the search terms is listed in online supplemental appendix A. The search terms were joined by Boolean

operators. The search strategy was created with the assistance of a clinical librarian (NM) at our institution.

Ovid MEDLINE, Excerpta Medica dataBASE (EMBASE), PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane database of systematic reviews and Google Scholar databases were searched independently by two authors (CM and BB) for all publication types, with the last search conducted on April 13, 2020.

Eligibility criteria

Articles eligible for inclusion were those written in English language, describing the use of PENG block in adult or pediatric patients, in the context of pain originating from the hip caused by either fracture or surgery. The hip was considered as the articulation between the acetabulum and the proximal femur (head-neck-trochanter). There were no restrictions in the included number of patients. Search was conducted for articles published from January 2018 onward, given the date of the inaugural publication describing PENG block. Excluded were studies describing the use of PENG block for other indications (such as femoral shaft fractures, pelvic fractures, periprosthetic femoral fractures, urological, soft tissue or vascular surgery), studies not available in English language and studies for which full-text was not available.

Article selection and inclusion

Two authors (CM and BB) independently screened titles and abstracts of the search results selecting articles for full-text review, which described the use of PENG block in adult or pediatric patients, in the context of pain originating from the hip caused by either fracture or surgery (figure 1).

Next, full-text review of potentially relevant articles was performed by the same two authors. Reference lists of articles selected for full-text assessment were reviewed for potentially additional articles of relevance.

A third author (D-YL) was consulted to mediate discussion in the event of disagreement.

Data extraction and quality assessment

The following data were extracted by the two authors (CM and BB) to a predefined extraction chart from the included articles: author, year of publication, country of origin, type of publication (case report/case series), number of included patients, adult or pediatric study population, setting (hip fracture analgesia/hip surgery postoperative analgesia/hip relocation/anesthesia/other), PENG block technique (ultrasound probe type, local anesthetic solution used, use of a nerve catheter), additional analgesia used, analgesia outcomes and adverse events.

RESULTS

Database screening yielded 345 articles, of which 20 articles met the inclusion criteria, with a total number of 74 patients. All 20 articles were case reports or case series, published

between November 2018 and April 2020 and summarized in table 1. A flowchart of article selection is shown in figure 1. Articles identified for inclusion originated from Canada, India, Turkey, Saudi Arabia, Costa Rica, Nepal, Italy, Spain, Colombia and Portugal.

Analgesic outcomes

PENG block in isolation

The use of PENG block as a regional analgesia technique without other nerve blocks has been described in 11 studies, in a total of 35 adult patients and one pediatric patient, in a variety of settings including hip relocation, hip fracture analgesia and hip surgery.[5 7–16] The included studies reported that PENG block provides analgesia in these settings, with reduced or no need for oral or intravenous opioid analgesia. In one study, including a total of five patients, it was reported that after hip fracture surgery a few of the patients experienced pain in the distribution of the lateral femoral cutaneous nerve.[9]

PENG block in combination with other regional analgesia techniques
PENG block in combination with local anesthetic infiltration, or other nerve blocks such as femoral nerve block or lateral femoral cutaneous nerve block, has been described in nine studies in a total of 32 adult patients and one pediatric patient.[9 17–22] These patients underwent hip arthroscopy, hip arthroplasty, hip fracture surgery or removal of osteosynthetic material. All reports indicated sufficient analgesia with no to minimal opioid require- ments up to 72hours postoperatively.

In three hip arthroplasty patients, PENG block was combined with a lumbar level erector spinae plane block. In these patients, the maximum reported pain score 24 hours postoperatively was 3/10 with a maximum use of 8 mg intravenous morphine equivalents.[23] The combination of PENG block and lumbar erector spinae block was also reported in one pediatric patient under- going surgery for congenital hip dysplasia with a maximum post- operative pain score of 1/10 and no requirement for additional postoperative opioid analgesia.[24]

Anesthesia outcomes

Notably, PENG block was used as the sole anesthetic technique for hip relocation in two adult patients, without requiring general anesthesia, neuraxial anesthesia or sedation.[25]

Technical aspects of PENG block

Varying techniques have been described with 10 studies reporting the use of curvilinear low-frequency ultrasound probes, four using linear high-frequency ultrasound probes and six studies not stating what type of ultrasound probe was used. No study compared the effect of different ultrasound probe selection.

In 19 studies, patients received single-shot nerve blocks except for the study by Santos *et al*,[16] who described the use of a contin- uous nerve catheter and local anesthetic infusion in

a single adult patient undergoing hip arthroplasty. This patient required no further analgesia for up to 72hours postoperatively.

No study reported the effective duration of PENG block, the effect of varying local anesthetic concentrations or the effect of additives in the local anesthetic solutions.

Motor weakness

One study reported two patients who experienced quadriceps muscle weakness after PENG block. PENG block placement was technically difficult in both patients, likely resulting in femoral nerve block caused by deposition of local anesthetic outside of the PENG block anatomical location in the musculo-fascial plane between the psoas tendon anteriorly and the pubic ramus posteriorly.[8] In both patients, the quadriceps weakness resolved within 48hours.

Adverse events

None of the studies reported any local anesthetic systemic toxicity, anaphylaxis, permanent nerve injury or other serious adverse events after PENG block.

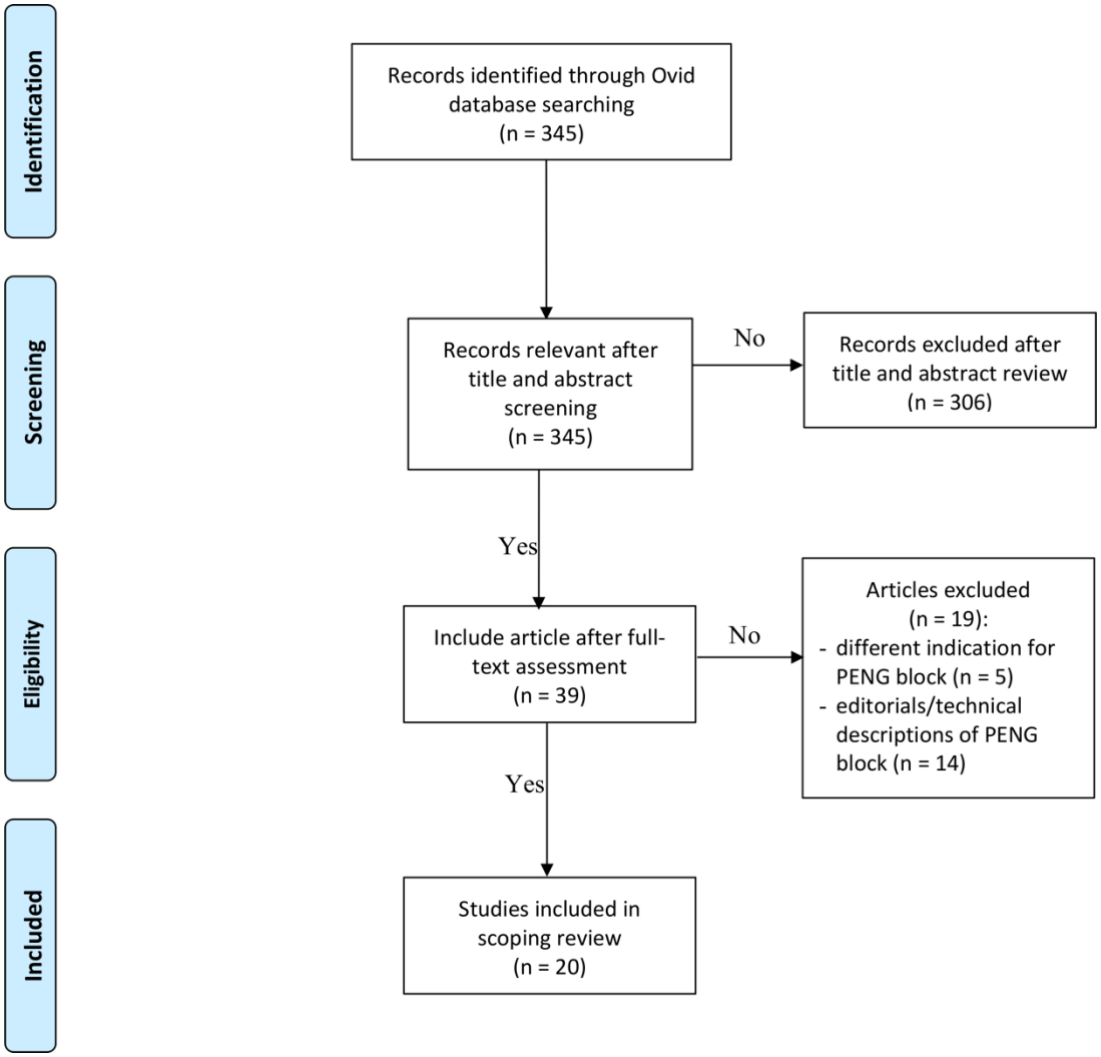

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for selection of studies for the current review. PENG, pericapsular nerve group.

Table 1 Summary of literature of PENG block for hip pain

First author, publication date, country (reference)	Type of report	Setting	Number of patients	Intervention	Additional nerve blocks used
PENG block in isolation for analgesia					
Giron-Arango L, Nov-18, Canada[5]	Case series	Hip fracture analgesia	Five adults	PENG block with either 20 mL of 0.25% bupivacaine with 1:400 000 epinephrine or 20 mL of 0.5% ropivacaine with 1:200 000 epinephrine plus 4 mg dexamethasone	None
Mistry T, Mar-19, India[7]	Case series	Hip fracture analgesia	Five adults	PENG block (local anesthetic solution not specified)	None
Yu HC, May-19, Canada[8]	Case report	Hip fracture surgery	Two adults	PENG block with either 20 mL 0.25% or 0.5% bupivacaine and 1:400 000 epinephrine+50 mcg/mL dexamethasone	None
Roy R, Jun-19, India[9]	Case series	Hip fracture surgery	Five patients initially— age not stated	PENG block—local anesthetic solution not described	None
Rocha Romero A, Jun-19, Costa Rica[10]	Case report	Hip fracture analgesia	One adult	PENG block with neurolytic injection of 10 mL of 6% phenol	None
Ueshima H, Sep-19, Japan[11]	Case report	Hip arthroplasty	Two adults	PENG block with 20 mL of 0.25% levobupivacaine	None
Acharya U, Mar-19, Nepal[12]	Case series	Hip fracture analgesia	Ten adults	PENG block with 20 mL 0.125% bupivacaine and 4 mg dexamethasone	None
Ahiskalioglu A, Nov-19, Turkey[13]	Case report	Hip fracture analgesia	One adult	PENG block with 15 mL 0.5% bupivacaine and 15 mL 2% lignocaine	None
Bilal, Jan-20, Turkey[14]	Case report	Hip fracture surgery	Two adults	PENG block with 30 mL 0.25% bupivacaine	None
Aksu C, May-20, Turkey[15]	Case report	Open reduction congenital hip dysplasia	One pediatric	PENG block with 10 mL 0.25% bupivacaine	None
Santos O, Jun-19, Portugal[16]	Case report	Hip arthroplasty	One adult	PENG block with 20 mL 0.5% ropivacaine and 4 mg dexamethasone	Nerve catheter - additional 15 mL 0.5% ropivacaine intra-operatively+5 mL/ hour 0.2% ropivacaine for 48 hours
PENG block in combination with local anesthetic infiltration for analgesia					
Sandri M, Mar-2020, Italy[17]	Case series	Hip arthroplasty	Ten patients	PENG block preoperatively with 40 mL 0.25% levobupivacaine and 4 mg dexamethasone	10 mL 1% mepivacaine at surgical incision site
Fusco P, Apr-19, Italy[18]	Case series	Hip arthroplasty	Four patients	PENG block preoperatively with 20 mL solution containing 0.375% levobupivacaine and 4 mg dexamethasone	None
PENG block in combination with LFCN block for analgesia					
Roy R, Jun-19, India[9]	Case series	Hip fracture surgery	Five later patients— age not stated	PENG block—local anesthetic solution not described	LFCN block—local anesthetic solution not described
Reza PC, Jan-20, Spain[19]	Case series	Hip arthroplasty, acetabular fracture surgery	Seven patients	PENG block with 20 mL 0.375% bupivacaine	LFCN block—5 mL 0.375% bupivacaine
Thallaj A, Oct/Dec-19, Saudi Arabi[20]	Case report	Hip arthroplasty	One adult	PENG block with 30 mL 0.25% bupivacaine	LFCN block with 5 mL 0.25% bupivacaine
PENG block in combination with femoral nerve block for analgesia					
Orozco S, Apr-19, Colombia[21]	Case series	Hip arthroscopy	Five adults	PENG block preoperatively with 20 mL of 0.75% bupivacaine and 1% lignocaine	FNB with 20 mL of 0.75% bupivacaine+1% lignocaine
PENG block in combination with LFCN block and femoral nerve block for analgesia					

Orozco S, Apr-19, Colombia[22]	Case report	Hip surgery—osteosynthetic material retrieval	One pediatric	PENG block with 10 mL 0.5% bupivacaine	FNB with 15 mL 1% lignocaine/0.75% levobupivacaine and LFCN block with 5 mL 1% lignocaine/0.75% levobupivacaine
PENG block in combination with lumbar erector spinae block for analgesia					
Ince, I, Jan-20, Turkey[23]	Case report	Congenital hip dislocation surgery	One pediatric	PENG block with 8 mL 0.25% bupivacaine	Lumbar erector spinae plane block with 12 mL 0.25% bupivacaine
Ince I, Jan-20, Turkey[24]	Case series	Hip arthroplasty	Three adults	PENG block with 10 mL 0.5% bupivacaine and 10 mL 2% lignocaine	Lumbar erector spinae plane block with 30 mL 0.25% bupivacaine
PENG block as a sole anesthetic technique for analgesia					
Ueshemia H, Sep-19, Japan[25]	Case report	Reduction of hip dislocation	Two adults	PENG block with 10 mL of 1% lignocaine	None

Table 1 Continued

First author, publication date, country (Reference)	Local anesthetic infiltration	Outcomes—analgesic efficacy	Outcomes—adverse effects	Comparison group
PENG block in isolation for analgesia				
Giron-Arango L, Nov-18, Canada[5]	NA	Reduction in NRS pain scores at rest (median reduction 7) and on movement at 30 min	None reported	Compared with patients pre-PENG block pain scores
Mistry T, Mar-19, India[7]	NA	All patients reported dynamic pain relief after 10–15 min without any motor weakness	None reported	None
Yu HC, May-19, Canada[8]	NA	Additional opioids required for postoperative analgesia in both patients	Description of 2 patients who experienced motor weakness post PENG block attributed to incorrect needle positioning	NA
Roy R, Jun-19, India[9]	NA	A few patients required rescue opioids for dermatomal pain	None reported	Authors describe that in their experience PENG block provides satisfactory reduction in pain for hip surgeries compared with other blocks available
Romero A, Jun-19, Costa Rica[10]	NA	Complete analgesia, no motor block	None reported	NA
Ueshemia H, Sep-19, Japan[11]	NA	Additional analgesics not required, uneventful perioperative course, no clear description of pain outcomes/analgesic medications	None reported	NA
Acharya, U. Mar-19, Nepal[12]	NA	Marked reduction in NRS pain scores when compared with pre-block, able to self-position for sitting spinal anesthesia in 9/10 cases with mild pain only on movement, able to sit without support post block	None reported	Compared with patients pre-PENG block NRS pain scores
Ahiskalioglu A, Nov-19, Turkey[13]	NA	VAS preprocedure 9 at rest, at 10 min post-PENG block 1 at rest, on movement 2	None reported	Compared with patients pre-PENG block pain scores
Bilal, Jan-20, Turkey[14]	NA	Maximum post-operative pain score during first 24 hours 3/10.No postoperative opioids required	None reported	NA
Aksu C, May-20, Turkey[15]	NA	Single-dose Ibuprofen 10 hours postoperatively, no additional analgesia required	None reported	NA
Santos O, Jun-19, Portugal[16]	NA	At 8 hours pain 2/10 at rest and 2/10 on movement. At 24 hours and 48 hours pain 0/10 at rest and 0/10 on movement with no further analgesia required	None reported	NA
PENG block in combination with local anesthetic infiltration for analgesia				

Sandri M, Mar-2020, Italy[17]	Yes	All 10 patients underwent surgery with 'light- moderate sedation', general anesthesia not required, maximal postoperative pain score reported 4/10, nil postoperative opioids required	None reported	NA
Fusco P, Apr-19, Italy[18]	Yes	Pain at rest on Numerical Rating Scale 'two controls', pain on movement 'four controls', patient reported lower perceived pain and 'very satisfied', no supplementary opioids/non-steroidal anti- inflammatory drugs	None reported	NA
PENG block in combination with LFCN block for analgesia				
Roy R, Jun-19, India[9]	NA	No rescue opioids required	None reported	NA
Reza PC, Jan-20, Spain[19]	NA	Pain outcomes not reported, only opioid consumption, 4 patients no opioids required postoperatively, 3 patients 6 mg or less intravenous morphine in first 24 hours	None reported	NA
Thallaj A, Oct/Dec-19, Saudi Arabi[20]	NA	Analgesia with paracetamol only postoperatively. 0–24 hours pain at rest 0/10, at 36 hours pain 2/10 at rest, at 48 hours pain 3/10 on movement	None reported	NA
PENG block in combination with femoral nerve block for analgesia				
Orozco S, Apr-19, Colombia[21]	NA	Highest VAS in the 24 hours postoperatively 3/10, after 48–72 hours all patients none or very low levels of pain requiring no opioid analgesia	None reported	NA
PENG block in combination with LFCN block and femoral nerve block for analgesia				
Orozco S, Apr-19, Colombia[22]	NA	72 hours follow-up maximum pain score 2/10, no additional analgesia required	None reported	NA
PENG block in combination with lumbar erector spinae block for analgesia				
Ince, I, Jan-20, Turkey[23]	NA	FLACC score maximum 1 for 24 hours follow-up. No postoperative opioids required	None reported	NA

Table 1 Continued

First author, publication date, country (Reference)	Local anesthetic infiltration	Outcomes—analgesic efficacy	Outcomes—adverse effects	Comparison group
Ince I, Jan-20, Turkey[24]	NA	Highest pain score in first 24 hours postoperatively 3/10, highest postoperative opioid consumption 8 mg intravenous morphine equivalent	None reported	NA
PENG block as a sole anesthetic technique				
Ueshima H, Sep-19, Japan[25]	NA	Successful reduction of hip dislocation in both patients without need for additional analgesia/ anesthesia	None reported	NA

FLACC, face legs, arms, cry, consolability pain scale; FNB, femoral nerve block; LFCN, lateral femoral cutaneous nerve; NA, not applicable; NRS, Numerical Rating Scale; PENG, pericapsular nerve group; VAS, Visual Analog Scale.

DISCUSSION

In this first scoping review of PENG block as regional analgesia or anesthesia technique for pain originating from the hip, we found that there is currently insufficient evidence to recommend PENG block. Within the limitations of current evidence, PENG block may provide analgesia, but since to date literature is limited to case reports and case series only, there is a high risk of publication bias, making it hard, if not impossible comment on safety and efficacy.

In theory, PENG block has potential advantages over traditional forms of regional analgesia for pain originating from the hip, such as femoral nerve or fascia iliaca blocks. One of these potential advantages includes a wider and more complete coverage of sensory nerves innervating the hip, leading to more effective regional analgesia with the potential to reduce postoperative pain. This may lead to increased patient satisfaction and reduced postoperative opioid consumption, potentially causing less opioid-related adverse events and fewer patients with long- term opioid dependency, as this can be triggered after a prescription from a medical professional.[26] Furthermore, if studies with large patient numbers confirm the absence of motor blockage after PENG block, it may allow early patient mobilization and participation in rehabilitation, contributing to an early recovery. The currently available reports are insufficient to comment on PENG block as a sole anesthesia technique for hip relocation or other procedures.

The easily identifiable sonographic landmarks of the anterior inferior iliac spine, the iliopubic eminence and the psoas tendon make the technical performance of PENG block comparable with other nerve blocks at the least.[5] This is supported by current literature not describing any serious adverse events after PENG block such as permanent nerve injury, major vascular damage or local anesthetic systemic toxicity, although it has to be borne in mind that current literature is too limited to conclude this. Additionally, several concerns have been raised regarding the safety of PENG block.[27] For instance, performing PENG block in patients with coagulation disorders or those on anticoagulant medication could potentially be dangerous.[27] Furthermore, when performing PENG blockage there is potential for the needle path to trans- verse either the femoral nerve or the lateral femoral cutaneous nerve.[27] In the current review, two patients experienced femoral nerve block after PENG block. In these patients, however, it was suspected that the local anesthetic agent was deposited in a different anatomical location, since the femoral nerve blockage was transient.[8] To avoid traversing of nerves, leading to permanent damage, from happening, it has been suggested to identify the femoral nerve in the ‘scanning phase’ prior to performing PENG block.[27] The lateral femoral cutaneous nerve, on the contrary, has a smaller caliber, follows a less predictable path and is more difficult to identify on ultrasound. Finally, there is the potential that damage to the pelvic part of the ureter could occur if a more medial insertion site or a medial to lateral technique would be used.[27] Despite these concerns, however, none of these adverse events have been reported in the articles included in the current review.

Some limitations identified in the current review have to be addressed. It is possible that we may have missed PENG block articles published in languages other than English due to our review methods. English, however, is the most regular published language in medical literature. Due to the heterogeneity of the current PENG block reports in terms of indications, combinations with other nerve blocks, different local anesthesia solutions used, differences in follow-up and reporting of outcomes, it is not possible to draw firm conclusions on its efficacy based on the current data. Therefore, the current study was in the form of a scoping review to describe and map current evidence to identify areas for future research. Currently, there are no observational studies including large patient numbers or comparative trials of PENG blockage available and, as shown in the current review, literature is limited to case reports and case series. In view of this, randomized-controlled trials comparing PENG block to other nerve blocks, such as the fascia iliaca block, femoral nerve block, lumbar erector spinae block or a combination of blocks, are needed to provide evidence if PENG block is effective in providing analgesia for pain originating from the hip. We note that there are currently several registered randomized-controlled trials comparing PENG block to placebo blocks (NCT04231123) and to other nerve blocks for patients with pain derived from the hip (ACTRN12620000298910, ACTRN12619001410145, NCT04210700, NCT03783247, NCT04373577) with the aim to provide better evidence on the efficacy of PENG block for hip pain. Additionally, a large cohort study will be required to investigate its safety.

Conclusions

This scoping review summarizes current available evidence on the use of PENG block as a regional analgesia and anesthesia technique for pain originating from the hip. Current literature suggests that PENG block is feasible and promising as a regional analgesia technique. Clinical trials and cohort series are required to determine its safety and efficacy.

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Contributors CM was responsible for review design, search, reviewing results and manuscript preparation. BB was responsible for review design, search, reviewing results and manuscript editing. D-YL was responsible for review design and manuscript editing. RJ was responsible for manuscript editing. HK was responsible for review oversight and manuscript editing. All authors contributed to the manuscript and all authors approved submission.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Correction: *Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review*

Morrison C, Brown B, Lin D, *et al*. Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review. *Reg Anesth Pain Med* 2021;46:169–175. doi:10.1136/rapm-2020-101826

The authors wish to direct the readers' attention to the retraction of two case reports cited in this review that been retracted due to academic misconduct.[1]

The first retracted article 'Clinical experiences of the pericapsular nerve group (PENG) block for hip surgery' was consistent with other articles described in the scoping review and thus the conclusion remains unchanged.[2]

The second retracted article 'Pericapsular nerve group (PENG) block is effective for dislocation of the hip joint' was the only article describing the PENG block as a sole anesthetic technique.[3] Thus on page three the paragraph subtitled 'Anesthesia outcomes' and on page four the tabled results subtitled 'PENG block as a sole anesthetic technique for analgesia' should be disregarded.

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2. 2 Ueshima H, Otake H. Retracted: clinical experiences of pericapsular nerve group (PENG) block for hip surgery. *J Clin Anesth* 2018;51:60–1.
3. 3 Ueshima H, Otake H. Retracted: Pericapsular nerve group (PENG) block is effective for dislocation of the hip joint. *J Clin Anesth* 2019;52:83.

Appendix A

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to April 18, 2020>
Search Strategy:
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1. 1 pericapsular nerve group.ti,ab,kf. [standalone term]
2. 2 Autonomic Nerve Block/
3. 3 nerve block*.ti,ab,kf.
4. 4 plane block*.ti,ab,kf.
5. 5 PENG.ti,ab,kf.
6. 6 or/2-5 [nerve block concept]
7. 7 hip/ and (exp Orthopedic Procedures/ or Surgical Procedures, Operative/)
8. 8 hip/su
9. 9 (hip* adj5 (surg* or operat* or orthopedic* or orthopaedic* or fractur* or arthroplast* or

arthroscop* or relocation or dislocat* or pain* or joint*)).ti,ab,kf.
10 ((femur* or femor*) adj3 (surg* or fractur* or arthroplast* or arthroscop* or relocation or dislocat*)).ti,ab,kf.
11 ((trochant* or pertrochant* or intertrochant* or subtrochant*) adj3 (surg* or fractur* or arthroplast* or arthroscop* or relocation or dislocat*)).ti,ab,kf.
12 ((intracapsular* or extracapsular*) adj3 (surg* or fractur* or arthroplast* or arthroscop* or relocation or dislocat*)).ti,ab,kf.

13. 13 lower extremit*.kf.
14. 14 (thigh adj4 surg*).ti,ab,kf.
15. 15 or/7-14 [hip surgeries concept]
16. 16 and/6,15 [joining nerve block and hips]
17. 17 or/1,5,16 [adding in standalone term]
18. 18 limit 16 to yr="2018-Current”

Part I, Chapter 2

Pericapsular nerve group (PENG) block provides improved short-term analgesia compared with the femoral nerve block in hip fracture surgery: a single- center double-blinded randomized comparative trial

Chapter 2

The Pericapsular Nerve Group (PENG) Block Provides Improved Short-Term Analgesia Compared to the Femoral Nerve Block in Hip Fracture Surgery: A Single-Centre Double-Blinded Randomized Comparative Trial.

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Contribution: This author assisted with protocol implementation, and approved the final manuscript.

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Contribution: This author assisted with protocol implementation, and approved the final manuscript.

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Contribution: This author conceived, assisted with designing, writing and submitting the protocol to Ethics and Governance, realized the study, lended departmental support, revised the drafts, and approved the final manuscript.

LIST OF ABBREVIATIONS

FNB: Femoral nerve block

PENG block: Pericapsular nerve group block

RCT: Randomized comparative trial

NRS: Numeric rating scale

FMC: Flinders Medical Centre

NTR: Netherlands Trial Registry

CONSORT: Consolidated Standards of Reporting Trials

PROMs: Patient reported outcome measures

PROMIS: Patient-reported outcomes measurement information system

BPI: Brief Pain Inventory

QoR-15 questionnaire: Quality of Recovery-15 questionnaire

SD: Standard Deviation

ABSTRACT

Background: The femoral nerve block (FNB) may be used for analgesia in hip fracture surgery. The pericapsular nerve group (PENG) block is a novel regional technique and may provide better pain reduction while preserving motor function, but these blocks have not been directly compared.

Methods: In a single-center double blinded randomized comparative trial, patients presenting for hip fracture surgery received analgesia with either FNB or PENG block. The primary outcome measure was pain scores (numeric rating scale 0 to 10). Secondary outcomes were: postoperative quadriceps strength, opiate use, complications, length of hospital stay, and patient-reported outcomes.

Results: Sixty patients were randomized and equally allocated between groups. Baseline demographics were similar. Postoperatively in Recovery (Day 0), the PENG group experienced less pain compared to the FNB group. (In the PENG group 63% experienced no pain, 27% mild pain, and 10% moderate to severe pain. In comparison, 30% of the FNB group reported no pain, 27% mild pain, and 36% moderate to severe pain; p=0.04). This was assessed using an 11-point Likert numeric rating scale (NRS). Quadriceps strength was better preserved in the PENG group in the Recovery Unit (Assessed using Oxford muscle strength grading, 60% intact in the PENG group versus none intact in the FNB group; p<0.001) and on Day 1 (90% intact versus 50%, respectively; p=0.004). There was no difference in other outcomes.

Conclusions: Patients receiving a PENG block for intra- and postoperative analgesia during hip fracture surgery experience less postoperative pain in the recovery room with no difference detected by postoperative day 1. Quadriceps strength was better preserved with

the PENG block. Despite the short-term analgesic benefit and improved quadriceps strength, there were no differences detected in the quality of recovery.

Key words: anesthesia, analgesia, regional analgesia, hip fractures, PENG, pericapsular nerve group block, femoral nerve block, pain, patient reported outcome measures, PROMs

INTRODUCTION

Approximately 1.5 million people experience a hip fracture globally each year. Due to the growing and aging population, this is projected to increase to 7 - 21 million by 2050. (4) Seventy percent of the patients with a hip fracture are 80 years or older, with an often frail pre-operative status and extensive comorbidities. (5) The United Kingdom's National Hip Fracture Database has named key performance indicators, to guide patient care in this vulnerable population, including prompt mobilisation after surgery.(6)

Anesthesiologists aim to decrease perioperative pain through regional analgesia techniques such as the femoral nerve block (FNB), as adequate pain management has been shown to decrease complications and facilitate postoperative mobilization (7). Previous studies have shown that the FNB results in a numeric rating scale (NRS) pain score reduction of 3.4 points on an 11-point Likert scale. (18) However, its benefits are offset by the FNB resulting in quadriceps weakness, impeding postoperative mobility. (19) The ideal regional technique for hip surgery would be one with a high pain score reduction that does not cause delayed mobilisation and discharge.

In 2018, Giron-Arango et al. described a novel technique for regional hip analgesia, and named it the pericapsular nerve group (PENG) block. (8) They reported a NRS pain score reduction of 7 points (out of 10) compared to a baseline of intravenous opiates only for analgesia. They noted a purely sensory blockade, so without motor impairment. These claims were based on a small case series of only five patients who received the PENG block. Additional series have not included large patient numbers either. (20) Therefore, the current study was conducted to test the PENG block in a double blinded randomized comparative fashion.

PATIENTS AND METHODS

This is a single-center, double blinded, randomized comparative trial conducted at Flinders Medical Centre (FMC), a tertiary trauma hospital in Adelaide, Australia. Institutional ethics approval was obtained (SALHN/HREC/218.19), and written informed consent was acquired from all participants. The trial was registered prior to commencement (NTR; NL8043; principal investigator: D-Y.L; date of registration: 12th of September 2019, URL: https://www.trialregister.nl/trial/8043).This study conforms to the Consolidated Standards of Reporting Trials (CONSORT) and the CONSORT extension for trials reporting patient-related outcomes. (21, 22) The study ran from February 12 to September 25, 2020 and was paused temporarily from March 18 to May 5, 2020 due to local SARS-2 Covid-19 virus pandemic restrictions.

The inclusion criteria were patients with a hip fracture presenting for surgery, aged 45 years and over, without contraindications for regional anesthesia, who were able to provide informed consent and reliably report symptoms to the research team. The exclusion criterion was an inability to provide first party consent due to cognitive impairment or a language barrier.

RANDOMIZATION, BLINDING AND STUDY INTERVENTION

Randomization was performed by an online randomization computer generator (www.sealedenvelope.com) on a 1:1 basis.

Members of the surgical, anesthetic, Acute Pain Service (APS), study and nursing staff were blinded for the intervention, as well as the patient. To ensure blinding, the anesthesiologist

placing the block preoperatively was different from the anesthesiologist managing the patient intra- and postoperatively.

The allocated block was placed 15-45 minutes preoperatively using ultrasound guidance. All blocks used 20mLs of ropivaicaine 0.75%. (See Appendix 1 for the technical descriptions and ultrasound images of block placement)

Surgical technique and type of anesthesia were performed at the discretion of the treating physicians, using a local protocol which allowed for variation within a small range. The study was designed to represent daily practice, and to achieve high external validity.

Pain scores were recorded using a NRS ranging from 0 to 10, with 0 being the absence of pain and 10 the worst pain imaginable. Pain scores were obtained preoperatively (baseline), 4-hours postoperatively in the Recovery Unit (Day 0), and on postoperative Day 1. The maximum pain score during active movement (quadriceps strength test) was the pain score used.

OUTCOME MEASURES

Primary outcome was the postoperative NRS pain score measured in the Recovery Unit (Day 0) at 4 hours postoperatively.

Secondary outcomes were: NRS pain scores on Day 1 post-operatively, postoperative quadriceps strength, perioperative opiate use, postoperative complications, length of hospital stay, patient satisfaction and patient reported outcomes measures (PROMs).

Quadriceps strength was assessed using the knee extension test (23) and Oxford muscle strength grading (24) with grouped scores of intact (5/5), reduced (1-4/5) and absent (0/5).

Opiate use was reported as use intraoperatively, on Day 0, use for each postoperative day for three days, and the total opiate use. Quantities were converted to oral morphine equivalents.

On Day 1, parameters of patient satisfaction, pain experienced, and quality of recovery were evaluated using the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks for evaluation of depression and pain interference, Brief Pain Inventory (BPI) and the Quality of Recovery (QoR-15) questionnaires. (Appendix 2) The APS assessed patient satisfaction and pain management on Day 1. Patients were asked to recall the time the block wore off, defined as return of motor (if initially impaired) and/or sensory recovery.

Complications were reported according to the Clavien-Dindo classification. (25)

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSES

The *a priori* power calculation was carried out using PASS 14 Power Analysis and Sample Size Software (Kaysville, Utah, USA) based on pain score reductions reported in previous publications. (8, 18) These reports showed a mean pain score reduction after FNB of 3.4 points, and 7 points after PENG block (both out of 10) on the day of the procedure, with a standard deviation of 2 points. (8) There are no studies directly comparing the two, hence we have compiled the results for FNB from the Cochrane review, and the PENG block from the case series. We incorporated that, despite clinical familiarity with the PENG block, we would be less experienced than the group who described the PENG block first, and selected a standard deviation of 3. A two-tailed independent-samples t-test for the difference between two unpaired means with an alpha-error of 0.05, beta-error of 0.2, and power of 0.95 were used. This showed that, to detect a pain score difference of 3 (out of 10) with a standard deviation of 3 points, 30 patients in each arm would be required, including an attrition rate of 15%, giving a total number of 60 patients for more than 95% power.

Data entry and statistical analyses were conducted in a blinded fashion. The analysis was performed on an intention-to-treat basis using SPSS version 27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software, La Jolla, Calif, USA). Parametricity of continuous variables was determined using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean with standard deviation, and nonparametric variables as median with range. Univariate analysis was carried out using the chi-squared test or Fisher's exact test for categorical variables; the Mann-Whitney U-test for nonparametric continuous variables and the Student's t-test for parametric continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 159 patients were admitted to FMC with a hip fracture requiring surgery and screened for eligibility. Ninety-three patients did not meet the inclusion criteria: 14 were younger than 45 years old, and 79 patients had dementia, other cognitive impairments or a language barrier. Three patients declined to participate and another three could not be recruited due to logistical reasons, leaving 60 patients who were consented and randomized equally between both groups for inclusion. (Flowchart 1) All patients completed the study and could be included in the final analysis as intention to treat without loss to follow up.

The preoperative demographics of both groups were similar, including baseline NRS pain scores, incidence of chronic pain and anxiety or depression. Anaesthetic and surgical techniques used were also similar between both groups. (Table 1)

Table 1: Patient and preoperative characteristics.

	Femoral nerve block (n=30)	**PENG** (n=30)	**p-value**
Age in years, mean (±SD)[a]	79.7 (±11.5)	77.2 (±11.6)	0.39
Gender, n (%)[d]			
Male	7 (23)	14 (47)	0.10
Female	23 (77)	16 (53)	
Weight in kg, mean (±SD)[a]	65.0 (±15.7)	65.6 (±17.8)	0.89
BMI in kg/m^2, median (IQR)[b]	23.8 (20.8-27)	24.5 (20-28)	0.84
Mobility, n (%)[e]			
Independent, no aids	17 (57)	19 (63)	0.60
Assisted (stick, walker or wheelchair)	13 (43)	11 (37)	
Residence, n (%)[d]			
Home	28 (93)	24 (80)	0.25
Assisted living or nursing home	2 (7)	6 (20)	
ASA score, n (%)[e]			
I	2 (7)	1 (3)	0.68

II III IV	3 (10) 21 (70) 4 (13)	5 (17) 22 (73) 2 (7)	
Chronic opiate use, n (%)[d] Yes No	7 (23) 23 (77)	12 (40) 18 (60)	0.27
Anxiety and/or depression, n (%)[e] Yes No	10 (33) 20 (67)	14 (47) 16 (53)	0.29
Mechanism of injury, n (%)[e] Mechanical fall Medical collapse High velocity trauma	25 (84) 4 (13) 1 (3)	28 (94) 1 (3) 1 (3)	0.37
Fracture side, n (%)[e] Left Right	12 (40) 18 (60)	14 (47) 16 (53)	0.60
Type of fracture, n (%)[d]			

Intracapsular	10 (33)	9 (30)	0.66
Extracapsular	20 (67)	21 (70)	
Type of surgical repair, n (%)[e]			
Gamma nail	13 (43)	11 (36)	0.95
Cannulated screw	5 (17)	5 (17)	
Hemiarthroplasty	8 (27)	9 (30)	
Total hip replacement	4 (13)	5 (17)	
Preoperative pain score (NRS), n (%)[e]			
None (0)	0 (0)	0 (0)	0.49
Mild (1-4)	4 (13)	2 (7)	
Moderate (5-7)	6 (20)	4 (13)	
Severe (8-10)	20 (67)	24 (80)	
Preoperative pain score (NRS), median (IQR)[b]	8 (7-10)	9 (8-10)	0.25
Type of anaesthesia for surgery, n (%)[e]			
General	20 (67)	18 (60)	0.43
Spinal	10 (33)	13[c] (43)	

Intrathecal morphine, n (%)[d]			
Yes	2 (7)	5 (17)	0.42
No	28 (93)	25 (83)	
Intravenous dexamethasone, n (%)[e]			
No	13 (43)	10 (33)	0.16
4mg	8 (27)	4 (13)	
8mg	9 (30)	16 (54)	

[a] Student's t-test used.

[b] Mann-Whitney U-test used.

[c] One patient converted from spinal to general anaesthesia.

[d] Fisher's exact test used.

[e] Chi-squared test used.

Abbreviations: SD: standard deviation, PENG: pericapsular nerve group block, NRS: numeric rating scale.

PRIMARY OUTCOME

Postoperative pain scores in the Recovery Unit (Day 0) were significantly different between groups, with 19 patients (63%) in the PENG group experiencing no pain, compared to 9 patients (30%) in the FNB group (p=0.04). In both groups, 8 patients (27%) reported mild

pain, defined as a NRS score of 1-4 points. In the PENG group, a total of 3 patients (10%) experienced moderate or severe pain, compared to 11 patients (36%) in the FNB group. (Table 2)

Two patients could not provide answers to the questions due to sedation or confusion in Recovery.

Table 2: Postoperative pain and motor outcomes.

	Femoral nerve block (n=30)	**PENG** (n=30)	**P-value**
Maximum postoperative pain score (NRS) in Recovery Unit (Day 0), n (%)[a]			
None (0)	9 (30)	19 (63)	**0.04**
Mild (1-4)	8 (27)	8 (27)	
Moderate (5-7)	7 (23)	1 (3)	
Severe (8-10)	4 (13)	2 (7)	
Unable to assess due to delirium	*2 (7)*	*0 (0)*	
Quadriceps strength in recovery, n (%)[a]			
Intact	0 (0)	18 (60)	**<0.001**

Reduced	11 (37)	8 (26)	
Absent	12 (40)	2 (7)	
Unable to assess	*7 (23)*	*2 (7)*	
Maximum postoperative pain score (NRS) on Day 1, n (%)[a]			
None (0)	2 (7)	6 (20)	0.53
Mild (1-4)	11 (37)	12 (40)	
Moderate (5-7)	7 (23)	7 (23)	
Severe (8-10)	7 (23)	5 (17)	
Unable to assess due to delirium	*3 (10)*	*0 (0)*	
Quadriceps strength on Day 1, n (%)[a]			
Intact	15 (50)	27 (90)	**0.004**
Reduced	10 (33)	2 (7)	
Absent	0 (0)	0 (0)	
Unable to assess	*5 (17)*	*1 (3)*	

[a] Chi-squared test used.

[b] Fisher's exact test used.

Abbreviations; PENG: Pericapsular nerve group block, NRS: Numeric rating scale.

SECONDARY OUTCOMES

On Day 1, pain scores were similar between both groups (p=0.53). Three patients were unable to report a pain score due to confusion or delirium.

Quadriceps strength was better preserved in the PENG group, both in the Recovery Unit (Day 0) (p<0.001) and on Day 1 (p=0.004). In Recovery, eighteen patients (60%) in the PENG group had intact quadriceps strength, eight (26%) had reduced quadriceps strength, and two (7%) had no motor capability. Two patients (7%) could not be assessed due to confusion or refusal. In comparison: No patient in the FNB group had intact quadriceps strength, 11 (37%) had reduced strength and in 12 patients (40%) had no motor capability. Seven patients (23%) could not be assessed. (Table 2)

On the 0 to 5 Clavien-Dindo scale, as well as the pooled categories, complication rates were similar between both groups. Specifically, the incidence of delirium was also similar: 6 patients (20%) in each group. (Table 3)

Patients were more satisfied with the analgesia received in the PENG group: 29 patients (97%) were satisfied, and one (3%) was ambivalent. No patient was dissatisfied. In the FNB group, 21 patients (70%) were satisfied, eight (27%) ambivalent, and one patient (3%) was dissatisfied (p=0.02). There was no difference in the patient-reported outcomes in the questionnaires. (Table 4) Twelve patients (six in each group) could not complete the postoperative questionnaires due to delirium, and three declined to complete the questionnaires due to general malaise or tiredness.

Postoperative opiate use was similar between both groups. (Table 5)

Table 3: Postoperative outcomes.

	Femoral nerve block (n=30)	**PENG** (n=30)	**P-value**
Complications, n (%)			
Pneumonia	2 (7)	4 (13)	
Renal failure	3 (10)	2 (7)	
Blood transfusion	7 (23)	3 (10)	
Wound infection	1 (3)	0 (0)	
Reoperation	1 (3)	0 (0)	
Delirium	6 (20)	6 (20)	
In hospital collapse	1 (3)	3 (10)	
STEMI/NSTEMI	1 (3)	2 (7)	
Unplanned ICU admission	3 (10)	1 (3)	
Death	1 (3)	0 (0)	
In hospital falls, n (%)[d]			
Fall as inpatient	2 (7)	0 (0)	0.50
No fall recorded	28 (93)	30 (100)	
Clavien-Dindo complication scale, n (%)[e]			

0 I II III IV V	14 (47) 1 (3) 9 (30) 2 (7) 3 (10) 1 (3)	15 (50) 8 (27) 6 (20) 0 (0) 1 (3) 0 (0)	0.07
Grouped Clavien-Dindo complications, n (%)[d] None-mild (grade 0-II) Moderate-severe (grade III-V)	 24 (80) 6 (20)	 29 (97) 1 (3)	 0.10

[d] Fisher's exact test used.

[e] Chi-squared test used.

Abbreviations: N/A: Not applicable, PENG: Pericapsular nerve group block, STEMI: S-T elevation myocardial infarction, NSTEMI: Non S-T elevation myocardial infarction.

Table 4: Patient outcome questionnaires.

	Femoral nerve block (n=20)[c]	**PENG** (n=25)[d]	**P-value**
QOR-15, mean (±SD)[a]	94.1 (±4.6)	94.0 (±4.1)	0.99
Brief Pain Inventory, mean (±SD)[a]	2.0 (±0.8)	2.50 (±0.5)	0.80
PROMIS Pain Inference, median (IQR)[b]	21 (18-24)	23.5 (18-26)	0.49
PROMIS Emotional Distress, median (IQR)[b]	14 (12-20)	12 (10-17)	0.49
Patient satisfaction, n (%)[e]			
Unsatisfied	1 (3)	0 (0)	**0.02**

Satisfied Ambivalent	21 (70) 8 (27)	29 (97) 1 (3)	
Would have the block again, n (%)[e] Yes No Ambivalent	 26 (87) 1 (3) 3 (10)	 30 (100) 0 (0) 0 (0)	 **0.02**

[a] Student's t-test used.

[b] Mann-Whitney U-test used.

[c] 9 patients were unable to complete surveys due to delirium or patient refusal.

[d] 6 patients were unable to complete surveys due to delirium or patient refusal.

[e] Chi-squared test used.

Abbreviations: SD standard deviation, PENG: Pericapsular nerve group block, QoR-15: Quality of Recovery 15, PROMIS: Patient-Reported Outcomes Measurement Information, System: SD: Standard deviation.

Table 5: Postoperative opiate use.

	Femoral nerve block (n=30)	**PENG** (n=30)	**P-value**
Postoperative opiate use in morphine equivalents (mg), median (IQR)[a]			
Intraoperative	22.5 (8.8-53)	20 (0-50)	0.37
Day 0 (total)	55 (36.5-80.1)	53.25 (32.3-86)	0.85
Day 1	17.5 (8-33.8)	13.5 (8-32)	0.59
Day 2	12.25 (7-32.5)	8 (0-28.5)	0.41
Day 3	8 (0-16.8)	0 (0-17.8)	0.62
Total	105.25 (54.6-175)	82.5 (0-165.5)	0.65

[a] Mann-Whitney U-test used.

Abbreviations: PENG: Pericapsular nerve group block, mg: milligrams.

ADVERSE EVENTS AND PROTOCOL DEVIATIONS

In one case, the patient and the APS became unblinded for which block the patient had received, after unintentional mention of this by an observing trainee anesthesiologist. Another patient had their spinal anesthesia converted to general anesthesia due to a large haemoptysis and aspiration during surgery.

DISCUSSION

This randomized comparative trial shows that the PENG block provides better perioperative analgesia than the FNB. Postoperative pain scores were significantly improved in the PENG group compared to the FNB group.

Previous publications on the PENG block have been limited to case series including small numbers of patients only. Giron-Arango, et al. included 5 patients and suggested a post-procedure 7 point NRS reduction. (8) This is consistent with other published case series. (26, 27, 28, 29) The authors of the first PENG block publication compared the PENG block efficacy with already published results of the FNB from a Cochrane systematic review by Guay et al. (18) . The FNB showed a pain score reduction of 3.4 points. The current randomized comparative trial now confirms these preliminary conclusions that the PENG block offers improved pain relief compared to the FNB.

Postoperative quadriceps strength in the Recovery Unit on Day 0 and on Day 1 was significantly better maintained in the PENG group compared to the FNB group. Better preserved quadriceps strength allows patients to mobilise earlier following their hip fracture surgery, which is associated with less complications, lower mortality, less pain and shorter length of stay. (30, 31, 32)

Some PENG patients did experience loss in muscle strength. Both patients with no motor capability had received spinal anaesthesia, and the motor effect was bilateral at 4 hours postoperative. Hence, we believe this is likely a residual effect of the spinal anesthetic.(33, 34) Also, we found that patients were sometimes still residually sedated in Recovery, or

couldn't fully understand instructions. It could also be due to the high concentration of local anesthetic used in this trial for both the FNB and PENG block (ropivacaine 0.75% 20mLs). It is possible that this produces some motor weakness, which is an aspect that would have to be investigated further. This could have resulted in a higher than expected impedence of quadriceps strength after PENG and FNB blocks. In future studies, we plan to decrease our concentration of local anesthesia as the pain relief is likely to be sufficient also at a lower dose.

There were two in-hospital falls recorded in the FNB group, while none were seen in the PENG group. The effect of the FNB could have been a contributing factor, although the number of incidents was too low to show this statistically, as the trial was not powered for this complication (p=0.50). (35)

Furthermore, no adverse events directly related to block placement were reported in either group.

Patient satisfaction was significantly better after PENG block (p=0.02). The other PROMs were similar between groups. The relatively high number of patients who declined to complete the questionnaires due to general malaise, especially in the FNB group, could have been a contributing factor to this. The scores obtained from the QoR-15 in both groups were lower than those reported by Myles et al. However, these PROMs were conducted in younger and less frail patients. (36) Trials involving elderly patients with extensive comorbidities reported similar QoR-15 scores to those found in this study. (37)

The similar opiate use in both groups could have been due to the advanced age of the hip fracture patients, their low baseline opiate use and the hospital's threshold to administer opioids in view of its side-effects in elderly. This study was not powered to detect a

difference in opiate use between the groups; a much larger cohort study would be needed to investigate this in the future.

LIMITATIONS

Some limitations of the study have to be addressed. This trial was conducted in a relatively small number of patients. However, because the power calculation was based on small PENG reports, we decided to increase the patient numbers for the current trial in the power calculations in order to minimize the risk of an underpowered study. Therefore, we are confident that the significant difference between groups for the primary outcome (postoperative pain) reflects a true difference between both blocks. It is possible that the secondary outcomes would have also reflected a difference, but our power calculation was based on the primary outcome. Hence, this study is likely too small to detect differences in the secondary outcomes such as opiate use reduction and incidence of complications, specifically in hospital falls.

We adopted a pragmatic approach, allowing surgeons and anesthesiologists to select their own treatments. This was to allow daily practice to be reflected in this study, as variation at our centre is minimal due to institutional standards of care. Further sensitivity analysis did not show a trend towards significance for the choice of spinal or general anesthesia.

Hip fracture patients are mostly elderly and frail, with a high incidence of dementia. (38) Due to our stringent patient selection to eliminate patients with any degree of cognitive impairment, a large number of patients had to be excluded, potentially inflicting a selection bias. The next step to further investigate the PENG block would be a large cohort study in the general hip fracture population.

Ideally, we would have conducted the PROMs preoperatively also, to obtain a baseline for each patient. This, however, was not feasible due to the emergency nature of hip fracture surgery.

CONCLUSION

Patients receiving a PENG block for intra- and postoperative analgesia during hip fracture surgery experience less postoperative pain in the recovery room with no difference detected by postoperative day 1. Quadriceps strength was better preserved with the PENG block. Despite the short-term analgesic benefit and improved quadriceps strength, there were no differences detected in the quality of recovery. For hip fracture surgery, the PENG block should be considered to reduce perioperative pain.

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DISCLOSURES

None.

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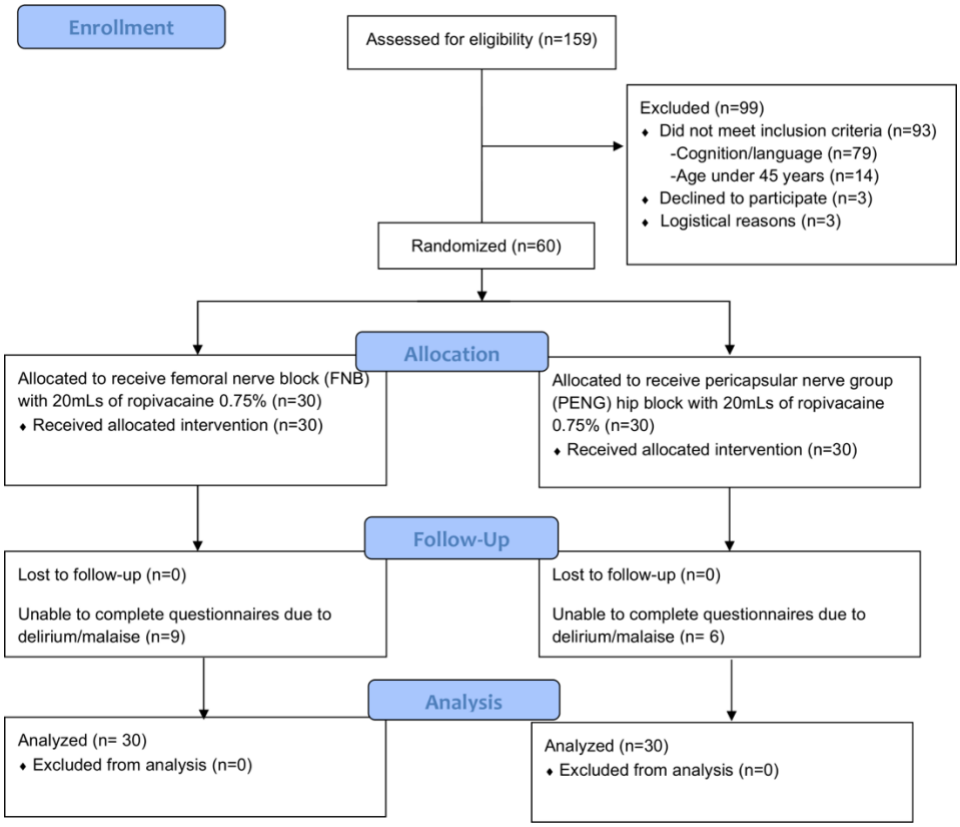


Figure 1 CONSORT study flowchart. CONSORT, Consolidated Standards of Reporting Trials; FNB, femoral nerve block; PENG block, pericapsular nerve group block.

APPENDIX 1.

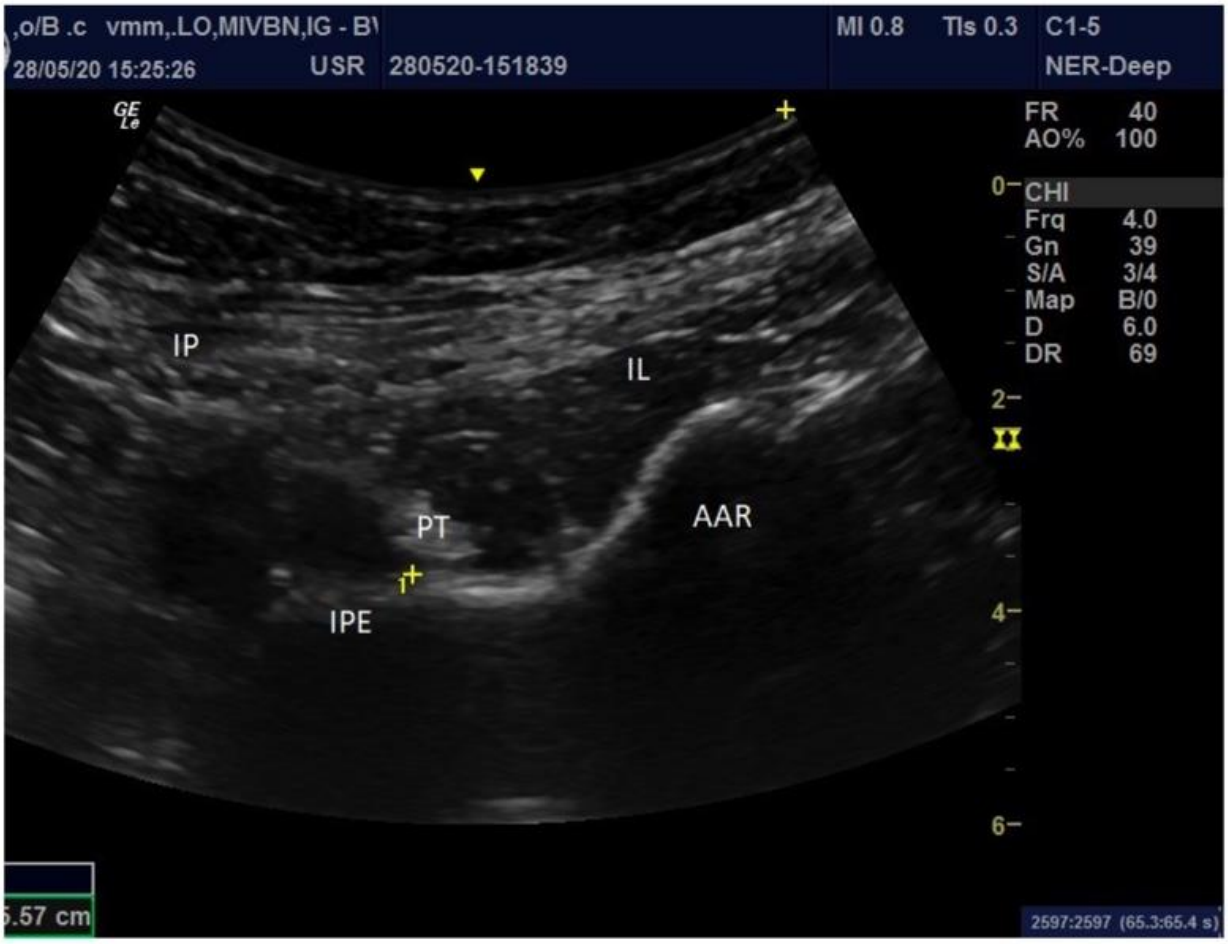
TECHNICAL DESCRIPTION OF PENG AND FNB BLOCK PLACEMENT

For placement of the PENG block, a low frequency (2.5-5MHz) curvilinear ultrasound probe was used. The transducer was placed in a longitudinal plane with the lateral edge over the anterior inferior iliac spine. The median edge of the probe was rotated caudally to obtain an adequate view of the fascial plane under the psoas tendon along the acetabulum. (Figure 1) A 21-Gauge 100mm Sonoplex needle (Pajunk, Geisingen, Germany) was inserted and an aspiration check performed prior to a 20 mL injection of local anesthetic solution into the sub-psoas fascial plane. (Figure 2). The local anesthetic was ropivacaine 0.75%, unless the patient weighed less than 50 kilograms in which case the concentration was adjusted for a maximum of 3mg/kg, and volume maintained at 20mLs.

To perform the FNB, a high frequency (5-10MHz) linear ultrasound transducer was used, placed over the inguinal crease, and the femoral nerve was visualised at this level. A 21-Gauge 50mm Sonoplex needle was inserted and an aspiration check performed prior to perineural local anaesthetic injection of 20mLs.

FIGURE LEGENDS

Figure S1: Ultrasound sonoanatomy of PENG block
Ultrasound image obtained for PENG block placement using a curvilinear probe.

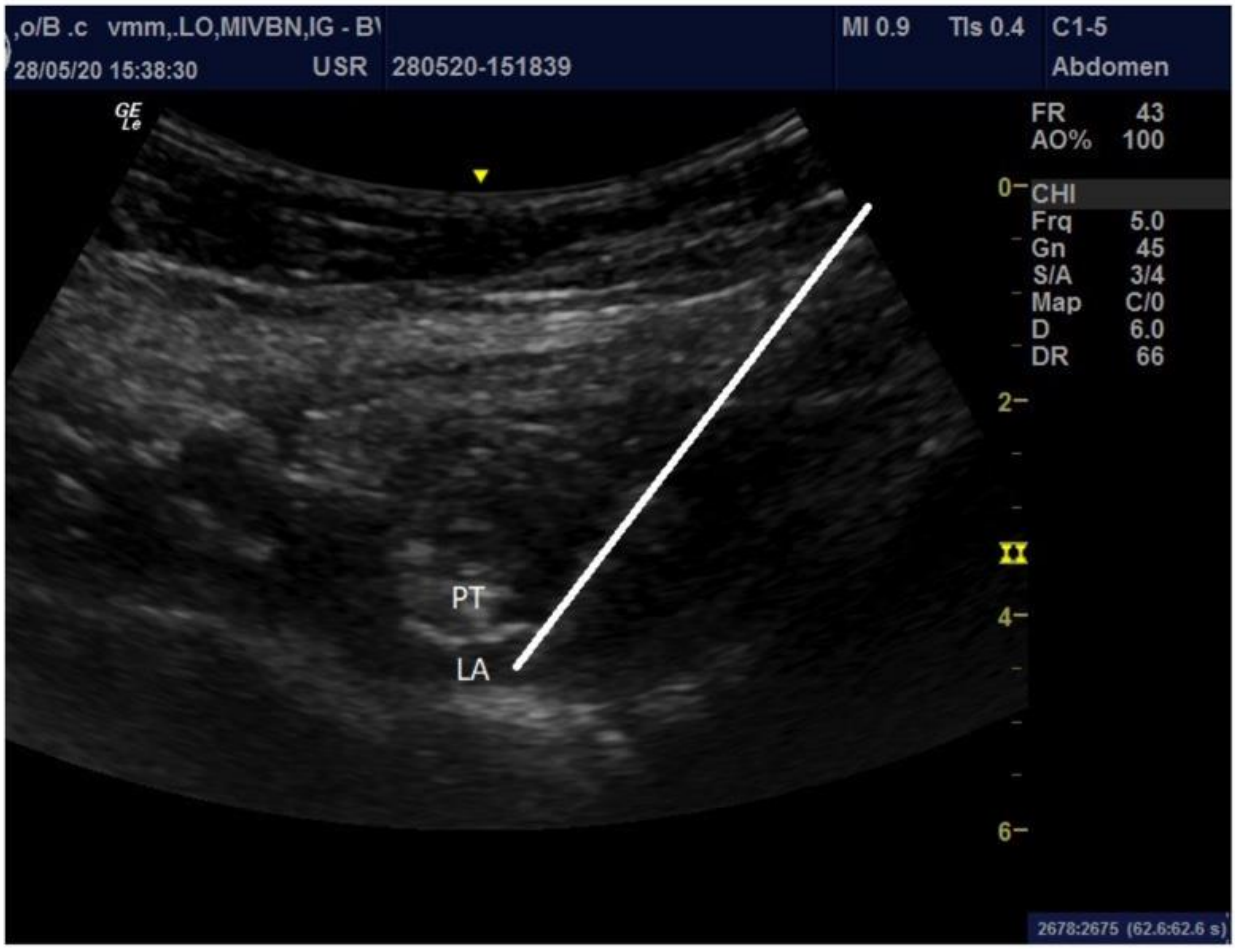


IPE: iliopubic eminence
AAR: anterior acetabular rim
PT: psoas tendon

IL: iliacus muscle IP: iliopsoas muscle

Figure S2: Injection and spread of local anesthetic in PENG block placement

Injection of local anesthetic into the tissue plane under the psoas tendon. Hydrodissection with a white fascial layer above is clearly seen. The path of the needle is demarcated by the white line.



PT: psoas tendon

LA: local anesthetic

APPENDIX 2.

QUESTIONNAIRES

The QoR-15 is a multidimensional patient reported item bank. It is used to assess functional recovery. Cronbach reliability is estimated at an alpha of 0.836. (1) The QoR-15 assesses five areas: pain, emotional state, comfort, physical independence and psychological support. (2) A QoR-15 global score (maximum 150 points) of 118 is considered to correlate with a good recovery (3).

The short form of the Brief Pain Inventory (BPI) questionnaire was designed to measure pain and interference from pain with the patient's physical and emotional functionality. (4) Cronbach reliability ranges from an alpha of 0.78 to 0.96. Complete relief is scored with a 0, and no relief corresponds to a score of 10. A lower global BPI score corresponds to less interference and less pain. There were two Patient-Related Outcomes Measurement Information System (PROMIS) used: the pain interference and depression item banks. These have been developed using item response theory, and have been validated in the orthopaedic population. (4-6)

The PROMIS pain interference questionnaire assesses the impact of pain on general enjoyment, concentration, daily activities, recreational enjoyment, tasks, and socialization. Cronbach reliability is estimated at an alpha of 0.99.(7) A higher score corresponds to a greater degree of interference. The PROMIS depression item bank has been designed to assess emotional distress from depressive symptoms. Cronbach reliability ranges from an alpha of 0.88 to 1.0.(8) A higher score corresponds to more depressive symptomology.

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Part I, Chapter 3

The Association of Anesthesia and Analgesia with Long Term Mortality after Hip Fracture Surgery: An Analysis of the Australian and New Zealand Hip Fracture Registry.

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LIST OF ABBREVIATIONS

ANZHFR: Australian and New Zealand Hip Fracture Registry

OR: Odds ratio

HR: Hazard ratio

IQR: Interquartile range

SD: Standard deviation

ED: Emergency department

KPI: Key performance indicator

MAR: Missing at random

TMLE: Targeted maximum likelihood estimation (Appendix 1.)

ABSTRACT

Introduction: Hip fractures are a common frailty injury affecting a vulnerable geriatric population. It is debated if anesthetic and analgesic techniques are associated with altered risk for outcomes in hip fracture patients. This study aimed to determine the association of anesthesia and regional analgesia with all cause 12-month mortality and even longer-term mortality after hip fracture surgery in Australia and New Zealand.

Methods: Data from the Australian and New Zealand Hip Fracture Registry (ANZHFR) collected from 2016 to 2018, with a minimum follow-up of 12 months, were reviewed. Anesthesia type and use of regional nerve blocks were investigated. The primary outcome was all cause 12-month mortality.

Results: 12-month mortality was 30.6% (n=5,410) in a total of 17,635 patients. There was no difference in 12-month mortality between patients who received spinal or general anesthesia (p=0.238). The administration of a combination of general and spinal anesthesia for surgery to repair the fracture was an independent predictor of higher 12-month mortality (unadjusted complete case hazard ratio (HR)= 1.17 (1.04, 1.31); p<0.001). Nerve blocks performed in both the emergency department (ED) and the operating theatre (OT) were associated with reduced long-term mortality (median follow-up 21 months) with an unimputed unadjusted HR=0.86 (0.77, 0.96; p=0.043).

Conclusion: There was no difference in the association of 12-month mortality between general and spinal anesthesia in patients undergoing hip fracture surgery. However, there was an association with a higher risk of 12-month mortality in patients who received both general and spinal anesthesia for the same surgery. Patients who received a regional nerve block in both ED and OT possibly had a lower association of 12-month and longer-term

mortality risk. The reasons for these findings remain unknown and should be the subject of further research investigation.

Summary:

The long term (12+ months) mortality effects of anesthesia and analgesia for fragility fracture surgery are not well known.

This retrospective analysis of a large international registry dataset suggests that there is a higher risk of mortality if both a general and spinal anesthetic are administered for one hip fracture repair surgery.

This was examined by complete case analysis using Kaplan-Meier method and multivariable Cox regression modelling to assess 12-month mortality and longer-term associations.

There was possibly a lower risk of long term mortality if both the treating Emergency Department physician and anesthesiologist administer a regional analgesia technique.

There was no difference in association with long term mortality between spinal and general anesthesia.

This may influence practitioners to include regional nerve blocks in their analgesia regime, and to carefully consider all factors when selecting a primary form of anesthesia for hip fracture surgery.

INTRODUCTION

Hip fractures are a common and debilitating injury, occurring predominantly in the older population. (1) Seventy percent of the hip fracture population are aged 80 years or older and often have a frail preoperative status with multiple medical comorbidities. (2) The required hip fracture surgery and associated anesthetic can pose a significant risk. In-hospital or short-term mortality is relatively low, but long-term mortality is significantly higher with 12-month mortality rates reported as high as 21-33%. (3-5). While the causes of longer-term mortality are certainly multifactorial, anesthetic technique May influence long-term mortality through reduction of harm associated with perioperative cardiac, respiratory or cognitive disturbances. Currently, the optimal anesthetic and analgesic technique to minimise long term mortality is not known. (6-9) (10) A Cochrane review found no difference in short-term (30-day) mortality between spinal and general anesthesia, and highlighted the paucity of evidence examining the combination of both spinal and general anesthesia for the same surgery. (11) The REGAIN study found no difference in 60-day mortality between spinal and general anesthesia. (12) Two meta-analyses found no or limited difference in long-term mortality between techniques, but due to limited evidence, both studies concluded that further studies were required. (13, 14) The RAGA study (15) did not find a difference in the incidence of delirium between spinal or general anesthesia, and a secondary outcome of 30-day all-cause mortality was not significantly different between the two groups.

The effect of regional block analgesia on mortality in hip fracture surgery is also inconclusive; a Cochrane meta-analysis concluded there was no change in mortality after their use, but noted that numbers were insufficient for proper analysis. (10) Despite the

limited research findings, there has been increased uptake of regional nerve blocks for hip fracture analgesia and their use as analgesia adjuncts is recommended in some national guidelines. (16, 17) Therefore incidence of associated morbidity and mortality are important to understand.

The Australian and New Zealand Hip Fracture Registry (ANZHFR) is a comprehensive international prospective database in which peri-operative data including long-term follow-up (12 months and longer) are collected from hospitals in Australia and New Zealand performing hip fracture surgery. In 2021, over 10,000 patients were added to the ANZHFR. Due to its size, prospective nature and long-term follow up, the ANZHFR has the potential to investigate long-term effects on a population level. Therefore, this study aimed to identify anesthetic and regional analgesic associations for 12-month and even longer term all cause mortality after hip fracture surgery by analysing the ANZHFR.

METHODS

The ANZHFR is a comprehensive international database to which 67 public hospitals from Australia and New Zealand who perform hip fracture surgery contribute. Thirty-six variables are collected from medical records and operative notes using a standardized format. (18) Institutional ethics approval for this study was obtained (SALHN/HREC/262.19). Reporting was according to the STROBE guidelines for observational trials. (19)

This is a retrospective analysis of a large international database. Twelve month mortality was defined as death from any cause within 12 months from the index surgery. Even longer term mortality was defined as death from any cause during the follow up period of the ANZHFR, which was a median of 21 months (range 0-48).

The first primary outcome was the impact of type of anesthetic on 12 month mortality. This could be general, spinal or both. The second primary outcome was the effect on mortality of administering a regional block to the participant. This could be a block performed in the emergency department, in the operating theatre, or both. Secondary outcomes were longer term mortality after 12 months for both categories. All other statistical explorations functioned as sensitivity checks only (see Statistical Analyses). Study variables and categories are listed in Table 1.

Twelve month mortality and even longer term mortality following hip fracture surgery is relevant in this patient population and used as a key performance indicator (KPI) in some databases. (5, 38, 39) 12-month mortality is seen to be a useful indicator of medium-term follow-up and might potentially be different to the results for longer term mortality.

Study participants

Patients recorded in the ANZHFR, admitted and discharged between 1st January 2016 and 31st December 2018 with a minimum follow-up of one year (31st December 2019) or until death, whichever occurred earlier, were included. Patients were excluded if the date of surgery or the date of hospital discharge was not documented, or if the type of anesthesia or regional analgesia data were missing.

Subjects with no value for the date of death variable were assumed to have not died, as this is how the ANZHFR data entry was intended. The ANZHFR is cross-linked with other Australian and New Zealand government data registries, including the Registry of Births and Deaths, lending the mortality data a high degree of reliability.

Follow-up time for the survival analysis was calculated in days as the time between the date of surgery and either the date of death or the 31st December 2019, whichever occurred earlier. Subjects that remained alive at the end of follow-up were censored.

Anesthesia and Analgesia Type (Independent Variables)

Variables of interest were type of anesthesia and use of regional analgesia in the emergency department and operating theatre. Types of anesthetic analyzed were general anesthesia, spinal anesthesia, or both. Analgesia was a documented regional nerve block prior to surgery in the emergency department (ED), the operating theatre (OT), both, or neither.

Mortality (Dependent Variable)

Outcomes were 12-month and long-term (at end of follow-up) mortality.

Patient characteristics were described according to their vital status (alive/deceased at the end of follow-up) using mean and standard deviation (SD) as all continuous variables were

normally distributed (Shapiro-Wilk test). Univariable and multivariable Cox regression were used to assess the association between type of anesthetic, type and location (ED/OT) of the regional analgesia, and 12-month mortality from the date of surgery.

Covariates

Participant clinical characteristics, which were used as covariates in the multivariable Cox regression analyses, were obtained from the ANZHFR. The characteristics and categorisation are provided in Table 1 for each variable.

Variables were included a priori based upon clinical relevancy. Categorical variables were described as frequency counts and percentage. Differences in patient characteristics and unadjusted outcomes were assessed using independent t-test and chi-square test as appropriate.

The multivariable Cox regression models were adjusted for age, gender, ASA grade, usual residence, dementia/delirium, pre-admission walking status, use of bone protective medications, fracture type, surgery delay, time-to-surgery, type of operation, mobilization after surgery, postoperative pressure ulcers, and postoperative ward type. This was based on the availability of variables in the dataset provided by the ANZHFR.

Statistical Analyses

The effect of the type of anesthetic, and the type and location of regional nerve block on long-term mortality (at the end of follow-up) were assessed using the Kaplan-Meier method and using univariable and multivariable Cox regression models with type of anesthetic, and type and location of regional block included as the two independent variables of interest.

For each analysis, the test of proportional hazard was assessed by checking the parallel structure of the log-log plot of the survival curves for each covariate of interest (anesthesia and analgesia) and the closeness of the Kaplan-Meier and the predicted survival curves. The 95% Confidence Intervals for the Kaplan-Meier curves were calculated using the exponential Greenwood formula.

For the Cox regression analysis, four different analyses were conducted for anesthesia type and the type and location of regional analgesia: a univariable analysis without imputation, a univariable analysis with imputation, and a multivariable analysis with and without imputation. The complete case analysis for 12 month mortality served as the primary analysis. Any case with a missing value was discarded. The other analyses functioned as sensitivity checks only (Appendix 1.)

A two-sided type 1 error of alpha=0.05 was used for significance testing. Descriptive statistics, regression analysis, and multiple imputation were performed using Stata version 17.0 (StataCorp, USA). Kaplan-Meier curves were estimated and plotted using Python (version 3.8.3) with the “lifelines” package (version 0.26.3).

RESULTS

Patients

The dataset included 17,635 patients (Figure 1). Of these, twenty-eight percent had at least one covariate missing and were excluded from the primary non-imputed analyses, reducing the cohort to 12,840. These 12,840 patients were treated as the complete case dataset for analysis.

Outcome Data

Of the total 17,635 patients, 12,225 survived until the end of follow-up (31st December 2019) and 5,410 (30.6%) had died. There were significant differences in patient characteristics between groups for age, gender, usual residence, ASA-grade, dementia, bone protective medication use, pre-admission walking ability, type of fracture, days to surgery after the fracture, delayed surgery, type and location (ED/OT) of regional analgesia given during surgery, type of operation, mobilization post-surgery, and the development of pressure ulcer postoperatively (p<0.001 for all). (Table 1)

Table 1: Demographic, clinical characteristics and completeness of data by vital status at the end of follow-up.

	Survived (n=8,774)	Died (n=4,066)	p-value
Gender, n (%)			
Male	6,428 (73.2)	2,540 (62.5)	<0.001
Female	2, 346 (26.7)	1,526 (37.5)	
Age (years), mean (SD)	82.2 (8.1)	86.1 (7.5)	<0.001
Age category, n (%)			
65-75 years	1,999 (22.7)	399 (9.8)	<0.001
76-81 years	1,861 (21.2)	623 (15.3)	
82-85 years	1,558 (17.8)	653 (16.1)	
86-90 years	1,962 (22.4)	1,156 (28.4)	

91-108 years	1,394 (15.9)	1,235 (30.4)	
ASA Grade, n (%)			
1	312 (3.6)	89 (2.2)	<0.001
2	1,948 (22.2)	217 (5.3)	
3	5,238 (59.7)	2,289 (56.3)	
4	1,264 (14.4)	1,453 (35.8)	
5	12 (0.1)	18 (0.4)	
Usual residence, n (%)			
Private residence (including unit in retirement village)	6,950 (79.2)	2,198 (54.1)	<0.001
Residential aged care facility	1,788 (20.4)	1,853 (45.6)	
Other	36 (0.4)	15 (0.3)	
Dementia, n (%)			
No	6,162 (70.2)	1,765 (43.4)	<0.001
Yes	2,612 (29.8)	2,301 (56.6)	
Pre-admission walking ability, n (%)			
without walking aids	4,672 (53.3)	1,177 (28.9)	<0.001
with stick or crutch	1,158 (13.2)	507 (12.5)	
walks with aids/frame	2,756 (31.4)	2,186 (53.8)	
wheelchair/bedbound	188 (2.1)	196 (4.8)	
Preoperative bone medication use, n (%)			
None	5,581 (63.6)	2,456 (60.4)	<0.001
Calcium/Vitamin D	2,365 (27.0)	1,290 (31.7)	
Bisphosphonates / strontium / Denosumab / Teriparitide	828 (9.4)	320 (7.9)	
Fracture type, n (%)			
Not a pathological or atypical fracture	8,476 (96.6)	3,902 (96.0)	<0.001
Pathological	106 (1.2)	104 (2.6)	
Atypical	192 (2.2)	60 (1.4)	
Delayed surgery, n (%)			
No	7,233 (82.4)	3,080 (75.8)	<0.001
Yes	1,544 (17.6)	986 (24.2)	
Days to surgery after fracture, n (%)			
Less than one	665 (7.6)	318 (7.8)	<0.001
One	4,885 (55.7)	1,975 (48.6)	
Two or more	3,224 (36.7)	1,773 (43.6)	
Anaesthesia type, n (%)			
General	5,061 (57.7)	2,401 (59.1)	0.238
Spinal	2,621 (29.9)	1,156 (28.4)	

Both	1,092 (12.4)	509 (12.5)	
Analgesia type and location, n (%)			
Nerve block in emergency department	3,243 (37.0)	1,475 (36.3)	<0.001
Nerve block in operating theatre	1,531 (17.4)	820 (20.2)	
Both	3,164 (36.1)	1,330 (32.7)	
Neither	836 (9.5)	441 (10.8)	
Operation, n (%)			
Cannulated screws (e.g., multiple screws)	396 (4.5)	155 (3.8)	<0.001
Sliding hip screw	1,624 (18.5)	845 (20.8)	
Intramedullary nail short	1,614 (18.4)	773 (19.1)	
Intramedullary nail long	1,413 (16.1)	680 (16.7)	
Hemiarthroplasty stem cemented	2,522 (28.8)	1,356 (33.3)	
Hemiarthroplasty stem uncemented	250 (2.9)	166 (4.1)	
Total hip replacement stem cemented	751 (8.6)	73 (1.8)	
Total hip replacement stem uncemented	186 (2.2)	18 (0.4)	
Postoperative ward type, n (%)			
Hip fracture unit/Orthopaedic ward/ Preferred ward	7, 968 (90.8)	3,685 (90.6)	0.152
Outlying ward	726 (8.3)	329 (8.1)	
HDU / ICU / CCU	80 (0.9)	52 (1.3)	
Postoperative mobilisation, n (%)			
Allowed to mobilise at day 1	8,231 (93.8)	3,579 (88.0)	<0.001
Not allowed to mobilise at day 1	543 (6.2)	487 (12.0)	
New pressure ulcer(s) postoperatively, n (%)			
No	8,562 (97.6)	3,895 (95.8)	<0.001
Yes	212 (2.4)	171 (4.2)	
Follow-up time (months), mean (SD)	26.64 (9.67)	10.39 (10.63)	<0.001

Main Results

Table 2: Risk of 12-month mortality (hazard ratio) for type of anesthetic and analgesic used for n=12,840 with complete covariates
Reference category for anaesthetic type is general
Reference category for regional nerve block is no block

	12-month vital status			
	Alive n (%)	**Died n (%)**	**Unadjusted HR (95%CI)**	**Adjusted[1] HR (95%CI)**
	10,210 (79.5)	2,630 (20.5)		
Anesthetic				
General only	5,959 (58.4)	1,503 (57.1)	1.00 (Reference)	1.00 (Reference)
Spinal only	3,025 (29.6)	752 (28.6)	0.99 (0.90, 1.08)	1.02 (0.94, 1.12)
General and spinal	1,226 (12.0)	375 (14.3)	**1.17 (1.04, 1.31)**	1.09 (0.98, 1.23)
Analgesia				
Nerve block in ED only	3,756 (36.8)	962 (36.6)	0.94 (0.82, 1.07)	1.00 (0.88, 1.15)
Nerve block in OT only	1,835 (18.0)	516 (19.6)	1.00 (0.86, 1.15)	0.98 (0.84, 1.13)
Neither	1,000 (9.8)	277 (10.5)	1.00 (Reference)	1.00 (Reference)
Both	4,346 (42.6)	995 (37.8)	0.89 (0.77, 1.01)	0.94 (0.82, 1.08)

[1]Adjusted for age category, gender, ASA grade, atypical fracture, dementia/delirium, pre-admission walking status, use of bone medications, mobilisation after surgery, type of operation, presence of pressure ulcers, surgery delay, usual residence, ward type and time-to-surgery.
HR=Hazard ratio, ED=emergency department, OT=operating theatre.

Table 2 describes the 12-month mortality for all cases with complete data available. Analysis for anesthesia was based on type of anesthetic, and for analgesia it was based on the location of regional analgesia administration.

Anesthesia: Main Results

The unadjusted analysis showed a positive association between performing both a general and spinal anesthetic and 12 month mortality (HR=1.17 (1.04, 1.31), p<0.001).

Table 3 shows the results of the Cox regression analysis for long-term mortality (at the end of follow-up: median 21 months, range 0-48 months). The non-imputed unadjusted multivariable analyses (HR=1.20 (1.10, 1.31); p<0.001 and HR=1.12 (1.02, 1.24); p=0.021 respectively) showed an association between the simultaneous use of a general and a spinal anesthetic and higher long-term mortality.

The Kaplan-Meier curve describing the associations between anesthesia (Figure 2) and long-term mortality showed that patients who received both a general and spinal anesthetic had a higher long-term mortality after surgery (p<0.001).

Table 3: Risk of long-term mortality (hazard ratio) at end of follow-up (median 21 months, range 0-48 postoperatively) for type of anesthesia and analgesia (n=12,840 fully observed).
Reference category for anaesthetic type is general
Reference category for regional nerve block is no block

	Vital status at end of follow-up (range: 0-48 months)		Complete case analysis	
	Alive n (%)	**Died n (%)**	**Unadjusted HR (95%CI) (n=16,649)**	**Adjusted[1] HR (95%CI) (n=12,840)**
Total cohort	11,528 (69.2)	5,121 (30.8)		
Anesthetic				
General only	6,799 (59.0)	3,053 (59.6)	1.00 (Reference)	1.00 (Reference)
Spinal only	3,330 (28.9)	1,424 (27.8)	1.00 (0.94, 1.06)	1.03 (0.96, 1.11)
General and spinal	1,399 (12.1)	644 (12.6)	**1.20 (1.10, 1.31)**	**1.12 (1.02, 1.24)**
Analgesia				
Nerve block in ED only	4,522 (39.2)	1,987 (38.8)	0.93 (0.84, 1.04)	0.93 (0.90, 1.11)
Nerve block in OT only	2,000 (17.3)	1,029 (20.1)	0.98 (0.87, 1.10)	0.93 (0.83, 1.05)
Neither	1,192 (10.3)	578 (11.3)	1.00 (Reference)	1.00 (Reference)
Both	3,814 (33.2)	1,527 (29.8)	**0.86 (0.77, 0.96)**	0.90 (0.81, 1.01)

[1]Adjusted for age category, gender, ASA grade, atypical fracture, dementia, pre-admission walking status, use of bone medications, mobilisation after surgery, type of operation, presence of pressure ulcers, surgery delay, usual residence, ward type and time-to-surgery. HR=hazard ratio, ED=emergency department, OT=operating theatre.

Anesthesia: Sensitivity Analysis Results

There was no missing data for date of death which was calculated based on the date of admission and the number of days recorded for “time from date of admission to death”. The total 17,635 patients were included for the multiply imputed analyses which functioned as secondary analyses (Appendix 1.)

In the non-imputed multivariable analysis, the results were not significant (OR=1.15 (0.99, 1.32); p=0.059). Both imputed sensitivity analyses in Appendix 1 reflected an association between combined general and spinal and a higher risk of 12 month all-cause mortality. Hence, patients who received both general and spinal anesthetic for surgery had poorer survival at 12 months.

Analgesia: Main Results

Patients who received a regional nerve block in both the ED and the OT had lower 12-month mortality in the unadjusted analysis (OR=0.86 (0.74, 0.99); p=0.048). Patients who received both a regional nerve block in ED and in OT had improved long-term survival (p<0.001; Figure 3). Patients who only received a regional block one time in one department (either ED or OT) had no difference in association with 12 month or longer term mortality.

Analgesia: Sensitivity Analysis Results

In the Cox regression analysis for long-term mortality, all four models for anesthesia and analgesia met the assumptions of proportional hazards according to the parallel nature of the log-log survival plots when comparing the fit of the observed (Kaplan-Meier) and predicted survival curves.

These associations were not significant in the multivariable analysis for 12 month mortality. In the imputed model (Appendix 1) the result was not significant in either analysis.

There was an association between the use of a regional nerve block both in the ED and in the OT and decreased long-term mortality in the non-imputed unadjusted analysis (HR=0.86 0.77, 0.96); p=0.006), but not in the non-imputed multivariable analysis (HR=0.90 (0.81, 1.01); p=0.071).

DISCUSSION

Anesthesia: Key Results

This analysis of the ANZHFR found that performing both general and spinal anesthetic in a patient may be associated with a higher risk of medium and long-term mortality after hip fracture surgery. Time-to-death is a reflection of the risk (hazard) and a hazard ratio >1 implies a reduced time to death. Both the 12 month and longer term mortality for the unadjusted complete case analyses had a higher hazard ratio for combined general/spinal compared to general anesthesia or spinal anesthesia alone.

This analysis showed no difference in 12-month mortality for patients who received either a spinal or a general anesthetic. This has long been a topic of debate among anesthesiologists

aiming to minimize morbidity and mortality in the elderly and frail population. Identifying no difference between these two techniques reinforces previously published literature. (6-9)

Anesthesia: Interpretation

The increased risk of long-term mortality in patients who underwent both general and spinal anesthesia is likely multifactorial. The need to convert from spinal to general anesthesia mid-case may herald a complicated or prolonged surgery in which more blood loss or bone manipulation occurs, all of which can disrupt homeostasis. Agitation secondary to delirium or cognitive impairment during a spinal anesthetic may result in poor patient compliance and the need to convert to a general anesthetic. The additive effects of two types of anesthetic can impact the risk of peri-operative hypotension which has associated risks of renal injury, myocardial infarction and death, with magnified effect in the geriatric population. (20-23) (24) A longer duration and greater severity of hypotension under anesthesia has been suggested as a predictor of postoperative complications following hip fracture surgery. (25) It has also been suggested that postoperative complications at any time point may influence mortality up to and including 30 months following surgery. (26) Anesthesiologists who are confronted with a clinical scenario in which spinal anesthesia may be insufficient should consider an anesthetic plan which accounts for a prolonged duration of surgery rather than risk doubling up anesthetic type during one case. This phenomenon, known as 'getting it right the first time', has previously been highlighted as one of the ten general principles of anesthesia for fragility surgery. (27) Interestingly, not much has previously been known about the mortality risk of simultaneous use of general and spinal

anesthesia in hip fracture surgery, with only one previously published high-quality study from 1980 that found no difference in 60 randomised participants. (28)

Regional Analgesia: Key Results

The administration of a regional analgesia technique in both the ED as well as in the OT was associated with a lower risk of 12 month and even longer-term mortality. This was significant only for the unadjusted complete case analysis for long term mortality, and not for 12 month mortality.

Analgesia: Interpretation

This result is in line with published works, including several international guidelines and a Cochrane review supporting the routine use of nerve blocks for analgesia in hip fracture. Regional blocks commonly performed include the femoral nerve block, fascia iliaca block, or the pericapsular nerve group block. (29) The benefit in long term mortality may be due to improved analgesia and an opioid sparing effect with reduced risk of postoperative delirium or respiratory depression . (10, 16, 17) (30) (33) The administration of regional nerve blocks by the emergency physician as well as the anesthesiologist may be a surrogate marker for quality of care given the growing recommendations for the use of these techniques. (31, 32) It may also reflect the admission of the patient to an institution which is more accustomed to treating hip fractures with a well established care pathway which has been shown to decrease the rate of perioperative complications (34). The development of any postoperative complication has been suggested to be an independent risk factor for higher long term mortality (34) with an increase in the relative risk if the complication occurred earlier in the postoperative trajectory. (26) The implementation of a hip fracture care

pathway to ensure high quality routine standardized treatment from admission, including performing regional blocks in ED, may help in complication reduction and therefore impact mortality outcomes.

Generalizability

The Australia and New Zealand Hip Fracture Registry is the international database collecting hip fracture data in Australia and New Zealand. In 2016 it had a moderate level of data accuracy and a very high level of data completeness, according to a data quality audit. (35) Since surgical and anesthetic practice in Australia and New Zealand are in accordance with standard international practice, this database allows for a high level of generalizability and external validity. The only exception would be that the use of combined spinal-epidural (CSE) techniques for hip fracture surgery is not routine . (36, 37) During the three-year inclusion period (2016-2018), there were no significant changes in surgical or anesthetic practice on a multinational level..

Limitations

Despite the size and international data included in the ANZHFR database, some limitations must be addressed. The data incorporated in this study, while important, are mostly of observational value. There is the limitation of potential effect of residual confounding on the associations. For the complete case analysis of long-term mortality and the adjusted HR=1.12 (1.02, 1.24), based on the use of the e-Value calculator (40), a single confounder with a hazard ratio of 1.49 would be sufficient to remove this observed association. This suggests that the potential for residual confounding (such as by clinical indication) could

potentially remove the observed association. Thus, while our findings are interesting, they do not imply causality.

Our postulated mechanism for long term mortality following surgery for hip fracture repair is an increased chance of postoperative complications, either due to increased surgical duration, underlying patient factors or intraoperative hypotensive episodes. However, the dataset lacks the ability to comprehensively check for the mediating effect of postoperative complications and thus this mechanism cannot be confirmed by this study.

Twenty eight percent of patients had missing datapoints during follow-up, necessitating the use of a multiply imputed model as a sensitivity analysis (Appendix 1). There is the potential for selection bias by excluding those with missing data in the complete case analysis; however, associations persisted in the sensitivity analyses.

The data were assumed missing at random (MAR) conditional on the covariates included in the multivariate analysis. Together, we believe that they would be able to account for any non-random missingness since there were no other factors that we could consider as potential causes of missingness, and which were not measured. However, since we cannot test this assumption, it is a limitation of the study.

The ANZHFR data fields do not contain surgery specific variables such as duration of surgery, complexity of the surgery, relative unit value, quantity of blood loss or further details concerning the regional block including type. It also does not include a comorbidity index. It is a relatively uncommon practice in Australia and New Zealand to place an epidural or combined spinal epidural for hip fracture surgery. There are other countries where this is routine, and hence could limit generalizability of these findings.

The ANZHFR was updated after the period of this study to include ethnicity of patients, which is a data point of interest to examine. In 2018 this information was not yet collected

and hence the absence of this variable is a limitation. Future studies could include this added information.

In conclusion:

Hip fracture surgery is commonly performed on a frail and elderly patient population. Assessing the impact of anesthetic and analgesic techniques is important for evaluation of continuing best medical practice. This retrospective study analyzed 12,840 patients from the ANZHFR database from 2016 to 2018.

This study observed no difference in association with 12-month mortality between spinal and general anesthesia after hip fracture surgery. Patients who received both a general and spinal anesthetic for the same surgical procedure were associated with a higher risk of 12-month and even longer term mortality than those who received either a spinal or general anesthetic. Patients who received a regional nerve block both in the ED and in the OT prior to surgery were associated with a lower risk of 12 month and even longer term all cause mortality than patients who received one or no nerve block. It should be noted that this data is observational in nature and conclusions regarding causality cannot be drawn.

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The patient data in this study were used with permission from the Australian and New Zealand Hip Fracture Registry. Restrictions apply to the availability of this patient information.

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Figure Legends

- Figure 1: Flowchart of included patients from Australian and New Zealand Hip Fracture Registry
- Figure 2: Kaplan-Meier plots of estimated survival time by type of anaesthesia.
- Figure 3: Kaplan-Meier plots of estimated survival time by regional nerve block administration.

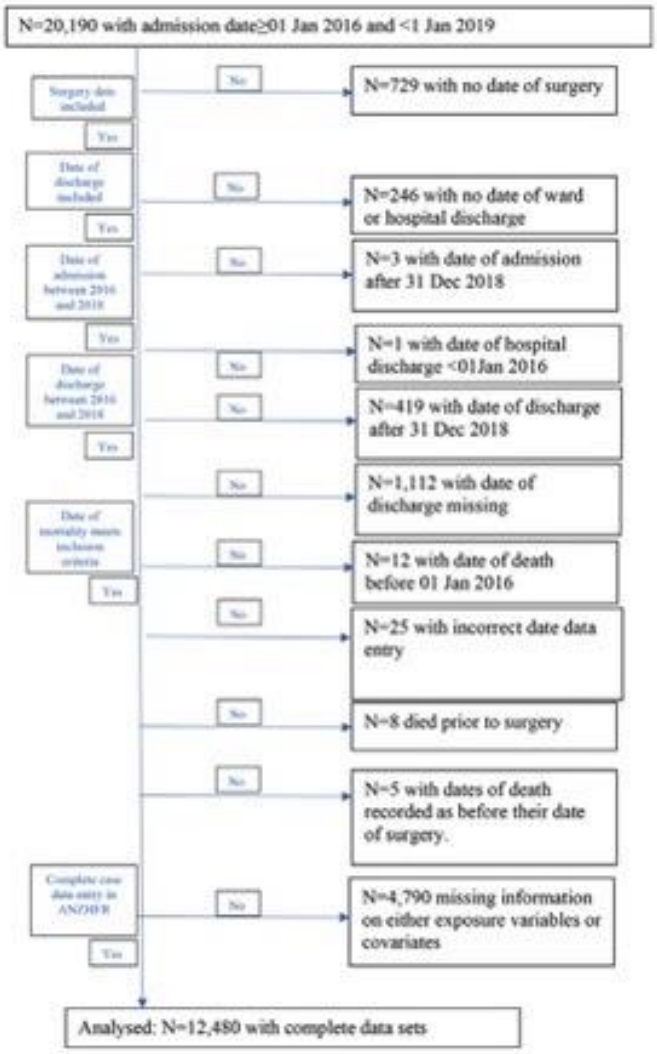


Figure 1 Flow chart of included patients from Australian and New Zealand hip fracture registry. ANZHFR, Australian and New Zealand Hip Fracture Registry.

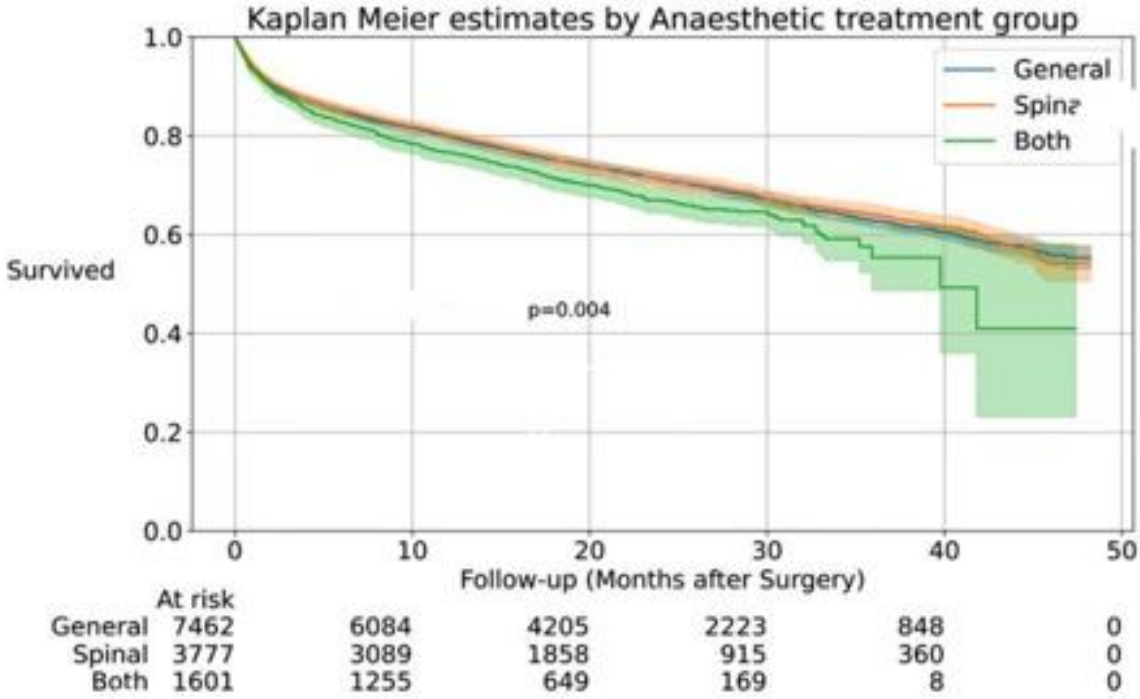
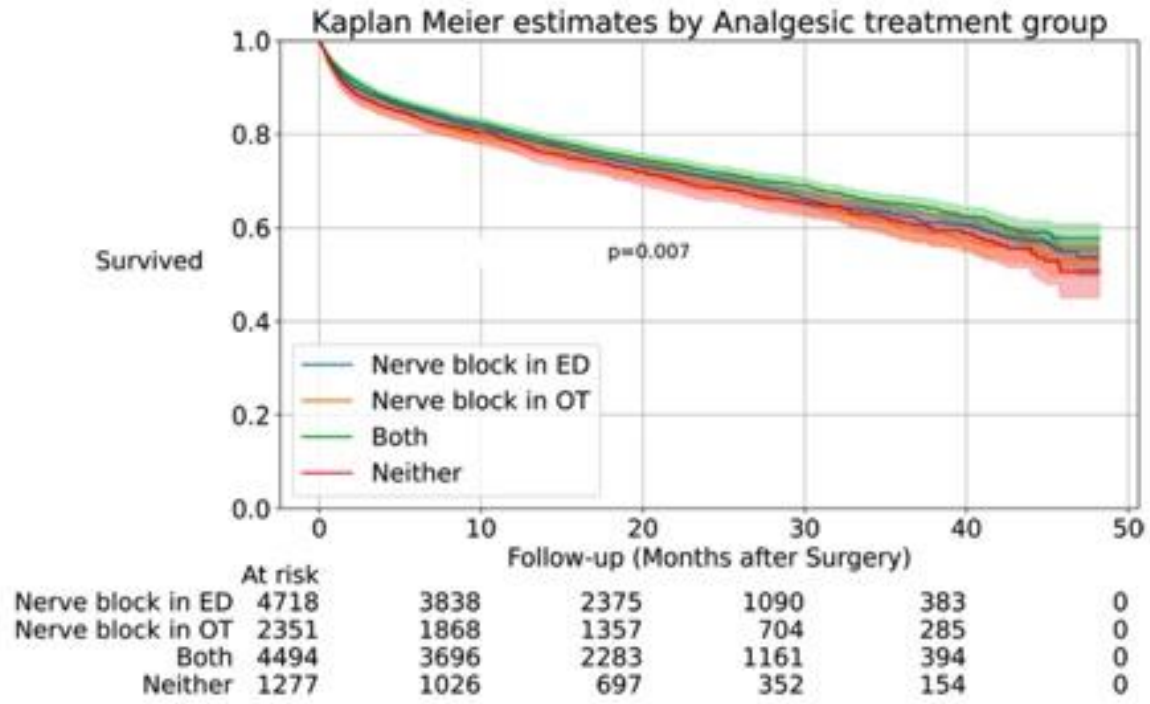


Figure 2 Kaplan-Meier plots of estimated survival time by type of anesthesia.



ED: Emergency department
OT: Operating theatre

Figure 3 Kaplan-Meier plots of estimated survival time by regional nerve block administration. ED, emergency department; OT, operating theater.

Appendix 1. Additional Statistical Analyses: Imputed Univariable and Multivariable Analyses, and Causal Effect Analysis Utilising Targeted Maximum Likelihood Estimation

Methods: *Imputed Analyses*

To prevent loss of participants from the imputed analyses included here as Appendix 1, imputations were performed using chained equations to obtain 20 datasets, each with complete covariate values for all observations. The use of multiple imputation using chained equations has as an assumption that all missing data are missing at random (MAR), that is,

that they are missing at random conditional on the other observed covariates. Although it is not possible to verify this assumption, we consider it a reasonable assumption for this dataset given that it is unlikely that anaesthesia and analgesia would be systematically missing for reasons beyond those that might be explainable by the included covariates. These were used for repeat regression analyses using the appropriate Stata regression commands for multiply imputed datasets. Variables in the imputation process included all the covariates used in the regression analyses. Missing data strategy and reporting of multiple imputation approach was as according to Sterne et al. (39)

Table 1: Risk of 12-month mortality (odds ratio) for type of anesthetic and analgesic used for n=17,635 after multiple imputation for missing covariate values

Reference category for anaesthetic type is general
Reference category for regional nerve block is no block

	12-month vital status		**Using multiple imputation[2]**	
	Alive n (%)	**Died n (%)**	**Unadjusted OR (95%CI) (n=17,635)**	**Adjusted[1] OR (95%CI) (n=17,635)**
Total cohort	13,343 (80.1)	3,306 (19.9)		
Anaesthetic				
General only	7,939 (59.5)	1,913 (57.9)	1.00 (Reference)	1.00 (Reference)
Spinal only	3,830 (28.7)	924 (27.9)	1.00 (0.91, 1.09) P=0.916	1.06 (0.97, 1.17) P=0.216
General and spinal	1,574 (11.8)	469 (14.2)	**1.25 (1.11, 1.40) P<0.001**	**1.21 (1.07, 1.37) P=0.003**
Analgesia				
Neither	1,412 (10.6)	358 (10.8)	1.00 (Reference)	1.00 (Reference)

Nerve block in ED only	5,211 (39.0)	1,298 (39.3)	0.98 (0.86, 1.12) P=0.745	1.05 (0.91, 1.21) P=0.496
Nerve block in OT only	2,374 (17.8)	655 (19.8)	1.07 (0.93, 1.25) P=0.337	1.04 (0.88, 1.22) P=0.659
Both	4,346 (32.6)	995 (30.1)	0.89 (0.78, 1.02) P=0.095	0.96 (0.83, 1.11) P=0.559

[1]Adjusted for age category, gender, ASA grade, atypical fracture, dementia/delirium, pre-admission walking status, use of bone medications, mobilisation after surgery, type of operation, presence of pressure ulcers, surgery delay, usual residence, ward type and time-to-surgery. [2]Using chained equations and n=20 multiply imputed datasets.
OR=odds ratio, ED=emergency department, OT=operating theatre.

Table 1 describes the 12-month mortality for multiply imputed analysis based on type of anesthetic, and location of department responsible for regional analgesia given. The primary complete case univariable analysis showed a positive association of the simultaneous use of both a general and spinal anesthetic, and death within 12 months (OR=1.23 (1.10, 1.39); p<0.001). This was reflected in the imputed multivariable (OR=1.21 (1.07,1.37); p=0.003) and imputed univariable analysis (OR=1.25 (1.11, 1.40); p=0.001), but in the non-imputed multivariable analysis this was not significant (OR=1.15 (0.99, 1.32); p=0.059).
Patients who received a regional nerve block both in the ED and in the OT had lower 12-month mortality in the univariable analysis of the non-imputed dataset (OR=0.86 (0.74, 0.99); p=0.048). However, these associations were not significant in the multivariable complete case analysis, nor either of the sensitivity analyses. This shows there was likely confounding present in the unadjusted (univariate) results.

Table 2: Risk of long-term mortality (hazard ratio) at end of follow-up (median 21 months, range 0-48 postoperatively) for type of anesthesia and analgesia (n=17,635 after using multiple imputation for missing covariate values).
Reference category for anaesthetic type is general
Reference category for regional nerve block is no block

	Vital status at end of follow-up (range: 0-48 months)		**Using multiple imputation[2]**	
	Alive n (%)	**Died n (%)**	**Unadjusted HR (95%CI) (n=17,635)**	**Adjusted[1] HR (95%CI) (n=17,635)**
Total cohort	11,528 (69.2)	5,121 (30.8)		
Anesthetic				
General only	6,799 (59.0)	3,053 (59.6)	1.00 (Reference)	1.00 (Reference)
Spinal only	3,330 (28.9)	1,424 (27.8)	1.00 (0.94, 1.06) P=0.953	1.05 (0.99, 1.11) P=0.123
General and spinal	1,399 (12.1)	644 (12.6)	**1.27 (1.17, 1.38) P<0.001**	**1.23 (1.13, 1.34) P<0.001**
Analgesia				
Neither	1,192 (10.4)	578 (11.3)	1.00 (Reference)	1.00 (Reference)
Nerve block in ED only	4,522 (39.2)	1,987 (38.9)	0.97 (0.88, 1.06) P=0.456	1.02 (0.93, 1.12) P=0.682
Nerve block in ED only	2,000 (17.3)	1,029 (20.1)	1.02 (0.92, 1.13) P=0.728	0.98 (0.88, 1.09) P=0.699
Both	3,814 (33.1)	1,527 (29.7)	**0.87(0.79, 0.96) P=0.005**	0.92 (0.84, 1.02) P=0.107

[1]Adjusted for age category, gender, ASA grade, atypical fracture, dementia, pre-admission walking status, use of bone medications, mobilisation after surgery, type of operation, presence of pressure ulcers, surgery delay, usual residence, ward type and time-to-surgery.
[2]Using multiple imputation with chained equations; n=20 datasets.
HR=hazard ratio, ED=emergency department, OT=operating theatre.

Table 2 shows the results of the Cox regression analysis for long-term mortality (at the end of follow-up: median 21 months, range 0-48 months). The non-imputed univariable and multivariable analyses (HR=1.20 (1.10, 1.31); p<0.001 and HR=1.12 (1.02, 1.24); p=0.021 respectively) showed an association between the simultaneous use of a general and a spinal anesthetic and higher long-term mortality. A similar result was returned in the sensitivity analyses; imputed univariable (HR=1.27 (1.17, 1.38); p<0.001,) and imputed multivariable analysis (HR=1.23 (1.13, 1.34); p<0.001)

There was an association between the use of a regional nerve block both in the ED and in the OT and decreased long-term mortality in the non-imputed univariable analysis (HR=0.86 0.77, 0.96); p=0.006), but not in the non-imputed multivariable analysis (HR=0.90 (0.81, 1.01); p=0.071). Sensitivity analysis also showed a similar pattern of observation. The imputed univariable analysis was significant (HR=0.87 (0.79, 0.96); p=0.005) whereas the imputed multivariable analysis was not (HR=0.92 (0.84, 1.02); p=0.107).

An additional analysis for causal effect utilising Targeted Maximum Likelihood Estimation (TMLE) was performed for 12 month mortality. TMLE is a semiparametric framework which allows machine learning models to estimate a certain value, but while placing minimal assumptions on what the distribution of data is. (40) The results were very similar to the primary analysis, which would imply that the impact of the measured observations is accurate.

Discussion

Our results showed an increased risk of mortality for both 12-month and longer-term mortality for patients treated with both General and Spinal anaesthesia. The strength of the associations were attenuated after adjustment for potential confounding, but remained significant for longer-term mortality. In addition, when using multiple imputation to account for missingness, the associations for both 12-month and longer-term mortality were significant both with and without adjustment.

There was also some evidence for a reduced risk of longer-term mortality when a nerve block was applied both in the OT and ED. However, the significant associations were also attenuated after adjustment for potential confounders, and were non-significant in both the complete cases and imputed datasets.

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Part II, Chapter 4

The Pericapsular Nerve Group (PENG) block combined with Local Infiltration Analgesia (LIA) compared to placebo and LIA in hip arthroplasty surgery: a multi-center double-blinded randomized-controlled trial

The Pericapsular Nerve Group (PENG) block combined with Local Infiltration Analgesia (LIA) compared to placebo and LIA in hip arthroplasty surgery: a multi-center double-blinded randomized-controlled trial

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Abstract

Background: The PEricapsular Nerve Group (PENG) block is a novel regional analgesia technique that provides improved analgesia in patients undergoing hip surgery while preserving motor function. In this study the PENG block was investigated for analgesia in elective total hip arthroplasty (THA).

Methods: In this multi-centre double-blinded randomized-controlled trial, in addition to spinal anesthesia and local infiltration analgesia (LIA), THA patients received either a PENG block or a sham block. The primary outcome was pain score (numeric rating scale 0–10) 3 h postoperatively (Day 0). Secondary outcomes were postoperative quadriceps muscle strength, postoperative Day 1 pain scores, opiate use, complications, length of hospital stay, and patient- reported outcome measures.

Results: Sixty patients were randomized and equally allocated between groups. Baseline demographics were similar. Postoperative Day 0, the PENG group experienced less pain compared to the sham group (PENG: 14 (47%) patients no pain, 14 (47%) mild pain, 2 (6%) moderate/severe pain versus sham: 6 (20%) no pain, 14 (47%) mild pain, 10 (33%) moderate/severe pain; $p = 0.03$). There was no difference in quadriceps muscle strength between groups on Day 0 (PENG: 23 (77%) intact versus sham: 24 (80%) intact; $p = 0.24$) and there were no differences in other secondary outcomes.

Conclusions: Patients receiving a PENG block for analgesia in elective THA experience less postoperative pain on Day 0 with preservation of quadriceps muscle strength. Despite these short-term benefits, no quality of recovery or longer lasting postoperative effects were detected.

Introduction

Total hip arthroplasty (THA) is a cost-effective treatment for osteoarthritis through reduction in pain and improvement in quality of life [1]. It is increasingly performed in an aging population with a total of 32,929 THAs performed in Australia in 2017—2018 (133:100,000 population) [2]. THA is associated with significant post- operative pain and high rates of analgesia use, [3] with incidences of opioid prescribing following THA as high as 89.7% [4, 5].

Adequate pain management following THA is impor- tant as quality analgesia has been shown to decrease complication rates and facilitate postoperative mobiliza- tion [6, 7]. Previous THA studies have suggested a multi- modal analgesia approach to decrease reliance on opioid based medications to reduce associated side-effects [3, 8]. Regional analgesia is an important part of this mul- timodal approach. Commonly performed regional anal- gesia techniques include the femoral nerve block, fascia iliaca block, or the lumbar plexus block. The major dis- advantage of these regional techniques commonly used for THA is that they have only been partially effective in reducing pain and frequently result in motor weaknesses, delaying mobilization [9, 10].

In 2018, Giron-Arango et al. described a novel regional technique for hip analgesia; the pericapsular nerve group (PENG) block [11]. The PENG block is a plane block placed under ultrasound guidance at the level of the ante- rior inferior iliac spine, targeting the articular branches of the femoral nerve, obturator nerve, and accessory obtu- rator nerve [12]. Randomized-controlled trials investigat- ing the efficacy of PENG have shown improved analgesia while preserving motor function and quadriceps mus- cle strength, enabling postoperative mobilization and improved quality of recovery [13–15].

A common technique used for THA is spinal anesthe- sia in combination with local infiltrating analgesia (LIA). However, this approach is largely based on favourable results of LIA in knee arthroplasty with limited effect in postoperative pain control in THA [16]. Little is known of the addition of PENG in THA with LIA. This double- blinded randomized-controlled trial was conducted to test the efficacy of the addition of PENG in THA com- pared with the standard of LIA alone, using a sham block as control.

The primary outcome was the NRS pain score at Day 0. Secondary outcomes were: NRS pain score (at Day 1), Day 0 and 1 quadriceps muscle strength, perioperative opiate use, postoperative complications, length of hospi- tal stay, patient satisfaction and PROMs.

Methods

This multi-centre double-blinded randomized-controlled trial was conducted at two teaching hospitals in Adelaide, Australia; Noarlunga Health Services (NHS) and Flinders Medical Centre (FMC). Institutional ethics approval was obtained (SALHN/HREC/292.20) and written informed consent was acquired from all participants. The trial was registered prior to commencement (NTR; NL9147; principal investigator: D-Y.L; date of registration: 25th of December 2020, URL: https://www.trialregister.nl/trial/ 9147). This study conforms to the Consolidated Stand- ards of Reporting Trials (CONSORT) and the CONSORT extension for

trials reporting patient-related outcomes [17, 18]. The study ran from June 28 to November 8 2021.

The inclusion criteria were adult patients presenting for primary elective THA under spinal anesthesia, without contraindications for regional analgesia, who were able to provide informed consent and reliably report symptoms to the research team. Exclusion criteria were an inability to provide first party consent (e.g. due to cognitive impairment or language barrier) and contraindications for or patient refusal of spinal anesthesia and/or regional analgesia.

Randomization, blinding and study intervention

Patients were randomized to either PENG block (intervention) or sham block (control). Randomization was performed by the principal investigator only via an online randomization computer generator (www.sealedenve lope.com) on a 1:1 basis. Members of the surgical team, members of the Acute Pain Service (APS), nursing staff and patients were all blinded to the intervention. To ensure blinding, the anaesthesiologist performing the preoperative block was different from the anaesthesiologist managing the patient intraoperatively and conducting the postoperative assessments.

Block techniques

Following the administration of spinal anaesthesia, the allocated block was placed using ultrasound guidance with a curvilinear probe (2.5-5 MHz).

PENG: 20 mL of ropivacaine 0.5% (100 mg) prepared by the anaesthesiologist performing the block was used. The area was aseptically prepped and draped. The curvilinear probe was placed transversely, medial to the anterior inferior iliac spine with the medial end of the probe rotated in a caudad direction to align to the superior pubic ramus. A 100 mm sonoplex needle was inserted in- plane under ultrasound guidance. 20mLs of local anaesthetic was injected as a plane block between the psoas fascia and superior pubic rami.

Sham

This block was simulated by the anaesthesiologist by prepping, scanning and draping as per PENG block pro- tocol. The probe and a blunt needle, with a 20 mL syringe filled with saline attached, were held against the skin similar to the PENG block and a sufficient pause to simulate the block being performed was conducted, without actual administration of any medicine.

Following placement of either block, a small cross was drawn with a surgical marker to cover the puncture site or absence thereof.

The study was designed to represent daily practice and to achieve high external validity. Anaesthetic technique was standardized to a spinal anaesthesia with 0.5% Isobaric bupivacaine (range 10-14 mg) without use of intrathecal opioids. A single 8 mg intravenous dose of dexamethasone was administered at the time of the block. Surgical technique was performed at the discretion of the treating orthopaedic surgeon, including rou- tine use of

LIA in all patients at a dose of 100 mL of 0.1% ropivacaine with 1 mg epinephrine. Postoperative analgesia regime was standardized with round-the-clock acetaminophen and NSAIDs if no contraindication, and if needed tramadol, oxycodone, and/or fentanyl on a nurse administered basis.

The rationale for using isobaric bupivacaine is to reflect usual practice at our institution, where the longer duration is suited to the surgery [19].

Outcomes

Pain

Preoperatively, individual patient pain experience was evaluated using the Pain Catastrophizing Scale [20]. Pain scores were obtained preoperatively (baseline), 3-h post-operatively in the Recovery Unit (Day 0), and on postoperative Day 1 (16 to 22 h postoperatively, standardized), marking the maximum pain score during active movement (quadriceps muscle strength test) at each time point. Pain scores were recorded using a numeric rating scale (NRS) ranging from 0 (absence of pain) to 10 (worst pain imaginable) and grouped as no (NRS 0), mild (NRS 1–4), moderate (NRS 5–7) or severe pain (NRS 8–10).

Perioperative opiate doses were recorded preoperatively, intraoperatively, on day 0 and each postoperative day for three days with quantities converted to oral morphine equivalents. Chronic opioid use and chronic preoperative pain were defined as daily opioid use or pain interfering with activities of daily living for a duration of greater than three months.

Mobilization: Postoperatively at Day 0 once the spinal had recessed, and Day 1, a blinded anaesthesiologist assessed quadriceps muscle strength using the Oxford muscle strength grading with grouping of results into intact (5/5), reduced (1–4/5) and absent (0/5). If a patient reported reduced or absent quadriceps muscle strength, the test was carried out on the non-operative side to ensure it was not due to residual spinal effect. Day 0 measurements of dynamic pain and quadriceps strength were standardised to three hours from end time of surgery. A Timed Up-and-Go test was conducted preoperatively and on Day 1 postoperatively by physiotherapists.

In this test, the patient starts in a seat at standard height, stands, walks ten feet, turns around, walks back, and sits back down [21].

Patient-reported outcome measures (PROMs)

Baseline preoperative anxiety and depression were noted using the validated Patient-reported outcomes measurement information system (PROMIS) anxiety and depression item banks [22]. These PROMs, along with the Pain Catastrophizing Scale, assess factors that have previously shown to influence pain experience and function [23]. Preoperatively and on Day 1, quality of recovery was evaluated using the Quality of Recovery (QoR-15) questionnaire [24].

The APS assessed patient satisfaction and pain management on Day 1 in a blinded fashion. Pain scores as a maximum on movement, quadriceps muscle strength, patient satisfaction and PROMs were collected using a scripted format. Complications throughout hospital admission, according to Clavien-Dindo classification grade, time to first mobilization and time to discharge were also recorded [25]. First mobilisation was accompanied by physiotherapy and assessment for suitability was twice a day.

The primary outcome was the NRS pain score at Day 0. Secondary outcomes were: NRS pain score (at Day 1), Day 0 and 1 quadriceps muscle strength, perioperative opiate use, postoperative complications, length of hospital stay, patient satisfaction and PROMs.

Sample size calculation and statistical analyses

A *priori* power calculation was carried out using PASS 14 Power Analysis and Sample Size Software (Kaysville, Utah, USA) based on pain scores from a pilot study and a previous PENG randomized-controlled trial. This showed a mean pain score of 4 out of 10 points after THA on Day 0 without placement of PENG block. This was reduced to a score of 2 out of 10 points with placement of PENG block, with a standard deviation (SD) of 2 [13, 14]. A two-tailed independent-samples t-test for the difference between the two unpaired means with an alpha-error of 0.05 and power of 0.80 showed that 18 patients in each arm were required to detect a difference, 36 total. Given the high attrition rate in the pilot study, we accounted for a 40% dropout which brought numbers to 26. This was rounded up to 30.

Data collection and entry, and statistical analyses were conducted in a blinded fashion. The analysis was per- formed on an intention-to-treat basis using SPSS version 27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9 (GraphPad Software, La Jolla, Calif, USA). Para- metricity of continuous variables was determined using the Shapiro–Wilk test. Normally distributed continuous

variables are expressed as mean (SD), and nonparametric variables as median (range). Univariate analysis was carried out using the chi^2 test or Fisher's exact test (for $n<10$) for categorical variables, and the Mann–Whitney U-test for nonparametric continuous variables or the Student's t-test for parametric continuous variables. A p-value of < 0.05 was considered statistically significant.

Results

During the study period, 75 patients were admitted for elective THA and screened for eligibility. Seven patients were excluded on the basis of cognitive impairment or a language barrier. Eight patients declined to participate, due to a preference for general anesthesia instead of the standardized spinal anesthesia, leaving 60 patients who were consented and randomized equally between both groups. (Fig. 1) All patients completed the study and were included in the final intention to treat analysis with- out loss to follow up.

The preoperative demographics of both groups were similar, including baseline NRS pain scores, pain catastrophising scores, incidence of chronic pain and anxiety or depression. (Table 1).

Primary outcome

Day 0 pain scores in PENG block patients were significantly lower than in the sham block group: 14 patients (47%) in the PENG group reported no pain, compared to 6 patients (20%) in the sham group (p=0.03). In both groups, 14 patients (47%) reported mild pain, and 2 patients (6%) in the PENG group experienced moderate or severe pain, compared to 10 patients (33%) in the sham group. (Table 2) These pain scores were maximum and on mobilisation, as quadriceps strength was tested immediately prior.

Secondary outcomes

On Day 1, pain scores were similar between both groups (p = 0.82). Quadriceps muscle strength was preserved in the PENG group and was similar when compared to the sham block group on Day 0 (p=0.24) and Day 1 (p = 0.75): On Day 0, 23 (77%) PENG patients and 24 (80%) sham block patients had intact quadriceps muscle strength (p=0.24), and on Day 1 this was 24 (80%) and 22 (73%) respectively (p = 0.75). (Table 2).

Complication rates were similar between both groups. One patient in the sham group had uncontrolled postoperative pain on the ward, requiring maximalisation of oral analgesia, commencement of a fentanyl patient-controlled analgesia pump, and at the end of Day 1 placement of a PENG block. (Table 3). These measures were largely effective. This patient was regarded as a sham patient as per intention-to-treat, and the primary and most secondary outcome measures had already been collected.

There were no differences in PROMs, Timed Up-and- Go tests, patient satisfaction, time to first mobilization, time to discharge and postoperative opiate use between groups. (Tables 4 and 5).

Figure 1. CONSORT Flow Diagram

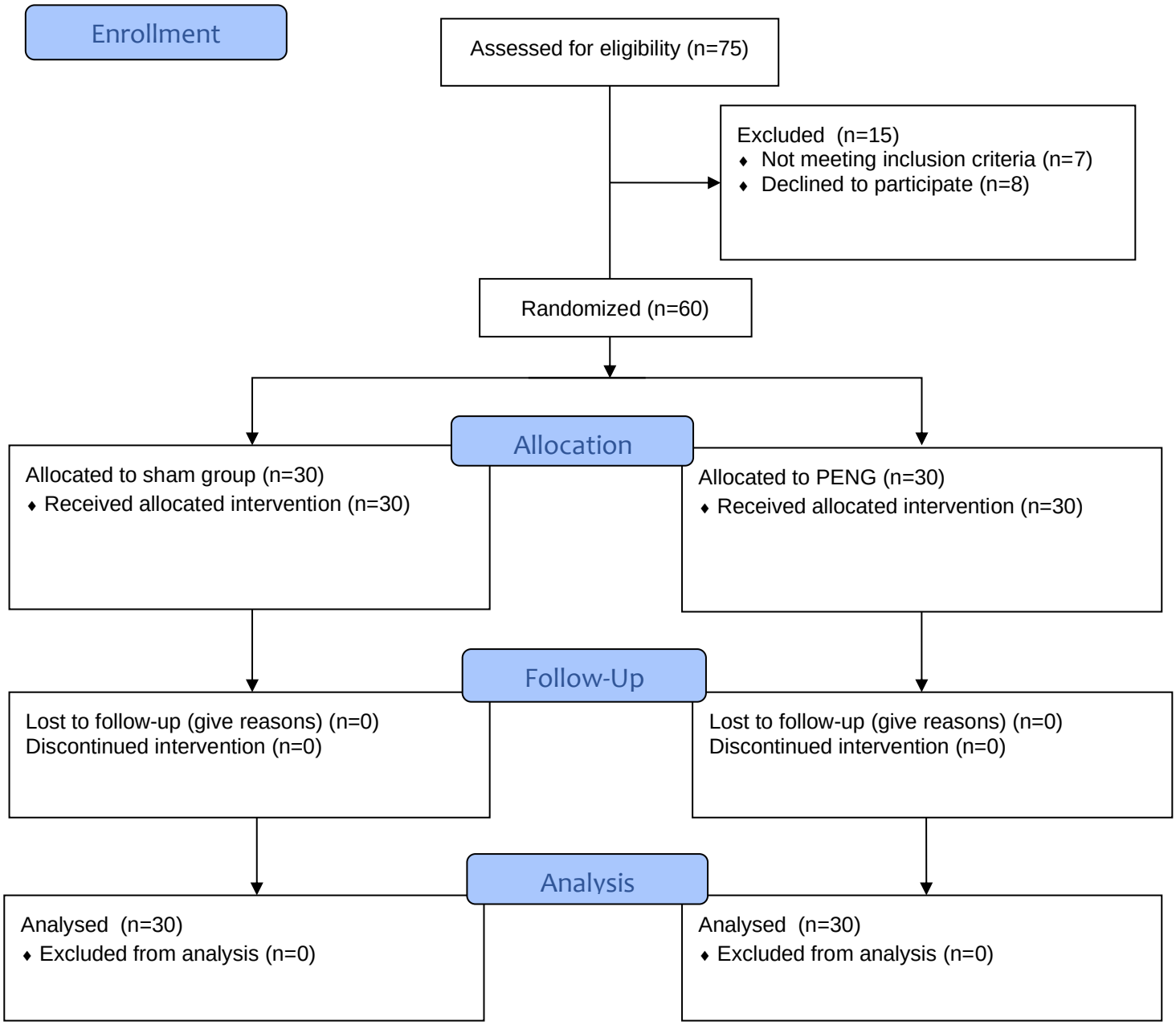

Table 1 Patient and preoperative characteristics

	Sham ($n=30$)	PENG ($n=30$)	*P*-value
Age in years, mean (± SD)[a]	68.3 (± 10.9)	68.6 (± 9.5)	0.91
Gender, n (%)[b]			
Male	14 (47)	13 (43)	0.80
Female	16 (53)	17 (57)	
Weight in kg, mean (± SD)[a]	84.8 (± 20.8)	88.6 (± 21.9)	0.51
BMI in kg/m^2, median (IQR)[c]	30.8 (27.5–32.8)	33.2 (28.3–36.7)	0.09
Mobility, n (%)[b]			
Independent (no aids)	16 (53)	10 (33)	0.13
Assisted (stick/walker/ wheelchair)	14 (47)	20 (67)	
Residence, n (%)[d]			
Home	30 (100)	29 (97)	1.00
Assisted living	0 (0)	1 (3)	
ASA score, n (%)[b]			
I	0 (0)	0 (0)	0.14
II	19 (63)	13 (43)	
III	10 (33)	17 (57)	
IV	1 (3)	0 (0)	
History of anxiety and/or depression, n (%)[d]			
Yes	7 (23)	3 (10)	0.30
No	23 (77)	27 (90)	
Chronic pain, n (%)[d]			
Yes	30 (100)	28 (93)	0.49
No	0 (0)	2 (7)	
Preoperative pain score (NRS), n (%)[b]			
None (0)	0 (0)	0 (0)	0.44
Mild (1–4)	0 (0)	0 (0)	
Moderate (5–7)	7 (23)	3 (10)	
Severe (8–10)	23 (77)	27 (90)	
Preoperative pain score (NRS), median (IQR)[c]	8 (7.8–10)	9 (8–10)	0.20
Preoperative Pain Catastrophising Scale Score median (IQR)[c]	14.5 (6.75–38)	17 (6–41)	0.72
Preoperative PROMIS Depression T Score, median (IQR)[c]	52.3 (37.1–61.2)	53.3 (37.1–62)	0.88
Preoperative PROMIS Anxiety T Score, median (IQR)[c]	49.4 (37.1–58.4)	47.7 (37.1–60.7)	0.74
Chronic opiate use, n (%)[d]			
Yes	7 (23)	9 (30)	0.56
No	23 (77)	21 (70)	
Gabapentinoid use preoperatively, n (%)[d]			
Yes	3 (10)	3 (10)	1.00
No	27 (90)	27 (90)	
Operative side, n (%)[b]			
Left	14 (47)	14 (47)	1.00
Right	16 (53)	16 (53)	
Surgical procedure, n (%)[d]			
Non-cemented total	9 (30)	8 (27)	0.77
Cemented total	21 (70)	22 (73)	
Surgical approach, n (%)[b]			
Direct anterior	15 (50)	18 (60)	0.44
Posterior	15 (50)	12 (40)	
Type of anaesthesia for surgery, n (%)[d]			
General	1 (3)	1 (3)	1.00
Spinal	29 (97)	29 (97)	

Abbreviations: *IQR* Interquartile range, *SD* Standard deviation, *PENG* Pericapsular nerve group block, *NRS* Numeric rating scale, *PROMIS* Patient-Reported Outcomes Measurement Information System

[a] Student's t-test used

[b] Chi^2 test used

[c] Mann–Whitney U-test used

[d] Fisher's exact test used

Table 2 Postoperative pain and motor outcomes

	Sham ($n=30$)	PENG ($n=30$)	*P*-value
Maximum postoperative pain score (NRS) in Recovery Unit (Day 0), n (%)[a]			
None (0)	6 (20)	14 (47)	**0.03**
Mild (1–4)	14 (47)	14 (47)	
Moderate (5–7)	9 (30)	2 (6)	
Severe (8–10)	1 (3)	0 (0)	
Quadriceps muscle strength in Recovery Unit (Day 0), n (%)[a]			
Intact	24 (80)	23 (77)	0.24
Reduced	4 (13)	7 (23)	
Absent	2 (7)	0 (0)	
Maximum postoperative pain score (NRS) on Day 1, n (%)[a]			
None (0)	2 (6)	1 (3)	0.82
Mild (1–4)	8 (27)	7 (23)	
Moderate (5–7)	12 (40)	11 (37)	
Severe (8–10)	8 (27)	11 (37)	
Quadriceps muscle strength on Day 1, n (%)[a]			
Intact	22 (73)	24 (80)	0.75
Reduced	6 (20)	5 (17)	
Absent	0 (0)	0 (0)	
Unable to assess	1 (3)	1 (3)	

Abbreviations: *PENG* Pericapsular nerve group block, *NRS* Numeric rating scale

[a] Chi^2 test used

Adverse events and protocol deviations

In two patients, one in each group, it was technically not possible to perform a spinal anaesthesia. Both had multiple failed attempts at locating a vertebral interspace for neuraxial injection. Therefore, both received a general anaesthetic for surgery.

Table 3 Other (post)operative outcomes

	Sham ($n=30$)	PENG ($n=30$)	*P*-value
Length of operation in minutes, mean (± SD)[a]	108.07 (± 21.3)	105.57 (± 28.7)	0.70
Time to first mobilization in minutes, median (range)[b]	1450 (1263.5–1592.5)	1374 (1257.5–1560)	0.30
Time to discharge in days, median (range) [b]	2 (1.75–3)	2 (1–3)	0.97
Clavien-Dindo complication grade, n (%)[c]			
0	24 (80)	25 (83)	0.55
I	4 (13)	5 (17)	
II	0 (0)	0 (0)	
III	1 (3)	0 (0)	
IV	1 (3)	0 (0)	
V	0 (0)	0 (0)	
Complications, n (%)			
Wound infection	0 (0)	0 (0)	N/A
Reoperation	0 (0)	0 (0)	
STEMI/NSTEMI	1 (3)	0 (0)	
Extreme postoperative pain	1 (3)	0 (0)	
Death	0 (0)	0 (0)	

Abbreviations: *N/A* Not applicable, *PENG* Pericapsular nerve group block, *STEMI* S-T elevation myocardial infarction, *NSTEMI* Non S-T elevation myocardial infarction

[a] Student's t-test used

[b] Mann–Whitney U-test used

[c] Chi^2 test used

Table 4 Patient outcome questionnaires and Timed Up-and-Go tests

	Sham ($n=30$)	PENG ($n=30$)	*P*-value
Preoperative QoR-15, mean (±SD)[a]	107 (±20.6)	99.1 (±27.4)	0.22
Postoperative QoR-15, mean (±SD)[a]	103 (±22.8)	96.6 (±13.6)	0.19
Timed up-and-go in seconds, preoperative, n (%)[b]			
0–15	12 (40)	9 (30)	0.61
16–30	7 (23)	8 (27)	
31–45	4 (13)	5 (17)	
46+	2 (7)	5 (17)	
Unable to perform	5 (17)	3 (9)	
Timed up-and-go in seconds, postoperative on Day 1, n (%)[b]			
0–15	0 (0)	1 (3)	0.58
16–30	11 (37)	9 (30)	
31–45	9 (30)	10 (33)	
46+	9 (30)	8 (27)	
Unable to perform	1 (3)	2 (7)	
Patient satisfaction, n (%)[b]			
Unsatisfied	1 (3)	1 (3)	1.00
Satisfied	23 (77)	23 (77)	
Ambivalent	6 (20)	6 (20)	

Abbreviations: *SD* Standard deviation, *IQR* Interquartile range, *PENG* Pericapsular nerve group block, *QoR-15* Quality of Recovery 15, *SD* Standard deviation

[a] Student's t-test used

[b] Chi^2 test used

Table 5 Postoperative opiate use

	Sham ($n=30$)	PENG ($n=30$)	*P*-value
Postoperative opiate use in morphine equivalents (mg), median (IQR)[a]			
Day 0	30 (18.9–73.0)	30 (8.0–57.5)	0.31
Day 1	49 (21.0–93.3)	46 (15.0–73.2)	0.41
Day 2	30 (0–47)	8 (0–45.0)	0.24
Day 3	0 (0–15)	0 (0–8.0)	0.81
Total	122 (56.5–232.5)	97.5 (30.5–164.3)	0.23

Abbreviations: *PENG* Pericapsular nerve group block, *mg* Milligrams, *IQR* Interquartile range

[a] Mann–Whitney U-test used

Discussion

This double-blinded randomized-controlled trial shows that the PENG block significantly reduces short-term postoperative pain in elective THA when spinal anaesthesia and LIA are used. (p = 0.03). The direct postoperative analgesic advantage of the PENG block in this setting does not remain after surgery on Day 1.

Regional analgesia in THA has traditionally been per- formed using a femoral nerve or fascia iliaca block. Although partially effective, these blocks result in a decrease in muscle strength [26]. Since the PENG block affects only the articular branches of the femoral and accessory obturator nerves, it is believed to achieve adequate analgesia while also preserving motor function and muscle strength. In the current study, postoperative quadriceps muscle strength was similar in both groups. This allows patients to mobilize early following surgery, which, in itself is associated with fewer complications, shorter length of hospital stay and lower mortality [27– 29]. Patients who received the PENG block were thus able to mobilize as soon as the sham group patients, with less pain.

The motor sparing effect is consistent with previous studies focused on anatomy suggesting that the PENG block targets the articular branches of the femoral, obturator, and accessory obturator nerves [12]. It must be mentioned that on Day 0 and Day 1, respectively seven and six PENG patients did experience reduction in quadriceps muscle strength, however, this incidence was similar in the sham group (6 and 7 patients respectively; p=0.24 and p=0.75). This could reflect a reluctance to actively move the newly operated hip, or possible spread from the LIA to the femoral nerve, consistent in both groups. Notably, no adverse events directly related to block placement were reported and patient satisfaction was similar across both groups.

A variety of PROMs and outcome measures were used with the aim to objectively quantify possible recovery benefits of the PENG block. Preoperative patient PROMs, quantified using the Pain Catastrophizing Scale, PROMIS anxiety and depression item banks, were all similar between groups. Postoperative PROMs, quality of recovery and the Timed Up-and-Go tests were also similar. This could possibly be due to the timing of these tests on Day 1 postoperatively, after the analgesic effect of the PENG block had finished. A recent RCT comparing PENG to sham in combination with intra-articular injection also showed only short term benefit, without differences in longer term out- comes [30].

The similar opiate use in both groups, despite a difference in pain scores, may be due to the advanced age of the included patients and their low baseline opiate use. It is also important to note that the study was not powered to detect a difference in opiate use nor in PROMs between both groups, for which larger studies will be required to investigate this in the future.

Limitations

Some limitations have to be addressed. As indicated above, this trial was conducted on a relatively small number of patients and could not identify differences in secondary outcomes. However, it was powered on the primary outcome, showing a significant difference between both groups.

Quadriceps strength was measured by a blinded clinician. A standardised dynamometric measurement tool would have been more accurate, but this was not avail- able. We recognise that this makes the secondary out- come less reliable due to interobserver variation, but have addressed this by grouping the intermediate scores together.

Due to the standardized spinal anaesthesia in the study protocol, 11% (8/75) patients approached, chose not to participate, potentially inflicting some selection bias. However, randomization took place after inclusion to reduce this bias. In the future, a next randomized-controlled trial to further investigate the efficacy of PENG block in THA patients could therefore be in patients having either spinal or general anesthesia.

Conclusion

Patients receiving an additional PENG block for analgesia during total hip arthroplasty experience less direct (Day 0) postoperative pain, with preserved quadriceps muscle strength and similar time to mobilization compared to patients having spinal anesthesia and local infiltration analgesia only. For total hip arthroplasty, the PENG block should be considered as part of multimodal analgesia.

Abbreviations

THA: Total hip arthroplasty; PENG block: Pericapsular nerve group block; RCT : Randomized controlled trial; NRS: Numeric rating scale; NHS: Noarlunga Health Services; FMC: Flinders Medical Centre; NTR: Netherlands Trial Registry; CONSORT: Consolidated Standards of Reporting Trials; APS: Acute Pain Service; LIA: Local infiltration analgesia; PROMs: Patient reported outcome measures; PROMIS: Patient-reported outcomes measurement information system; QoR-15 questionnaire: Quality of Recovery-15 questionnaire; SD: Standard Deviation.

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Ethics approval and consent to participate

This multi-centre double-blinded randomized-controlled trial was conducted at two teaching hospitals in Adelaide, Australia; Noarlunga Health Services (NHS) and Flinders Medical Centre (FMC). Institutional ethics approval was obtained (SALHN/HREC/292.20) and written informed consent was acquired from all participants.

All methods were carried out in accordance with relevant guidelines and regulations.

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Part II, Chapter 5

A Multi-Disciplinary Program for Opioid Sparse Arthroplasty Results in Reduced Long-Term Opioid Consumption: A Four Year Prospective Study.

A Multi-Disciplinary Program for Opioid Sparse Arthroplasty Results in Reduced Long-Term Opioid Consumption: A Four Year Prospective Study.

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List of abbreviations

PROMs: Patient reported outcome measures
LIA: Local infiltration analgesia
PENG: Pericapsular nerve group block
BMI: Body mass index
OKS: Oxford Knee Score
OHS: Oxford Hip Score

Abstract

Introduction: The current opioid epidemic poses patient safety and economic burdens to healthcare systems worldwide. Postoperative prescriptions of opioids contribute, with reported opioid prescription rates following arthroplasty as high as 89%. In this multi-centre prospective study, an opioid sparing protocol was implemented for patients undergoing knee or hip arthroplasty. The primary outcome is to report our patient outcomes in the context of this protocol, and to examine the rate of opioid prescription on discharge from our hospitals following joint arthroplasty surgery. This is possibly associated with the efficacy of the newly implemented Arthroplasty Patient Care Protocol.

Methods: Over three years, patients underwent perioperative education with the expectation to be opioid-free after surgery. Intraoperative regional analgesia, early postoperative mobilisation and multimodal analgesia were mandatory. Long-term opioid medication use was monitored and PROMs (Oxford Knee/Hip Score (OKS/OHS), EQ-5D-5L) were evaluated pre-operatively, and at 6 weeks, 6 months and 1 year postoperatively. Primary and secondary outcomes were opiate use and PROMs at different time points.

Results: A total of 1,444 patients participated. Two (0.2%) knee patients used opioids to one year. Zero hip patients used opioids postoperatively at any time point after six weeks ($p<0.0001$). The OKS and EQ-5D-5L both improved for knee patients from 16 (12-22) pre-operatively to 35 (27-43) at 1 year postoperatively, and 70 (60-80) preoperatively to 80 (70-90) at 1 year postoperatively ($p<0.0001$). The OHS and EQ-5D-5L both improved for hip patients from 12 (8-19) preoperatively to 44 (36-47) at 1 year postoperatively, and 65 (50-75) preoperatively to 85 (75-90) at 1 year postoperatively ($p<0.0001$). Satisfaction improved between all pre- and postoperative time points for both knee and hip patients ($p<0.0001$).

Conclusions: Knee and hip arthroplasty patients receiving a peri-operative education program can effectively and satisfactorily be managed without long-term opioids when coupled with multimodal perioperative management, making this a valuable approach to reduce chronic opioid use.

Introduction

The current opioid epidemic poses significant economic and patient safety burdens to healthcare systems. (41, 42) This is an issue of growing concern around the world. In the United States, for instance, opioid prescriptions have tripled from 1999 to 2014, leading to a three-fold increase of opioid-related overdoses, and in Australia over 70% of opioid overdoses are prescription related. (43)

Orthopedic surgery is in the top 5 specialties who provide opioid prescriptions, and one of the largest providers of postoperative narcotics. (44, 45) Arthroplasty surgery is associated with high incidences of new opioid prescriptions in previously opioid naïve patients, with reported incidences of 17.4 to as high as 89%, with an upwards trend in opioid prescription rates in some countries. (46, 47) In the last decade, there has been a conscious shift away from opioid based medications to treat postoperative pain in orthopaedic surgery. (48) In an effort to reduce rates of new opioid prescriptions, some studies have reported successful implementation of novel opioid sparing protocols for postoperative care following procedures normally accompanied with high rates of opioid prescriptions, including arthroplasty surgery. (49, 50, 51, 52) These studies show a tendency towards higher rates of opioid prescription. Our study describes a protocol that aims to safely reduce the incidence of postoperative opioid prescription while achieving good patient satisfaction and patient related outcomes.

Sabatino et al (44) described a median prescription rate of ninety 5-mg oxycodone or equivalent pills per patient who underwent total hip or knee arthroplasty with a large proportion of these medications going unused. This would seem to indicate that opioids are perhaps overprescribed following TKR/THR, and that there is room for reducing these prescriptions postoperatively.

In view of this growing opioid problem, the Departments of Anesthesiology and Orthopedic Surgery of our large teaching hospitals have implemented an Arthroplasty Patient Care Protocol (Addendum 1), focused on intensive pre-operative education and early postoperative mobilisation with the aim to limit postoperative opioid subscriptions and with the expectation of an opioid-free postoperative trajectory. The aim of this study was to evaluate if this protocol is indeed effective in decreasing longer-term opioid use, while maintaining patient satisfaction and early recovery.

Outcomes

The primary outcome is to report our patient related outcomes in the context of this protocol, and to examine the rate of opioid prescription on discharge from our hospitals following joint arthroplasty surgery. Time points are preoperative, six weeks postoperative, three months postoperative and one year postoperative.

Three validated patient reported outcome measures (PROMs) scores were taken: the Oxford Knee Score (OKS) or Oxford Hip Score (OHS) (53), the EQ-5D-5L score (54), and a 5-point Likert scale for patient satisfaction. Also recorded were the use of opioids at all time points.

Patients and Methods

This is a multi-centre prospective observational study. This study was conducted at two tertiary teaching hospitals (FMC and NH) in Adelaide, Australia. Orthopaedic surgeons and anesthesiologists work routinely across both sites, performing 500-600 arthroplasty procedures per year. Due to SARS Covid-19 related restrictions on elective operations, this number was reduced in 2020 to 307.

All consecutive adult patients who underwent elective knee or hip arthroplasty were approached for informed consent to participate over a three-year period. Patients were prospectively enrolled from 8th January 2018 to 1st of October 2020, with a 1 year follow up. The local Human Research Ethics Committee granted multi-centre approval (SALHN/329.17).

At both hospitals, the Arthroplasty Patient Care Protocol (Addendum 1) was implemented in 2018.

This protocol, based on previous publications (55, 56, 57, 58), was created with multidisciplinary input from orthopaedic surgeons, anesthesiologists, physiotherapists and nursing staff. In short, the protocol involves the following. Preoperative: To qualify for surgery, patients are to taper or cease opioids and attend compulsory educational sessions. These sessions are in a group-based format and include explanations of prehabilitation techniques, the operative procedure including the anesthetic, early postoperative mobilisation, and postoperative pain and pain relief. There are also interactive question and answer components with the treating orthopaedic surgeon, physiotherapists and nurses. Emphasis is placed on the expectation for patients to be comfortably opioid-free long term postoperatively, but with low threshold to discuss pain management options. The use of simple analgesic alternatives (paracetamol and non-steroidal anti-inflammatory drugs if not contraindicated) is encouraged with education provided for dosing intervals. All hospital prescribers undergo mandatory education regarding the opioid sparse program prior to patient contact. Intra-operative: Spinal anesthesia without intrathecal morphine is the preferred anesthesia method with local infiltration analgesia (LIA) by the surgeon. Standard regional anesthesia was an adductor canal block for knee, and from 2019 a pericapsular nerve group (PENG) block for hip arthroplasty was added. (9, 59) Postoperative: Anesthesiologists and the Acute Pain Service review all patients daily, reinforcing the expectation of opioid-free recovery with administration of regular simple oral analgesia.

Patients are allowed opioids as an inpatient if indicated. The inpatient stay is extended if indicated by acute (on chronic) pain and subsequent opioid titration, until the multidisciplinary team determines that the patient is optimised to proceed comfortably as an opioid sparse outpatient. Patients are discharged with a maximum of ten tablets of opioid medication (oxycodone or tramadol) without repeat prescriptions. There is some flexibility if inpatient opioid use indicates that 10 tablets is unlikely to be adequate, but this is by extremely infrequent exception. Postoperative: Orthopaedic surgical follow-up takes place at six weeks and three months. If a patient requires review for postoperative pain, there are appointment slots available in the outpatient clinic. If these are not possible for logistical reasons, the patient is encouraged to see their treating primary care physician who has had a letter sent to them communicating that a joint replacement has been carried out and the opioid sparse expectation of the postoperative trajectory.

This approach is also supported on a national level by a revision to the Pharmaceutical Benefit Scheme in Australia, implemented since 1 June 2020. Postsurgical patients with acute non-cancer pain only qualify for financial cover for a half-pack (10 tablets) of opioid based medication. Any prescription above this amount is paid for by the patient themselves. Long term opioid prescribing requires registration of the patient, and completion of an 'Authority Prescription' process with written or telephone approval from a central government agency. Currently, a program known as Script Check is being implemented in Australia, which allows a registered medical practioner to check if a patient has had multiple opioid prescriptions. It allows the program user to check in real-time the prescribing history of a particular patient for high-risk prescriptions, including all opioid based medications. It will shortly be mandatory to cross reference a patient using this system prior to providing such a prescription.

Protocol follow-up for this study took place at four different time points: preoperatively, and at six weeks, six months and one year postoperatively. Data were recorded by a dedicated research assistant, using scripted questionnaires either via telephone or via a posted written survey. The same script was used at all four time points. Three validated patient reported outcome measures (PROMs) scores were taken: the Oxford Knee Score (OKS) or Oxford Hip Score (OHS) (53), the EQ-5D-5L score (54), a 5-point Likert scale for patient satisfaction, and the use of opioids at all time points. Data were entered into a password secured database stored on the hospital computer network. The database was subdivided into knee or hip arthroplasty. A random sample of patients (n=52) were called by a separate research assistant to corroborate entered data.

The primary outcome was opiate use at the different time points. Secondary outcomes were the PROMs at the different time points.

The analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software, La Jolla, Calif, USA). The Shapiro-Wilk test showed that all continuous variables were nonparametric and are therefore described as median with interquartile range (IQR). Categorical variables are described as frequency with percentages. Univariate analyses were carried out using the chi-squared test or Fisher's exact test (for $n<20$) for categorical variables, and the Mann-Whitney U-test for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

Out of 1,728 consecutive patients who were invited to participate, 1,444 (84%) provided informed consent.

Knee arthroplasty group

A total of 917 patients underwent knee arthroplasty. The majority was female (n=613; 67%) with a median age of 73 (IQR 65-80), median body mass index (BMI) of 32 kg/m^2 (IQR 28-36) and most had surgery for a primary replacement, 909 (99%). Of the knee arthroplasty patients, 232 (25%) used opioids preoperatively. At baseline, 655 (72%) patients reported no or minimal anxiety/depression (EQ-5D-5L score), moderate anxiety/depression was reported by 198 (21%) and 64 (7%) had severe or extreme preoperative anxiety/depression. (Table 1)

Of the 917 patients who consented to participate in the questionnaire follow-up, 59 (6.4%) were lost to follow-up at six weeks (a slightly higher number of 86 (9.3%) for the satisfaction component). 179 (19.5%) were lost to follow up at six months, and 353 (38.5%) did not respond to the 1 year questionnaire.

Two (0.2%) patients used long-term opioids postoperatively, at six weeks, six months and one year after surgery (p<0.0001 compared to preoperatively). (Table 3.1) Both were using opioids preoperatively.
The total Oxford Knee Score improved significantly after surgery from 16 points (range 12-22) preoperatively to 35 points (range 27-43) at one year (p<0.0001). Similarly, the total EQ-5D-5L score improved from 70 points (range 60-80) preoperatively, to 80 points (range 70-90) at one year (p<0.0001). (Table 3.2)

At 6 weeks postoperatively, anxiety/depression had improved to 749 (85%) with no or minimal anxiety/depression, 103 (12%) with moderate symptoms, and 31 (3%) with severe or extreme anxiety/depression (p<0.0001 compared to preoperatively).

At 6 weeks postoperatively, 433 (49%) patients reported no or slight pain, 358 (41%) had moderate pain, and 94 (10%) reported severe or extreme pain. At six months, 529 (71%) had no or slight pain, 166 (22%) moderate and 52 (7%) had severe or extreme pain. At one year, 434 (75% of 578 respondents) had absent or minimal pain, 105 (18%) had moderate pain symptoms, and 39 (7%) had severe or extreme pain. Both patients who continued using opioids reported severe or extreme pain at one-year follow-up. These incidences are significantly improved compared to preoperative baseline (p<0.0001).
At six weeks 651 (78%) patients were satisfied, 122 (15%) were ambivalent and 58 (7%) were dissatisfied with their overall experience and surgery (86 lost to follow up for satisfaction questionnaire at six weeks).
PROMs showed an upwards trend across all questionnaires and domains within the questionnaires, consistent with improving function. The Oxford Knee Score showed a significant median postoperative improvement of 11 points at six weeks, and 19 points at one year. (Table 3) Improvements were made at all time points across all PROMs (p<0.0001).

Hip arthroplasty group

527 (36%) patients received a hip arthroplasty, who were predominantly female (n=333; 63%), with a median age of 73 (IQR 66-81) and median BMI of 30 kg/m^2 (28-36). 187 (35%) patients reported using opioid based medication prior to operation. (Table 2)

Of the 527 patients who consented to participate in the questionnaire follow-up, 59 (11.2%) were lost to follow-up at six weeks (a slightly higher number of 60 (11.4%) for the satisfaction component). 180 (34.2%) were lost to follow up at six months, and 256 (48.6%) did not respond to the 1 year questionnaire.

At baseline, 344 (66%) patients had no or slight anxiety or depression, moderate anxiety or depression was present in 106 (20%) patients, and 57 (10%) had severe or extreme anxiety or depression. This had improved by six weeks postoperative to 421 (88%) with no or minimal anxiety or depression as part of the EQ-5D-5L PROM, and 47(10%) with moderate symptoms. 9 (2%) patients had severe and zero had extreme depression/anxiety.
Zero patients in the hip group used opioid based medication after six weeks, this continued out to a year. (Table 4.1)
At six weeks, 318 (60%) patients had no or slight pain, 134 (25%) had moderate pain, and 26 (5%) reported severe pain. At six months, 297 (85%) had no or slight pain, 39 (11%) moderate and 11 (4%) had severe or extreme pain. At one year, 252 (93% of 271 respondents) had absent or minimal pain, 17 (6%) had moderate pain symptoms, and 2 (1%) had severe or extreme pain. At all postoperative follow-up points, comparison to preoperative incidences were significantly improved ($p<0.0001$).
At 6 weeks postoperative 412 (78%) patients were satisfied, 22 (4%) were ambivalent, 27 (6%) were dissatisfied 66 (13%) were lost to follow-up. This remained consistent at six months and one year. This represented a significant change in incidence ($p<0.0001$).
The Oxford Hip Score showed a median postoperative improvement of 19 points at six weeks, and 31 points at a year. (Table 4.2) Statistically significant improvements were made at all time points across all PROMs ($p<0.0001$).

Discussion

This study demonstrates that a patient education protocol with emphasis on patient expectation management coupled with a multi-disciplinary approach to pain management can result in a long-term opioid free recovery. This is supported on a national level in Australia by multiple programs designed to restrict and monitor opioid prescribing. Similar programs in other countries have also shown success in previous studies. (60, 61)
The subject of opioid use for pain management is 'one of intense international interest', according to Morgan et al. (62) Dependence can develop following the use of prescription opioids after surgery. (63) Health systems internationally have flagged this as an area of concern and strategies aimed at minimising postoperative opioid prescriptions are increasingly suggested. (64) That said, opioids are a cornerstone of postoperative pain management and inadequate analgesia can result in delayed mobilisation and recovery. (65)
The results of the current prospective study, however revealed no decrease in PROM outcomes during an opioid free postoperative phase, showing that joint arthroplasty surgery can be managed with simple analgesia postoperatively without compromising quality of recovery. Pain scores are also comparable with previously published studies, if not lower. (66, 67) Pain scores at 6 weeks postoperatively for TKA were described in previous studies as moderate (approximately 5 on a 11 point Likert scale), and decreasing for the following 12 months postoperatively. Another study found at 12 months postoperatively for TKA that 40% of patients had moderate to severe pain. Chronic pain and dissatisfaction have been reported as being as high as 10-34% of patients at 12 months after TKA. (68) Our study describes perhaps less pain, with a majority reporting only slight pain at 6 weeks and moderate pain being the second most common response with a similar pattern of pain improvement over the 12 months of follow-up.
Patient satisfaction rates at our institution are consistent or better than reported incidences from other tertiary centres, (69) describing dissatisfaction rates of up to 20% under a classic opioid prescribing regime. (70) This may, however, not be related to the opioids specifically, but likely also to the hands-on care, meticulous preoperative preparation, and extensive follow up.
Twenty-five (5%) hip patients reported severe or extreme postoperative pain, and 94 (10%) knee patients at six weeks postoperatively. The limitation to this result is that data collection did not specify the location of and frequently patients were reporting pain in the contralateral joint, likely due to the same underlying pathology. Interestingly, these patients did not report dissatisfaction with the surgery, nor did they use postoperative opioids, making it plausible their pain was indeed not related to the operated joint.
The two patients who remained on opioids postoperatively both recorded preoperative opioid use and severe anxiety and/or depression at all time points. PROM improvements were consistent with average results from the group. One patient reported low patient satisfaction, and both had continuing severe pain despite the prescription of opioid medication.
We compare our incidence of 2/1444 patients who remained on long term opioid medications with previously published incidences of Australian hip and knee arthroplasty patients who followed a traditional regime, ie not opioid sparse. It has been described in a similar population as our own as 10% at 6 months postoperatively following TKR, and 4% at 6 months postoperatively following THR. (71)

Despite the common use of prescription opioids for chronic non-cancer pain, there remains no strong scientific evidence to support this routine practice. (72) This study illustrates that recovery from arthroplasty surgery can be achieved with good patient satisfaction and high-quality PROM outcomes, while remaining opioid sparse. Furthermore, opioid use is associated with an increase in long-term utilisation of health care services, as well as inflicting a significant economic burden. (73)
PROM surveys and long-term opioid based data collection will be integrated shortly into the national Australian Orthopaedic Association joint registry database. (74) This promises to provide an interesting look into opioid prescription and recovery on a large scale in the future. It is likely that the presence of an Acute Pain Service, as well as the use of novel regional anaesthesia assisted in this outcome.

Limitations

Despite the favourable outcomes described in this study, some limitations do need to be addressed. There is unfortunately no historical data collection at our centre prior to implementation of this protocol, and hence we cannot definitively conclude that a change has been actuated. We have compared to published data in other centres, with similar patient populations and more classic opioid regimes to illustrate the difference. These prescription rates are self-reported by patients, which is also a limitation.
We acknowledge that there may in fact be a cultural component to the result of a low opioid prescription rate, where the team approach is to 'just say no' to continuing postoperative opioids. We would argue that if that is a factor in our positive outcomes, that it is not necessarily a weakness. Our high patient satisfaction rate and good PROM results despite our low opioid prescription rates show that it is attainable.
It is also possible that the patients who were lost to follow-up were taking opioids. It is unfortunately not possible for us to determine if this is the case. The pattern of lost to follow-up is that the percentage attrition is greater the further away from index surgery, which is not consistent with attrition due to opioid prescribing rates in the acute postoperative phase continuing from surgery. Non-responders had comparable baseline characteristics to responders, ie. were not more likely to be using opioids preoperatively. The attrition rate, for example 6.4% at 6 weeks for TKA, is also lower than most opioid prescribing rates described in previously published studies. We hope that in the near future with the implementation in Australia of Script Check, that it becomes easier to determine patient opioid use across all health providers.

Conclusion

In conclusion, the results of this multi-centre prospective study show no decrease in PROM outcomes or patient satisfaction during an opioid free postoperative phase for the vast majority of patients. This illustrates that joint arthroplasty surgery can be managed with non-opiod analgesia postoperatively between six weeks and one year, without compromising pain scores or quality of recovery. This topic should be considered for future investigation by means of a randomized controlled trial.

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	Knees (n=917)
Age in years, median (IQR)	73 (65-80)
Gender, n (%) Male Female	 304 (33) 613 (67)
Weight in kg, median (IQR)	88.9 (75.1-100)
BMI in kg/m^2, median (IQR)	32 (28-36)
Type of surgery, n (%) Primary Revision	 909 (99) 8 (1)
Operative side, n (%) Left Right	 403 (44) 514 (56)

Table 1: Characteristics for knee arthroplasty patients.
Abbreviations: IQR: interquartile range.

Table 2: Characteristics for hip arthroplasty patients.

	Hips (n=527)
Age in years, median (IQR)	73 (66-81)
Gender, n (%) Male Female	 194 (37) 333 (63)
Weight in kg, median (IQR)	83.0 (70.6-97.2)
BMI in kg/m^2, median (IQR)	30 (26.2-34.9)
Type of surgery, n (%) Primary Revision	 519 (98.5) 8 (1.5)
Operative side, n (%) Left Right	 219 (42) 308 (58)
Pre-operative opiate use, n (%) Yes No	 187 (35) 340 (65)

Abbreviations: IQR: interquartile range.

Table 3.1: Pre- and postoperative opiate use and patient Reported Outcome Measures (PROMs) for knee arthroplasty.

	Knees (n=917)	**p-value** (comparison to pre-operative)
Opiate use, n (%)[a]		
pre-operative	232 (25)	-
6 weeks postoperative[1]	2 (0.2)	<0.0001*
6 months postoperative[2]	2 (0.2)	<0.0001*
1 year postoperative[3]	2 (0.2)	<0.0001*
Oxford Knee Score total, median (IQR)[b]		
pre-operative	16 (12-22)	-
6 weeks postoperative[1]	27 (21-33)	<0.0001*
6 months postoperative[2]	34 (27-40)	<0.0001*
1 year postoperative[3]	35 (27-43)	<0.0001*
EQ-5L-5D Health Questionnaire total, median (IQR)[b]		
pre-operative	70 (60-80)	-
6 weeks postoperative[1]	80 (70-90)	<0.0001*
6 months postoperative[2]	80 (70-90)	<0.0001*
1 year postoperative[3]	80 (70-90)	<0.0001*

Table 3.2: Pre- and postoperative patient Reported Outcome Measures (PROMs) for knee arthroplasty.

	Pre-operatively	**6 weeks**	**6 months**	**1 year**	**p-value**
EQ-5L-5D pain/discomfort score, n (%)[c]	n=917	n=885	n=747	n=578	
No pain	12 (1)	60 (7)	164 (22)	186 (32)	<0.0001[*]
Slight pain	74 (8)	373 (42)	365 (49)	248 (43)	
Moderate pain	349 (38)	358 (41)	166 (22)	105 (18)	
Severe pain	410 (45)	83 (9)	46 (6)	37 (6)	
Extreme pain	72 (8)	11 (1)	6 (1)	2 (1)	
Lost to follow up	-	*32*	*170*	*339*	
EQ-5L-5D anxiety/depression score, n (%)[c]	n=917	n=883	n=742	n=574	
Not anxious/depressed	386 (42)	530 (60)	468 (63)	367 (64)	<0.0001[*]
Slightly anxious/depressed	269 (30)	219 (25)	171 (23)	152 (26)	
Moderately anxious/depressed	198 (21)	103 (11)	86 (12)	49 (9)	
Severely anxious/depressed	47 (5)	26 (3)	17 (2)	6 (1)	
Extremely anxious/depressed	17 (2)	5 (1)	0	0	
Lost to follow up	-	*34*	*175*	*343*	
Likert patient satisfaction, n (%)[c]	n=917	n=831	n=708	n=564	
Very satisfied		350 (42)	340 (48)	267 (47)	<0.0001[$]
Satisfied		301 (36)	210 (30)	170 (30)	
Ambivalent		122 (15)	100 (14)	77 (14)	
Dissatisfied		46 (6)	46 (6)	38 (7)	
Very dissatisfied		12 (1)	12 (2)	12 (2)	
Lost to follow up		*86*	*209*	*353*	

IQR: interquartile range.

[*] p-values for pre-operative vs. each individual postoperative time point.

[$] p-values for six-week vs. each individual postoperative time point.

[1] 59 lost to follow up; [2] 179 lost to follow up; [3] 353 lost to follow up.

[a] Fisher's exact test, [b] Mann-Whitney U test; [c] Chi-squared test.

Table 4.1: Pre- and postoperative opiate use and patient Reported Outcome Measures for (PROMs) for hip arthroplasty.

	Hips (n=527)	**p-value**
Opiate use, n (%)[a]		
pre-operative	187 (35)	-
6 weeks postoperative[1]	0	<0.0001*
6 months postoperative[2]	0	<0.0001*
1 year postoperative[3]	0	<0.0001*
Oxford Hip Score total, median (IQR)[b]		
pre-operative	12 (8-19)	-
6 weeks postoperative[1]	31 (24-37)	<0.0001*
6 months postoperative[2]	38 (31-44)	<0.0001*
1 year postoperative[3]	44 (36-47)	<0.0001*
EQ-5L-5D Health Questionnaire total, median (IQR)[b]		
pre-operative	65 (50-75)	-
6 weeks postoperative[1]	80 (70-90)	<0.0001*
6 months postoperative[2]	80 (70-90)	<0.0001*
1 year postoperative[3]	85 (75-90)	<0.0001*

Table 4.2: Pre- and postoperative patient Reported Outcome Measures (PROMs) for hip

	Pre-operatively	**6 weeks**	**6 months**	**1 year**	**p-value**
EQ-5L-5D pain/discomfort score, n (%)[c]	n=527	n=477	n=347	n=271	
No pain	3 (1)	111 (23)	181 (52)	200 (73)	<0.0001[*]
Slight pain	32 (6)	207 (43)	116 (33)	52 (19)	
Moderate pain	152 (29)	134 (28)	39 (11)	17 (6)	
Severe pain	187 (235)	24 (5)	10 (3)	1 (1)	
Extreme pain	153 (29)	1 (1)	1 (1)	1 (1)	
Lost to follow up	-	*50*	*180*	*256*	
EQ-5L-5D anxiety/depression score, n (%)[c]	n=507	n=477	n=345	n=269	
Not anxious/depressed	199 (38)	332 (70)	257 (74)	210 (78)	<0.0001[*]
Slightly anxious/depressed	145(28)	89 (18)	62 (18)	43 (16)	
Moderately anxious/depressed	106 (20)	47 (10)	20 (6)	13 (5)	
Severely anxious/depressed	34 (6)	9 (2)	6 (2)	3 (1)	
Extremely anxious/depressed	23 (4)	0	0	0	
Lost to follow up	*20*[^]	*50*	*182*	*258*	
Likert patient satisfaction, n (%)[c]	n=527	n=461	n=317	n=240	
Very satisfied		291 (63)	203 (64)	157 (65)	<0.0001[$]
Satisfied		121 (26)	80 (25)	60 (25)	
Ambivalent		22 (5)	17 (5)	11 (5)	
Dissatisfied		8 (2)	5 (2)	3 (1)	
Very dissatisfied		19 (4)	12 (4)	9 (4)	
Lost to follow up		*66*	*210*	*287*	

arthroplasty.

IQR: interquartile range.

[*] p-values for pre-operative vs. each individual postoperative time point.

[^] declined to answer.

[$] p-values for six-week vs. each individual postoperative time point.

[1] 59 lost to follow up; [2] 180 lost to follow up; [3] 256 lost to follow up.

[a] Fisher's exact test, [b] Mann-Whitney U test; [c] Chi-squared test.

Addendum 1.

Arthroplasty Patient Care Protocol

PREOPERATIVE
Patient is booked for surgery and stratified according to urgency
Patient is referred to Anesthesiology for assessment, and physiotherapy for prehabilitation
Primary care physician is advised of upcoming surgery, and to taper dose of any opioid medications
Regular use of simple analgesia is advised
Patient attends a mandatory patient education session 4 weeks prior to surgery

INTRAOPERATIVE
Premedication of oral paracetamol
Anesthesia technique is suggested to be spinal anesthesia, and use of regional blocks:
PENG (Pericapsular Nerve Group) block for hip replacement is recommended
Adductor canal +/- IPACK (Infiltration between the Popliteal Artery and Condyles of the Knee) block for knee replacement
No intrathecal morphine, or low dose (100mcg) only
LIA (Local Infiltration Analgesia) 100mLs of 0.1% ropivacaine

POSTOPERATIVE
Early mobilisation with physiotherapy, same day as surgery
Regular simple analgesia
Opioid based medication allowed on a PRN only basis, if indicated as inpatient
Cessation of any slow-release opioid medication
Daily or twice daily physiotherapy
Daily ward rounds with reinforcement that the patient should be aiming to be opioid free
Daily review by Acute Pain Service with reinforcement that the patient should be aiming to be opioid free

DISCHARGE
Advised to continue regular simple analgesia if needed
Preference for no opioid on discharge. If opioid discharge script given- provided for a maximum of ten tablets, no repeats
Follow-up appointments with arthroplasty team at six weeks and three months
Written communication to primary care physician, reinforcing expectation of opioid-free postoperative trajectory
Follow-up with research assistant at six weeks, six months and one year to assess PROMs, patient satisfaction and opioid use.

Part III, Chapter 6

A Longitudinal Validation of the EQ-5D-5L and EQ-VAS Stand-Alone Component Utilising the Oxford Hip Score in the Australian Hip Arthroplasty Population

A Longitudinal Validation of the EQ-5D-5L and EQ-VAS Stand-Alone Component Utilising the Oxford Hip Score in the Australian Hip Arthroplasty Population

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ABSTRACT

Purpose: To evaluate the measurement properties of the Oxford Hip Score (OHS), EQ-5D-5L utility index and EQ-5D-5L visual analogue scale (EQ-VAS) in patients undergoing elective total hip arthroplasty in Australia.
Methods: In this prospective multi-centre study, the OHS and EQ-5D-5L were collected preoperatively, six weeks (6w) and six months (6m) postoperatively. The OHS, EQ-VAS and EQ-5D-5L index were evaluated for concurrent validity, predictive validity (Spearman's Rho of predicted and observed values from a generalised linear regression model (GLM)), and responsiveness (effect size (ES) and standard response mean (SRM)).
Results: 362 patients were included in this analysis for 6w and 269 for 6m. The EQ-5D-5L index showed good concurrent validity with the OHS (r=0.71 preoperatively, 0.61 at 6w and 0.59 at 6m). Predictive validity for EQ-5D-5L index was similar to OHS when regressed (GLM). Responsiveness was good at 6w (EQ-5D-5L index ES 1.53, SRM 1.40; OHS ES 2.16, SRM 1.51) and 6m (EQ-5D-5L index ES 1.88, SRM 1.70; OHS ES 3.12, SRM 2.24). The EQ-VAS returned poorer results, at 6w an ES of 0.75 (moderate) and SRM 0.8. At 6m the EQ-VAS had an ES of 0.92 and SRM of 1.00. It, however, had greater predictive validity.
Conclusions: The EQ-5D-5L index and the OHS demonstrate strong concurrent validity. The EQ-5D-5L index demonstrated similar predictive validity at 6w and 6m, and both PROMs had adequate responsiveness. The EQ-VAS should be used routinely together with the EQ-5D-5L index. The EQ-5D-5L is suitable to quantify health-related quality of life in Australian hip arthroplasty patients.

INTRODUCTION

Total hip arthroplasty (THA) is a common operation, with 32,929 replacements performed annually in Australia (133 per 100,000) in 2017-2018. (10) Learmonth et al. called it "the operation of the century" in *The Lancet*, (11) citing improvements in quality of life following this procedure and naming cost-effectiveness as the main factor that would determine further developments in this area. Health economics and patient recovery are used as part of the evaluation of patient outcomes. Patient outcomes can be measured using patient-related outcome measures (PROMs).

The 3-level version of the EuroQol 5 Dimensions (EQ-5D-3L) is such a PROM. It is a standardized health-related quality of life (HRQoL) questionnaire that was developed in 1990 and designed to assess general health at three different levels for five dimensions. (54) (75) In 2011, it was further revised to a 5-level version (EQ-5D-5L) with five levels and five dimensions. (76) This was done to measure more nuanced differences in health response and reduce the ceiling effect. The EQ-5Dsuite of questionnaires are some of the most widely used PROMs globally. In the United Kingdom, for instance, the EQ-5D is an instrument recommended by the National Institute for Health and Clinical Excellence (NICE), the premier health technology assessment body, for calculating quality adjusted life years used in cost-utility analysis (77) (78, 79)

A validated outcome measure is one that has been tested to ensure the production of reliable, accurate results. The EQ-5D-5L has not yet been validated for the Australian orthopaedic population for HRQoL assessment. The results of the PROM are converted into 'vectors'. These are five-digit codes representing a health state. For example, 11111 is full health, and 55555 represents the worst health. There are 3,125 possible health states. These health states are then mapped onto a single EQ-5D-5L utility index using a country-specific value set. If a country-specific value set is not yet validated, the scores can be examined using the EQ-5D-3L value sets using a "crosswalk" method. (80) Alternatively, the generic Western Preference Pattern (81) can be used. Both of these choices come with issues related to nonspecificity and lack of validation. To date, 28 countries have validated country-specific EQ-5D-5L value sets, including England, Uruguay, Japan, Canada, The Netherlands and South Korea. (82)

The EQ-VAS is a stand-alone component of the EQ-5D-5L, a rating system for the patient to self-report how they feel their general health is. The EQ-VAS is seen as a simple and unambiguous manner for a patient to communicate overall functionality and is conceptually different to the question-and-answer based nature of the rest of the PROM. (83) The Oxford Hip Score (OHS) is a PROM that was specifically developed to assess function and pain in patients undergoing a THA. (84) It has been previously utilised for assessing the concurrent validity of the EQ-5D-5L index score in THA patients in other countries. (85) A copy of the Oxford Hip Score PROM is attached as Appendix 1, while that for the EQ-5D-5L PROM is attached as Appendix 2.

This study aims to test the concurrent and predictive validity of the EQ-5D-5L (EQ-5D-5L utility index and the EQ-VAS) when compared against the OHS in the Australian hip arthroplasty population. We test concurrent and predictive validity. Concurrent validity

describes the extent to which the measure to be tested correlates with an established method to measure the same. In this case, the measure to be tested is the EQ-5D-5L, and the established measurement tool is the OHS. Predictive validity describes the association between baseline and follow-up outcomes. Predictive validity is highly valued in this cohort, as this has implications for surgical suitability for individual patients. We also test responsiveness, which is defined as a measure of the sensitivity of PROMs to reflect the change in health status over time.

PATIENTS AND METHODS

This multi-centre prospective study was conducted at two tertiary teaching hospitals in Australia. Orthopaedic surgeons operate routinely at both hospitals, performing approximately 500 hip arthroplasty procedures per year. Due to SARS Covid-19 related restrictions on elective operations, in 2020, this number was reduced to approximately 300 patients. The local Human Research Ethics Committee granted multi-centre approval (SALHN/329.17).

All consecutive adult patients undergoing elective total hip arthroplasty surgery were prospectively enrolled over an almost three-year period from 8th January 2018 to 1st of October 2020, with a six-month follow-up until 2nd April 2021. Informed consent was obtained from all participants. Baseline demographics were recorded for all patients, including age, gender, body mass index (BMI) and Charlson comorbidity index (CCI). (86) Data were recorded by a dedicated research assistant, using scripted questionnaires either via telephone or via a written survey sent by postal mail. The same English language script was used at three different time points: preoperatively and six weeks and six months postoperatively. At all three time points, two validated PROMs were used: the Oxford Hip Score (OHS) (87) and the EQ-5D-5L (54) including the EQ-VAS stand-alone component. Data were entered into a password secured database and stored on the hospital computer network.

Patients were included for analysis if they had complete quality of life data. This was defined as completing the EQ-5D-5L and OHS preoperatively and at six weeks postoperatively. The validation of the EQ-5D-5L utility values was established using a discrete choice experiment approach. (88)

OXFORD HIP SCORE

The OHS is a joint-specific PROM (89) that has been used extensively over the last 20 years. (90, 91, 92) It assesses six fields, each with 2 questions (12 questions total). These fields are pain, walking, physical activity, function, quality of life and psychological wellbeing. Each question is scored on a 5-point discrete visual analogue scale, with higher numbers correlating with better function. (Appendix 1). The final score is a total of the individual question scores. In this study, it effectively functioned as a comparative control.

EQ-5D-5L INDEX AND EQ-VAS

The EQ-5D-5L is a standardized health-related quality of life (HRQoL) PROM that the EuroQol Group designed to quantify generic health in the adult population in the fields of mobility, self-care, usual activities, anxiety/depression and pain/discomfort. Response levels are on a 5-point scale of none, slight, moderate, severe and extreme/unable to perform. Based on Australian general population preference weights determined through a discrete choice experiment approach (88), a utility index ranging from −0.676 to 1 can be attached to each of the EQ-5D-5L health states. Higher utilities represent better HRQoL.

The EQ-VAS is a vertical visual analogue scale that forms part of the EQ-5D-5L. It asks patients to rate their general health from 0 to 100. Higher numeric scores represent better patient function.

STATISTICAL ANALYSIS

All statistical analyses were performed using STATA version 17 (StataCorp, Texas, USA). Continuous variables (age, BMI, CCI) were expressed as mean and standard deviation, whereas the categorical variable (gender) was expressed as percentages (counts). A p-value of <0.05 was considered statistically significant.

Concurrent Validity, Predictive Validity and Agreement

For analysis of concurrent validity, the Spearman's correlation coefficient (rho, ρ) was utilised to compare the EQ-5D-5L index score, dimension scores of the EQ-5D-5L and EQ-VAS against the OHS. The strength of the relationship was considered low/weak ($\rho < 0.25$), fair ($\rho = 0.25–0.50$), good ($\rho = 0.50–0.75$), and excellent ($\rho > 0.75$). This magnitude of rank order correlations was sourced from previous publications on the same area. (93, 94) Predictive validity was ascertained using a regression framework whilst controlling for confounders. We utilised generalized linear models with the 6-week and 6-month postoperative PROMs as the dependant variables and preoperative values and baseline characteristics as independent variables. The average marginal effect regarding preoperative score was used to compare models if different distribution families were utilised. Agreement between the EQ-5D-5L index score and the OHS was measured using Krippendorff's alpha, which is a reliability coefficient designed to measure the agreement among observers, coders, judges, raters, or measuring instruments. (78, 95) The following interpretations of agreement were applied: below 0.0 – poor, 0.00 to 0.20 – slight, 0.21 to 0.40 – fair, 0.41 to 0.60 – moderate, 0.61 to 0.80 - substantial and 0.81 to 1.00 - almost perfect. (96)Two measures of absolute agreement were considered as alternatives to Krippendorff's alpha: Lin's Concordance Correlation Coefficient (CCC), which is robust to departures from normality (97)and Intraclass Correlation Coefficient (ICC), with PROM data transformed using power analysis to conform to assumptions of normality and stable variance required for ICC. (98, 99, 100) The ICC was based on a two-way mixed-effect model where the individual effect was random and the effect of the instrument was fixed. Data were analyzed using **Intercooled Stata software** version 17.1 for Windows (**Stata Corp**. **College Station**, **TX**, USA). Values of the ICC and CCC higher than 0.9 were considered to indicate excellent reliability, good between 0.9 and 0.75, moderate between 0.75 and 0.5, and poor below 0.5. (98)

Responsiveness

Responsiveness is a measure of the sensitivity of PROMs to reflect the change in health status over time. For this study, we compared measures at baseline and at 6 weeks and 6 months follow-up using paired t-tests. Further assessment of responsiveness was quantified using effect size (ES) and standardized response mean (SRM).

Effect size was calculated using the formula:

$$ES = \frac{Mean\ Difference\ from\ Baseline}{Standard\ Deviation\ at\ Baseline}$$

Standard response mean was calculated using the formula:

$$SRM = \frac{Mean\ Difference\ from\ Baseline}{Standard\ Deviation\ of\ Difference}$$

ES and SRM were classified according to Cohen's rule of thumb, as large (≥ 0.8), moderate (0.5–0.79) or small (< 0.5). Both ES and SRM are standardized measures of change over time in health, independent of sample size.

Influence of Baseline Characteristics on PROMs

Regression analysis using generalised linear models was performed with respect to baseline characteristics (age, gender, BMI and CCI), using the preoperative EQ-5D-5L index score, EQ-VAS and OHS as independent variables. The postoperative PROMs were used as the dependent variables. Depending on the distribution of the dependant variable, an appropriate distribution family and canonical link function were chosen. Multiple families were trialled when there was difficulty ascertaining the appropriate family of distribution, and the best fitting model was selected based on low Akaike's Information Criteria and Bayesian Information Criteria score. The coefficient, standard error and p-values were recorded.

Since the EQ-5D-5L index scores had negative values, it was determined that the Gaussian family of distribution with a canonical identity link was most appropriate. Both OHS and EQ-VAS had a non-negative distribution. Multiple families and their canonical links were fitted, including Gaussian, inverse Gaussian, Poisson, and Gamma distributions were tested for best fit. In both OHS and EQ-VAS, it was determined that the Gamma distribution provided the best fit and was hence used for the final model.

RESULTS

In total, 362 hip arthroplasty patients were identified from the database. These had complete data for preoperative and 6 weeks postoperatively and could be included in these two analyses. Of these, 269 were included in the study, with postoperative PROMs at 6 months available. This is due to a 26% attrition rate at 6 months.

The mean age of our cohort at the time of surgery was 68.5 (SD = 12.5) years old, and 55.8% (202/362) were female. The mean preoperative BMI was 30.8 (SD = 5.6), and the mean CCI was 73.7% (SD = 22.5). A summary of baseline characteristics can be found in Table 1. Boxplots for the distributions of scores at baseline (preoperative), 6 weeks and 6 months is shown in Figure 1.

Concurrent Validity, Predictive Validity and Agreement

The EQ-5D-5L index showed good concurrent validity when compared to OHS at baseline, 6 weeks, and 6 months postoperative, with a Spearman's coefficient of 0.71, 0.61 and 0.59, respectively. EQ-VAS had good concurrent validity at 6 weeks when compared to OHS, and fair concurrent validity at baseline and 6 months, with a Spearman's coefficient of 0.53, 0.37 and 0.45, respectively (Table 2).

In Table 3, the dimensions of the EQ-5D-5L index showed good concurrent validity when compared to the corresponding OHS at baseline, 6 weeks, and 6 months postoperative, with a Spearman's coefficient ranging from 0.52 to 0.62 (good) for Mobility, Self-Care, Usual

Activities and Pain. Concurrent validity was only fair for the Anxiety/Depression dimension, with a Spearman's coefficient of 0.28 (preoperative), 0.33 (6 weeks) and 0.37 (6 months).

The predictive validity of each score generated by the three different scores was determined using generalized linear models, with regression to baseline scores and covariates. In all cases, the distribution that provided the best model fit was the Gamma distribution with a canonical negative inverse link. The average marginal effects for the preoperative score were recorded and displayed in Table 2. The EQ-5D-5L index score showed similar predictive validity when compared to OHS at 6 weeks (average marginal effect of 0.19 and 0.18 respectively) and 6 months (average marginal effect of 0.23 and 0.16 respectively). However, EQ-VAS showed greater predictive validity than both OHS and EQ-5D-5L index score at 6 weeks and 6 months (average marginal effect of 0.37 and 0.31 respectively).

As shown in Table 4, the agreement between the EQ-5D-5L utility and OHS total scores ranged from moderate to substantial/good when measured using all three agreement indices (Krippendorff's alpha, ICC and CCC). The best agreement was seen at the preoperative stage, while the least agreement was at 6 weeks. There was less agreement between the EQ-VAS and OHS total scores, ranging from poor/fair to moderate. The best agreement was seen at 6 weeks, while the least agreement was at the preoperative stage.

Responsiveness

These findings are detailed in Table 5. At 6 weeks, all three PROMs showed significant differences between baseline and follow-up scores. Both OHS and EQ-5D-5L had a large ES and SRM. The ES for OHS and EQ-5D-5L index was 2.16 and 1.53, respectively, and the SRM was 1.51 and 1.40, respectively, $p<0.0001$. The EQ-VAS had a moderate ES of 0.75 and a large SRM of 0.80, $p<0.0001$.

At 6 months, all three PROMs again showed a significant difference between baseline and follow-up scores: The ES for OHS, EQ-5D-5L index and EQ-VAS was 3.12, 1.88 and 0.92, respectively, and the SRM was 2.24, 1.70 and 1.00, respectively.

Influence of Baseline Characteristics on PROMs

There was a statistically significant positive association between higher preoperative OHS scores on one end and both male gender and BMI. However, higher EQ-5D-5L index and EQ-VAS scores were only significantly associated with higher BMI and male gender, respectively.

DISCUSSION

This analysis is an empirical validation of the EQ-5D-5L for suitability of HRQoL assessment for hip arthroplasty patients using experienced-based patient data from a prospective multi-centre study database, with the correlation between the Oxford Hip Scores, EQ-VAS, and the EQ-5D-5L PROMs examined. The findings support the utilization of EQ-5D-5L index score as a valid and reliable instrument in assessing HRQoL amongst these patients.

The limits of agreement were good between the EQ-5D-5L index score and the OHS, and they can be considered similar to each other in terms of concurrent validity. However, the OHS is a joint-specific PROM, whereas the EQ-5D-5L index score is designed to assess overall

functionality. For example, someone who can compensate enough to perform daily tasks and cope well with the mental burden of an arthritic hip on the EQ-5D-5L index score, may record gait disturbances and set specific difficulties with mobility on the OHS. We chose the OHS as a comparator for this validation as it is a widely used PROM, with significant overlap in terms of items with the EQ-5D-5L index score. For example, both feature mobility, pain/discomfort and usual activities. This was shown in more detail when the OHS was compared against the dimensions of the EQ-5D-5L. There is a high degree of correlation between the dimensions for the EQ-5D-5L and the OHS for the most part. The exception is the relationship between the Anxiety/Depression dimension of the EQ-5D-5L and the OHS, where the correlation is only fair. This is in line with evidence from the literature (101, 102, 103) that shows that strong correlations exist between instruments and dimensions that measured similar constructs. Hence, they should be utilised concurrently to complement each other, instead of being considered as substitutes for one another.
The longitudinal nature of this study with multiple time points lends itself well to assessing incremental changes in the population and detecting differences in the performance of both PROMs. The experience-based and prospective nature of this data is also a strong point.
The EQ-VAS as a stand-alone measure showed a smaller ES than the EQ-5D-5L index score at both six weeks (0.75 versus 1.53 respectively, $p<0.0001$) and six months (0.80 versus 1.40 respectively, $p<0.0001$). SRM was also large for both scores at the six-week and six-month time points. However, the EQ-VAS has better predictive validity than the EQ-5D-5L index score and OHS. This suggests that it has a higher predictive value for postoperative recovery and should be routinely used as an adjunct to the EQ-5D-5L index score. A reason for this better predictive validity may be the much broader nature of the VAS (i.e. not proscribed by the domains or items as in the OHS or EQ-5D-5L descriptive system) which allows the patients to include more in their subjective rating of health. This is beneficial for patient stratification and counselling with regards to realistic rehabilitation expectations and postsurgical results.
An assessment of the agreement between the EQ-5D-5L and the EQ-VAS on one hand and the OHS on the other showed acceptable agreement (moderate to good/substantial for most comparisons). This suggests that while the ratings from the instruments were not identical, they were moderately close and should be considered complements rather than substitutes of one another.

Some limitations of this study have to be addressed. There were approximately 25% missing data for patients at six months. Therefore, these patients had to be excluded, introducing a response bias. There was also an incomplete recording of patients' baseline characteristics, with 90.6% (328/362) patients having their BMI recorded and 94.2% (341/362) having their CCI recorded.

CONCLUSIONS
In conclusion, The EQ-5D-5L index score and the Oxford Hip Score demonstrate good concurrent validity in this study. The EQ-5D-5L index score revealed a large effect size at six weeks and six months postoperatively, and both PROMs had adequate responsiveness. The EQ-5D-5L index score PROM is suitable to quantify general health-related quality of life in the Australian hip arthroplasty patient population.

TABLES

Table 1: Baseline Characteristics

Age (mean ± SD)	68.5 ± 12.0
Gender (M/F)	160/202
BMI (mean ± SD)	30.8 ± 5.6
CCI (mean ± SD)	73.7 ± 22.5

Table 2: Concurrent and Predictive Validity

Concurrent Validity				
	EQ-5D-5L		EQ-VAS	
Preoperative	0.71 (Good)		0.37 (Fair)	
6 Weeks	0.61 (Good)		0.53 (Good)	
6 Months	0.59 (Good)		0.45 (Fair)	
Predictive Validity[a]				
	6 Weeks		6 Months	
	Average Marginal Effect (Standard Error)	Model (Link)	Average Marginal Effect (Standard Error)	Model (Link)
OHS[b]	0.19 (0.06) (Low)	Gamma (Negative Inverse)	0.23 (0.08) (Low)	Gamma (Negative Inverse)
EQ-5D-5L[b]	0.18 (0.04) (Low)	Gaussian (Identity)	0.16 (0.05) (Low)	Gaussian (Identity)
EQ-VAS[b]	0.37 (0.04) (Fair)	Gamma (Negative Inverse)	0.31 (0.04) (Fair)	Gamma (Negative Inverse)

[a]Regression analysis for predictive validity was performed using generalised linear models (GLMs) with baseline characteristics age, gender, CCI and BMI as the dependent variables.

[b]OHS= Oxford Hip Score, EQ5D-5L = EQ-5D-5L utility index score, EQ-VAS = Visual analogue score of the EQ-5D-5L

Table 3: OHS[a] as compared to EQ-5D-5L dimensional components over time (Spearman's correlation)

	EQ-5D-5L[a] dimensions				
	Mobility	Self-care	Usual Activities	Pain /Discomfort	Anxiety/ Depression
OHS[a] - Preoperative	0.6171 (Good)	0.5302 (Good)	0.6342 (Good)	0.6677 (Good)	0.2822 (Fair)
OHS[a] – 6 weeks	0.5639 (Good)	0.5065 (Good)	0.5934 (Good)	0.5881 (Good)	0.3328 (Fair)
OHS[a] – 6 months	0.5564 (Good)	0.5296 (Good)	0.5725 (Good)	0.5182 (Good)	0.3673 (Fair)

[b]OHS= Oxford Hip Score, EQ5D-5L = EuroQol 5 dimensions 5 level instrument

Table 4: Measuring agreement between the PROMs[a]

	EQ-5D-5L[b] vs OHS[b]	EQ-VAS[b] vs OHS[b]

Preoperative	Krippendorff's alpha	0.704 (0.648, 0.752) – Substantial	0.382 (0.289, 0.465) – Fair
	ICC[c]	0.827 (0.787, 0.859) - Good	0.553 (0.450, 0.636) – Moderate
	CCC[c]	0.704 (0.652, 0.756) - Moderate	0.381 (0.292, 0.469) - Poor
6 weeks	Krippendorff's alpha	0.640 (0.575, 0.697) – Substantial	0.519 (0.439, 0.590) – Moderate
	ICC[c]	0.781 (0.731, 0.822) - Good	0.684 (0.611, 0.743) - Moderate
	CCC[c]	0.640 (0.579, 0.701) - Moderate	0.519 (0.443, 0.594) – Moderate
6 months	Krippendorff's alpha	0.658 (0.583, 0.719) – Substantial	0.462 (0.361, 0.550) – Acceptable
	ICC[c]	0.793 (0.737, 0.837) - Good	0.632 (0.532, 0.710) - Moderate
	CCC[c]	0.656 (0.588, 0.725) - Moderate	0.461 (0.366, 0.555) - Poor

[a]PROMs = patient related outcome measures
[b]OHS= Oxford Hip Score, EQ5D-5L = EQ-5D-5L utility index score, EQ-VAS = Visual analogue score of the EQ-5D-5L
[c] ICC = Intraclass Correlation Coefficient; CCC = Lin's Concordance Correlation Coefficient

Table 5: Responsiveness of PROMs[a]

(a) 6 Weeks

	Preoperative	6 Weeks	Mean Difference	Paired t-Test	Effect Size	Standard Response Mean
OHS[b]	13.73 ± 7.32	30.10± 9.08	16.37 ± 10.85	<0.0001	2.16 (Large)	1.51 (Large)
EQ-5D-5L[b]	0.08 ± 0.36	0.63 ± 0.27	0.56 ± 0.40	<0.0001	1.53 (Large)	1.40 (Large)
EQ-VAS[b]	61.57 ± 20.11	76.64 ± 15.83	15.07 ± 18.82	<0.0001	0.75 (Moderate)	0.80 (Large)

(b) 6 Months

	Preoperative	6 Months	Mean Difference	Paired t-Test	Effect Size	Standard Response Mean
OHS[b]	13.71 ± 7.59	37.41 ± 9.23	23.70 ± 10.56	<0.0001	3.12 (Large)	2.24 (Large)
EQ-5D-5L[b]	0.10 ± 0.37	0.78 ± 0.26	0.69 ± 0.40	<0.0001	1.88 (Large)	1.70 (Large)
EQ-VAS[b]	62.00 ± 20.19	80.59 ± 13.90	18.59 ± 18.64	<0.0001	0.92 (Large)	1.00 (Large)

[a] PROMs = Patient reported outcome measures
[b]OHS= Oxford Hip Score, EQ5D-5L = EQ-5D-5L utility index score, EQ-VAS = Visual analogue score of the EQ-5D-5L

FIGURES

Figure 1: Boxplots Showing Distribution of PROMs Scores over Time

LIST OF ABBREVIATIONS

THA: Total hip arthroplasty
6w: Six weeks
6m: Six months
ES: Effect size
SRM: Standardized response mean
PROMs: Patient reported outcome measures
OHS: Oxford Hip Score
VAS: Visual Analogue Scale
CCI: Charleson Comorbidity Index
HRQoL: Health Related Quality of Life
TMLE: Targeted Maximum Likelihood Estimation
BMI: Body mass index
TTO: Time Trade Off

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Problems with your hip

During the past 4 weeks..

✓tick one box for every question.

1. ***During the past 4 weeks*****.....**

How would you describe the pain you usually had from your hip?

None	Very mild	Mild	Moderate	Severe
❑	❑	❑	❑	❑

2. ***During the past 4 weeks*****.....**

Have you had any trouble with washing and drying yourself (all over) because of your hip?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

3. ***During the past 4 weeks*****.....**

Have you had any trouble getting in and out of a car or using public transport because of your hip? *(whichever you tend to use)*

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

4. ***During the past 4 weeks*****.....**

Have you been able to put on a pair of socks, stockings or tights?

Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, Impossible
❑	❑	❑	❑	❑

5. ***During the past 4 weeks*****.....**

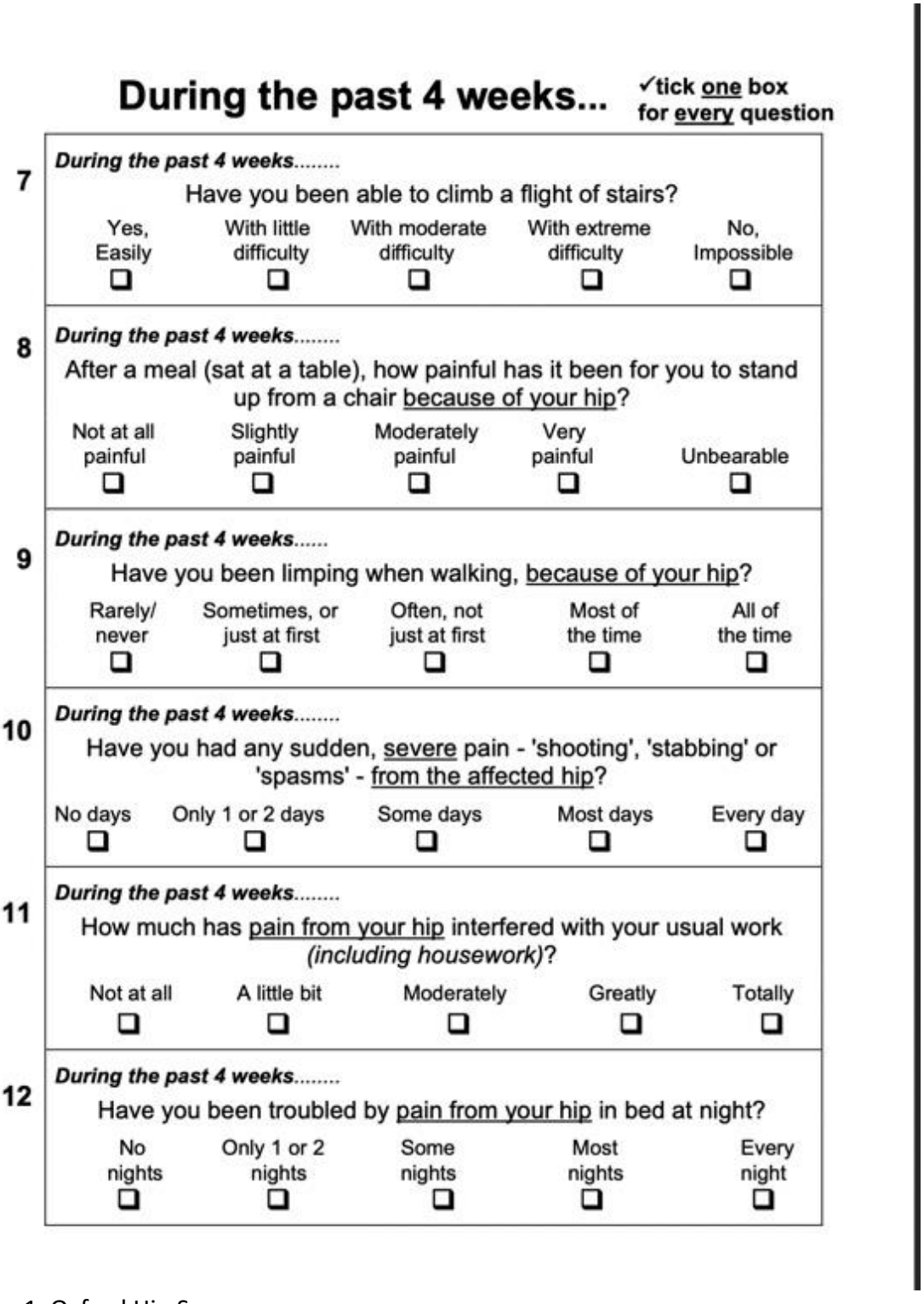
Could you do the household shopping on your own?

Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, Impossible
❑	❑	❑	❑	❑

6. ***During the past 4 weeks*****.....**

For how long have you been able to walk before pain from your hip becomes severe? (*with or without a stick)*

No pain/ More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all -pain severe on walking
❑	❑	❑	❑	❑



Addendum 1. Oxford Hip Score

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ 1 I have no problems in walking about
- ☐ 2 I have slight problems in walking about
- ☐ 3 I have moderate problems in walking about
- ☐ 4 I have severe problems in walking about
- ☐ 5 I am unable to walk about

SELF-CARE

- ☐ 1 I have no problems washing or dressing myself
- ☐ 2 I have slight problems washing or dressing myself
- ☐ 3 I have moderate problems washing or dressing myself
- ☐ 4 I have severe problems washing or dressing myself
- ☐ 5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ 1 I have no problems doing my usual activities
- ☐ 2 I have slight problems doing my usual activities
- ☐ 3 I have moderate problems doing my usual activities
- ☐ 4 I have severe problems doing my usual activities
- ☐ 5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have slight pain or discomfort
- ☐ 3 I have moderate pain or discomfort
- ☐ 4 I have severe pain or discomfort
- ☐ 5 I have extreme pain or discomfort

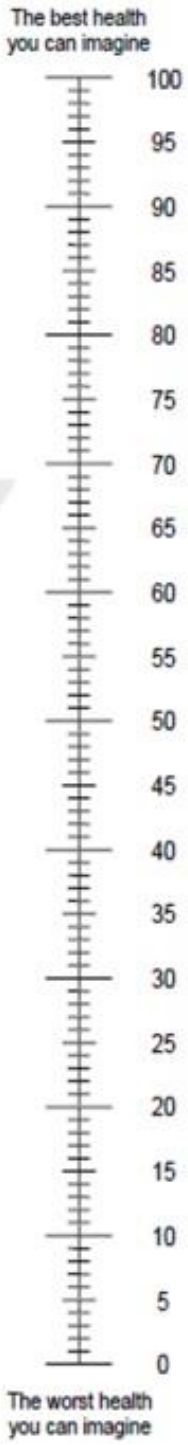
ANXIETY / DEPRESSION

- ☐ 1 I am not anxious or depressed
- ☐ 2 I am slightly anxious or depressed
- ☐ 3 I am moderately anxious or depressed
- ☐ 4 I am severely anxious or depressed
- ☐ 5 I am extremely anxious or depressed

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



Addendum 2. EQ-5D-5L

Part III, Chapter 7

Evaluation of the EQ-5D-5L, EQ-VAS Stand-Alone Component and Oxford Knee Score in the Australian Knee Arthroplasty Population Utilising Minimally Important Difference, Concurrent Validity, Predictive Validity and Responsiveness

Evaluation of the EQ-5D-5L, EQ-VAS Stand-Alone Component and Oxford Knee Score in the Australian Knee Arthroplasty Population Utilising Minimally Important Difference, Concurrent Validity, Predictive Validity and Responsiveness

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ABSTRACT

Purpose: To evaluate the Oxford Knee Score (OKS), EQ-5D-5L utility index and EQ-5D visual analogue scale (EQ-VAS) for health-related quality of life outcome measurement in patients undergoing elective total knee arthroplasty (TKA) surgery.
Methods: In this prospective multi-centre study, the OKS and EQ-5D-5L index scores were collected preoperatively, six weeks (6w) and six months (6m) following TKA. The OKS, EQ-VAS and EQ-5D-5L index were evaluated for minimally important difference (MID), concurrent validity, predictive validity (Spearman's Rho of predicted and observed values from a generalised linear regression model (GLM)), responsiveness (effect size (ES) and standard response mean (SRM)). The MID for the individual patient was determined utilising two approaches; distribution-based and anchor-based.
Results: 533 patients were analysed. The EQ-5D-5L utility index showed good concurrent validity with the OKS (r=0.72 preoperatively, 0.65 at 6w and 0.69 at 6m). Predictive validity for the EQ-5D-5L index was lower than OKS when regressed. Responsiveness was large for all fields at 6w for the EQ-5D-5L and OKS (EQ-5D-5L ES 0.87, SRM 0.84; OKS ES 1.35, SRM 1.05) and 6m (EQ-5D-5L index ES 1.31, SRM 0.95; OKS ES 1.69, SRM 1.59). The EQ-VAS returned poorer results, at 6w an ES of 0.37 (small) and SRM of 0.36 (small). At 6m, the EQ-VAS had an ES of 0.59 (moderate) and SRM of 0.47 (small). It, however, had similar predictive validity to the OKS, and better than the EQ-5D-5L index. MID determined using anchor approach, was shown that for OKS at 6 weeks it was 8.84 ± 9.28 and at 6 months 13.37 ± 9.89. For the EQ-5D-5L index at 6 weeks MID was 0.23 ± 0.39, and at 6 months 0.26 ± 0.36.
Conclusions: The EQ-5D-5L index score and the OKS demonstrate good concurrent validity. The EQ-5D-5L index demonstrated lower predictive validity at 6w, and 6m than the OKS, and both PROMs had adequate responsiveness. The EQ-VAS had poorer responsiveness but better predictive validity than the EQ-5D-5L index.
This article includes MID estimates for the Australian knee arthroplasty population.

INTRODUCTION

Total knee arthroplasty (TKA) is a safe and cost-effective surgery for patients with osteoarthritis who do not respond to medical therapy alone (104) and in Australia, a total of 54,102 replacements were performed per year from 2017 – 2018 (218 per 100,000). (10) Despite the well-established safety data and patient improvements published over the last 20 years (104), the measurement of patient-related outcomes, including functional change or improvement, are not as clear-cut for TKA compared to other orthopaedic surgery such as total hip arthroplasty. (105, 106)

Patient-reported outcome measures (PROMS) are used as a measurement tool to evaluate patient and health economic outcomes, with an example being the 5-level version of the EuroQol 5 Dimensions (EQ-5D-5L index score). This standardized health-related quality of life (HRQoL) questionnaire was initially developed in 1990 as a 3-level version designed to assess general health for five dimensions. (54) (75) In 2011, it was revised to a 5-level version (EQ-5D-5L index) with five levels and five dimensions to reduce granularity in health response and reduce the ceiling effect. (76) The EQ-5D questionnaires are some of the most widely used PROMs globally; in some countries, such as the United Kingdom, it is used to calculate quality adjusted life years used in cost-utility analysis (77) (78, 79)

While extensively used in other parts of the world, the EQ-5D-5L index score has not yet been well validated for the Australian orthopaedic population for HRQoL assessment. (107) The results of the EQ-5D-5L index score PROM are converted into vectors which are five-digit codes representing a health state. For example, 11111 is full health, and 55555 represents the worst health. There are 3,125 possible health states. These are mapped onto a single utility index using a country-specific value set. To date, more than 25 countries have validated country-specific EQ-5D-5L value sets for various patient populations. (82)

The EQ-VAS is a stand-alone component of the EQ-5D-5L index, in which a patient self-reports their impression of their general health and functionality. Compared with the in-depth, question-and-answer format of the ED-5D-5L index, the EQ-VAS is seen as a simpler and less ambiguous format. (83) The Oxford Knee Score (OKS) is a validated PROM specifically developed to assess function and pain in patients undergoing TKA. (84) It had been utilised to assess the concurrent validity of the EQ-5D-5L index in TKA patients in other countries. (85)

The minimally important difference is defined as the smallest PROM score change, which is perceived significantly by patients or clinicians. (108) The MID is 'anchored' by using a satisfaction survey to identify patients who experienced a change in their functional status considered perceptible and clinically important. Changes in functional status were measured using a five-point Likert scale at one year postoperatively scored as either (1) "very satisfied", (2) "satisfied" (3) "neither satisfied nor dissatisfied", (4) "dissatisfied", or (5) "very dissatisfied". Patients whose functional change was 4 or 2 were considered to have experienced some change equivalent to the MID. (109) It is generally considered that the anchor-based approach is the optimal method for evaluation of MID as it yields a direct expression of the patient's preferences and values. (108) The distribution-based method of

MID estimation assesses the distribution of scores around the mean of the measurement of interest, for example standard deviation. (110)

Concurrent validity describes the extent of the method being tested to assess an outcome correlates with an established method to measure the same. Here the EQ-5D-5L index will be tested against the established OKS. Predictive validity describes the association between baseline and follow-up outcomes which is highly valued in this cohort, as it has implications for surgical suitability for individual patients. Responsiveness, a measure of the sensitivity of PROMs to reflect a change in health status over time, is also tested.

OUTCOME MEASURE

This study aims to compare the EQ-5D-5L utility index and EQ-VAS against the OKS in Australian patients undergoing total knee arthroplasty using the minimally important difference (MID), concurrent and predictive validity.

PATIENTS AND METHODS

This multi-centre prospective trial was conducted at two large tertiary teaching hospitals in Adelaide, Australia. A group of orthopaedic surgeons operate routinely at both sites, performing approximately 300 knee arthroplasty surgeries annually. However, the number of patients operated on in 2020 was reduced to approximately 150 due to SARS Covid-19-related restrictions. The local governing Human Research Ethics Committee granted multi-centre approval (SALHN/329.17).

All consecutive adult patients undergoing elective total knee arthroplasty surgery were prospectively enrolled over a nearly three-year period from 8th January 2018 to 1st of October 2020, with a six-month follow-up until 2nd April 2021. Indication for surgery was predominantly osteoarthritis, all joint replacements were primary operations only. Informed consent was obtained from all participants, and baseline demographics were recorded for all patients, including age, gender, body mass index (BMI) and the Charlson comorbidity index (CCI). (86) (111)

Data were recorded at three different time points (preoperatively, six weeks and six months postoperatively) by one dedicated research assistant, using scripted questionnaires via telephone or a written survey sent by postal mail. At all three time points, two validated PROMs were used: the Oxford Knee Score (OKS) (87) and the EQ-5D-5L index score (54) including the EQ-VAS stand-alone component. Data were keyed into a password-secured database and stored on the hospital computer network.

Patients were included for analysis if they had complete quality of life data. This was defined as completing the EQ-5D-5L index score and OKS for the three time points.

OXFORD KNEE SCORE

The OKS is a joint-specific PROM (112, 113) which has been extensively utilised over the last 20 years. It assesses six fields (pain, walking, physical activity, function, quality of life and psychological wellbeing), with each field containing 2 questions, making up a total of 12 questions. Each question is scored on a 5-point discrete visual analogue scale where higher scores indicate better function. The final score is a sum tally of the individual question scores, with a range of 0 to 48. The OKS has previously been utilised as a comparator for

responsiveness with PROMs such as the EQ-5D-3L and SF-12 in a similar patient population, albeit in different countries than Australia. (114, 115)

EQ-5D-5L INDEX AND EQ-VAS

The EuroQol Group designed the EQ-5D-5L index to quantify general health in adults. Using a 5-point scale (none, slight, moderate, severe and extreme/unable to perform), it evaluates the fields of mobility, self-care, usual activities, anxiety/depression and pain/discomfort. Based on the general Australian population, preference weights can be attached to each of the EQ-5D-5L health states. These were determined through a discrete choice experiment approach (88). Utility indices vary from −0.676 to 1, with higher utilities signifying a better HRQoL.

The EQ-VAS is a vertical visual analogue scale which constitutes a part of the EQ-5D-5L index score and can also be used as a stand-alone component. Patients are to rate their general health from 0 to 100, with higher numeric scores denoting a better function. The EQ-5D-5L index questionnaire is established on specific national value sets or the generic Western Preference Pattern. (81) It has been validated in approximately 28 countries as of 2022 (116, 117, 118, 119).

STATISTICAL ANALYSIS

All statistical analyses were performed utilising STATA version 17 (StataCorp, Texas, USA). Continuous variables (age, BMI, CCI) were expressed as means and standard deviations. The categorical variable (gender) was expressed as percentages (counts). A p-value of <0.05 was considered statistically significant.

Concurrent Validity, Predictive Validity and Agreement

For analysis of concurrent validity, Spearman's correlation coefficient (rho, ρ) was utilised to compare the EQ-5D-5L index and EQ-VAS against the OKS. The strength of the relationship can be assessed as low/weak ($\rho < 0.25$), fair ($\rho = 0.25$ to <0.50), good ($\rho = 0.50–0.75$), or excellent ($\rho > 0.75$). This magnitude of rank order correlations was sourced from previous publications on the same area. (93, 94)

Predictive validity was ascertained using a regression framework, whilst controlling for confounders. We utilised generalized linear models with the 6-week and 6-month postoperative PROMs as the dependent variable, and the preoperative values and baseline characteristics as independent variables. Depending on the distribution of the dependant variable, the most appropriate distribution family and canonical link function were chosen. Multiple families (including the Gaussian, inverse Gaussian, Poisson, and Gamma distributions) were trialled when there was difficulty ascertaining the appropriate family of distribution. The best fitting model was then selected based on low Akaike's Information Criteria and Bayesian Information Criteria scores. The average marginal effect with respect to preoperative score was used to compare models if different distribution families were utilised.

The agreement between the EQ-5D-5L index and the OKS was measured using Bland-Altman analysis at all three measurement points.

Responsiveness

Responsiveness is a measure of the sensitivity of PROMs to reflect the change in health status over time. For this study, we compared measurements at baseline, 6 weeks and 6 months follow-up using paired t-tests. Further assessment of responsiveness was quantified using effect size (ES) and standardized response mean (SRM).
The effect size was calculated using the formula: effect size equals the mean difference from baseline divided by the standard deviation at baseline.
The standard response mean was calculated using the formula: standard response mean equals mean difference from baseline divided by the standard deviation of difference.
ES and SRM were classified according to Cohen's rule of thumb, as large (≥ 0.8), moderate (0.5–0.79) or small (< 0.5). (120) Both ES and SRM are standardized measures of change over time in health, independent of sample size.

Influence of Baseline Characteristics on PROMs
Regression analysis of the baseline characteristics (age, gender, BMI and CCI) was performed using generalised linear models with the preoperative EQ-5D-5L index, EQ-VAS and OKS as independent variables. The preoperative PROMs were used as the dependant variables, and depending on the distribution, an appropriate distribution family and canonical link function were chosen using the same approach taking in the predictive validity analysis. The coefficient, standard error and p-values were recorded.
Determination of Minimally Important Difference
Minimally important difference (MID) is defined as the smallest change in score, which is perceived as important by patients or clinicians. (121) The MID for the cohorts was defined as the change in PROM score for patients who responded as satisfied (2) or dissatisfied (4) to the anchor question at one year. The MID was determined using two approaches: distribution-based approach, and the anchor-based approach.
The distribution-based approach defined MID as half the baseline standard deviation of the PROM scores (122) For both the anchor-based approach, we quantified satisfaction based on the anchor question (satisfaction rating). We then calculated Spearman's correlation coefficient to assess the correlation between the measured score and the satisfaction rating. The MID calculation would not be performed if the correlation coefficient was less than 0.25. While calculating the MID using the anchor-based approach, we considered a satisfaction score of 2 or 4 as having experienced some MID-equivalent change. The MID was then taken as the mean changes in scores of the patients who scored 2 or 4.

RESULTS
In total, the database had 797 patients, of which 96 were excluded as they did not have a preoperative questionnaire completed, 115 did not have any postoperative questionnaires answered, and a further 9 had their operation cancelled. There were statistically insignificant differences in characteristics between those with complete data and those with missing data for nearly all demographic characteristics. Out of 12 comparisons, only 2 statistically significant differences were seen with another borderline significant (Appendix 1). Therefore, complete case analysis was conducted.

673 knee arthroplasty patients with preoperative and postoperative questionnaires completed were identified from the database. Of these, 140 had preoperative and 6w data, and the further 533 had complete data for preoperative, 6w and also 6 months. All 673 with both pre- and postoperative data were included in the study. The mean age of our cohort at the time of surgery was 68.3 ± 9.6 years old, and 59.14% (398/673) were female. The mean preoperative BMI was 31.9 ± 5.7 and the

mean CCI was 72.0 ± 22.4%. A summary of baseline characteristics can be found in Table 1. Early complications of arthroplasty recorded at 6 weeks included 20 cases of venous thromboembolism, 19 cases of additional antibiotic use, eight cases of peri-prosthetic fractures, seven cases of myocardial infarctions, five cases of cerebrovascular events, four cases of postoperative stiffness limiting rehabilitation and two cases of periprosthetic infections requiring re-operation. Eleven patients had more than one complication, and 610 patients of the total 673 included reported no complications. Of the 533 patients who were followed up until 6 months, 53 of them had early complications.

Boxplots for the distributions of scores at baseline (preoperative), 6 weeks and 6 months are shown in Figure 1.

Number of patient responses to the satisfaction survey at one year were as follows:

- 1 (Very satisfied): 196 (48.2%)
- 2 (Satisfied): 114 (28%)
- 3 (Neither Satisfied Nor Dissatisfied): 62 (15.2%)
- 4 (Dissatisfied): 24 (5.9%)
- 5 (Very Dissatisfied): 11 (2.7%)

A summary of baseline characteristics can be found in Table 1.

Concurrent Validity, Predictive Validity and Agreement

EQ-5D-5L index showed good concurrent validity when compared to OKS at baseline, 6 weeks, and 6 months postoperative, with a Spearman's coefficient of 0.72, 0.65 and 0.69, respectively. EQ-VAS had fair concurrent validity when compared to OKS at baseline, 6 weeks, and 6 months postoperative, with a Spearman's coefficient of 0.31, 0.46 and 0.49 respectively (Table 2).

Predictive validity for each of the three different PROMs score was determined using generalized linear models, with regression to baseline scores and covariates. In all cases, the distribution that provided the best model fit was the Gamma distribution with a canonical negative inverse link. The average marginal effects for the preoperative score were recorded and displayed in Table 2. The EQ-5D-5L index score showed lower predictive validity when compared to OKS at 6 weeks and 6 months. EQ-VAS, however, showed similar predictive validity compared to OKS at 6 weeks and 6 months.

Bland Altman's plot showed good agreement between OKS and EQ-5D-5L index at preoperative, 6 weeks and 6 months, with approximately 95% of data points within the limits of agreement. These plots are shown in Figures 2, 3 and 4.

Responsiveness

At 6 weeks, all three PROMs showed significant differences between baseline and follow-up scores. Both OKS and EQ-5D-5L index had a large ES and SRM, although the actual estimate for OKS was larger. The ES for OKS and EQ-5D-5L index was 1.35 and 0.87, respectively, and the SRM was 1.05 and 0.84, respectively. The EQ-VAS had a small ES and SRM of 0.37 and 0.36, respectively.

At 6 months, all three PROMs again showed a significant difference between baseline and follow-up scores: The ES for OKS, EQ-5D-5L index, and EQ-VAS were 1.69, 1.31 and 0.59, respectively, and the SRM was 1.59, 0.95 and 0.47 respectively. These findings are detailed in Table 3.

Influence of Baseline Characteristics on PROMs

Since EQ-5D-5L scores had negative values, it was determined that the Gaussian family of distribution with a canonical identity link was most appropriate compared to both OKS and EQ-VAS, which had non-negative distributions. Therefore, the Gamma distribution provided the best fit and was hence used for the final model. All three preoperative PROMs were significantly affected by CCI. EQ-VAS was additionally significantly affected by BMI (Table 4).

Minimally Important Difference

As measured using the distribution-based method, the MID for OKS and EQ-5D-5L index were 3.70 and 0.18, respectively. When the anchor-based technique was utilised, the MID for OKS at 6 weeks and 6 months was 8.84 ± 9.28 and 13.37 ± 9.89, respectively. The MID for the EQ-5D-5L index scores were 0.23 ± 0.39 and 0.26 ± 0.36 at 6 weeks and 6 months, respectively.

DISCUSSION

This analysis is an empirical validation of the EQ-5D-5L index's suitability in assessing HRQoL amongst knee arthroplasty patients using experienced-based patient data from a prospective multi-centre study database, with the correlation between the Oxford Knee Scores, EQ-VAS, and the EQ-5D-5L index PROMs. The findings support the utilization of the EQ-5D-5L index as a valid and reliable instrument in assessing HRQoL amongst these patients, but it must be noted that the OKS outperformed the EQ-5D-5L index in all fields. The EQ-VAS had poorer responsiveness than the EQ-5D-5L index, but better predictive validity.

The EQ-VAS as a stand-alone measure showed a smaller ES than the EQ-5D-5L index at both six weeks (0.37 versus 0.87 respectively, $p<0.0001$) and six months (0.59 versus 1.31 respectively, $p<0.0001$). The SRM was large for the EQ-5D-5L index score at the six-week and six-month time points, but only small for the EQ-VAS. However, the EQ-VAS had better predictive validity than the EQ-5D-5L index but comparable validity to the OKS. This suggests a higher predictive value for postoperative recovery and could be used as an adjunct to the EQ-5D-5L index score. An explanation for this may be the broader nature of the EQ-VAS (ie. not proscribed by the domains or items as in the OKS or EQ-5D-5L index descriptive system), which allows the patients to consider more quality of life constructs in their subjective rating of health. This is beneficial for patient stratification and counselling regarding realistic rehabilitation expectations and postsurgical results.

The EQ-VAS standalone component was only fair in terms of concurrent validity. The OKS is a joint-specific PROM, whereas the EQ-5D-5L index is designed to assess overall functionality. For example, someone who can compensate enough to perform daily tasks and cope well with the mental burden of an arthritic knee on the EQ-5D-5L index, may record gait disturbances and set specific difficulties with mobility on the OKS. We chose the OKS as a comparator for this validation as it is widely used and has significant items that overlap with the EQ-5D-5L index. For example, both feature mobility, pain/discomfort and usual activities. Hence, they should be utilised concurrently to complement each other, instead of being considered as substitutes for one another.

This study analysed MID via two approaches; anchor-based and distribution-based. An estimate of MID in this patient population is important clinically as it will indicate when a particular patient would notice a benefit from knee arthroplasty surgery. It is important in study design, as any new treatment being investigated should aim to detect a difference at least equal to the MID. Non-inferiority studies should aim to show that the difference between groups is less than the MID for the Australian orthopaedic population. (123)
The longitudinal nature of this study with multiple time points allows evaluation of the incremental changes in the population and the differences in the performance of both PROMs. The experience-based and prospective nature of this data is also a strong point. Generalizability of this study is high, as surgical technique and perioperative management is consistent with standard practice in Australia, and worldwide.
The EQ-5D-5L index has been assessed against other PROMs in the TKA population in previous publications, and found to to be more responsive (ES and SRM) than other scores in reflecting health related changes in this group. (124) Conner-Spady et al. found a MID of 0.20 for TKA patients for the EQ-5D-5L index. (85) They reported a wide variation in the MID with the percentage agreement of responder classification using 2SEM versus MID ranging from 79.6 to 99.6% for the EQ-5D-5L and from 69.4 to 94.8% for the Oxford scores. Recommendations included utilising multiple PROMs for HRQoL assessment in future studies. Our study also found a wide variation, with a similar MID result to those found by the previous studies.
There is a paucity of literature for TKA and concurrent and predictive validity, but comparable literature for total hip arthroplasty in the Australian population has previously illustrated that the EQ-5D-5L index and the OHS demonstrate strong concurrent validity. The EQ-5D-5L index had similar predictive validity at 6w and 6m. (107)
Some limitations of this study have to be addressed. There were approximately 21% missing data for patients at six months. Therefore, these patients had to be excluded, introducing a response bias.
Future research should include further validation of these clinically relevant PROMs, as well as perhaps corroboration of the baseline MID for knee arthroplasty patients in Australia.

CONCLUSIONS

In conclusion, The EQ-5D-5L index and the Oxford Knee Score demonstrate good concurrent validity in this study. EQ-5D-5L index revealed a large effect size at six weeks and six months postoperatively, but smaller than the OKS at all time points. Both PROMs had adequate responsiveness. However, the OKS outperformed the EQ-5D-5L in all fields. The EQ-VAS had poorer responsiveness than the EQ-5D-5L index, but better predictive validity when used as a stand-alone component.
The EQ-5D-5L index PROM is suitable to quantify general health-related quality of life in the Australian knee arthroplasty patient population. Still, given the OKS superior performance in terms of predictive validity and responsiveness, it should be favoured for use above the EQ-5D-5L. Ideally, both can be used to complement each other with an assessment of a joint specific PROM in OKS and a more generalised health assessment in EQ-5D-5L.
This article establishes a baseline MID for the Australian knee arthroplasty patient population, which can be incorporated into further research or utilised for patient counselling in the perioperative phase.

TABLES

Table 1: Baseline Characteristics
SD: Standard Difference
M/F: Male/Female
BMI: Body Mass Index
CCI: Charlson Comorbidity Index

Age (mean ± SD)	68.3 ± 9.6
Gender (M/F)	275/398
BMI (mean ± SD)	31.9 ± 5.6
CCI (mean ± SD)	72.0+/- 22.4

Table 2: Concurrent and Predictive Validity
OKS : Oxford Knee Score

Concurrent Validity (Spearman's Coefficients)				
	EQ-5D-5L		EQ-VAS	
Preoperative	0.72 (Good)		0.31 (Fair)	
6 Weeks	0.65 (Good)		0.46 (Fair)	
6 Months	0.69 (Good)		0.49 (Fair)	
Predictive Validity				
	6 Weeks		6 Months	
	Average Marginal Effect (Standard Error)	Model (Link)	Average Marginal Effect (Standard Error)	Model (Link)
OKS	0.33 (0.05)	Gamma (Negative Inverse)	0.37 (0.06)	Gamma (Negative Inverse)
EQ-5D-5L index	0.25 (0.03)	Gaussian (Identity)	0.23 (0.04)	Gaussian (Identity)
EQ-VAS	0.34 (0.04)	Gamma (Negative Inverse)	0.31 (0.04)	Gamma (Negative Inverse)

Table 3: Responsiveness of PROMs
OKS : Oxford Knee Score

(c) 6 Weeks

	Preoperative	6 Weeks	Mean Difference	Paired t-Test	Effect Size	Standard Response Mean
OKS	17.23 ± 7.41	27.25 ± 8.62	10.02 ± 9.58	<0.0001	1.35 (Large)	1.05 (Large)
EQ-5D-5L index score	0.30 ± 0.35	0.61 ± 0.26	0.31 ± 0.37	<0.0001	0.87 (Large)	0.84 (Large)
EQ-VAS	67.71 ± 19.07	74.79 ± 16.54	7.08 ± 19.76	<0.0001	0.37 (Small)	0.36 (Small)

(d) 6 Months

	Preoperative	6 Months	Mean Difference	Paired t-Test	Effect Size	Standard Response Mean
OKS	17.20 ± 7.33	33.26 ± 9.52	16.07 ± 10.08	<0.0001	1.69 (Large)	1.59 (Large)
EQ-5D-5L index score	0.30 ± 0.35	0.67 ± 0.28	0.36 ± 0.38	<0.0001	1.31 (Large)	0.95 (Large)
EQ-VAS	67.81 ± 19.14	77.05 ± 15.62	9.24 ± 19.68	<0.0001	0.59 (Moderate)	0.47 (Small)

Table 4: Regression Analysis with respect to Baseline Characteristics using Preoperative PROMs as the Dependant Variables
BMI: Body Mass Index
CCI: Charlson Comorbidity Index

	Oxford Knee Score	EQ-5D-5L Index Score	EQ-VAS Score

	Coefficient	SE	p-Value	Coefficient	SE	p-Value	Coefficient	SE	p-Value
Age	1.00	0.00	0.305	1.00	0.00	0.343	1.00	0.00	0.112
Gender – Male	1.00	0.00	0.100	1.01	0.03	0.816	1.00	0.00	0.129
BMI	1.00	0.00	0.862	1.00	0.00	0.384	1.00	0.00	0.014*
CCI	0.98	0.01	0.004*	1.23	0.10	0.011*	1.00	0.00	0.001*

Table 5 : Minimum Important Difference (MID)
OKS : Oxford Knee Score

	Spearman's Correlation	Distribution Technique (0.5*Baseline SD)	Anchor Technique
OKS at 6 Weeks	0.34	3.70	8.84 ± 9.28
OKS at 6 Months	0.53		13.37 ± 9.89
EQ-5D-5L index at 6 Weeks	0.34	0.18	0.23 ± 0.39
EQ-5D-5L index at 6 Months	0.50		0.26 ± 0.36

FIGURES

Figure 1: Boxplots Showing Distribution of PROMs Scores over Time

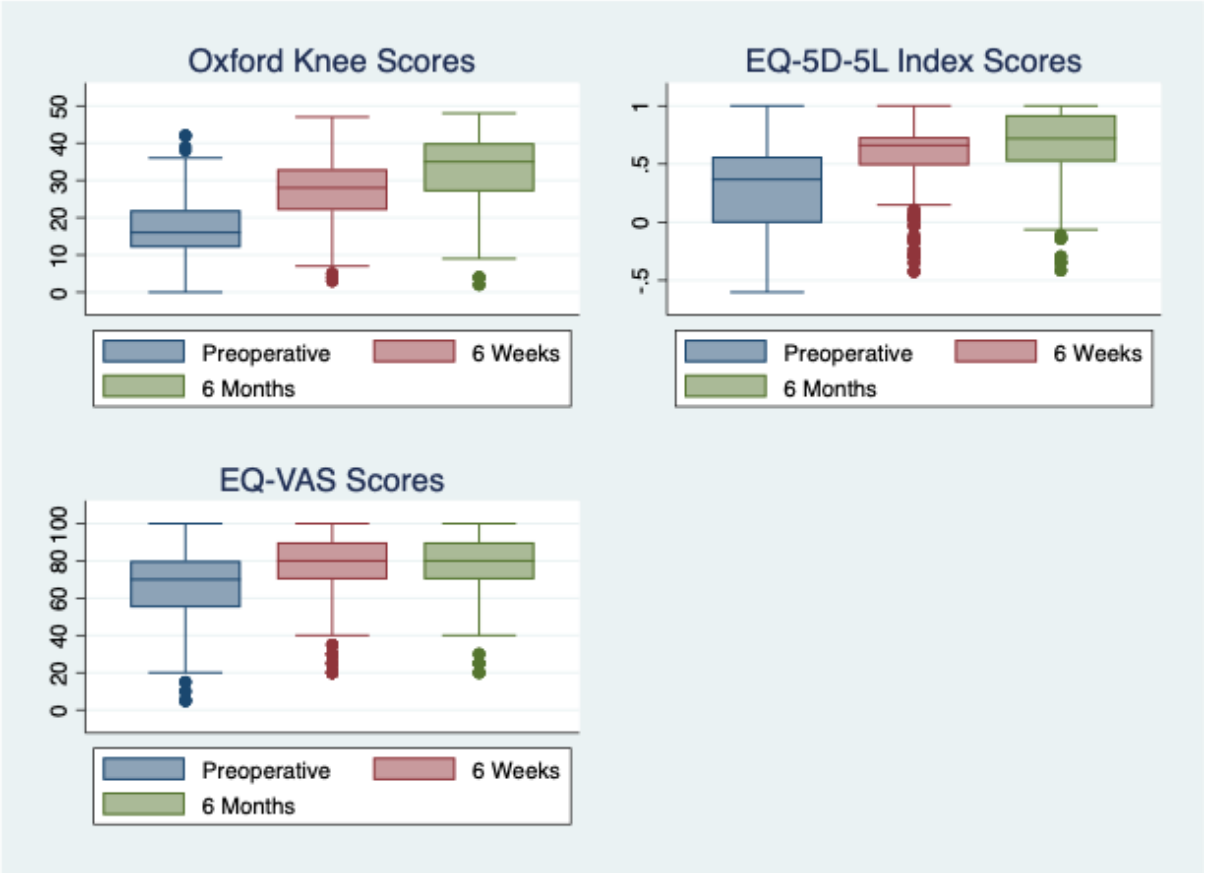


Figure 2: Preoperative Bland Altman Plots

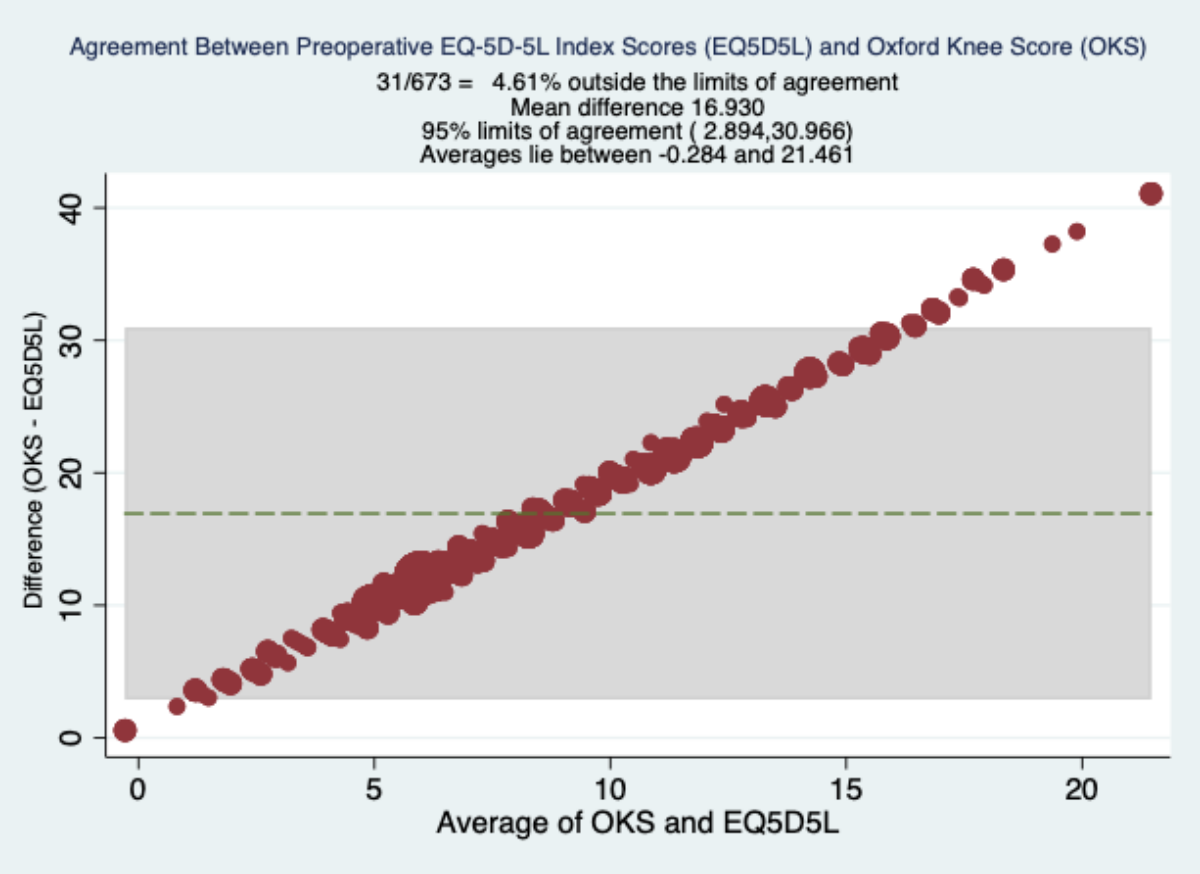


Figure 3: Bland Altman Plots at 6 Weeks

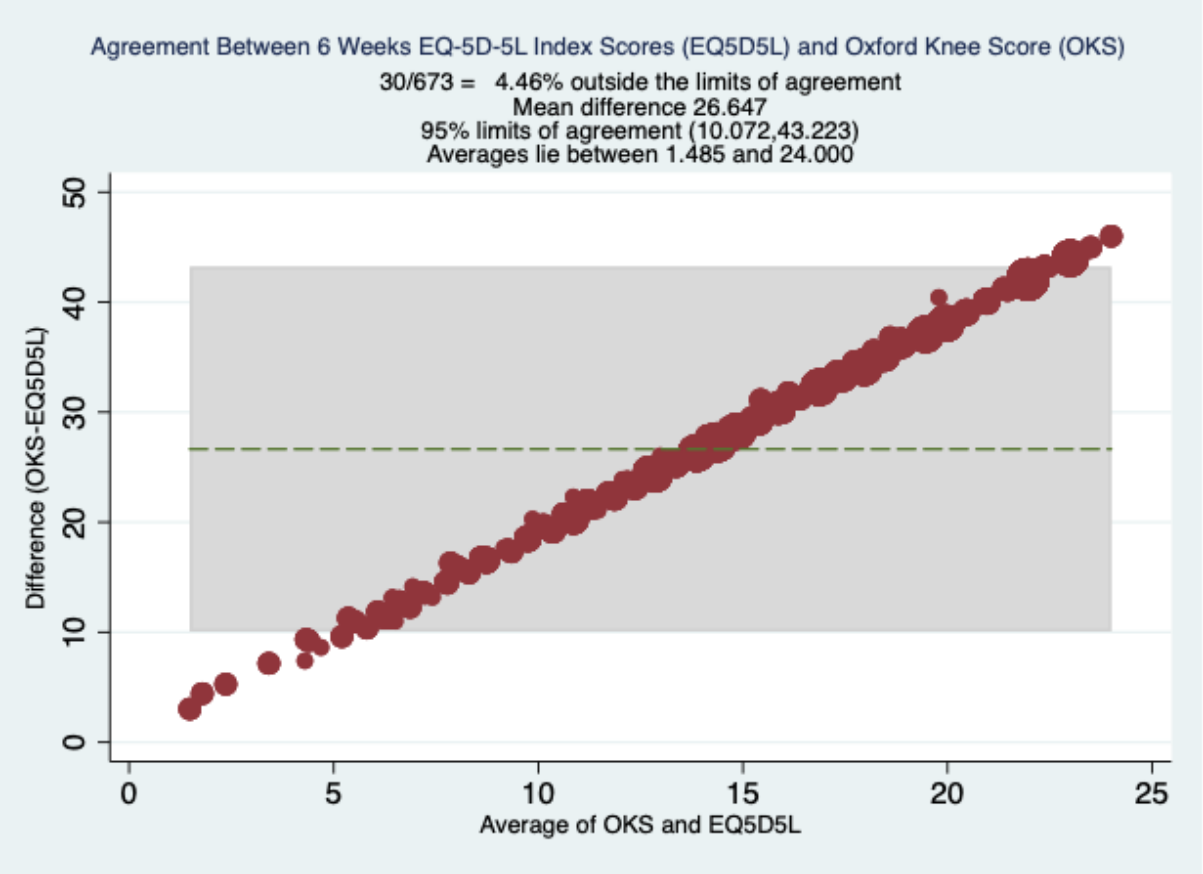
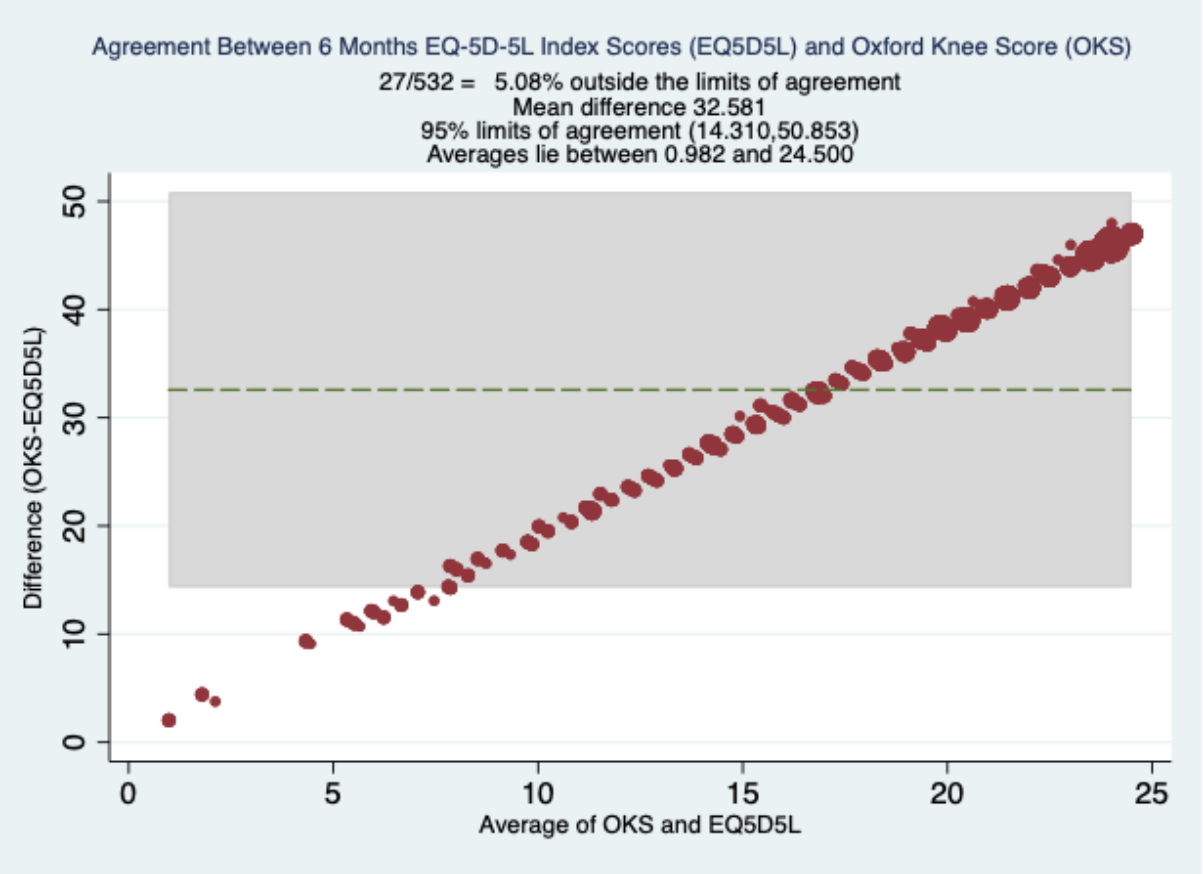


Figure 4 Bland Altman Plots at 6 Months



LIST OF ABBREVIATIONS

TKA: Total knee arthroplasty
6w: Six weeks
6m: Six months
ES: Effect size
SRM: Standardized response mean
PROMs: Patient reported outcome measures
OKS: Oxford Knee Score
VAS: Visual Analogue Scale
CCI: Charlson Comorbidity Index
HRQoL: Health Related Quality of Life
MID: Minimally Important Difference
TMLE: Targeted Maximum Likelihood Estimation
BMI: Body mass index
TTO: Time Trade-Off

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Appendix 1.

There were statistically insignificant differences in characteristics between those with complete data and those with missing data for nearly all demographic characteristics. Out of 12 comparisons, only 2 statistically significant differences were seen with another borderline. Crucially, there were statistically significant differences in the PROM scores between the two groups (please see results below).

Sorted by Complications at 6W

Baseline Demographics

Age: No Difference on t test (p=0.118)

1. No complications: 68.09 +/- 9.64
2. Complications: 70.07 +/- 9.03

Gender (M/F): No Difference on Chi2 (p=0.639)

3. No Complications: 251/359
4. Complications: 24/39

BMI: No difference on t test (p=0.374)

5. No Complications: 31.98 +/- 5.81
6. Complications: 31.28 +/- 5.03

CCI: **Those with complications had a significantly lower CCI** (p=0.004)

7. No Complications: 72.76 +/- 21.68
8. Complications: 64.13 +/- 27.64

PROMS Baseline

OKS: No significant difference on t test (p=0.055)

9. No Complications: 17.41 +/-7.39
10. Complications: 15.52 +/-7.41

EQ5D5L (Index): No significant difference on t test (p=0.556)

11. No Complications: 0.30 +/- 0.35
12. Complications: 0.33 +/- 0.37

Sorted by Complications at Presence of Follow Up at 6 Months

Baseline Demographics

Age: No Difference on t test (p=0.066)

13. No FU: 66.95 +/- 9.38

14. FU: 68.63 +/- 9.63

Gender (M/F): **Greater male dominance in the FU group on Chi2 (p=0.049)**
15. No FU: 47/93
16. FU: 228/305

BMI: No difference on t test (p=0.328)
17. No FU: 32.35 +/- 6.42
18. Complications: 31.81 +/- 5.55

CCI: **Those with FU had a significantly lower CCI** (p=0.043)
19. No FU: 75.49 +/- 21.58
20. FU: 71.06 +/- 22.56

PROMS Baseline

OKS: No significant difference on t test (p=0.820)
21. No FU: 17.36 +/-7.72
22. FU: 17.20 +/-7.33

EQ5D5L (Index): No significant difference on t test (p=0.710)
23. No FU: 0.29 +/- 0.35
24. FU: 0.30 +/- 0.35

Given the above, we felt that assuming that data were missing completely at random was appropriate as common methods of dealing with missing data (such as mean and multiple imputation) can lead to over or underestimation of MIDs in an instance such as ours. (125)

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Part III, Chapter 8

Short -Term Difference Only in Reported Outcomes (PROMs) after Anterior or Posterior Approach to Total Hip Arthroplasty: A Four Year Prospective Multi-Centre Observational Study.

Short -Term Difference Only in Reported Outcomes (PROMs) after Anterior or Posterior Approach to Total Hip Arthroplasty: A Four Year Prospective Multi-Centre Observational Study.

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LIST OF ABBREVIATIONS

DAA: Direct anterior approach

THA: Total hip arthroplasty

PA: Posterior approach

PROMs: Patient reported outcome measures

OHS: Oxford Hip Score

LOS: Length of stay

BMI: Body mass index

ABSTRACT

Background: The direct anterior approach (DAA) in total hip arthroplasty (THA) may demonstrate better functional recovery compared to the posterior approach (PA).

Methods: In this prospective multi-centre study, patient-related outcome measures (PROMs) and length of stay (LOS) were compared between DAA and PA THA patients. The Oxford Hip Score (OHS), EQ-5D-5L, pain and satisfaction scores were collected at four perioperative stages.

Results: 337 DAA and 187 PA THAs were included. The OHS PROM was significantly better in the DAA group at 6 weeks postoperatively (OHS: 33 vs. 30, p=0.02, EQ-5D-5L: 80 vs 75, p=0.03), but there were no differences at 6 months and at 1 year. EQ-5D-5L scores were similar between both groups at all time points. LOS as inpatient was significantly different, in favour of DAA (median 2 days (IQR 2-3) vs PA 3 (IQR 2-4), p=<0.0001)

Conclusions: Patients undergoing DAA THA have shorter LOS and report better short-term Oxford Hip Score PROMs at 6 weeks, but DAA did not convey long-term benefits over PA THA.

INTRODUCTION

The direct anterior approach (DAA) to facilitate total hip arthroplasty (THA) was first described by Carl Heuter in 1881. (12) This is a minimally invasive technique that utilises the tissue plane between the tensor fascia lata and rectus femoris. (13) It was later modified into the Smith-Petersen method, (14) with increasing uptake in recent years. Some evidence suggests that the DAA results in improved early functional recovery and lower postoperative pain scores, when compared to the more traditional posterior approach (PA), but these results have not been consistently supported (15, 16, 17). Furthermore, there is a paucity of evidence for long-term outcomes supporting DAA as a standard approach for THA. (126, 127, 128)

In this study, we aimed to determine if DAA THA resulted in improved patient-reported quality of recovery, shorter LOS and lower long-term pain outcomes compared to PA THA.

PATIENTS AND METHODS

This multi-centre prospective study was conducted across two tertiary teaching hospitals in Adelaide, Australia. Orthopaedic surgeons operate routinely at both hospitals, performing approximately 500 arthroplasty procedures per year. Due to SARS Covid-19 related restrictions on elective operations, this number was reduced in 2020 to approximately 300. Each orthopaedic surgeon has a preference for performing DAA or PA, and hence both

approaches were performed by different surgeons. Allocation of patient to surgeon is determined in a multidisciplinary discussion, with the orthopaedic surgeons present. The data includes DAA training curves for both some attending surgeons as well as senior trainee surgeons. 100% of cases were supervised by a senior consultant orthopaedic surgeon, and in 70% of cases a training consultant surgeon, fellow or senior trainee were the supervised primary surgeon.

All consecutive adult patients at both hospitals undergoing elective THA were prospectively enrolled over a three-year period from 8th January 2018 to 1st of October 2020, with a year follow-up until 2nd October 2021. Indication for elective THA was for the vast majority osteoarthritis, zero trauma patients were included. The local Human Research Ethics Committee granted multi-centre approval (SALHN/329.17). Informed consent was obtained from all participants. This trial was retrospectively registered (Netherlands Trial Registry: NL9803).

Data for this study were recorded by a dedicated research assistant, using scripted questionnaires either via telephone or via a posted written survey. The same script was used at four different time points: preoperatively, and postoperatively at 6 weeks, 6 months and 1 year. At all four times, two validated patient reported outcome measures (PROMs) were used: the Oxford Hip Score (OHS) (53, 87) and the EQ-5D-5L Health Questionnaire, including pain/discomfort and anxiety/depression scores (54). These have previously been used in similar studies for THA outcomes. (129) Also recorded were LOS, opioid use at all four time points as well as a 5-point Likert scale for patient satisfaction postoperatively. Data were entered into a password secured database stored on the hospital computer network.

STATISTICAL ANALYSIS

The analysis was performed using SPSS version 27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software, La Jolla, Calif, USA). Continuous variables were tested for parametricity (Shapiro-Wilk test). Nonparametric variables are described as median with interquartile range (IQR). Univariate analysis was carried out using the chi-squared test for categorical variables, and the Mann-Whitney U-test for nonparametric continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

557 consecutive patients were approached to participate, of whom 527 (95%) provided informed consent. Eight patients were excluded due to use of an approach other than DAA or PA (namely lateral), the remaining 519 were included in this analysis: 337 underwent a DAA, and 182 a PA.

There were more female patients in the DAA group than in the PA group (204 (60.5%) vs. 93 (51.1%) respectively, p=0.038), but no difference in median age (70 year (IQR 63-76) vs. 71 (60-79) respectively, p=0.18). The median body mass index (BMI) was lower in the DAA group than in PA (29.6kg/m^2 (IQR 26.0-34.0) vs. 31.3 (27.0-35.9) respectively, p=0.005). (Table 1.)

Length of stay as an inpatient was significantly different between the two groups, p=<0.0001. Patients who underwent a DAA had a shorter LOS of 2 days, IQR 2-3. PA patients had a median of 3 days IQR 2-4.

Use of preoperative opioid based medication was similar between both groups (DAA 108 patients (32%) vs. PA 55 (30%), p=0.67), but the DAA group had more preoperative pain/discomfort than the PA cohort (254 (76%) patients had severe or extreme pain vs. 122

(67%) respectively, p=0.02). (Table 2) No patient in either group used postoperative opioid based medication at 6 weeks, 6 months and 1 year. The Oxford Hip Scores were similar between both groups preoperatively and showed a median postoperative improvement of 21 points at 6 weeks in the DAA group (33 points, IQR 25-38), which was significantly higher than the 18-point improvement in the PA group (30 points, IQR 23-36, p=0.02). At 6 months and 1 year, there was no difference in the Oxford Hip Scores between the two groups: the DAA group had a median score of 41 (IQR 33-45) at 6 months, which was 37 (IQR 30-44) in the PA group (p=0.10) and at 1 year, this was 44 points for both groups (p=0.56). (Table 2.) At 6 weeks' follow-up, the following OHS items were significantly different between the two groups ($p < 0.05$), all showing better outcomes in the anterior group (Appendix Tables): being troubled by pain from the hip in bed at night; Sudden, severe pain (shooting, stabbing, or spasms) from affected hip; Ability to walk before the pain in the hip becomes severe (with or without a walking aid); ability to climb a flight of stairs and ability to put on a pair of socks, stockings or tights. The breakdown of subgroups for both PROMs can be found as Appendix 1.

Postoperative scores for all dimensions of the EQ-5D 5L (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) remained similar between both groups at all time points. At 6 weeks, between 175 to 193 (84 – 93%) DAA patients and 94-101 (86-93%) PA patients had no or slight problems in their EQ-5D 5L dimensions, while between 11 and 25 (5-12%) and between 6 and 11 (6-10%) had moderate pain ($p>0.05$). At 6 months and one year there was no difference in these scores between both groups either ($p>0.05$).

The EQ-5D-5L utility scores were also similar preoperatively between groups (DAA: -0.030 (IQR -0.676-0.911) and PA: -0.024 (IQR -0.176-0.367), p=0.47). At 6 weeks DAA: 0.672 (IQR 0.521-0.805) and PA: 0.672 (IQR 0.502-0.805), p=0.69); 6 months (DAA: 0.860 (IQR 0.661-1.000) and PA: 0.884 (IQR 0.661-1.000), p=0.70) and at 1 year (1.000 points (IQR 0.860-1.000) and 1.000 (IQR 0.733-1.000) respectively, p=0.07) there was no significant difference between groups. (Table 3.1)

There was no difference in pre and postoperative anxiety and/or depression scores across both groups. (Table 3.2.)

Patient satisfaction scores were also similar between both groups at all time points. (Table 3.3.)

Discussion

The aim of this prospective multi-centre trial was to determine if there was a difference between the direct anterior approach and the posterior approach for total hip arthroplasty surgery in terms of length of stay, long-term functional recovery and pain scores.

This prospective multi-centre study found that patients undergoing a direct anterior approach for total hip arthroplasty report improved quality of recovery with shorter LOS and better PROMs at 6 weeks postoperatively compared to patients undergoing a posterior approach. There are no long-term benefits between both surgical approaches.

The Oxford Hip Score and EQ-5D-5L Health Questionnaire are validated PROMs, widely used to assess joint related disability and functional recovery in orthopaedic surgery. (130, 131) Internal consistency is high for both questionnaires; Cronbach alpha=0.94 for the Oxford Hip Score, (132) and 0.86 for the EQ-5D-5L. (133) In the current study, the OHS showed an early improvement in favour of DAA patients at 6 weeks. The EQ-5D-5L showed no difference

between the two groups at any time point. At 6 months and at one year there was no difference in functional recovery between the two groups. A reason for the EQ-5D-5L not being different between groups while the OHS was, is that the OHS is.a joint specific PROM while the EQ-5D-5L measures general health. It may thus be that the OHS can detect more joint specific improvement whereas the EQ-5D-5L is more granular in this regard.
Previous analyses have also reported superior early recovery of DAA compared to PA, which is likely due to the minimally invasive nature of the technique. Most of these studies, however, have been limited in their duration of follow-up, of low quality, have not formally assessed functionality using a validated PROM, or have not achieved minimally clinical important difference in the PROMs. (134) Previous studies that have reported long-term outcomes have also not been able to show a benefit of either technique. (135) In the current study we confirm these outcomes, but now with a prospective cohort design, and systematic use of PROMs.

Earlier studies have often focussed on gait analysis, radiographic outcomes, dislocation rates, or length of stay as primary end points. We aimed to assess global recovery and functionality utilising LOS, and the Oxford Hip Score and the EQ-5D-5L questionnaires. There is a training curve for the DAA approach, which represents a significant investment for both the surgeon and the patients involved. It is also well recognised that certain patient types lend themselves better to the DAA approach, such as the non-obese patient for example. Hence, careful patient selection and a risk-benefit analysis must form a part of the consideration for each individual surgeon when choosing a surgical approach.
Some limitations of the current study have to be addressed. 17% of patients were lost to follow up at six weeks and 38% at six months. Similar losses to follow up at similar time

points were reported in previous studies of THA outcomes. (136) Baseline characteristics between both groups were not balanced as the DAA group had a lower BMI, a greater proportion of females, and had more preoperative pain. This represents a selection bias, as these characteristics make the patient more suitable for the DAA approach. Due to the team-based approach to patient selection for surgery and allocation to individual surgeons who favour one approach above the other, this was a conscious decision made to optimise patient outcome and allow surgeons training in the DAA the most optimal conditions in which to begin. That this study suggests favorable outcomes for the DAA compared to PA, despite the inclusion of training data, speaks to the possible short-term benefits of this technique. (137, 138) It is also dubious if a BMI difference between the two groups of 1.7kg/m^2 would be clinically significant, despite the statistical significance.

In conclusion, the results of this multi-centre prospective study complement previous studies showing early functional improvement in favour of the DAA approach. However, there is no difference in long term PROM outcomes, pain scores or patient satisfaction between the two approaches. Future direction for investigation should include well designed multicentre randomized controlled trials to compare long term effects of both approaches.

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TABLE LEGEND

	Anterior (n=337)	**Posterior** (n=182)	**p-value**
Age in years, median (IQR)	70 (63-76)	71 (60-79)	0.18[a]
Gender, n (%) Male Female	 133 (39.5) 204 (60.5)	 89 (48.9) 93 (51.1)	**0.038**[b]
Weight in kg, median (IQR)	82.5 (71.3-93.8)[1]	83.2 (70.0-98.0)[2]	0.37[a]
BMI in kg/m^2, median (IQR)	29.6 (26.0-34.0)[3]	31.3 (27.0-35.9)[4]	**0.005**[a]
Operative side, n (%) Left Right	 150 (44.5) 187 (55.4)	 82 (45.0) 100 (55.0)	0.91[b]

Table 1: Baseline characteristics for anterior and posterior hip arthroplasty patients.
IQR: interquartile range.
[a] Mann-Whitney U test; [b] Chi-squared test.
[1] n=190, [2] n=129, [3] n=299, [4] n=160.

Table 2: Pre- and postoperative opiate use, and Patient Reported Outcome Measures (PROMs) for anterior and posterior hip arthroplasty.

	Anterior (n=337)	**Posterior** (n=182)	**p-value**
Opiate use, n (%)[a]			
pre-operative	108 (32)	55 (30)	0.67[a]
6 weeks postoperative	0 (0)[1]	0 (0)[4]	-
6 months postoperative	0 (0)[2]	0 (0)[5]	-
1 year postoperative	0 (0)[3]	0 (0)[6]	-
Oxford Hip Score total, median (IQR)[b]			
pre-operative	12 (8-20)	12 (7-18)	0.41[b]
6 weeks postoperative	33 (25-38)[1]	30 (23-36)[4]	**0.02**[b]
6 months postoperative	41 (33-45)[2]	37 (30-44)[5]	0.10[b]
1 year postoperative	44 (40-47)[3]	44 (33-48)[6]	0.56[b]
EQ-5L-5D Health Questionnaire Utility Scores, median (IQR)[b]			
pre-operative	-0.030 (-0.676-0.911)	-0.024 (-0.176-0.367)	0.47[b]
6 weeks postoperative	0.672 (0.521-0.805)[1]	0.672 (0.502-0.805)[4]	**0.69**[b]
6 months postoperative	0.860 (0.661-1.000)[2]	0.884 (0.661-1.000)[5]	0.70[b]
1 year postoperative	1.000 (0.860-1.000)[3]	1.000 (0.733-1.000)[6]	0.07[b]

IQR: interquartile range.

[a] Chi-squared test, [b] Mann-Whitney U test.

[1] 57 lost to follow up, [2] 128 lost to follow up, [3] 187 lost to follow up, [4] 25 lost to follow up, [5] 70 lost to follow up, [6] 93 lost to follow up.

Table 3.1: Pre- and postoperative Patient Reported Outcome Measure (PROM) for EQ-5L-5D pain/discomfort score.

[a] Chi-squared test.

	Anterior	**Posterior**	**p-value**
EQ-5L-5D pain/discomfort score pre-operatively, n (%)[a]	n=337	n=182	
No pain	1 (0)	0 (0)	**0.02**[a]
Slight pain	14 (4)	2 (1)	
Moderate pain	68 (20)	58 (32)	
Severe pain	195 (58)	91 (50)	
Extreme pain	59 (18)	31 (17)	
Lost to follow up	-	-	
EQ-5L-5D pain/discomfort score at 6 weeks, n (%)[a]	n=280	n=157	
No pain	63 (23)	46 (29)	0.17[a]
Slight pain	136 (48)	60 (38)	
Moderate pain	67 (24)	44 (28)	
Severe pain	14 (5)	7 (5)	
Extreme pain	0 (0)	0 (0)	
Lost to follow up	*57*	*25*	
EQ-5L-5D pain/discomfort score at 6 months, n (%)[a]	n=209	n=112	
No pain	112 (54)	64 (57)	0.91[a]
Slight pain	69 (33)	35 (31)	
Moderate pain	22 (11)	10 (9)	
Severe pain	5 (2)	3 (3)	
Extreme pain	1 (0)	0 (0)	
Lost to follow up	*128*	*70*	
EQ-5L-5D pain/discomfort score at 1 year, n (%)[a]	n=150	n=89	
No pain	119 (79)	63 (71)	0.35[a]
Slight pain	24 (16)	20 (22)	
Moderate pain	6 (4)	5 (6)	
Severe pain	0 (0)	1 (1)	
Extreme pain	1 (1)	0 (0)	
Lost to follow up	*187*	*93*	

Table 3.2: Pre- and postoperative Patient Reported Outcome Measure (PROM) for EQ-5L-5D

	Anterior	**Posterior**	**p-value**
EQ-5L-5D anxiety/depression score pre-operatively, n (%)	n=337	n=182	
Not anxious/depressed	116 (34)	64 (35)	0.65[a]
Slightly anxious/depressed	86 (26)	45 (25)	
Moderately anxious/depressed	109 (32)	53 (29)	
Severely anxious/depressed	14 (4)	13 (7)	
Extremely anxious/depressed	12 (4)	7 (4)	
Lost to follow up	-	-	
EQ-5L-5D anxiety/depression score at 6 weeks, n (%)	n=280	n=157	
Not anxious/depressed	199 (71)	113 (72)	0.56[a]
Slightly anxious/depressed	53 (19)	24 (15)	
Moderately anxious/depressed	23 (8)	18 (12)	
Severely anxious/depressed	5 (2)	2 (1)	
Extremely anxious/depressed	0 (0)	0 (0)	
Lost to follow up	*57*	*25*	
EQ-5L-5D anxiety/depression score at 6 months, n (%)	n=209	n=112	
Not anxious/depressed	156 (75)	90 (80)	0.62[a]
Slightly anxious/depressed	38 (18)	14 (13)	
Moderately anxious/depressed	11 (5)	6 (5)	
Severely anxious/depressed	4 (2)	2 (2)	
Extremely anxious/depressed	0 (0)	0 (0)	
Lost to follow up	*128*	*70*	
EQ-5L-5D anxiety/depression score at 1 year, n (%)	n=150	n=89	
Not anxious/depressed	121 (81)	71 (80)	0.97[a]
Slightly anxious/depressed	22 (15)	13 (15)	
Moderately anxious/depressed	5 (3)	4 (4)	
Severely anxious/depressed	2 (1)	1 (1)	
Extremely anxious/depressed	0 (0)	0 (0)	
Lost to follow up	*187*	*93*	

anxiety/depression scores.

[a] Chi-squared test.

	Anterior	Posterior	p-value
Patient satisfaction at 6 weeks, n (%)	n=280	n=157	
Very satisfied	176 (63)	103 (66)	0.66[a]
Satisfied	80 (28)	39 (25)	
Ambivalent	8 (3)	7 (4)	
Dissatisfied	3 (1)	3 (2)	
Very dissatisfied	13 (5)	5 (3)	
Lost to follow up	*57*	*25*	
Patient satisfaction at 6 months, n (%)	n=209	n=112	
Very satisfied	135 (65)	79 (71)	0.69[a]
Satisfied	52 (25)	25 (22)	
Ambivalent	10 (5)	4 (4)	
Dissatisfied	3 (1)	2 (1.5)	
Very dissatisfied	9 (4)	2 (1.5)	
Lost to follow up	*128*	*70*	
Patient satisfaction at 1 year, n (%)	n=150	n=89	
Very satisfied	102 (68)	62 (70)	0.56[a]
Satisfied	34 (23)	21 (24)	
Ambivalent	5 (3)	4 (4)	
Dissatisfied	1 (1)	1 (1)	
Very dissatisfied	8 (5)	1 (1)	
Lost to follow up	*187*	*93*	

Table 3.3: Postoperative patient satisfaction.
[a] Chi-squared test.

Appendix tables:

Tabulation of subgroups of EQ-5D-5L as frequencies and percentages

Tabulation of EQ5D5L_Mobility Group when TIMEPOINT is Pre-operatively

	Group		
Mobility	Anterior	Posterior	Total
No problems walking about	126	63	189
	82.89	68.48	77.46
Slight problems walking about	20	24	44
	13.16	26.09	18.03
Moderate problems walking about	5	4	9
	3.29	4.35	3.69
Severe problems walking about	1	0	1
	0.66	0.00	0.41
Unable to walk about	0	1	1
	0.00	1.09	0.41
Total	152	92	244
	100.00	100.00	100.00

Pearson Chi2 = 9.28 Prob = 0.0544
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Mobility Group when TIMEPOINT is 6-weeks

	Group		
Mobility	Anterior	Posterior	Total
No problems walking about	119	57	176
	57.21	52.29	55.52
Slight problems walking about	60	39	99
	28.85	35.78	31.23
Moderate problems walking about	23	11	34
	11.06	10.09	10.73
Severe problems walking about	6	2	8
	2.88	1.83	2.52
Total	208	109	317
	100.00	100.00	100.00

Pearson Chi2 = 1.79 Prob = 0.6178
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Mobility Group when TIMEPOINT is 6-months

	Group		
Mobility	Anterior	Posterior	Total
No problems walking about	83	44	127
	30.29	28.39	29.60
Slight problems walking about	102	51	153
	37.23	32.90	35.66
Moderate problems walking about	77	47	124
	28.10	30.32	28.90
Severe problems walking about	12	13	25
	4.38	8.39	5.83
Total	274	155	429
	100.00	100.00	100.00

Pearson Chi2 = 3.54 Prob = 0.3160
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Mobility Group when TIMEPOINT is 1-year

	Group		
Mobility	Anterior	Posterior	Total
No problems walking about	5	2	7
	1.74	1.20	1.54
Slight problems walking about	18	10	28
	6.25	6.02	6.17
Moderate problems walking about	74	38	112
	25.69	22.89	24.67
Severe problems walking about	174	98	272
	60.42	59.04	59.91
Unable to walk about	17	18	35
	5.90	10.84	7.71
Total	288	166	454
	100.00	100.00	100.00

Pearson Chi2 = 3.90 Prob = 0.4191
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Selfcare Group when TIMEPOINT is Pre-operatively

	Group		
Self-care	Anterior	Posterior	Total
No problems	129	71	200
	84.87	77.17	81.97
Slight problems	15	16	31
	9.87	17.39	12.70
Moderate problems	8	4	12
	5.26	4.35	4.92
Unable to peform	0	1	1
	0.00	1.09	0.41
Total	152	92	244
	100.00	100.00	100.00

Pearson Chi2 = 4.72 Prob = 0.1938
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Selfcare Group when TIMEPOINT is 6-weeks

	Group		
Self-care	Anterior	Posterior	Total
No problems	140	74	214
	67.31	67.89	67.51
Slight problems	46	26	72
	22.12	23.85	22.71
Moderate problems	17	7	24
	8.17	6.42	7.57
Severe problems	4	2	6
	1.92	1.83	1.89
Unable to perform	1	0	1
	0.48	0.00	0.32
Total	208	109	317
	100.00	100.00	100.00

Pearson Chi2 = 0.92 Prob = 0.9224
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Selfcare Group when TIMEPOINT is 6-months

	Group		
Self-care	Anterior	Posterior	Total
No problems	137	81	218

	50.00	52.26	50.82
Slight problems	84	45	129
	30.66	29.03	30.07
Moderate problems	45	20	65
	16.42	12.90	15.15
Severe problems	7	7	14
	2.55	4.52	3.26
Unable to perform	1	2	3
	0.36	1.29	0.70
Total	274	155	429
	100.00	100.00	100.00

Pearson Chi2 = 3.38 Prob = 0.4971
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Selfcare Group when TIMEPOINT is 1-year

	Group		
Self-care	Anterior	Posterior	Total
No problems	46	34	80
	15.97	20.48	17.62
Slight problems	73	29	102
	25.35	17.47	22.47
Moderate problems	75	48	123
	26.04	28.92	27.09
Severe problems	87	46	133
	30.21	27.71	29.30
Unable to perform	7	9	16
	2.43	5.42	3.52
Total	288	166	454
	100.00	100.00	100.00

Pearson Chi2 = 7.34 Prob = 0.1189
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_UsualActivities Group when TIMEPOINT is Pre-operatively

	Group		
Usual activities	Anterior	Posterior	Total
No problems	123	66	189
	80.92	71.74	77.46
Slight problems	20	18	38
	13.16	19.57	15.57
Moderate problems	8	7	15
	5.26	7.61	6.15
Severe problems	1	0	1
	0.66	0.00	0.41
Unable to perform	0	1	1
	0.00	1.09	0.41
Total	152	92	244
	100.00	100.00	100.00

Pearson Chi2 = 4.90 Prob = 0.2972
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_UsualActivities Group when TIMEPOINT is 6-weeks

	Group		
Usual activities	Anterior	Posterior	Total
No problems	118	59	177
	56.73	54.13	55.84
Slight problems	57	35	92

	27.40	32.11	29.02
Moderate problems	25	9	34
	12.02	8.26	10.73
Severe problems	7	6	13
	3.37	5.50	4.10
Unable to perform	1	0	1
	0.48	0.00	0.32
Total	208	109	317
	100.00	100.00	100.00

Pearson Chi2 = 2.90 Prob = 0.5749
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_UsualActivities Group when TIMEPOINT is 6-months

	Group		
Usual activities	Anterior	Posterior	Total
No problems	69	39	108
	25.18	25.16	25.17
Slight problems	113	51	164
	41.24	32.90	38.23
Moderate problems	69	43	112
	25.18	27.74	26.11
Severe problems	17	16	33
	6.20	10.32	7.69
Unable to perform	6	6	12
	2.19	3.87	2.80
Total	274	155	429
	100.00	100.00	100.00

Pearson Chi2 = 5.23 Prob = 0.2643
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_UsualActivities Group when TIMEPOINT is 1-year

	Group		
Usual activities	Anterior	Posterior	Total
No problems	8	3	11
	2.78	1.81	2.42
Slight problems	23	12	35
	7.99	7.23	7.71
Moderate problems	81	41	122
	28.12	24.70	26.87
Severe problems	139	83	222
	48.26	50.00	48.90
Unable to perform	37	27	64
	12.85	16.27	14.10
Total	288	166	454
	100.00	100.00	100.00

Pearson Chi2 = 1.89 Prob = 0.7569
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Pain_Discomfort Group when TIMEPOINT is Pre-operatively

	Group		
Pain/Discomfort	Anterior	Posterior	Total
No problems	122	65	187
	80.26	70.65	76.64
Slight problems	23	21	44
	15.13	22.83	18.03
Moderate problems	6	5	11

	3.95	5.43	4.51
Severe problems	0	1	1
	0.00	1.09	0.41
Unable to perform	1	0	1
	0.66	0.00	0.41
Total	152	92	244
	100.00	100.00	100.00

Pearson Chi2 = 5.11 Prob = 0.2761
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Pain_Discomfort Group when TIMEPOINT is 6-weeks

	Group		
Pain/Discomfort	Anterior	Posterior	Total
No problems walking about	110	63	173
	52.88	57.80	54.57
Slight problems walking about	70	33	103
	33.65	30.28	32.49
Moderate problems walking about	22	10	32
	10.58	9.17	10.09
Severe problems walking about	5	3	8
	2.40	2.75	2.52
Unable to walk about	1	0	1
	0.48	0.00	0.32
Total	208	109	317
	100.00	100.00	100.00

Pearson Chi2 = 1.27 Prob = 0.8672
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Pain_Discomfort Group when TIMEPOINT is 6-months

	Group		
Pain/Discomfort	Anterior	Posterior	Total
No problems walking about	62	45	107
	22.63	29.03	24.94
Slight problems walking about	133	60	193
	48.54	38.71	44.99
Moderate problems walking about	65	43	108
	23.72	27.74	25.17
Severe problems walking about	14	7	21
	5.11	4.52	4.90
Total	274	155	429
	100.00	100.00	100.00

Pearson Chi2 = 4.46 Prob = 0.2158
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Pain_Discomfort Group when TIMEPOINT is 1-year

	Group		
Pain/Discomfort	Anterior	Posterior	Total
No problems walking about	1	0	1
	0.35	0.00	0.22
Slight problems walking about	14	2	16
	4.86	1.20	3.52
Moderate problems walking about	68	42	110
	23.61	25.30	24.23
Severe problems walking about	151	90	241
	52.43	54.22	53.08
Unable to walk about	54	32	86

	18.75	19.28	18.94
Total	288	166	454
	100.00	100.00	100.00

Pearson Chi2 = 4.77 Prob = 0.3113
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Anxiety_Depression Group when TIMEPOINT is Pre-operatively

	Group		
Anxiety/Depression	Anterior	Posterior	Total
No problems	122	73	195
	80.26	79.35	79.92
Slight problems	23	13	36
	15.13	14.13	14.75
Moderate problems	5	5	10
	3.29	5.43	4.10
Severe problems	2	1	3
	1.32	1.09	1.23
Total	152	92	244
	100.00	100.00	100.00

Pearson Chi2 = 0.71 Prob = 0.8702
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Anxiety_Depression Group when TIMEPOINT is 6-weeks

	Group		
Anxiety/Depression	Anterior	Posterior	Total
No problems	155	87	242
	74.52	79.82	76.34
Slight problems	38	14	52
	18.27	12.84	16.40
Moderate problems	11	6	17
	5.29	5.50	5.36
Severe problems	4	2	6
	1.92	1.83	1.89
Total	208	109	317
	100.00	100.00	100.00

Pearson Chi2 = 1.56 Prob = 0.6696
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Anxiety_Depression Group when TIMEPOINT is 6-months

	Group		
Anxiety/Depression	Anterior	Posterior	Total
No problems	194	112	306
	70.80	72.26	71.33
Slight problems	52	24	76
	18.98	15.48	17.72
Moderate problems	23	17	40
	8.39	10.97	9.32
Severe problems	5	2	7
	1.82	1.29	1.63
Total	274	155	429
	100.00	100.00	100.00

Pearson Chi2 = 1.59 Prob = 0.6621
First row has *frequencies* and second row has *column percentages*

Tabulation of EQ5D5L_Anxiety_Depression Group when TIMEPOINT is 1-year

Anxiety/Depression	Group

	Anterior	Posterior	Total
No problems	117	62	179
	40.62	37.35	39.43
Slight problems	85	46	131
	29.51	27.71	28.85
Moderate problems	59	38	97
	20.49	22.89	21.37
Severe problems	15	13	28
	5.21	7.83	6.17
Unable to function	12	7	19
	4.17	4.22	4.19
Total	288	166	454
	100.00	100.00	100.00

Pearson Chi2 = 1.87 Prob = 0.7604

First row has *frequencies* and second row has *column percentages*

Tabulation of subgroups of Oxford Hip Score as frequencies and percentages

Tabulation of UsualPain Group when TIMEPOINT is Pre-operatively

	Group		
UsualPain	Anterior	Posterior	Total
Severe	93	41	134
	37.80	30.83	35.36
Moderate	3	2	5
	1.22	1.50	1.32
Mild	6	5	11
	2.44	3.76	2.90
Very mild	23	19	42
	9.35	14.29	11.08
None	121	66	187
	49.19	49.62	49.34
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 3.66 Prob = 0.4537
First row has *frequencies* and second row has *column percentages*

Tabulation of UsualPain Group when TIMEPOINT is 6-weeks

	Group		
UsualPain	Anterior	Posterior	Total
Severe	62	46	108
	23.05	29.49	25.41
Moderate	11	4	15
	4.09	2.56	3.53
Mild	19	6	25
	7.06	3.85	5.88
Very mild	80	55	135
	29.74	35.26	31.76
None	97	45	142
	36.06	28.85	33.41
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 6.48 Prob = 0.1659
First row has *frequencies* and second row has *column percentages*

Tabulation of UsualPain Group when TIMEPOINT is 6-months

	Group		
UsualPain	Anterior	Posterior	Total
Severe	29	19	48
	9.57	11.18	10.15
Moderate	42	22	64
	13.86	12.94	13.53
Mild	96	44	140
	31.68	25.88	29.60
Very mild	87	57	144
	28.71	33.53	30.44
None	49	28	77

	16.17	16.47	16.28
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 2.42 Prob = 0.6593
First row has *frequencies* and second row has *column percentages*

Tabulation of UsualPain Group when TIMEPOINT is 1-year

	Group		
UsualPain	Anterior	Posterior	Total
Severe	189	101	290
	55.92	55.19	55.66
Moderate	121	65	186
	35.80	35.52	35.70
Mild	23	14	37
	6.80	7.65	7.10
Very mild	3	2	5
	0.89	1.09	0.96
5	2	1	3
	0.59	0.55	0.58
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 0.19 Prob = 0.9958
First row has *frequencies* and second row has *column percentages*

Tabulation of PainAtNight Group when TIMEPOINT is Pre-operatively

	Group		
PainAtNight	Anterior	Posterior	Total
Every night	93	41	134
	37.80	30.83	35.36
Most nights	0	1	1
	0.00	0.75	0.26
Some nights	8	6	14
	3.25	4.51	3.69
Only 1 or 2 nights	16	15	31
	6.50	11.28	8.18
No nights	129	70	199
	52.44	52.63	52.51
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 5.82 Prob = 0.2134
First row has *frequencies* and second row has *column percentages*

Tabulation of PainAtNight Group when TIMEPOINT is 6-weeks

	Group		
PainAtNight	Anterior	Posterior	Total
Every night	61	48	109
	22.68	30.77	25.65
Most nights	1	1	2
	0.37	0.64	0.47
Some nights	26	4	30
	9.67	2.56	7.06
Only 1 or 2 nights	54	58	112
	20.07	37.18	26.35
No nights	127	45	172
	47.21	28.85	40.47
Total	269	156	425

	100.00	100.00	100.00

Pearson Chi2 = 28.92 Prob = 0.0000
First row has *frequencies* and second row has *column percentages*

Tabulation of PainAtNight Group when TIMEPOINT is 6-months

	Group		
PainAtNight	Anterior	Posterior	Total
Every night	26	14	40
	8.58	8.24	8.46
Most nights	7	3	10
	2.31	1.76	2.11
Some nights	70	53	123
	23.10	31.18	26.00
Only 1 or 2 nights	120	48	168
	39.60	28.24	35.52
No nights	80	52	132
	26.40	30.59	27.91
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 7.55 Prob = 0.1097
First row has *frequencies* and second row has *column percentages*

Tabulation of PainAtNight Group when TIMEPOINT is 1-year

	Group		
PainAtNight	Anterior	Posterior	Total
Every night	63	32	95
	18.64	17.49	18.23
Most nights	103	51	154
	30.47	27.87	29.56
Some nights	112	73	185
	33.14	39.89	35.51
Only 1 or 2 nights	49	13	62
	14.50	7.10	11.90
No nights	8	13	21
	2.37	7.10	4.03
5	3	1	4
	0.89	0.55	0.77
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 14.13 Prob = 0.0148
First row has *frequencies* and second row has *column percentages*

Tabulation of SuddenPain Group when TIMEPOINT is Pre-operatively

	Group		
SuddenPain	Anterior	Posterior	Total
Every day	93	41	134
	37.80	30.83	35.36
Most days	1	2	3
	0.41	1.50	0.79
Some days	9	7	16
	3.66	5.26	4.22
Only 1 or 2 days	22	20	42
	8.94	15.04	11.08
No days	121	63	184
	49.19	47.37	48.55
Total	246	133	379

	100.00	100.00	100.00

Pearson Chi2 = 5.98 Prob = 0.2006
First row has *frequencies* and second row has *column percentages*

Tabulation of SuddenPain Group when TIMEPOINT is 6-weeks

	Group		
SuddenPain	Anterior	Posterior	Total
Every day	60	46	106
	22.30	29.49	24.94
Most days	3	4	7
	1.12	2.56	1.65
Some days	29	10	39
	10.78	6.41	9.18
Only 1 or 2 days	77	59	136
	28.62	37.82	32.00
No days	100	37	137
	37.17	23.72	32.24
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 13.51 Prob = 0.0090
First row has *frequencies* and second row has *column percentages*

Tabulation of SuddenPain Group when TIMEPOINT is 6-months

	Group		
SuddenPain	Anterior	Posterior	Total
Every day	25	14	39
	8.25	8.24	8.25
Most days	12	17	29
	3.96	10.00	6.13
Some days	82	51	133
	27.06	30.00	28.12
Only 1 or 2 days	117	51	168
	38.61	30.00	35.52
No days	67	37	104
	22.11	21.76	21.99
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 9.09 Prob = 0.0588
First row has *frequencies* and second row has *column percentages*

Tabulation of SuddenPain Group when TIMEPOINT is 1-year

	Group		
SuddenPain	Anterior	Posterior	Total
Every day	51	26	77
	15.09	14.21	14.78
Most days	144	91	235
	42.60	49.73	45.11
Some days	116	51	167
	34.32	27.87	32.05
Only 1 or 2 days	23	9	32
	6.80	4.92	6.14
No days	2	5	7
	0.59	2.73	1.34
5	2	1	3
	0.59	0.55	0.58
Total	338	183	521

	100.00	100.00	100.00

Pearson Chi2 = 7.68 Prob = 0.1748
First row has *frequencies* and second row has *column percentages*

Tabulation of Limping Group when TIMEPOINT is Pre-operatively

	Group		
Limping	Anterior	Posterior	Total
All of the time	100	48	148
	40.65	36.09	39.05
Most of the time	3	3	6
	1.22	2.26	1.58
Often	16	8	24
	6.50	6.02	6.33
Sometimes	28	20	48
	11.38	15.04	12.66
Rarely/never	99	54	153
	40.24	40.60	40.37
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 1.99 Prob = 0.7374
First row has *frequencies* and second row has *column percentages*

Tabulation of Limping Group when TIMEPOINT is 6-weeks

	Group		
Limping	Anterior	Posterior	Total
All of the time	77	56	133
	28.62	35.90	31.29
Most of the time	15	4	19
	5.58	2.56	4.47
Often	29	15	44
	10.78	9.62	10.35
Sometimes	79	56	135
	29.37	35.90	31.76
Rarely/never	69	25	94
	25.65	16.03	22.12
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 9.26 Prob = 0.0548
First row has *frequencies* and second row has *column percentages*

Tabulation of Limping Group when TIMEPOINT is 6-months

	Group		
Limping	Anterior	Posterior	Total
All of the time	73	50	123
	24.09	29.41	26.00
Most of the time	24	20	44
	7.92	11.76	9.30
Often	94	38	132
	31.02	22.35	27.91
Sometimes	75	40	115
	24.75	23.53	24.31
Rarely/never	37	22	59
	12.21	12.94	12.47
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 5.96 Prob = 0.2020

First row has *frequencies* and second row has *column percentages*

Tabulation of Limping Group when TIMEPOINT is 1-year

	Group		
Limping	Anterior	Posterior	Total
All of the time	123	66	189
	36.39	36.07	36.28
Most of the time	121	67	188
	35.80	36.61	36.08
Often	73	34	107
	21.60	18.58	20.54
Sometimes	18	9	27
	5.33	4.92	5.18
Rarely/never	2	6	8
	0.59	3.28	1.54
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 6.37 Prob = 0.2722
First row has *frequencies* and second row has *column percentages*

Tabulation of WalkBeforePain Group when TIMEPOINT is Pre-operatively

	Group		
WalkBeforePain	Anterior	Posterior	Total
Not at all	100	46	146
	40.65	34.59	38.52
Around the house only	2	1	3
	0.81	0.75	0.79
5 to 15 minutes	6	7	13
	2.44	5.26	3.43
16 to 30 minutes	22	21	43
	8.94	15.79	11.35
No pain for 30 minutes or more	116	58	174
	47.15	43.61	45.91
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 6.64 Prob = 0.1563
First row has *frequencies* and second row has *column percentages*

Tabulation of WalkBeforePain Group when TIMEPOINT is 6-weeks

	Group		
WalkBeforePain	Anterior	Posterior	Total
Not at all	70	53	123
	26.02	33.97	28.94
Around the house only	9	3	12
	3.35	1.92	2.82
5 to 15 minutes	27	10	37
	10.04	6.41	8.71
16 to 30 minutes	57	46	103
	21.19	29.49	24.24
No pain for 30 minutes or more	106	44	150
	39.41	28.21	35.29
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 10.67 Prob = 0.0305

First row has *frequencies* and second row has *column percentages*

Tabulation of WalkBeforePain Group when TIMEPOINT is 6-months

	Group		
WalkBeforePain	Anterior	Posterior	Total
Not at all	57	42	99
	18.81	24.71	20.93
Around the house only	14	13	27
	4.62	7.65	5.71
5 to 15 minutes	76	35	111
	25.08	20.59	23.47
16 to 30 minutes	88	42	130
	29.04	24.71	27.48
No pain for 30 minutes or more	68	38	106
	22.44	22.35	22.41
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 5.24 Prob = 0.2637

First row has *frequencies* and second row has *column percentages*

Tabulation of WalkBeforePain Group when TIMEPOINT is 1-year

	Group		
WalkBeforePain	Anterior	Posterior	Total
Not at all	124	63	187
	36.69	34.43	35.89
Around the house only	80	50	130
	23.67	27.32	24.95
5 to 15 minutes	80	40	120
	23.67	21.86	23.03
16 to 30 minutes	43	22	65
	12.72	12.02	12.48
No pain for 30 minutes or more	10	7	17
	2.96	3.83	3.26
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 1.49 Prob = 0.9145

First row has *frequencies* and second row has *column percentages*

Tabulation of Stairs Group when TIMEPOINT is Pre-operatively

	Group		
Stairs	Anterior	Posterior	Total
No, impossible	98	44	142
	39.84	33.08	37.47
With extreme difficulty	6	5	11
	2.44	3.76	2.90
With moderate difficulty	11	8	19
	4.47	6.02	5.01
With little difficulty	25	21	46
	10.16	15.79	12.14
Yes, easily	106	55	161
	43.09	41.35	42.48
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 4.29 Prob = 0.3678

First row has *frequencies* and second row has *column percentages*

Tabulation of Stairs Group when TIMEPOINT is 6-weeks

	Group		
Stairs	Anterior	Posterior	Total
No, impossible	69	49	118
	25.65	31.41	27.76
With extreme difficulty	13	8	21
	4.83	5.13	4.94
With moderate difficulty	27	8	35
	10.04	5.13	8.24
With little difficulty	63	52	115
	23.42	33.33	27.06
Yes, easily	97	39	136
	36.06	25.00	32.00
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 11.45 Prob = 0.0220

First row has *frequencies* and second row has *column percentages*

Tabulation of Stairs Group when TIMEPOINT is 6-months

	Group		
Stairs	Anterior	Posterior	Total
No, impossible	34	26	60
	11.22	15.29	12.68
With extreme difficulty	22	23	45
	7.26	13.53	9.51
With moderate difficulty	70	42	112
	23.10	24.71	23.68
With little difficulty	83	40	123
	27.39	23.53	26.00
Yes, easily	93	39	132
	30.69	22.94	27.91
5	1	0	1
	0.33	0.00	0.21
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 9.57 Prob = 0.0883

First row has *frequencies* and second row has *column percentages*

Tabulation of Stairs Group when TIMEPOINT is 1-year

	Group		
Stairs	Anterior	Posterior	Total
No, impossible	108	60	168
	31.95	32.79	32.25
With extreme difficulty	100	60	160
	29.59	32.79	30.71
With moderate difficulty	81	44	125
	23.96	24.04	23.99
With little difficulty	38	13	51
	11.24	7.10	9.79
Yes, easily	10	5	15
	2.96	2.73	2.88
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521

	100.00	100.00	100.00

Pearson Chi2 = 2.71 Prob = 0.7438
First row has *frequencies* and second row has *column percentages*

Tabulation of Socks Group when TIMEPOINT is Pre-operatively

	Group		
Socks	Anterior	Posterior	Total
No, impossible	107	53	160
	43.50	39.85	42.22
With extreme difficulty	7	6	13
	2.85	4.51	3.43
With moderate difficulty	15	12	27
	6.10	9.02	7.12
With little difficulty	44	23	67
	17.89	17.29	17.68
Yes, easily	73	39	112
	29.67	29.32	29.55
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 2.03 Prob = 0.7307
First row has *frequencies* and second row has *column percentages*

Tabulation of Socks Group when TIMEPOINT is 6-weeks

	Group		
Socks	Anterior	Posterior	Total
No, impossible	83	65	148
	30.86	41.67	34.82
With extreme difficulty	12	13	25
	4.46	8.33	5.88
With moderate difficulty	39	10	49
	14.50	6.41	11.53
With little difficulty	75	42	117
	27.88	26.92	27.53
Yes, easily	60	26	86
	22.30	16.67	20.24
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 13.02 Prob = 0.0112
First row has *frequencies* and second row has *column percentages*

Tabulation of Socks Group when TIMEPOINT is 6-months

	Group		
Socks	Anterior	Posterior	Total
No, impossible	87	59	146
	28.71	34.71	30.87
With extreme difficulty	22	14	36
	7.26	8.24	7.61
With moderate difficulty	64	42	106
	21.12	24.71	22.41
With little difficulty	100	41	141
	33.00	24.12	29.81
Yes, easily	30	14	44
	9.90	8.24	9.30
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 5.24 Prob = 0.2639

First row has *frequencies* and second row has *column percentages*

Tabulation of Socks Group when TIMEPOINT is 1-year

	Group		
Socks	Anterior	Posterior	Total
No, impossible	126	62	188
	37.28	33.88	36.08
With extreme difficulty	134	77	211
	39.64	42.08	40.50
With moderate difficulty	57	29	86
	16.86	15.85	16.51
With little difficulty	17	11	28
	5.03	6.01	5.37
Yes, easily	3	3	6
	0.89	1.64	1.15
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 1.62 Prob = 0.8992
First row has *frequencies* and second row has *column percentages*

Tabulation of StandAfterMeal Group when TIMEPOINT is Pre-operatively

	Group		
StandAfterMeal	Anterior	Posterior	Total
Unbearable	96	43	139
	39.02	32.33	36.68
Very painful	1	2	3
	0.41	1.50	0.79
Moderately painful	13	7	20
	5.28	5.26	5.28
Slightly painful	34	27	61
	13.82	20.30	16.09
Not at all painful	102	54	156
	41.46	40.60	41.16
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 4.64 Prob = 0.3268
First row has *frequencies* and second row has *column percentages*

Tabulation of StandAfterMeal Group when TIMEPOINT is 6-weeks

	Group		
StandAfterMeal	Anterior	Posterior	Total
Unbearable	62	48	110
	23.05	30.77	25.88
Very painful	9	4	13
	3.35	2.56	3.06
Moderately painful	25	10	35
	9.29	6.41	8.24
Slightly painful	76	49	125
	28.25	31.41	29.41
Not at all painful	97	45	142
	36.06	28.85	33.41
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 5.34 Prob = 0.2541

First row has *frequencies* and second row has *column percentages*

Tabulation of StandAfterMeal Group when TIMEPOINT is 6-months

	Group		
StandAfterMeal	Anterior	Posterior	Total
Unbearable	27	14	41
	8.91	8.24	8.67
Very painful	7	9	16
	2.31	5.29	3.38
Moderately painful	64	49	113
	21.12	28.82	23.89
Slightly painful	119	52	171
	39.27	30.59	36.15
Not at all painful	86	46	132
	28.38	27.06	27.91
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 7.97 Prob = 0.0927
First row has *frequencies* and second row has *column percentages*

Tabulation of StandAfterMeal Group when TIMEPOINT is 1-year

	Group		
StandAfterMeal	Anterior	Posterior	Total
Unbearable	80	34	114
	23.67	18.58	21.88
Very painful	148	97	245
	43.79	53.01	47.02
Moderately painful	80	37	117
	23.67	20.22	22.46
Slightly painful	28	11	39
	8.28	6.01	7.49
Not at all painful	2	3	5
	0.59	1.64	0.96
5	0	1	1
	0.00	0.55	0.19
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 8.20 Prob = 0.1453
First row has *frequencies* and second row has *column percentages*

Tabulation of Car Group when TIMEPOINT is Pre-operatively

	Group		
Car	Anterior	Posterior	Total
Impossible to do	98	45	143
	39.84	33.83	37.73
Extreme difficulty	4	4	8
	1.63	3.01	2.11
Moderate trouble	13	14	27
	5.28	10.53	7.12
Very little trouble	27	19	46
	10.98	14.29	12.14
No trouble at all	104	51	155
	42.28	38.35	40.90
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 6.04 Prob = 0.1962

First row has *frequencies* and second row has *column percentages*

Tabulation of Car Group when TIMEPOINT is 6-weeks

	Group		
Car	Anterior	Posterior	Total
Impossible to do	68	52	120
	25.28	33.33	28.24
Extreme difficulty	10	6	16
	3.72	3.85	3.76
Moderate trouble	19	15	34
	7.06	9.62	8.00
Very little trouble	65	36	101
	24.16	23.08	23.76
No trouble at all	107	47	154
	39.78	30.13	36.24
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 5.66 Prob = 0.2258

First row has *frequencies* and second row has *column percentages*

Tabulation of Car Group when TIMEPOINT is 6-months

	Group		
Car	Anterior	Posterior	Total
Impossible to do	47	32	79
	15.51	18.82	16.70
Extreme difficulty	39	21	60
	12.87	12.35	12.68
Moderate trouble	43	28	71
	14.19	16.47	15.01
Very little trouble	110	65	175
	36.30	38.24	37.00
No trouble at all	64	24	88
	21.12	14.12	18.60
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 4.10 Prob = 0.3931

First row has *frequencies* and second row has *column percentages*

Tabulation of Car Group when TIMEPOINT is 1-year

	Group		
Car	Anterior	Posterior	Total
Impossible to do	209	112	321
	61.83	61.20	61.61
Extreme difficulty	86	48	134
	25.44	26.23	25.72
Moderate trouble	30	17	47
	8.88	9.29	9.02
Very little trouble	12	5	17
	3.55	2.73	3.26
No trouble at all	1	0	1
	0.30	0.00	0.19
5	0	1	1
	0.00	0.55	0.19
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 2.69 Prob = 0.7475

First row has *frequencies* and second row has *column percentages*

Tabulation of Washing Group when TIMEPOINT is Pre-operatively

	Group		
Washing	Anterior	Posterior	Total
Impossible to do	96	42	138
	39.02	31.58	36.41
Extreme difficulty	3	3	6
	1.22	2.26	1.58
Moderate trouble	13	12	25
	5.28	9.02	6.60
Very little trouble	17	17	34
	6.91	12.78	8.97
No trouble at all	117	59	176
	47.56	44.36	46.44
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 7.24 Prob = 0.1239

First row has *frequencies* and second row has *column percentages*

Tabulation of Washing Group when TIMEPOINT is 6-weeks

	Group		
Washing	Anterior	Posterior	Total
Impossible to do	66	48	114
	24.54	30.77	26.82
Extreme difficulty	6	2	8
	2.23	1.28	1.88
Moderate trouble	24	20	44
	8.92	12.82	10.35
Very little trouble	44	30	74
	16.36	19.23	17.41
No trouble at all	129	56	185
	47.96	35.90	43.53
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 7.12 Prob = 0.1298

First row has *frequencies* and second row has *column percentages*

Tabulation of Washing Group when TIMEPOINT is 6-months

	Group		
Washing	Anterior	Posterior	Total
Impossible to do	40	12	52
	13.20	7.06	10.99
Extreme difficulty	11	13	24
	3.63	7.65	5.07
Moderate trouble	65	40	105
	21.45	23.53	22.20
Very little trouble	58	35	93
	19.14	20.59	19.66
No trouble at all	129	70	199
	42.57	41.18	42.07
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 7.58 Prob = 0.1083

First row has *frequencies* and second row has *column percentages*

Tabulation of Washing Group when TIMEPOINT is 1-year

	Group		
Washing	Anterior	Posterior	Total
Impossible to do	138	70	208
	40.83	38.25	39.92
Extreme difficulty	89	55	144
	26.33	30.05	27.64
Moderate trouble	76	48	124
	22.49	26.23	23.80
Very little trouble	12	5	17
	3.55	2.73	3.26
No trouble at all	22	4	26
	6.51	2.19	4.99
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 6.38 Prob = 0.2713
First row has *frequencies* and second row has *column percentages*

Tabulation of Shopping Group when TIMEPOINT is Pre-operatively

	Group		
Shopping	Anterior	Posterior	Total
No, impossible	97	44	141
	39.43	33.08	37.20
With extreme difficulty	3	2	5
	1.22	1.50	1.32
With moderate difficulty	13	12	25
	5.28	9.02	6.60
With little difficulty	18	22	40
	7.32	16.54	10.55
Yes, easily	115	53	168
	46.75	39.85	44.33
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 10.70 Prob = 0.0301
First row has *frequencies* and second row has *column percentages*

Tabulation of Shopping Group when TIMEPOINT is 6-weeks

	Group		
Shopping	Anterior	Posterior	Total
No, impossible	69	52	121
	25.65	33.33	28.47
With extreme difficulty	8	3	11
	2.97	1.92	2.59
With moderate difficulty	25	15	40
	9.29	9.62	9.41
With little difficulty	60	41	101
	22.30	26.28	23.76
Yes, easily	107	45	152
	39.78	28.85	35.76
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 6.44 Prob = 0.1689
First row has *frequencies* and second row has *column percentages*

Tabulation of Shopping Group when TIMEPOINT is 6-months

	Group		
Shopping	Anterior	Posterior	Total
No, impossible	38	22	60
	12.54	12.94	12.68
With extreme difficulty	29	20	49
	9.57	11.76	10.36
With moderate difficulty	68	51	119
	22.44	30.00	25.16
With little difficulty	105	45	150
	34.65	26.47	31.71
Yes, easily	63	32	95
	20.79	18.82	20.08
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 5.50 Prob = 0.2396
First row has *frequencies* and second row has *column percentages*

Tabulation of Shopping Group when TIMEPOINT is 1-year

	Group		
Shopping	Anterior	Posterior	Total
No, impossible	120	76	196
	35.50	41.53	37.62
With extreme difficulty	145	70	215
	42.90	38.25	41.27
With moderate difficulty	59	28	87
	17.46	15.30	16.70
With little difficulty	13	8	21
	3.85	4.37	4.03
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 2.37 Prob = 0.6674
First row has *frequencies* and second row has *column percentages*

Tabulation of PainInterferWork Group when TIMEPOINT is Pre-operatively

	Group		
PainInterferWork	Anterior	Posterior	Total
No, impossible	110	50	160
	44.72	37.59	42.22
With extreme difficulty	8	9	17
	3.25	6.77	4.49
With moderate difficulty	17	12	29
	6.91	9.02	7.65
With little difficulty	17	15	32
	6.91	11.28	8.44
Yes, easily	94	47	141
	38.21	35.34	37.20
Total	246	133	379
	100.00	100.00	100.00

Pearson Chi2 = 6.06 Prob = 0.1947
First row has *frequencies* and second row has *column percentages*

Tabulation of PainInterferWork Group when TIMEPOINT is 6-weeks

PainInterferWork	Group

	Anterior	Posterior	Total
No, impossible	74	55	129
	27.51	35.26	30.35
With extreme difficulty	14	12	26
	5.20	7.69	6.12
With moderate difficulty	30	18	48
	11.15	11.54	11.29
With little difficulty	46	27	73
	17.10	17.31	17.18
Yes, easily	105	44	149
	39.03	28.21	35.06
Total	269	156	425
	100.00	100.00	100.00

Pearson Chi2 = 6.27 Prob = 0.1799
First row has *frequencies* and second row has *column percentages*

Tabulation of PainInterferWork Group when TIMEPOINT is 6-months

	Group		
PainInterferWork	Anterior	Posterior	Total
No, impossible	53	25	78
	17.49	14.71	16.49
With extreme difficulty	35	23	58
	11.55	13.53	12.26
With moderate difficulty	85	48	133
	28.05	28.24	28.12
With little difficulty	63	35	98
	20.79	20.59	20.72
Yes, easily	67	39	106
	22.11	22.94	22.41
Total	303	170	473
	100.00	100.00	100.00

Pearson Chi2 = 0.90 Prob = 0.9250
First row has *frequencies* and second row has *column percentages*

Tabulation of PainInterferWork Group when TIMEPOINT is 1-year

	Group		
PainInterferWork	Anterior	Posterior	Total
No, impossible	190	88	278
	56.21	48.09	53.36
With extreme difficulty	93	59	152
	27.51	32.24	29.17
With moderate difficulty	50	30	80
	14.79	16.39	15.36
With little difficulty	1	3	4
	0.30	1.64	0.77
Yes, easily	3	2	5
	0.89	1.09	0.96
5	1	1	2
	0.30	0.55	0.38
Total	338	183	521
	100.00	100.00	100.00

Pearson Chi2 = 5.61 Prob = 0.3457
First row has *frequencies* and second row has *column percentages*

Contextual Statement Part II: Summary and Conclusions

This thesis was aimed at answering the following questions:

1. Is the novel PENG block an effective regional analgesia technique for hip fractures?
2. What can we as anaesthetists do to improve outcomes in hip fracture care?
3. Is the novel PENG block an effective regional analgesia technique for hip arthroplasty?
4. What can we as anaesthetists do to improve outcomes in lower limb arthroplasty?

The Introduction of this thesis summarised the technical aspects of the PENG hip block, and the nature of the surgery and the patient populations who commonly present for both hip fracture surgery and hip arthroplasty surgery.

The first chapter, a scoping review by Dr C Morrison serves as an introduction to the PENG block, highlighting the paucity of evidence in 2020. At that time, current evidence of using PENG block for hip surgery or hip pain was limited to case reports and case series only. The PENG block was back then a promising regional analgesia technique as an alternative to other regional nerve blocks such as femoral nerve block or iliac fascia nerve block. Observational and experimental studies were required to determine the effectiveness, efficacy and safety of the PENG block, which we then actively addressed with two randomised controlled trials.

Chapter 2 was the first of the RCTs conducted as part of this thesis, but also the first RCT published worldwide on this block. It described sixty patients who were randomized and equally allocated between two groups- either PENG block or the femoral nerve block. Baseline demographics were similar between the two arms. Postoperatively in recovery (day 0), the PENG group experienced less pain compared with the femoral nerve block group. In the PENG group, 63% experienced no pain, 27% mild pain, and 10% moderate to severe pain. In comparison, 30% of the femoral nerve block group reported no pain, 27% mild pain, and 36% moderate to severe pain ($p=0.04$). This was assessed using an 11-point Likert numeric rating scale. Quadriceps strength was better preserved in the PENG group in the PACU on day of surgery. This was assessed using Oxford muscle strength grading. We found that 60% were intact in the PENG group, and no patients had intact muscle strength in the femoral nerve block group ($p<0.001$). On the first day after surgery, 90% in the PENG group had intact muscle strength and movement, whereas only 50% in the femoral nerve block could move that leg normally ($p=0.004$). There was no difference found in all other outcomes.
This randomized comparative trial showed that the PENG block gave better postoperative analgesia than the femoral nerve block. Pain scores were significantly better in the PENG group when compared to the femoral nerve block group postoperatively.
Previous published literature on the PENG block had at the time of this first randomized comparative study been limited to case series including little amounts of participants only. This was fitting given it was at the time a very new block in its infancy. Giron-Arango, et al. described in her landmark paper which detailed the PENG block for the first time a small number of only 5 patients. She suggested a staggering post-procedure 7 point pain score reduction. (8) This turned out to be consistent with case series which were then published afterwards exploring

the PENG block. (26, 27, 28, 29) The writers of the initial PENG block article compared the PENG block effectiveness with previously published outcomes of the femoral nerve block from a Cochrane systematic review written by Guay et al. (18) . The femoral nerve block showed a pain score reduction of 3.4 points. Our randomized comparative trial did confirm these early suppositions; namely that the PENG block offers superior analgesia when compared to the femoral nerve block.

Postoperatively, muscle strength in the PACU on Day 0 and on Day 1 was considerably better maintained in the PENG group when compared to the femoral nerve block group. Superior preservation of quadriceps strength allows participants to mobilise at an earlier time following their index surgery. This in turn is associated with fewer complications, reduced mortality, better pain experience and a shorter length of stay. (30, 31, 32)

We did note that some PENG patients did have a loss of muscle strength, namely two patients. Both patients with no motor ability had undergone spinal anaesthesia, and the motor effect was found to be bilateral at 4 hours after surgery. Therefore, we consider that this is likely a residuary influence of the spinal anaesthetic.(33, 34) Moreover, we discovered that patients were occasionally still residually sedated in PACU, or couldn't fully comprehend commands. This noted effect could also have been due to the high concentration of local anaesthetic used in this trial for both the femoral nerve block and PENG block, which was ropivacaine 0.75% 20mLs. It is definitely a possibility that this produces some reduction in motor strength, which was an aspect that we suggested should be investigated further as this could have caused a higher than projected inhibition of quadriceps strength after PENG and femoral nerve block blocks. For later studies featured in this thesis, we decreased our concentration of local anaesthetic used, as the analgesia was likely to be sufficient also at a less concentrated dose.

We also observed that there were two in-hospital falls recorded in the femoral nerve block group. No falls were seen in the PENG group. The effect of the femoral nerve block could have been a contributing factor, although the number of events was too small to show this statistically, as the sample was not powered for this complication (p=0.50). (35)

Additionally, no adverse occurrences directly related to block placement were reported in both groups.

Patient satisfaction was found to be considerably better after PENG block than femoral nerve block (p=0.02). The other PROMs were comparable between the two arms. The relatively high number of patients who declined to complete the surveys due to general malaise, especially in the femoral nerve block group, may have been a contributing factor to this lack of difference. The totals obtained from the QoR-15 in both arms were lower than those reported by the original studies describing them. However, these outcome measures were originally piloted in younger and more robust patients. (36) Studies involving elderly patients with extensive comorbidities reported comparable QoR-15 scores to those found by us here. (37)

The comparable amounts of opioid use in both arms may have been secondary to the higher age of the neck of femur fracture patients, and their altered geriatric pharmacodynamics. Also, their lower baseline opioid use and our institution's threshold to administer opioids in view of its side-effects in elderly is also higher- which combined may have contributed to the lack of difference noted between arms. This trial was also not powered to detect a dissimilarity in opiate use between the arms; for this, a much larger cohort trial would be needed to investigate this.

Some limitations of the study did have to be addressed. Our study was conducted in a comparatively low number of patients. However, since the power calculation was based on small PENG reports as previously described, we chose to increase the participant numbers for the study described in this chapter in the power calculations. This was in order to minimize the risk of an underpowered trial. Consequently, we are confident that the significant differences found between arms for our primary outcome (postoperative pain) reflects a true difference between the PENG and femoral nerve block. It is imaginable that the secondary outcomes would have also returned a difference, but the power calculation was based on the primary outcome. Therefore, this trial was likely too small to identify differences in the secondary outcomes as detailed above- such as opiate use reduction as well as the occurrence of complications, specifically in hospital falls.

For our study, we had a pragmatic method, permitting surgeons and anaesthesiologists to select their own management plans. This was to permit daily practice to be reproduced in this analysis, as variation at our hospitals is negligeable due to our institutional standards of care. Further sensitivity analysis did not show a trend towards significance for the choice of spinal or general anaesthesia.

Neck of femur fracture patients are by-and-large elderly and frail, with dementia as a not uncommon comorbidity. (38) Due to our rigorous patient selection to remove patients with any amount of cognitive impairment, a sizable number of patients had to be omitted, possibly causing a selection bias. The subsequent step to further examine the PENG block would be a greater cohort study in the overall hip fracture population including those with cognitive impairment.

Preferably, we would have conducted the surveys preoperatively as well, to find a baseline for each participant. This, however, was not feasible due to the emergency nature of hip fracture surgery. When we did our next randomized study described in a later chapter, this is what we did as the elective nature of hip replacement surgery allowed this.

In conclusion, patients having a PENG block for intra- and postoperative pain relief during neck of femur fracture surgery experienced less postoperative pain in the PACU. No difference was detected by day 1 after surgery. Muscle strength was better conserved with the PENG block. Notwithstanding the short-term analgesic benefit and improved muscle strength, there were no dissimilarities found in the quality of recovery. We therefore concluded that for hip fracture surgery, the PENG block should be considered as part of an anaesthetic plan to reduce perioperative pain.

Following the publication of this paper, which in a short time already received more than 100 citations, the PENG block has seen a large up take around the world. Our collaborators from Amsterdam to Boston and from Alice Springs to Curaçao all report the PENG block being used in their respective hospitals today.

Chapter 3 of this thesis describes a study which aimed to determine the association of anaesthesia and regional analgesia with all cause 12-month mortality and even longer-term mortality after hip fracture surgery in Australia and New Zealand. We employed data from the Australian and New Zealand Hip Fracture Registry gathered from 2016 to 2018, with a minimum follow-up of 12 months. Anaesthesia type and use of regional nerve blocks were examined. The

primary outcome was all cause 12-month mortality. 12-month mortality was 30.6% (n=5410) in a total of 17,635 patients. There was no difference detected in 12-month mortality between patients who received spinal or general anaesthesia (p=0.238). The administration of a simultaneous combination of general and spinal anaesthesia for surgery to repair the hip fracture was an independent predictor of higher 12-month mortality, with an unadjusted complete case hazard ratio of 1.17 (95% CI 1.04 to 1.31); p<0.001. Nerve blocks performed in both the emergency department and the operating theatre were correlated with reduced long-term mortality, with a median follow-up of 21 months. This had an unimputed unadjusted hazard ratio of 0.86 (95% CI 0.77 to 0.96); p=0.043.

Our analysis of the ANZHFR found that performing both general and spinal anaesthetic in for a single surgery may be correlated with an increased risk of medium and long-term mortality after index neck of femur fracture surgery. Time-to-death is a reflection of the risk (hazard) and an HR >1 implies a shorter time to death. Both the 12-month and longer-term mortality for the unadjusted complete case analyses had a higher hazard ratio for combined general/spinal when likened with general anaesthesia, or spinal anaesthesia alone.

This study indicated no distinction in 12-month mortality for patients who received either a spinal or a general anaesthetic. Anaesthesiologists aim to minimize morbidity and mortality in the elderly and frail population, and given the bourgeoning field of perioperative anaesthesia as a subspecialty it is no wonder that this particular topic has been hotly discussed. Finding no difference between these two techniques reinforced previously published literature (139, 140, 141, 142).

The higher risk of long-term mortality in patients who underwent both general and spinal anaesthesia is probably multifactorial. The need to convert from spinal to general anaesthesia mid-case may have been due to a complicated or prolonged surgery in which more blood loss or bony manipulation occurs, all of which can disturb homeostasis. Agitation due to delirium or cognitive impairment throughout an awake spinal anaesthesia may have caused poor patient compliance and the necessity of converting to a general anaesthetic. The additive effects of two forms of anaesthetic can affect the chance of perioperative hypotension. This in turn is associated with the probability of renal injury, myocardial infarction and death, with an increased effect in the geriatric population (143, 144, 145, 146, 147). A lengthier period and larger severity of hypotension under anaesthesia has been proposed as a predictor of postoperative complications following neck of femur fracture surgery (148). It has also been postulated that postoperative complications at any time point may influence mortality up to and including 30 months following index surgery (149).

Therefore, anaesthesiologists who are challenged with a clinical scenario in which spinal anaesthesia may be inadequate should contemplate an anaesthetic plan which accounts for a prolonged length of surgery rather than risk doubling up anaesthetic type during a single case. ‘Getting it right the first time’ has earlier been emphasised as one of the ten core general principles of anaesthesia for fragility surgery (150). Intriguingly, not much has earlier been known about the mortality risk of simultaneous use of general and spinal anaesthesia in hip

fracture surgery, with only one earlier published high-quality study from 1980 that found no difference in 60 randomized participants (151).

The administration of a regional analgesia technique in both the emergency department as well as in the operating theatre was correlated with a smaller risk of 12-month and even longer-term mortality. This was significant only for the unadjusted complete case analysis for long-term mortality, and not for 12-month mortality.

This outcome was in line with previously published works, including a number of international guidelines and a Cochrane review supporting the routine use of nerve blocks for analgesia in fragility fracture management. Regional blocks commonly performed included the femoral nerve block, fascia iliaca block, or the pericapsular nerve group block (9). The benefit in long-term mortality may be due to better pain relief and an opioid sparing effect with a reduction in risk of postoperative delirium and respiratory depression (152, 153, 154, 155, 156). The administration of regional nerve blocks by the emergency physician as well as the anaesthesiologist may also be a surrogate marker for quality of care given the mounting endorsements for the use of these procedures (157, 158). It may also mirror the admittance of the patient to a hospital which is more familiar with treating neck of femur fractures. This may even be supported with an established care pathway which has been shown to cut the rate of perioperative complications (159). The occurrence of any postoperative complication has been proposed to be an independent risk factor for higher long-term mortality (159), with an upturn in the relative risk if the complication occurred earlier in the postoperative course (149). The application of a hip fracture care pathway to ensure high-quality routine standardized treatment from admittance, containing performing regional blocks in the emergency department, may help in reduction of complications and consequently impact mortality outcomes.

For this chapter, we utilised the Australia and New Zealand Hip Fracture Registry. This is the international database collecting hip fracture data in Australia and New Zealand. A data quality audit (160) found that in 2016 it had a moderate level of data accuracy and a very high level of data completeness. Given that surgical and anaesthetic methods in Australia and New Zealand are in line with standard international practice, this databank allows for a high level of generalizability and external validity. The only omission would be that the use of combined spinal-epidural (CSE) techniques for hip fracture surgery is not routine (161) in Australia as it is in some other countries such as the United States of America. Throughout our inclusion stage (2016–2018), there were no significant changes in surgical or anaesthetic practice on a multinational level. We noted as a potential limitation that the data incorporated in this study, while significant, were of observational value. There was the limitation of potential effect of residual confounding on the associations. For the complete case analysis of long-term mortality and the adjusted HR=1.12 (95% CI 1.02 to 1.24), based on the use of the e-Value calculator (162), a single confounder with an hazard ratio of 1.49 would be enough to eradicate this observed association. This implies that the potential for residual confounding, such as confounding by clinical indication, could hypothetically remove the observed association. Thus,

while our findings were interesting, they do not imply causality. This is important to note before any clinical decisions are based on this.

Our proposed explanation for long-term mortality following index surgery for neck of femur fracture repair revolves around an increased likelihood of post-operative complications. This might stem from extended surgical durations, underlying patient-related factors, or occurrences of intraoperative hypotensive episodes. However, the dataset at hand lacks the means to systematically investigate the intermediate impact of postoperative complications. As a result, this mechanism cannot be definitively confirmed by the current study. A notable twenty-eight percent of patients exhibited missing data points during the follow-up period, necessitating the utilization of a multiply imputed model as part of a sensitivity analysis (See Supplemental Appendix 1 for the chapter). While there exists the potential for selection bias by excluding cases with missing data in the complete case analysis, associations persisted in the sensitivity analyses. We presumed the data to be missing at random, conditioned on the covariates incorporated into the multivariate analysis. Our belief is that these covariates could effectively account for any non-random missingness, given the absence of unmeasured factors that could contribute to such missingness. However, due to the inability to test this assumption, it does represent a limitation of the study.

The ANZHFR dataset fields lack surgical-specific variables, such as surgery duration, procedural complexity, relative unit value, volume of blood loss, or finer details about the regional block employed, including its type. Furthermore, the dataset doesn't encompass a comorbidity index. It's important to note that while it's relatively unusual in Australia and New Zealand to administer epidural or CSE for hip fracture surgery, this practice is routine in other countries, potentially constraining the generalizability of these findings.

It's worth mentioning that the ANZHFR database was updated post the study period to include patient ethnicity, which presents an additional point of interest for future examination. The absence of this variable in the 2016-2018 dataset represents a limitation.

To conclude, hip fracture surgery predominantly involves a frail and elderly patient demographic. Evaluating the influence of anaesthetic and analgesic techniques holds significance in ensuring the continued advancement of medical practices. This retrospective analysis encompassed 12,840 patients from the ANZHFR database spanning 2016 to 2018.

The study found no discernible difference in the association with 12-month mortality between spinal and general anaesthesia following hip fracture surgery. Notably, patients who underwent both general and spinal anaesthesia for the same surgical procedure exhibited a heightened risk of 12-month and longer-term mortality compared to those who received either spinal or general anaesthesia exclusively. Patients who received a regional nerve block both in the emergency department and the operating theatre before surgery demonstrated a reduced risk of 12-month and longer-term all-cause mortality, in contrast to those who received either one or no nerve blocks. It is important to acknowledge that the nature of this data is observational, and as such, causal conclusions cannot be drawn.

This article has been included in several summaries of what is noteworthy and new in clinical research in highly ranked journal editorials as well as UpToDate, a widely used medical clinician website that is highly utilised worldwide. (163, 164, 165)

The second randomized controlled trial (RCT) within this thesis examined the efficacy of the PENG block in hip arthroplasty surgery compared to a placebo. In this multi-centre double-blinded RCT, hip arthroplasty patients, in addition to spinal anaesthesia and local infiltration analgesia, were randomized to receive either a PENG block or a sham block. The primary outcome was the pain score (on a numeric rating scale of 0-10) three hours postoperatively (Day 0). Secondary outcomes included postoperative quadriceps muscle strength, pain scores on postoperative Day 1, opiate usage, complications, length of hospital stay, and patient-reported outcome measures. The study included sixty patients who were equally divided between the groups. Baseline demographics demonstrated no significant differences. On postoperative Day 0, the PENG group reported lower pain levels compared to the sham group (PENG: 14 (47%) patients experienced no pain, 14 (47%) had mild pain, and 2 (6%) reported moderate/severe pain, as opposed to the sham group: 6 (20%) with no pain, 14 (47%) with mild pain, and 10 (33%) with moderate/severe pain; p = 0.03). No significant variation in quadriceps muscle strength between the groups was noted on Day 0 (PENG: 23 (77%) intact versus sham: 24 (80%) intact; p = 0.24), and no differences emerged in other secondary outcomes. This double-blinded RCT demonstrates that the PENG block provides significant short-term postoperative pain relief in elective total hip arthroplasty when used alongside spinal anaesthesia and local infiltration analgesia (p = 0.03). However, the immediate postoperative analgesic benefit of the PENG block does not persist beyond Day 1. Regional analgesia in THA has traditionally been performed using a femoral nerve or fascia iliaca block. Although partially effective, these blocks result in a decrease in muscle strength (166). Since the PENG block affects only the articular branches of the femoral and accessory obturator nerves, it is believed to achieve adequate analgesia while also preserving motor function and muscle strength. In this study, postoperative quadriceps muscle strength was similar in both groups. This allowed patients to mobilize early following surgery, which, in itself is associated with fewer complications, shorter length of hospital stay and lower mortality (30, 31, 32). Patients who received the PENG block were thus able to mobilize as soon as the sham group patients, with less pain.

The motor sparing effect was consistent with previous studies focused on anatomy suggesting that the PENG block targets the articular branches of the femoral, obturator, and accessory obturator nerves (167). It's important to note that on Day 0 and Day 1, seven and six PENG patients respectively experienced a decrease in quadriceps muscle strength. Interestingly, a similar occurrence was observed in the sham group, with 6 and 7 patients respectively (p=0.24 and p=0.75). This phenomenon could potentially signify a reluctance to engage in active movement following hip surgery or the potential diffusion of effects from the LIA to the femoral nerve, which was consistent across both groups.

Noteworthy is the absence of any adverse events directly linked to the placement of the block, and patient satisfaction remained consistent between both groups.

To objectively assess the potential recovery advantages associated with the PENG block, a range of Patient-Reported Outcome Measures (PROMs) and outcome metrics were employed. Initial patient PROMs, evaluated through the Pain Catastrophizing Scale and PROMIS anxiety and depression item banks, exhibited no significant discrepancies between the groups. Similarly, postoperative PROMs, quality of recovery, and the Timed Up-and-Go tests displayed comparable outcomes. It's plausible that the timing of these assessments on Day 1 post-surgery might have contributed to this similarity, as they occurred after the analgesic effects of the PENG block had waned. An additional recent randomized controlled trial (RCT) comparing PENG to a sham in combination with intra-articular injection also demonstrated short-term benefits but failed to exhibit distinctions in longer-term outcomes (168).

The comparable opiate usage observed in both groups, despite differing pain scores, might be attributed to the advanced age of the included patients and their low baseline opiate consumption. It's worth highlighting that the study was not adequately powered to detect disparities in opiate use or Patient-Reported Outcome Measures (PROMs) between the groups. Larger studies in the future will be required to delve into these aspects more comprehensively.

Several limitations were inherent to this study. As elucidated in the chapter, this trial encompassed a relatively modest number of patients, which limited its ability to identify differences in secondary outcomes. Nonetheless, it was sufficiently powered for the primary outcome, revealing a significant distinction between the two groups. Quadriceps strength assessment was conducted by a blinded clinician. While a standardized dynamometric measurement tool could have provided greater accuracy, its unavailability mandated an alternative approach. It's acknowledged that this introduces some level of interobserver variation, which was mitigated by consolidating intermediate scores. Due to the standardized spinal anaesthesia in the study protocol, 11% (8/75) of approached patients declined participation, potentially introducing a degree of selection bias. However, randomization occurred post-inclusion to mitigate this bias. In subsequent randomized-controlled trials, investigating the efficacy of the PENG block in total hip arthroplasty, it might be worthwhile to consider patients undergoing either spinal or general anaesthesia.

In summary, individuals receiving an additional PENG block for analgesia during total hip arthroplasty encountered diminished immediate (Day 0) postoperative pain, while retaining quadriceps muscle strength and a comparable timeframe for mobilization compared to those receiving spinal anaesthesia and local infiltration analgesia alone. In the context of total hip arthroplasty, the inclusion of the PENG block should be contemplated as an integral component of a multimodal analgesia approach.

As our newest RCT, this has not received as many citations are the primary RCT- but the citation numbers are steadily increasing.

The subsequent chapter outlines the implementation of an opioid-sparing protocol for patients undergoing knee or hip arthroplasty. The ongoing opioid epidemic has placed substantial safety and financial burdens on healthcare systems worldwide. Postoperative opioid prescriptions significantly contribute to this crisis, with reported opioid prescription rates following arthroplasty surgeries soaring as high as 89%. In this multi-centre prospective study, our primary goal was to document patient outcomes within the framework of this protocol and examine the rate of opioid prescriptions upon discharge from our hospitals following joint arthroplasty procedures. This is potentially linked to the effectiveness of the newly introduced Arthroplasty Patient Care Protocol detailed in this study. Over a span of three years, we amassed data from patients who underwent perioperative education with the expectation of opioid-free recovery post-surgery. The protocol mandated intraoperative regional analgesia, early postoperative mobilization, and a multimodal analgesia approach. We monitored extended opioid use and assessed patient outcome measures (Oxford Knee/Hip Score, EQ-5D-5L) prior to surgery and at 6 weeks, 6 months, and 1 year post-surgery. Both primary and secondary outcomes encompassed opiate utilization and patient outcome measures at varying time intervals. A total of 1,444 patients participated in the study. Two (0.2%) knee patients used opioids to one year. Zero hip patients used opioids postoperatively at any time point after six weeks ($p<0.0001$). The Oxford Knee Score and EQ-5D-5L both improved for knee patients from 16 (12-22) pre-operatively to 35 (27-43) at 1 year postoperatively, and 70 (60-80) preoperatively to 80 (70-90) at 1 year postoperatively ($p<0.0001$). The Oxford Hip Score and EQ-5D-5L both improved for hip patients from 12 (8-19) preoperatively to 44 (36-47) at 1 year postoperatively, and 65 (50-75) preoperatively to 85 (75-90) at 1 year postoperatively ($p<0.0001$). Satisfaction improved between all pre- and postoperative time points for both knee and hip patients ($p<0.0001$). This study demonstrated that a patient education protocol with emphasis on patient expectation management coupled with a multi-disciplinary approach to pain management can result in a long-term opioid free recovery. This is supported on a national level in Australia by multiple programs designed to restrict and monitor opioid prescribing. Similar programs in other countries have also shown success in previous studies. (60, 61) The subject of opioid use for pain management is 'one of intense international interest', according to Morgan et al. (62) Dependence can develop following the use of prescription opioids after surgery. (63) Health systems internationally have flagged this as an area of concern and strategies aimed at minimising postoperative opioid prescriptions are increasingly suggested. (64) That said, opioids are a cornerstone of postoperative pain management and inadequate analgesia can result in delayed mobilisation and recovery. (65) The results of this prospective study, however revealed no decrease in PROM outcomes during an opioid free postoperative phase, showing that joint arthroplasty surgery can be managed with simple analgesia postoperatively without compromising quality of recovery. Pain scores are also comparable with previously published studies, if not lower. (66, 67) In previous studies, pain scores at 6 weeks postoperatively for Total Knee Arthroplasty (TKA) were characterized as moderate, averaging around 5 on an 11-point Likert scale. These scores tend to diminish over the subsequent 12 months following the procedure. In a separate investigation, it was noted that

12 months postoperatively for TKA, 40% of patients reported experiencing moderate to severe pain. The prevalence of chronic pain and patient dissatisfaction has been documented to range between 10% and 34% at the 12-month mark after undergoing TKA. (68) Our study described perhaps less pain, with a majority reporting only slight pain at 6 weeks and moderate pain being the second most common response with a similar pattern of pain improvement over the 12 months of follow-up.

Patient satisfaction rates at our institution are consistent or better than reported incidences from other tertiary centres, (69) describing dissatisfaction rates of up to 20% under a classic opioid prescribing regime. (70) However, this outcome might not solely be attributed to opioids but likely owes much to hands-on care, meticulous preoperative preparation, and extensive follow-up.

At the six-week postoperative mark, 25 (5%) of the hip patients and 94 (10%) of the knee patients reported severe or extreme postoperative pain. An inherent limitation of this finding is that the data collection did not specify the precise location of the pain. It's noteworthy that patients often reported pain in the contralateral joint, likely due to the shared underlying pathology. Interestingly, these individuals did not express dissatisfaction with the surgery, nor did they resort to postoperative opioids. This suggests the possibility that their pain might not have been linked to the operated joint.

Among the patients who continued to use opioids postoperatively, both had documented preoperative opioid consumption and exhibited severe anxiety and/or depression throughout the study period. The improvements in Patient-Reported Outcome Measures (PROMs) were consistent with the group's average results. One patient reported low satisfaction, and both continued to experience severe pain despite being prescribed opioid medications.

Our study's evaluation of the incidence of two out of 1444 patients who remained on long-term opioid medications was then compared with previously published incidences among Australian hip and knee arthroplasty patients following traditional regimes, that is, without opioid sparing. Comparable populations have shown rates of 10% at 6 months postoperatively following Total Knee Replacement (TKR) and 4% at 6 months postoperatively following Total Hip Replacement (THR) (71). Despite the common use of prescription opioids for chronic non-cancer pain, there remains no strong scientific evidence to support this routine practice. (72) This study effectively demonstrates that successful recovery from arthroplasty surgery can be attained, accompanied by favourable patient satisfaction and noteworthy improvements in Patient-Reported Outcome Measures (PROMs), all while adopting a strategy of minimizing opioid usage. Additionally, it's important to note that opioid consumption correlates with heightened long-term utilization of healthcare services, alongside imposing a substantial economic strain.(73)

PROM surveys and long-term opioid based data collection will be integrated shortly into the national Australian Orthopaedic Association joint registry database. (74) This study provides a promising glimpse into the potential of investigating opioid prescription and recovery on a larger scale in the future. The presence of an Acute Pain Service and the utilization of innovative

regional anaesthesia likely contributed to these positive outcomes. Notwithstanding the favourable results described, it's crucial to address certain limitations. Regrettably, there's no historical data collection available at our centre prior to the implementation of this protocol, preventing us from definitively concluding a causal change. We've resorted to comparing our findings to published data from other centres that share similar patient populations but employ more conventional opioid regimens, highlighting the discernible contrast. Nevertheless, it's important to recognize that these prescription rates are reliant on patients' self-reporting, presenting a limitation. We acknowledge the potential influence of cultural factors on our observed low opioid prescription rate, where a team approach of minimizing postoperative opioids may play a role. If such an approach contributes to our positive outcomes, we argue that it's not necessarily a weakness. The high patient satisfaction rate and positive PROM results, in spite of our minimal opioid prescription rates, strongly suggest its feasibility.

We should also consider the possibility that patients lost to follow-up were indeed using opioids. Unfortunately, we lack the means to determine this definitively. The pattern of attrition doesn't align with opioid prescribing rates in the acute postoperative phase continuing from surgery, as attrition increases further from index surgery. Non-responders had comparable baseline characteristics to responders, indicating they weren't inherently more prone to preoperative opioid usage. Furthermore, the attrition rate, such as the 6.4% at 6 weeks for TKA, is even lower than most opioid prescribing rates reported in prior studies. We anticipate that the implementation of Script Check in Australia will facilitate the determination of patient opioid use across all healthcare providers in the near future.

In conclusion, the outcomes of this multi-centre prospective study unequivocally demonstrate that for the vast majority of patients, there's no compromise in PROM outcomes or patient satisfaction when transitioning to an opioid-free postoperative phase. This underscores the feasibility of managing joint arthroplasty surgery with non-opioid analgesia in the six-week to one-year postoperative period, all without jeopardizing pain scores or the quality of recovery. This warrants consideration for future investigation through a randomized controlled trial.

This is a crucially important perspective, as the opioid epidemic is one of the greatest challenges pain medicine faces in this current time. We have received multiple invitations to present this protocol to hospitals also looking to set up their own long term opioid free/sparse regimes- and see this as such an important public health outcome that we have moved or cancelled other speaking engagements to facilitate this.

The objective of the sixth chapter was to assess the measurement properties of the Oxford Hip Score (OHS), EQ-5D-5L utility index, and EQ-5D-5L visual analogue scale (EQ-VAS) in patients undergoing elective total hip arthroplasty in Australia. This prospective multi-centre study collected OHS and EQ-5D-5L data preoperatively, as well as at six weeks and six months postoperatively. The study evaluated these measures for concurrent validity, predictive validity using Spearman's Rho of predicted and observed values from a generalized linear regression model (GLM), and responsiveness in terms of effect size (ES) and standard response mean (SRM).

A total of 362 patients' results were analyzed at six weeks, and 269 patients at six months. The EQ-5D-5L index demonstrated strong concurrent validity with the OHS, showing good correlation preoperatively (r = 0.71), at 6 weeks (r = 0.61), and at 6 months (r = 0.59). The predictive validity of the EQ-5D-5L index was comparable to the OHS when regressed using the GLM approach. Responsiveness was notable at both 6 weeks (EQ-5D-5L index ES 1.53, SRM 1.40; OHS ES 2.16, SRM 1.51) and 6 months (EQ-5D-5L index ES 1.88, SRM 1.70; OHS ES 3.12, SRM 2.24).

In contrast, the EQ-VAS exhibited lower results with an ES of 0.75 (moderate) and SRM of 0.8 at 6 weeks. At 6 months, the EQ-VAS showed an ES of 0.92 and SRM of 1.00, though it demonstrated greater predictive validity. Consequently, while the EQ-VAS had its strengths, the EQ-5D-5L index and OHS maintained stronger concurrent validity.

This analysis constitutes an empirical validation of the EQ-5D-5L's suitability for assessing Health-Related Quality of Life (HRQoL) in hip arthroplasty patients. It utilizes experienced-based patient data from a prospective multi-centre study database to examine the correlation between the Oxford Hip Scores, EQ-VAS, and EQ-5D-5L PROMs. The findings endorse the EQ-5D-5L index score as a valid and reliable tool for HRQoL assessment in these patients.

While the limits of agreement were satisfactory between the EQ-5D-5L index score and the OHS, it's crucial to recognize their differing scopes. The OHS is a joint-specific PROM, whereas the EQ-5D-5L index score evaluates overall functionality. Instances may arise where an individual could manage daily tasks well and cope with the mental toll of an arthritic hip on the EQ-5D-5L index score, but still report issues with mobility on the OHS. The OHS was chosen as a comparator due to its widespread use and substantial item overlap with the EQ-5D-5L index score, featuring items like mobility, pain/discomfort, and usual activities. Detailed comparison even revealed substantial correlation between dimensions of the EQ-5D-5L and the OHS, except for the Anxiety/Depression dimension, where the correlation was only fair. This is in line with evidence from the literature (101, 102, 103) that shows that strong correlations exist between instruments and dimensions that measured similar constructs. Hence, they should be utilised concurrently to complement each other, instead of being considered as substitutes for one another.

The longitudinal design of this study, incorporating multiple time points, lends itself adeptly to evaluating gradual changes within the population and pinpointing discrepancies in the performance of both Patient-Reported Outcome Measures (PROMs). The utilization of experience-based and prospective data serves as a robust aspect of this study.

When assessed as standalone measures, the EQ-VAS demonstrated a notably smaller Effect Size (ES) compared to the EQ-5D-5L index score at both six weeks (0.75 versus 1.53, $p<0.0001$) and six months (0.80 versus 1.40, $p<0.0001$). Similarly, the Standard Response Mean (SRM) was substantial for both scores at both time points. However, what sets the EQ-VAS apart is its superior predictive validity compared to the EQ-5D-5L index score and OHS. This suggests that the EQ-VAS holds a greater predictive value for postoperative recovery and should be routinely

incorporated as a complementary measure to the EQ-5D-5L index score. This heightened predictive validity might be attributed to the broader nature of the VAS, which isn't confined by specific domains or items, unlike the OHS or EQ-5D-5L descriptive system. This flexibility empowers patients to encompass a wider range of factors in their subjective health rating. This aspect proves beneficial for patient categorization and counselling, aiding in setting realistic rehabilitation expectations and offering insights into postoperative outcomes.

An evaluation of the agreement between the EQ-5D-5L index score and EQ-VAS, as well as with the OHS, unveiled acceptable concordance (ranging from moderate to good/substantial for most comparisons). This indicates that while the assessments derived from these instruments were not identical, they displayed a considerable level of alignment and should be perceived as complementary rather than interchangeable. Several limitations inherent to this study warrant consideration and clarification. Approximately 25% of the patient data were missing at the six-month mark, necessitating the exclusion of these cases. As a result, this introduces a response bias, potentially affecting the overall generalizability of the findings. Moreover, there were gaps in the recording of patients' baseline characteristics, with BMI being recorded for 90.6% (328/362) of patients and Charlson Comorbidity Index (CCI) for 94.2% (341/362) of patients. This incomplete data recording may affect the accuracy and comprehensiveness of the analysis.

It is noteworthy that the EQ-5D-5L index displayed consistent predictive validity at both the six-week and six-month intervals, with both Patient-Reported Outcome Measures (PROMs) demonstrating satisfactory responsiveness. Given this, it's advisable to regularly incorporate the EQ-VAS alongside the EQ-5D-5L index in assessments. Importantly, the EQ-5D-5L index emerges as a suitable tool for quantifying health-related quality of life in Australian hip arthroplasty patients.

In conclusion, while these limitations are acknowledged, the study outcomes underscore the significance of the EQ-5D-5L index in evaluating health-related quality of life for Australian hip arthroplasty patients. Its consistent predictive validity and robust performance, along with the endorsement of using the EQ-VAS in conjunction, emphasize the practicality and utility of these measures for guiding patient care and treatment decisions.

The primary objective of the seventh chapter was to assess the utility of the Oxford Knee Score (OKS), EQ-5D-5L utility index, and EQ-VAS for measuring health-related quality of life outcomes in patients undergoing elective total knee arthroplasty (TKA) surgery in Australia. This prospective multi-centre study collected OKS and EQ-5D-5L index scores preoperatively, at six weeks, and at six months post-TKA. The study evaluated these measures for the minimally important difference (MID), concurrent validity, predictive validity (using Spearman's Rho from a generalized linear regression model), and responsiveness (Effect Size (ES) and Standard Response Mean (SRM)). MID was determined using both anchor-based and distribution-based approaches.

The analysis encompassed data from 533 patients. The EQ-5D-5L utility index demonstrated strong concurrent validity with the OKS, exhibiting good correlation preoperatively ($r = 0.72$), at

6 weeks (r = 0.65), and at 6 months (r = 0.69). However, the EQ-5D-5L index's predictive validity was lower compared to the Oxford Knee Score when subjected to regression analysis. Responsiveness was notable at 6 weeks for both the EQ-5D-5L index and Oxford Knee Score, with substantial Effect Sizes (EQ-5D-5L ES 0.87, Oxford Knee Score ES 1.35) and Standard Response Means (EQ-5D-5L SRM 0.84, Oxford Knee Score SRM 1.05). At 6 months, similar trends persisted (EQ-5D-5L ES 1.31, Oxford Knee Score ES 1.69; EQ-5D-5L SRM 0.95, Oxford Knee Score SRM 1.59). Conversely, the EQ-VAS demonstrated weaker responsiveness, with an Effect Size of 0.37 (small) at 6 weeks and 0.59 (moderate) at 6 months, along with small SRMs for both time points.

The anchor-based approach revealed that the minimally important difference for the OKS was 8.84 ± 9.28 at 6 weeks and 13.37 ± 9.89 at 6 months. For the EQ-5D-5L index, the corresponding values were 0.23 ± 0.39 at 6 weeks and 0.26 ± 0.36 at 6 months.

This empirical validation of the EQ-5D-5L index's appropriateness in assessing health-related quality of life among knee arthroplasty patients employed real-world patient data from a prospective multi-centre study database. The correlation between the Oxford Knee Scores, EQ-VAS, and EQ-5D-5L index PROMs was investigated, affirming the EQ-5D-5L index's validity and reliability. However, it's worth noting that the OKS consistently outperformed the EQ-5D-5L index across all domains. Despite the EQ-VAS's weaker responsiveness, it exhibited better predictive validity compared to the EQ-5D-5L index and similar predictive validity to the OKS.

Comparing the EQ-VAS as a standalone measure to the EQ-5D-5L index, the EQ-5D-5L index demonstrated higher Effect Sizes at both six weeks (0.87 versus 0.37, $p<0.0001$) and six months (1.31 versus 0.59, $p<0.0001$), along with large SRMs at both time points. Although the EQ-VAS had lower responsiveness, it showcased stronger predictive validity compared to the EQ-5D-5L index, but comparable to the OKS. This likely stems from the EQ-VAS's broader scope, allowing patients to incorporate a wider spectrum of quality-of-life considerations in their subjective health rating. This feature holds valuable potential for patient stratification and counselling on realistic recovery expectations.

The EQ-VAS's standalone component demonstrated only moderate concurrent validity. The OKS, being a joint-specific PROM, and the EQ-5D-5L index, designed to assess overall functionality, may exhibit variations in patients' perceptions. For instance, someone capable of compensating effectively for daily tasks and managing the mental burden of an arthritic knee on the EQ-5D-5L index may report gait disturbances and specific mobility difficulties on the OKS. The OKS was chosen as a comparator due to its widespread use and substantial item overlap with the EQ-5D-5L index, featuring items like mobility, pain/discomfort, and usual activities. Consequently, it's advisable to use both the OKS and EQ-5D-5L index concurrently to supplement each other's assessments rather than considering them as substitutes.

The study assessment of the MID utilized both anchor-based and distribution-based approaches. This estimation of MID is crucial for clinical purposes, as it indicates when a patient could notice a beneficial change post-knee arthroplasty surgery. Furthermore, it's of paramount

importance in study design, as any new treatment under investigation should aim to identify differences equal to or greater than the MID. Non-inferiority studies should aim to show that the difference between groups is less than the MID for the Australian orthopaedic population. (123)

The strength of this chapter lies in its longitudinal design, which includes multiple time points, enabling the assessment of incremental changes in the study population and differences in the performance of the Patient-Reported Outcome Measures (PROMs). The prospective nature of the data collection also adds to the study's robustness.

Furthermore, the study's generalizability is enhanced by its adherence to standard surgical techniques and perioperative management practices that are consistent not only with Australian standards but also reflective of global norms. This approach increases the relevance and applicability of the study's findings beyond its specific geographic context.

The EQ-5D-5L index has been assessed against other PROMs in the TKA population in previous publications, and found to be more responsive (ES and SRM) than other scores in reflecting health related changes in this group. (124) Conner-Spady et al. found a MID of 0.20 for TKA patients for the EQ-5D-5L index. (85) They reported a wide variation in the MID with the percentage agreement of responder classification using 2SEM versus MID ranging from 79.6 to 99.6% for the EQ-5D-5L and from 69.4 to 94.8% for the Oxford scores. The study's recommendations emphasize the importance of employing multiple Patient-Reported Outcome Measures (PROMs) for assessing Health-Related Quality of Life (HRQoL) in future research. The wide variation observed in the study's findings aligns with similar Minimum Important Difference (MID) results identified in prior studies.

It is worthwhile noting that while there is a limited body of literature regarding concurrent and predictive validity in the context of Total Knee Arthroplasty (TKA), comparable research conducted on the Australian population, especially in the domain of Total Hip Arthroplasty (THA), has demonstrated strong concurrent validity between the EQ-5D-5L index and the Oxford Hip Score (OHS). This reinforces the robustness of the EQ-5D-5L index as a valid instrument for assessing HRQoL in these surgical contexts. The EQ-5D-5L index had similar predictive validity at 6 weeks and 6 months. (107)

Several limitations of this study needed to be addressed. Approximately 21% of patients had missing data at the six-month mark, leading to their exclusion and potentially introducing a response bias.

Future research endeavours should focus on further validating clinically relevant Patient-Reported Outcome Measures (PROMs) and corroborating the baseline Minimum Important Difference (MID) specifically for knee arthroplasty patients in Australia.

In conclusion, this study establishes that both the EQ-5D-5L index and the Oxford Knee Score exhibit good concurrent validity. The EQ-5D-5L index demonstrates a large effect size at six

weeks and six months postoperatively, albeit smaller than the OKS across all time points. Both PROMs show adequate responsiveness, yet the OKS outperforms the EQ-5D-5L in various aspects. While the EQ-VAS displays weaker responsiveness compared to the EQ-5D-5L index, it exhibits better predictive validity when used in isolation.

The EQ-5D-5L index is appropriate for quantifying general health-related quality of life in the Australian knee arthroplasty patient population. However, considering the OKS's superior performance in terms of predictive validity and responsiveness, it should be favoured over the EQ-5D-5L. Ideally, a combination of both can provide a comprehensive assessment, utilizing the OKS for joint-specific evaluation and the EQ-5D-5L for a broader health assessment.

This article also establishes a baseline Minimum Important Difference (MID) for knee arthroplasty patients in Australia, serving as a valuable reference point for future research and patient counselling during the perioperative phase.

The final study in this thesis aimed to compare the direct anterior approach (DAA) and posterior approach (PA) in total hip arthroplasty regarding functional recovery, with a focus on patient-related outcome measures (PROMs) and length of stay. The study included 337 DAA and 187 PA total hip arthroplasties. While the DAA group demonstrated significantly better Oxford Hip Score and EQ-5D-5L scores at 6 weeks postoperatively compared to the PA group, no differences were observed at 6 months and 1 year. The length of stay favoured DAA with a significantly shorter inpatient stay.

The study concluded that the direct anterior approach for total hip arthroplasty led to improved quality of recovery with shorter length of stay and better PROMs at 6 weeks postoperatively, although no significant long-term benefits were found between the two surgical approaches.

Both the Oxford Hip Score and EQ-5D-5L Health Questionnaire are established and validated PROMs widely used to assess joint-related disability and functional recovery in orthopaedic surgery.(130, 131) Internal consistency is high for both questionnaires; Cronbach alpha=0.94 for the Oxford Hip Score, (132) and 0.86 for the EQ-5D-5L. (133) In the current study, the OHS showed an early improvement in favour of DAA patients at 6 weeks. The EQ-5D-5L showed no difference between the two arms at any stage. At six months and at one year there was no disparity in functional recovery between the arms. A cause for the EQ-5D-5L not being unalike between arms while the Oxford Hip Score was, is that the Oxford Hip Score is a joint specific survey while the EQ-5D-5L examines general health. It may therefore be that the Oxford Hip Score can detect more joint specific improvement whereas the EQ-5D-5L is less fine in this area. Earlier analyses have also described better early recovery of direct anterior approach patients compared to posterior approach patients, which is possibly due to the minimally invasive nature of the method. Most of these trials, however, have been limited in their period of follow-up, or of low quality, or have not formally assessed functionality using a validated PROM, or have not attained minimally clinical important difference in the PROMs. (134) Earlier studies that have described long-term outcomes have also not been able to show a benefit of either technique. (135) In the current chapter's study we confirmed these outcomes, but now with a

prospective cohort design, and systematic use of PROMs. Previous trials have often focussed on gait analysis, radiographic outcomes, dislocation rates, or length of stay as primary outcomes. We targeted our study to assess global recovery and functionality using length of stay, and the Oxford Hip Score and the EQ-5D-5L surveys. There is a training curve for the direct anterior approach, which represents a significant outlay for both the surgeon and the participants involved. It is also well recognised that certain patient types lend themselves better to the direct anterior approach, such as the patient with a normal body mass index, for example. Therefore, meticulous patient choice and a risk-benefit exploration must form a part of the deliberation for each individual surgeon when choosing a surgical method. We did find that for this study some limitations had to be addressed. 17% of patients were lost to follow up at six weeks and 38% at six months. Comparable losses to follow up at comparable time points were reported in earlier studies of total hip arthroplasty results. (136) Baseline characteristics between both arms were not balanced as the direct anterior approach group had a lower body mass index, a larger percentage of females, and had more preoperative pain. This signifies a selection bias, as these characteristics make the patient more appropriate for the direct anterior approach. Due to the team-based method to patient selection for surgery and distribution to individual surgeons who prefer one approach above the other, this was a cognizant decision made to enhance patient outcome and permit surgeons training in the direct anterior approach the most ideal conditions in which to commence. That this study suggests favourable outcomes for the direct anterior approach compared to posterior approach, despite the presence of training data, speaks to the potential short-term benefits of this procedural approach. (137, 138) It is also doubtful if a BMI difference between the two groups of 1.7kg/m^2 would be clinically significant, despite the statistical significance. In conclusion, the outcomes of this multi-centre prospective study match previous studies showing early functional improvement in favour of the direct anterior approach. However, there is no difference in long term patient reported outcomes, pain scores or patient satisfaction between the two approaches. Future direction for investigation should contain well designed multicentre randomized controlled trials to compare long term effects of both approaches.

Before embarking upon the trials presented by prior publication in this thesis, the goal presented was to learn to be a beginner researcher in clinical medicine. At the end of the PhD journey and the beginning of a post-doctorate trajectory, looking back there has been a wealth of experience gained and knowledge acquired.

It Is one of the greatest benefits to a permanent position as a consultant in a large teaching hospital, that we can participate in clinical research. Many of our patients who come to our centres are willing to engage in these projects, and provide their valuable time and energy to the support of our research. We hope that in turn our studies may provide valuable insight which will improve their outcomes in the future. The honour of caring for a patient for a research project is enormous and not to be underestimated in its ability to engage us as researchers to do our utmost to obtain the best outcomes for them.

An incredible amount has been learned during the formation of this PhD; regarding hypothesis generation, study design, ethical conduction of research, guidelines for the different sorts of

trials that form quantitative analysis, (pre-study) statistics and health economic validation, and the requirements of journals for publication. The development of intrinsic motivation rather than extrinsic was also a key milestone. This has not been a stand-alone effort, but very much a team based journey.

The working group formed for orthopaedic anaesthesia at Flinders Medical Centre is a dynamic and highly productive team. This is no accident, as it is consciously built on a strong foundation of mutual respect and open communication. Starting with a blank slate, this was built up with small but high quality RCTs, database analyses and branched out into health economic explorations of PROMs.

Two articles written by our research group featured in the top 5 most cited articles of Regional Anesthesia and Pain Medicine (RAPM) in 2021, which is one of anaesthesia's first quartile and highest impact journals (https://rapmsite-d625817.vercel.bmj.com/pages/top-cited-articles). Speaking invitations and the keen interest shown in this research have been welcome returns. As it is linked to a very real and teach-able technique, which can be demonstrated to a trainee or attending anaesthetist in an hour; the PENG block technique has been taught to hundreds of anaesthetists and pain specialists throughout Australia, Canada, the Netherlands, Afghanistan, and New Zealand. With teaching engagements now fully booked until the start of 2025, this reflects the popularity of the PENG block and the impact the articles detailed in this PhD have made.

Based on the evidence presented in this thesis, the following conclusions can be drawn as answers to the questions postulated at the start of this summary:

1. **Is the novel PENG block an effective regional analgesia technique for hip fractures?**

In the short term, it is likely superior to the older nerve block analgesia techniques. It is more effective in reducing pain scores as well as being motor sparing. That it does not convey a long term benefit is fitting with the duration of the nerve block analgesia and not totally unexpected. Patients in the geriatric age category often have very low opiate requirements which would be a possible explanation for why we could not show a difference in opioid usage.

2. **What can we as anaesthetists do to improve outcomes in hip fracture care?**

It is likely that the basis of the anaesthetic technique (general or spinal) does not impact mortality. Just one of the two should be sufficient for surgical anaesthesia, and given the lack of reserve in this geriatric population the choice for which technique to perform primarily should be carefully considered by the treating anaesthetist. We can involve our emergency department colleagues actively in hip fracture care and perhaps aim to have a hip fracture pathway which includes regional nerve blocks in both the emergency department as well as the operating theatre.

3. **Is the novel PENG block an effective regional analgesia technique for hip arthroplasty?**

Once again, in the short term yes. The motor sparing effect of the PENG block is likely to facilitate earlier physiotherapy and discharge once the postoperative systems in place for hip arthroplasty care are also adjusted to fit an accelerated timeline.

4. **What can we as anaesthetists do to improve outcomes in lower limb arthroplasty?**

We can be actively involved in the evaluation of surgical results utilising validated outcome measures such as the EQ-5D-5L, and be mindful of the trend towards earlier discharge for these patients. They are inherently different to hip fracture patients, where the focus is more on optimisation of results rather than minimisation of mortality. Consideration of the larger picture is vital, whether it be on the individual level to facilitate better recovery outcomes or on a global scale to do what is possible to minimise harm in the context of opioid abuse or dependence.

Future Directions

The PENG block remains a relatively new regional anaesthesia technique, and future research directed at investigating its efficacy further is the next logical step. The studies included in this thesis stopped short of showing longer term benefit to the PENG block or a difference in opioid requirements. Perhaps a larger multicentre RCT with a factorial pragmatic design could perhaps add power as well as further external validation. The aspects of analgesia which fall into the secondary outcome category such as patient satisfaction, time to discharge and use of pain relief medications could be explored more comprehensively in a larger study.

We believe that a multidisciplinary approach to care for hip fractures as well as hip arthroplasty is vital and future research should focus on this. Consideration of the individual patient as well as consideration of their recovery as a whole should be optimised. We are planning further studies evaluating this, utilising supervised machine learning as well as traditional statistics.

Chapter 5 provided a promising glimpse into the potential of minimising opioid prescription and improving recovery in the future. This is a critical change in direction that clinical medicine needs to take in the age of the opioid epidemic. Our group has devoted considerable time to presenting these results with the simple message that this is a treatment pathway that exists and is possible. A future direction that would be of great value to us as a community would be to expand this opioid sparse recovery protocol to other forms of surgery and conduct larger studies investigating this.

This PhD established a baseline Minimum Important Difference (MID) for knee arthroplasty patients in Australia, serving as a valuable reference point for future research and patient counselling during the perioperative phase. Future research endeavours should focus on further validating clinically relevant Patient-Reported Outcome Measures (PROMs) and corroborating the baseline Minimum Important Difference (MID) specifically for knee arthroplasty patients in Australia.

These research projects have follow-on studies, which have been allocated as part of three further PhD projects (Drs Brigid Brown, Craig Morrison and Tim Soon Cheok). We are now exploring the field of grants and larger funded studies to further improve the quality of evidence we can bring to the wider medical community. Multicentre and international collaboration with other university hospitals is also being discussed. The research group are attracting a growing number of students and junior doctors, and hope to be able to return the trust they invest in us with appropriate learning opportunities and scope for career advancement. Physicians all remember the frustration and exhaustion associated with being a junior doctor, and the feeling of not making a difference in a large healthcare machine. We hope that by guiding them in meaningful projects that they can be offered some fulfillment and

the idea that there is indeed light at the end of the tunnel, as well as developing a unique skill set that will serve them well in the practice of evidence based medicine.

The Department of Anaesthesia at Flinders Medical Centre is also developing a research fellowship for a senior anaesthetic trainee looking to learn comprehensively about how to conduct research. This is a unique chance for a trainee who has completed all exams and requirements from the college of anaesthetists to then branch out into the field of research, which they may not have had a chance to do up until that time. This is facilitated by protected non-clinical time, teaching and learning opportunities and the expert guidance of the professorial members of this research group. Our research group has been elected to mentor these fellows, who represent a continuous stream of enthusiastic trainees who have chosen to devote time to developing a research interest.

I am also honoured and humbled to be chosen as the next National Scientific Convenor of the Australian Society of Anaesthetists National Scientific Congress, to be held in 2024. The Head Convenor is Brigid Brown, who shall be the next PhD candidate for the orthopaedic anaesthesia group at Flinders Medical Centre. The organisation of a large (1000 attendee) conference at a national level with international keynote speakers, sponsors, workshops, masterclasses, audits and plenaries has been a journey in itself. This would not have been possible without the organisational and critical appraisal skills developed during the course of this PhD trajectory.

The PENG block has also featured in the final fellowship exam of 2023 for anaesthesia, with a dedicated question in two parts. Candidates were asked to describe the innervation of the hip, and then to evaluate a motor sparing regional technique for hip surgery. This reflects the widespread use of PENG blocks, as questions in a fellowship exam must reflect experience reasonable to have been obtained during training, and relevant to function as a consultant following on from obtaining full qualification as an anaesthetist.

The research group has also been awarded the Jackson Rees Prize for 2023 by the Australian Society of Anaesthetists, for a future study on PENG blocks comparing them to intrathecal morphine in anterior hip replacements. This is the largest monetary grant available from our national association and a fiercely competitive grant. As we move away from small in kind studies done on clinical support time, and towards larger funded multicentre randomised controlled trials, this represents a natural progression in a researcher career. Through the judicious use of these and other funds, the level of evidence and size of trials able to be performed will increase.

Feedback from an anonymous reviewer of the awarded Jackson Rees Prize was:

"This research team, spearheaded by Drs. Lin and Brown, are doing several important things that have placed them on the regional anaesthesia research map.

1) They are prolific in publishing in the last few years.

2) They have multiple publications in a specific area: hip surgeries and hip pain.

3) They have pursued clinical research in a world where it is much easier to do data studies and SRMAs.

4) They have the expertise to design, execute, and publish clear, concise research.

5) They have been repeatedly published in very good journals.

… In the world filled with big data and meta-analyses, there will always be a place for randomized clinical research to answer important questions most clearly... I would have no concerns that the grant money would be effectively used to execute and publish this study as described."

The focus on anterior hip replacements alone, and not a mixed group with posterior approaches was also highlighted by the reviewers as an area of need in orthopaedic study.

In terms of concrete future studies, currently there is an exploration of machine learning training and testing of models based on the ANZHFR detailed here in Chapter 3. This shall for a risk stratification model for hip fracture patients based on individual patient characteristics, and the model shall be made freely available for use on the internet.

The validation of further PROMs and patient reported experience measures (PREMs) will continue with the development of a perioperative satisfaction score, as well as a to be validated metric to determine return-to-play readiness in elite sportspeople following orthopaedic surgery, a group that cannot be adequately assessed with everyday scales due to the ceiling effect.

The Acute Pain Service data collected at Flinders Medical Centre is currently being cleaned and missing variables filled in, with an eye to examining this for best practice in terms of anaesthetic techniques for health economics and patient outcomes in our specific population.

The facilitation of good pain relief for hip surgery on a larger scale is an important outcome, and by teaching the PENG block to a variety of communities on an international scale we hope to facilitate this. Notably, the PENG block has been taught in Darwin to aid in analgesia for rural and First Nations communities, as well as in Afghanistan where medications and medical supplies are limited.

The field of health care and its clinical delivery continues to evolve, with the evolution of artificial intelligence and the trend towards individualised risk assessment and safer and more comfortable perioperative journeys. The focus on day-case arthroplasty is growing, with this already being carried out in North America. It is easy to see how an effective form of analgesia which still allows a patient to mobilise could be useful here. Surgical techniques also advance, with the less invasive direct anterior approach to total hip replacements likely to be further

developed. Perhaps at some point this operation shall be so painless that no analgesia is required, but this is not yet the case for the vast majority of patients. The evaluation of patient outcomes utilising validated tools is crucial at this juncture to ensure we are not moving too quickly, and that patients remain safe and well cared for.

In conclusion, the synthesis of this thesis is that there is much still to improve in patient outcomes concerning orthopaedic surgery of the lower limb. The studies detailed in this manuscript illustrate where clinical practice is heading- better analgesia, opiate sparse surgical recovery and validation of evaluation methods utilised in medical studies. We are grateful for the support afforded us to be able to have conducted these studies and been able to educate other clinicians to translate these results into real-world medicine. The publications contained within this thesis perhaps go some way to furthering our knowledge towards more effective care of these patients at a time in their lives when they are especially vulnerable.

Abbreviations

PENG: Pericapsular nerve group block
OHS: Oxford Hip Score
RCT: randomised control trial
GLM: generalised linear regression model
ES: effect size
SRM: standard response mean
DAA: direct anterior approach
THA: total hip arthroplasty
PA: posterior approach
PROMs: patient-related outcome measures
PREMs: patient-related experience measures

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Curriculum vitae

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Training and Qualifications

2018	Fellow of the Australian and New Zealand College of Anaesthetists (FANZCA), Australia
2010 - 2016	Anaesthetic training, Erasmus Medical Centre, Rotterdam. Sub-specialism in cardiothoracic and regional anaesthesia
2000 - 2005	Bachelor of Medicine and Bachelor of Surgery (MBBS), Adelaide Medical School, University of Adelaide, Australia

Employment

2018 – current	Consultant cardiac anaesthetist, Flinders Medical Centre, Adelaide, Australia
2017 - 2018	Fellow orthopaedic and vascular anaesthesia, Flinders Medical Centre, Adelaide, Australia

Committees

-2023 – current: Research Fellow Supervisor for the Department of Anaesthesia, Flinders Medical Centre
-2023 – current: Intensive Care Clinical Lead Liaison for the Department of Anaesthesia, Flinders Medical Centre
-2023 – current: Senior Lecturer, Flinders University, Adelaide, Australia
-2021- current: Clinicians Special Purpose Fund Executive Committee, Southern Adelaide Local Health Network
-2021- 2022: Blood Transfusion Committee, Southern Adelaide Local Health Network
-2019 - 2023 Medical Ethics Committee, Southern Adelaide Local Health Network, Adelaide, Australia
-2018 – 2022: Clinical Lecturer, Flinders University, Adelaide, Australia

Prizes and Qualifications

-2023: Jackson Rees Grant (27,000 AUD) from the Australian Society of Anaesthetists
-2023: Graduate Certificate in Clinical Ultrasound, University of Melbourne
-2024: Diploma of Perioperative Medicine, Australian and New Zealand College of Anaesthetists (projected)

Publications

1. Kroon HM, Lin DY, Kam PC, Thompson JF. Safety and efficacy of isolated limb infusion with cytotoxic drugs in elderly patients with advanced locoregional melanoma. Ann Surg 2009;246:1008-13.
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10. Lin DY, Morrison C, Brown B, Saies A, Pawar R, Vermeulen M, Anderson SR, Lee TS, Doornberg J, Kroon H, Jaarsma R. In reply to: 'towards precision regional anesthesia: is the PENG block appropriate for all hip fracture surgeries?'. Reg Anesth Pain Med 2021;22:rapm-2021-102926.
11. Lin DY, Brown B, Morrison C, Saies A, Pawar R, Vermeulen M, Anderson SR, Lee TS, Doornberg J, Kroon H, Jaarsma R. In reply to: A letter to the recent publication: Pericapsular nerve group (PENG) block provides improved short-term analgesia compared with the femoral nerve block in hip fracture surgery: a single-center double-blinded randomized comparative trial. Reg Anesth Pain Med 2021;8:rapm-2021-103002.
12. Brown B, Lin DY, Morrison C, Jaarsma R. Letter to the editor in response to the recent publication: randomized comparison between pericapsular nerve group (PENG) block and suprainguinal fascia iliaca block for total hip arthroplasty. Reg Anesth Pain Med. 2021 Aug 27:rapm-2021-103080. doi: 10.1136/rapm-2021-103080.
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14. Lin DY. Erector Spinae Blocks, Keynote speaker, ANZCA Anaesthesia Continuing Education Meeting, March 2020, Adelaide, Australia
15. Lin DY. Novel fascial blocks of the lower limb, Keynote speaker, ANZCA Anaesthesia Continuing Education Meeting, March 2021, Adelaide, Australia

16. Lin DY, Brown B, Morrison C, Pawar R, Saies A, Vermeulen M, Lee TS, Anderson SR, Doornberg J, Kroon HM, Jaarsma R. The pericapsular nerve group (PENG) block provides improved analgesia compared to the femoral nerve block in hip fracture surgery: A secondary analysis of a randomized controlled trial. Australian and New Zealand College of Anaesthetists Annual Scientific Meeting, April 2021, Melbourne, Australia
17. Lin DY, Brown B, Morrison C, Pawar R, Saies A, Vermeulen M, Lee TS, Anderson SR, Doornberg J, Kroon HM, Jaarsma R. The pericapsular nerve group (PENG) block provides improved short-term analgesia compared to the femoral nerve block in hip fracture surgery: A single-centre double-blinded randomized comparative trial. 46th Annual Regional Anesthesiology and Acute Pain Medicine Meeting, May 2021, Disney Resort, Lake Buena Vista, FL, USA
18. Brown B, Lin DY, Morrison C, Pawar R, Saies A, Vermeulen M, Lee TS, Anderson SR, Doornberg J, Kroon HM, Jaarsma R. The pericapsular nerve group (PENG) block vs. femoral nerve block. Which is better in NOF surgery? Canadian Orthopaedic Association Annual Meeting, June 2021, invited tele-oral, Canada.
19. Morrison C, Brown B, Lin DY, Pawar R, Saies A, Vermeulen M, Lee TS, Anderson SR, Doornberg J, Kroon HM, Jaarsma R. The pericapsular nerve group (PENG) block provides improved analgesia compared to the femoral nerve block in neck of femur surgery. Orthopedic Research Society Annual Meeting, February 2021, Rosemont, IL, USA
20. The Pericapsular Nerve Group (PENG) Block Combined with Local Infiltration Analgesia (LIA) Provides Improved Short-Term Analgesia Without Loss of Motor Function Compared to Placebo and LIA in Hip Arthroplasty Surgery: A Multi-Center Double-Blinded Randomized-Controlled Trial. Shortlisted Gilbert Brown Prize, selection 2 May. Anaesthesia and Intensive Care publication of abstract attached to prize. Oral presentation. Brigid Brown, D-Yin Lin, Matthew Cehic, Craig Morrison, Nikolai Fraser, Cheryl Chooi, Michael Henningsen, Nikolina Sladojevic, David McLeod, Hidde Kroon, Ruurd Jaarsma
21. The Pericapsular Nerve Group (PENG) Block Combined with Local Infiltration Analgesia (LIA) Provides Improved Short-Term Analgesia Without Loss of Motor Function Compared to Placebo and LIA in Hip Arthroplasty Surgery: A Multi-Center Double-Blinded Randomized-Controlled Trial. Australian Orthopaedic Association SA State Meeting. Matthew Cehic, D-Yin Lin, Brigid Brown, Craig Morrison, Nikolai Fraser, Cheryl Chooi, Michael Henningsen, Nikolina Sladojevic, David McLeod, Hidde Kroon, Ruurd Jaarsma
22. The Pericapsular Nerve Group (PENG) Block Combined With Local Infiltration Analgesia (LIA) Provides Superior Short-Term Analgesia Compared to Non-Invasive Sham and LIA in Hip Arthroplasty Surgery. International Society for Technology in Arthroplasty, Maui Hawaii, August 2022. Chris Wilson, Matthew Cehic, Ruurd Jaarsma, Emma Jackman, D-Yin Lin, Brigid Brown, Hidde Kroon
23. Anesthetic and Analgesic Risk-Factors for Twelve-Month Mortality after Hip Fracture Surgery: A Population Analysis of the Australian and New Zealand Hip Fracture Registry. ANZCA Annual Scientific Meeting, (virtual) Perth, Australia April 2022, e-Poster. D-Yin Lin, Brigid Brown, Matthew Cehic, Craig Morrison, Nikolai Fraser, Cheryl Chooi, Michael Henningsen, Nikolina Sladojevic, David McLeod, Hidde Kroon, Ruurd Jaarsma
24. Valve Durability Following Surgery for Rheumatic Heart Disease. ANZSCTS Annual Scientific Meeting 2023, Wellington, New Zealand. Rohen Skiba, Jayme Bennetts, D-Yin Lin, Tim Soon Cheok, Robert Baker

The medical literature tells us that the most effective ways to reduce the risk of heart disease, cancer, stroke, diabetes, Alzheimer's, and many more problems are through healthy diet and exercise. Our bodies have evolved to move, yet we now use the energy in oil instead of muscles to do our work.
David Suzuki

Illness is the doctor to whom we pay most heed; to kindness, to knowledge, we make promise only; pain we obey.
Marcel Proust

The illiterate of the 21st century will not be those who cannot read and write, but those who cannot learn, unlearn, and relearn.
Alvin Toffler

You miss 100 percent of the shots you never take.
Wayne Gretzky

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.
William Osler

Enlightenment is the space between your thoughts
Eckhart Tolle

I'm not feeling very well - I need a doctor immediately. Ring the nearest golf course.
Groucho Marx

As to diseases, make a habit of two things — to help, or at least, to do no harm.
Hippocrates