Hemiplegic Shoulder Pain

Studies of Epidemiology, Assessment and Management

By

Dr Zoe Adey-Wakeling

FAFRM (RACP), BMBS, BAppSc (Physiotherapy)

Department of Rehabilitation and Aged Care

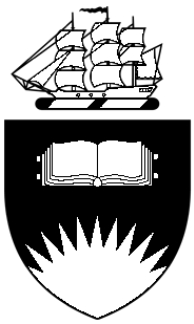
Faculty of Health Sciences, Flinders University

A thesis submitted for the degree of

Doctor of Philosophy

at

Flinders University



Submitted January 2016

Table of Contents

Summary

Rehabilitation focuses on maximising an individual's independence following disease or disability. With increasing survival following stroke, there is a growing rehabilitation population of patients with stroke-related disability. Whilst increasing attention has been directed towards motor deficits such as upper limb weakness following stroke, the common complications of such deficits such as shoulder pain are often overlooked.

Hemiplegic shoulder pain is a common complication of stroke, and the focus of this thesis. This thesis explores the current literature pertaining to this topic: its context within the broader upper limb deficits post stroke **(Publication 1)**, its definition, aetiology and evidence for prophylaxis and treatment. Building on this background, original research using data from a population based stroke incidence study then provides information on the local epidemiology, and the typical characteristics of shoulder pain presentation **(Publication 2)**. A greater understanding of typical presentations provides the clinician with context and understanding on which to build strategies for assessment and treatment.

Randomised controlled data provides insight into suprascapular nerve block as an evidence-based treatment option. The protocol paper **(Publication 3)** outlines the rationale for investigating this intervention, with the randomised controlled trial providing evidence on efficacy and effectiveness **(Publication 4)**. Post-hoc analysis **(Publication 5)** provides information on selecting patients who are likely to respond to this intervention. This pragmatic trial provides information which is highly relevant to patients under the care of all Australian rehabilitation units but the findings are generalizable to all patients with hemiplegic shoulder pain following stroke.

Whilst the experience of stroke and pain after stroke have previously been shown to impact on quality of life, the specific impact of hemiplegic shoulder pain has not been demonstrated. Using data from the population study on stroke the impact of hemiplegic shoulder pain occurring at any time during the first year after stroke on health-related quality of life is demonstrated **(Publication 6)**.

The findings of this thesis suggest that a new approach to the assessment and management of shoulder pain after stroke could be considered and tested. A possible protocol is suggested for future evaluation. The gap between research and implementation in clinical practice is well known and a review of possible barriers and facilitators to knowledge translation is discussed.

Hemiplegic shoulder pain after stroke affects more than one in four stroke survivors. Greater understanding of this common complication of stroke will enhance the clinical focus on appropriate evidence-based management options.

Publications arising from this research

Publications in Peer-Reviewed Journals

Adey-Wakeling Z, Crotty M. Upper Limb rehabilitation following stroke: current evidence and future perspectives. *Aging Health* 2013; 9(6):629-648

Allen ZA, Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83-88

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial.
Stroke 2013; 44: 3136-3141

Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal of Physical Medicine and Rehabilitation* 2015; 1(2):009

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study
American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending

Oral Presentations

Adey-Wakeling. Final PhD Seminar – Hemiplegic Shoulder Pain: Studies of Epidemiology, Assessment and Management. *Repatriation General Hospital*. October 20, 2015

Adey-Wakeling, Z. et al. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: A prospective population based study. *Australasian Faculty of Rehabilitation Medicine Annual Scientific Meeting*, held from 9-12 September 2014 in Adelaide, Australia

Adey-Wakeling, Z. Flinders Medical Centre Grand Round. Clinician's Special Purpose Prize Presentation. 6 March 2014

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular nerve block for shoulder pain in the first year after stroke. *Australasian Faculty of Rehabilitation Medicine Annual Scientific Meeting*, held from 17-20 September 2013 in Sydney, Australia.

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular nerve block for shoulder pain in the first year after stroke. *24st Annual Scientific Meeting of Stroke Society of Australia*, held from 31 July-2 August 2013 in Darwin, Australia.

Poster Presentations

Adey-Wakeling Z, Arima H, Crotty M and the SEARCH Investigators. Prevalence, Correlations and Prediction of Hemiplegic Shoulder Pain: A Prospective Population Based Study in South Australia. *International Stroke Conference*, held from 6-8 February 2013 in Hawaii, USA.

Adey-Wakeling Z, Arima H, Crotty M and the SEARCH Investigators. Prevalence, Correlations and Prediction of Hemiplegic Shoulder Pain: A Prospective Population Based Study in South Australia. *Rehabilitation Research Forum,* held March 2013 in Adelaide, SA

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular nerve block for shoulder pain in the first year after stroke: a randomised controlled trial ACR, Oct 2013 in San Diego, USA.

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

I am the primary author on all published manuscripts included in this thesis. The contribution to each analysis of the statisticians and my co-authors is stated at the beginning of each chapter.

Chapters 4 and 6 use data from an NHMRC funded population study on stroke (Project Grant 565402). One of my supervisors (MC) was a chief investigator on that project and I was allowed to select and include questions on shoulder pain during the design phase. In addition to selecting the questions on shoulder pain to be used I assisted in the data collection phase of the study with those patients who came to Flinders Medical Centre. I also trained the nurses who undertook the data collection to perform the shoulder assessments which are included in the study.

Please note that I have changed my surname through marriage, and as a result there are two names by which I have been published (Allen ZA, and Adey-Wakeling Z).

Zoe Adey-Wakeling

8 February 2016

Acknowledgements

This thesis represents a culmination of the generosity and efforts of the many trial participants and their treating teams across the participating stroke centres. The eagerness of volunteer participants to help future patients in similar situations is truly worthy of thanks.

I have been lucky to have two supervisors that have provided both expertise and mentorship throughout my candidature. Thanks go to Professor Maria Crotty and Associate Professor Michael Shanahan who have encouraged, prodded and inspired me along this journey.

Acknowledgment must also go to the Department of Rehabilitation and Aged Care, particularly the Research team, and the Rehabilitation wards. Special thanks go to Maayken Van Den Burg, Kelly Pinkney, Dasha Loutchkina, and Enwu Liu. I would like to also thank Foundation Daw Park for the initial grant which assisted in the completion of the randomised controlled trial. Thanks also to the NHMRC SEARCH investigators (and in particular the current Chief Investigator Jonathon Newbury) for allowing me input and access to the population-based data set. I owe a particular debt to Konrad Jamrozik (the original Chief Investigator, now deceased) who gave permission for me to have questions on shoulder and assessments inserted into the panel during the design phase.

Finally, to my family – thank you for encouraging me along this path. For providing the coffees, the gins and the hugs along the way! Special thanks to Tim, Archie, Daniel, Kym and Sandy.

Dedication

To those few who truly know, believe in, and sustain my ‘inner horse’

Michael Leunig

List of Tables

List of Figures

List of Appendices

List of Abbreviations

HSP	Hemiplegic Shoulder Pain
SSNB	Suprascapular Nerve Block
ICF	International Classification of Functioning, Disability and Health
EBRSR	Evidence-Based Review of Stroke Rehabilitation
PREP	Prediction of Recovery Potential
SULCS	Stroke Upper Limb Capacity Scale
NSF	National Stroke Foundation
PET	Positron Emission Tomography
fMRI	Functional Magnetic Resonance Imaging
BATRAC	Bimanual Arm Training with Rhythmic Auditory Cuing
CIMT	Constraint Induced Movement Therapy
mCIMT	Modified Constraint Induced Movement Therapy
TENS	Transcutaneous Electrical Nerve Stimulation
NMES	Neuromuscular Electrical Stimulation
FES	Functional Electrical Stimulation
NICE	National Institute of Healthcare and Excellence
rTMS	Repetitive Transcranial Magnetic Stimulation
tDCS	Transcranial Direct Current Stimulation
GPP	Good Practice Point
CNS	Central Nervous System
BoNT-A	Botulinum Toxin A
CRPS	Chronic Regional Pain Syndrome
CPSP	Central Post Stroke Pain
PSSP	Post Stroke Shoulder Pain

MMT	Manual Muscle Testing
VAS	Visual Analogue Scale
CI	Confidence Interval
LACS	Lacunar Syndrome
TACS	Total Anterior Circulation Syndrome
PACS	Partial Anterior Circulation Syndrome
POCS	Posterior Circulation Syndrome
NIHSS	National Institute of Health Stroke Scale
IQR	Inter-Quartile Range
OR	Odds Ratio
MMSE	Minimental Status Examination
mRS	Modified Rankin Scale
EQ	EuroQol
EQindex	EuroQol Utility Score
HR-QoL	Health-Related Quality of Life
QoL	Quality of Life
SD	Standard Deviation
MAS	Modified Ashworth Scale
GDS	Geriatric Depression Scale
ICP	Integrated Care Pathway
NH&MRC	National Health and Medical Research Council

Chapter One

Thesis Introduction and Rationale

1.1 Definitions used in this thesis:

Stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin"[1].

Rehabilitation is defined by The World Health Organisation[2] as "a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments". Stroke rehabilitation is "a progressive, dynamic, goal orientated process aimed at enabling a person with an impairment to reach their optimal physical, cognitive, emotional, communicative and / or social functional level"[3].

Definitions of Pain

The International Association for the Study of Pain[4] defines **pain** as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Multiple classifications of pain are encountered when reviewing the literature pertaining to pain following stroke. The author's accepted definition of hemiplegic shoulder pain (HSP), as outlined in the introduction, encompasses the following definitions, as HSP is widely accepted as having contributions from several aetiologies.

Nociceptive	Pain associated with actual or threatened tissue injury or damage
Neuropathic pain	Pain associated with injury or disease of nerve tissue
Acute pain	A self-limited pain caused by a specific disease / injury

Chronic pain Can be considered a disease state, in that it exists beyond the expected healing time from the causative factor(s)

Post stroke shoulder pain (PSSP) is an overarching term that includes both hemiplegic shoulder pain (HSP) and **chronic post stroke pain (CPSP).** CPSP may also be referred to **thalamic pain,** though central nervous system somatosensory pathways may not always involve the thalamus[5]. Hemiplegic shoulder pain and chronic post stroke pain may occur in combination, with HSP as a result of CPSP[6], or separately[5].

Hemiplegic shoulder pain, pain experienced in the contralesional upper limb, which is considered more complicated than simple nociceptive pain. Di Lorenzo and Domenico[7] define HSP as "pain perceived in the shoulder and arm after stroke, with a source that does not lie always in the shoulder muscles or joint".

1.2 Context of Thesis

Background

Hemiplegic shoulder pain is an important cause of suffering amongst stroke survivors. Despite this it is often approached by clinicians with a sense of therapeutic nihilism. The high prevalence and significant impact of this condition is poorly balanced with a lack of evidence-based management options to guide the clinician. This thesis aims to grow the body of knowledge in order to inform understanding, assessment and management of this condition for future patients.

The National Stroke Foundation estimates that there will be 50,000 new or recurrent strokes in Australia this calendar year[8]. Stroke is a leading cause of disability, with current national estimates of approximately 440,000 Australians living with disability secondary to stroke, and survival rates continually increasing[8]. Increasing survival with higher rates of disability requires focussed rehabilitation to optimise outcomes. Limb hemiparesis is the most prevalent impairment following stroke[9], with stroke survivors reporting upper limb hemiparesis as their most common problem[10]. Up to 80% of survivors have upper limb problems in the immediate post-stroke period[11] with studies reporting significant rates of persisting impairment ranging from 30%[11] up to as high as 75%[12]. Recovery of upper limb dexterity and function is reported in the range of 30%[13] with as few as 5-20% achieving full functional recovery[14]. Upper limb motor deficits are a standard therapy focus, but increased attention needs to be given to the assessment, prevention and treatment of potential complications of hemiparesis, such as swelling and pain

Epidemiology: Incidence and Impact of Hemiplegic Shoulder Pain

Hemiplegic shoulder pain has been described as one of the four most common medical complications following stroke[15], with others including depression, falls and urinary tract infections[1]. It is estimated that approximately 25% of individuals experience hemiplegic shoulder pain following a stroke[16], though earlier studies reported frequencies as high at 65-70%[17-19]. Australian statistics regarding epidemiology of hemiplegic shoulder pain are lacking, and there have been no previous Australian population studies investigating the incidence or associations of HSP following stroke.

Understanding HSP in an Australian context would assist in targeting clinical treatments for the condition. Hemiplegic shoulder pain has been shown to increase length of stay, interfere with the rehabilitation process[20, 21], and is associated with higher rates of depression [22] and a worse global outcome [23]. A recent systematic review[24] reported that post-stroke upper limb interventions can impact on health-related quality of life, but information specifically regarding the quantitative impact of hemiplegic shoulder pain in an unselected population sample is lacking. NEMESIS,[25] a large Australian population-based study, reported on variables associated with health-related quality of life following stroke. This study provides a valuable Australian comparison, but does not investigate HSP as an independent variable. With an incidence of approximately 25%,[26] it is hypothesised that HSP would adversely impact on health-related quality of life (HR-QoL).

Endorsed by the World Health Organisation in 2001, the International Classification of Functioning, Disability and Health (ICF) provides an international standard by which to describe and measure health and disability[27] (Figure 1). The ICF model is important in rehabilitation as it recognises the dynamic interactions between an individual's health condition, environment and personal factors. A

paper assessing correlations between upper limb function and the ICF model found shoulder pain to be the variable most associated with limitations in participation[28, 29]. The NEMESIS trial[25] highlights the concept that interventions focussing on participation can conceivably improve HRQoL, irrespective of impairment and activity contributors.

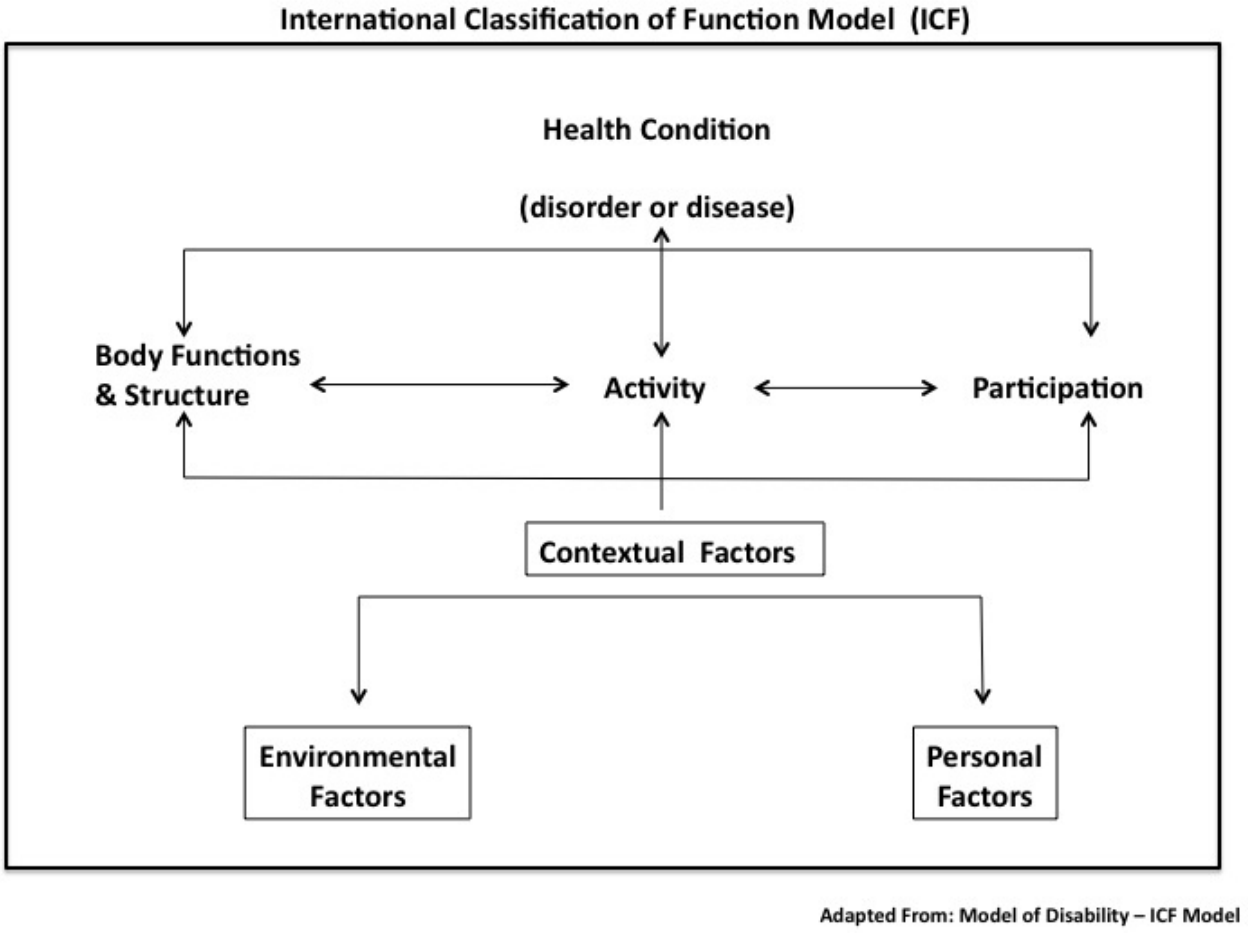


Figure 1. International Classification of Functioning, Disability and Health (ICF) Model

Aetiology of Hemiplegic Shoulder Pain

There are multiple aetiologies for hemiplegic shoulder pain[30], which may present in isolation or in combination. The three major aetiological categories outlined by Kalichman (2011) are soft tissue injuries, changes in motor control, and central nervous system alterations[31]. Initial loss of motor tone can contribute to instability and subluxation, which in turn can lead to soft tissue or nerve injury[31], though there is conflicting evidence regarding the role of subluxation in the development of hemiplegic shoulder pain[32]. Note is made of the dependence on musculotendinous integrity to provide stability of the shoulder complex. The most common non-central, musculoskeletal aetiologies of hemiplegic shoulder pain include adhesive capsulitis, subluxation and rotator cuff pathologies, with up to one-third of patients having multiple contributing factors[30]. Biomechanical changes result from a combination of paralysis, fluctuation in muscle tone and prolonged shoulder immobility which lead to postural malalignment[33]. Not all shoulder pain is associated with the complications of limb flaccidity, and some pain may be attributable to spasticity or central-pain. **Chapter 3.1.2** explores in detail the clinical considerations in assessment and diagnosis of the complex interplay of aetiologies of HSP, as required to optimise patient outcomes.

Treatment of Hemiplegic Shoulder Pain

The aetiological complexity is a challenge for the practicing clinician. Currently there is a deficiency in evidence based treatment options for hemiplegic shoulder pain[34]. This area is a priority for research as up to 20-30% of patients experience pain which is refractory to current treatment modalities[35].

The paucity of high-grade evidence for treatment options is reflected in current national and some international guidelines, which do not cite any evidence-based therapeutic options specific to a stroke population[36, 37]. In an overview of the challenges of managing shoulder pain after stroke[38], Price and Rodgers (1999)[38] conclude that the evidence on treatments does not allow the development of clinical guidelines and further efforts are required to examine intervention options. Management can be considered as either prophylaxis to avoid developing pain, or treatment of established hemiplegic shoulder pain (both allied health and medical interventions to be considered and **detailed in Chapter 3.1.4**).

Prophylaxis includes good practice recommendations of positioning and safe manual handling techniques, though there is no clear evidence base supporting these guidelines[39]. Older research outlines careful handling, electrical stimulation, movement with elevation, strapping and avoidance of overhead pulleys as potentially effective interventions to reduce or prevent hemiplegic shoulder pain[40].

Conflicting evidence complicates selection of treatment options for established hemiplegic shoulder pain. There is limited but growing evidence for intra-muscular Botulinum Toxin A for shoulder pain associated with spasticity as outlined by 2010 Cochrane review[41]. Of note, there are promising pilot studies exploring intra-articular use of Botulinum for shoulder pain not necessarily associated with spasticity aetiology[42]. The routine use of intra-articular corticosteroids is not recommended for hemiplegic shoulder pain[34], with evidence supporting use only in selected cases with clear musculoskeletal aetiology[43]. A 2001 Cochrane review found inconclusive evidence regarding electrical stimulation, though a systematic review and meta-analysis completed since this time demonstrated long term benefits of intramuscular electrical stimulation[34].

The suprascapular nerve supplies 70% of the pain sensation[44] to the shoulder complex and blockade of this nerve potentially offers a useful treatment option for pain of multiple aetiologies. The nerve block involves local injection of long acting local anaesthetic and corticosteroid to bathe the suprascapular nerve with the goal of blocking its sensory pathways. Suprascapular nerve block has been demonstrated to be a safe[45] and efficacious intervention for shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions[46-48], with anecdotal report of successful use of suprascapular nerve block in treating intractable hemiplegic shoulder pain[33]. **Chapter 3.2 explores in detail the evidence base** for use of suprascapular nerve block in both non-stroke and stroke populations. Due to the emerging nature of this procedure in stroke populations, published systematic reviews on management of shoulder pain following stroke have not included information on the use of suprascapular nerve block (SSNB). Therefore, this thesis examines the possibility that SSNB may be an efficacious treatment in the management of hemiplegic shoulder pain.

Evidence Gap

Australian data on the epidemiological perspectives of hemiplegic shoulder pain is lacking. Local population based data will provide increased evidence regarding the importance and behaviour of this common presentation, which in turn will provide the clinician with context and understanding on which to build strategies for assessment and treatment.

Treatment options have historically been based on the musculoskeletal components of HSP aetiology. Increasing understanding of the interplay between multiple aetiological contributors warrants investigation into treatment modalities with broader applications. No previous randomised controlled studies have investigated the role of the suprascapular nerve block in stroke population.

Robust research is required to assist in building a population-specific evidence base to assist in clinical management.

The demonstrated gap between research and implementation in practice is well known. This thesis aims to provide clinical context, a patient-centred focus, and an evidence-based treatment option that is easily reproducible, cost effective and efficacious in a ward or clinic setting. Greater understanding of this common complication of stroke will enhance the clinical focus on appropriate evidence-based management options and inform quality improvement in this field. Recommendations from the research provided in this thesis offer a framework for improved patient, clinician and training expectations.

Table 1. Context of Thesis: Evidence Gap

<table>
<tr><td>Current Evidence</td><td>Wide range of incidence of HSP reported (25-75%)
Population based data from overseas (Sweden, New Zealand) report more conservative incidence of approximately 25%</td><td>Significant impact of HSP on the individual

Research identifies pain as a contributor to reduced quality of life following stroke</td><td>Limited evidence-base to guide the clinician in treatment of HSP
Suprascapular nerve supplies 70% of pain fibres to shoulder SSNB safe and efficacious in non-stroke populations</td></tr>
<tr><td>Evidence Gap</td><td>No Australian population-based studies investigating hemiplegic shoulder pain incidence or associations</td><td>No population-based data (Australian or international) investigating the specific impact of hemiplegic shoulder pain on quality of life</td><td>No randomised controlled studies investigating the role of SSNB in a stroke population</td></tr>
<tr><td rowspan="2">Thesis Objectives</td><td>Objective I:
Describe hemiplegic shoulder pain within the broader context of upper limb dysfunction following stroke

Objective II:
To characterise the epidemiology, aetiology and clinical approaches to hemiplegic shoulder pain via a review of the literature

Objective IV:
To report the epidemiological patterns of hemiplegic shoulder pain incidence and associations within an Australian population</td><td>Objective VI:
To investigate the impact of hemiplegic shoulder pain on health-related quality of life</td><td>Objective III
To determine the current evidence for the use of suprascapular nerve block, including anatomy and description of the procedure, and summarise research in both non-stroke and stroke populations

Objective V:
To investigate SSNB as a treatment option for hemiplegic shoulder pain compared to placebo; and to characterise patient subtypes more likely to have a positive response to this treatment; Characterise the patient subtypes most likely to have positive response to this treatment</td></tr>
<tr><td colspan="3">Objective VII:
To synthesise the research findings into clinical recommendations</td></tr>
</table>

1.3 Research Objectives

The objectives of this thesis are to address the knowledge gaps as outlined above, and are identified as the following:

I. To describe hemiplegic shoulder pain within the broader context of upper limb dysfunction following stroke

II. To characterise the epidemiology, aetiology and clinical approaches to hemiplegic shoulder pain via a review of the literature

III. To determine the current evidence for the use of suprascapular nerve block, including anatomy and description of the procedure, and to summarise the search in both non-stroke and stroke populations

IV. To report the epidemiological patterns of hemiplegic shoulder pain incidence and associations within an Australian stroke population

V. To investigate suprascapular nerve block as a treatment option for hemiplegic shoulder pain compared to placebo; and to characterise patient subtypes more likely to have a positive response to this treatment

VI. To investigate the impact of hemiplegic shoulder pain on health-related quality of life

VII. To synthesise the research findings into clinical recommendations

Chapter Two

Overview - The Impact of Stroke on the Upper Limb

2.1 Introduction To Publication

Publication 1: Adey-Wakeling Z, Crotty M. Upper Limb rehabilitation following stroke: current evidence and future perspectives. *Aging Health* 2013; 9(6): 629-648

Purpose

The purpose of this review article is to provide an overview of shoulder pain within the clinical context of upper limb dysfunction following stroke. Hemiplegic shoulder pain is a recognised complication of upper limb hemiplegia and sits within the paradigm of upper limb deficits that was neglected for many years.

Many aspects of upper limb dysfunction have attracted recent research. This publication summarises the evidence regarding the impact of stroke on the upper limb and the treatments available to manage the subsequent complications.

Published in

Aging Health – A Future Medicine Journal

Impact Factor 1.477

5 year Impact Factor 2.102

Contribution from primary author

Primary Author – Dr Zoe Adey-Wakeling (ZAW)

ZAW conceptualised the manuscript, completed the literature review in its entirety, and was responsible for the majority of the writing. Supervision and review were provided by co-author Professor M Crotty.

2.2 Publication 1

Adey-Wakeling Z, Crotty M. Upper Limb rehabilitation following stroke: current evidence and future perspectives. *Aging Health* 2013; 9(6):629-648

Upper Limb rehabilitation following stroke: current evidence and future perspectives.

Keywords

stroke; rehabilitation; upper limb; therapy; future; implementation

Abstract / Summary

Stroke is a leading cause of disability worldwide, with risk increasing with age. Upper limb hemiparesis is common and associated with persistent impairments and associated disabilities. Older stroke populations often suffer multiple co-morbidities and restoring independence is complex. Recovery of upper limb function can be crucial for them to return to independent living and to participate in community life.

This review describes upper limb recovery post stroke, and some of the new therapeutic approaches available to promote recovery. Technologies (including virtual reality and telehealth) offer the opportunity for more home-based therapies, longer programs, and greater access to rehabilitation for older people; however the trials continue to exclude older people so acceptability is poorly understood. Upper limb rehabilitation remains a research frontier which has been energized by new

technologies but which is grounded in the basic need to find ways to allow older people to recover independence. This paper aims to review applicability and generalizability of current research to the older stoke survivor. This is undertaken in the context of the older mean age of persons in stroke rehabilitation, and the need to tailor future research priorities.

Introduction

The World Stroke Organization awareness campaign highlights the global burden of stroke, promoting the statistic that 1 in 6 persons worldwide will suffer a stroke in their lifetime. Whilst stroke can occur at any age, age is a significant risk factor with 75% of strokes occurring in people over the age of 65[49]. National Institute of Health[50] data reflect a doubling of stroke risk for each decade after 55 years of age. With an increasing ageing population, rehabilitation programs need to incorporate evidence that is relevant, acceptable and applicable to an elderly population. Despite this, the majority of published research is not targeted towards the aged patient [51]. This likely reflects selection of trial participants following exclusions of significant comorbidities more prominent in the aged population. Additionally, it is postulated that there might be a trend for younger stroke survivors to have greater familiarity with technology and hence a higher chance of trial consent.

With improved survival and an ageing population, stroke continues to rank as a leading cause of long-term disability[52]. Limb hemiparesis is the most prevalent impairment post stroke[9], with stroke survivors reporting upper limb hemiparesis as their most common problem[10]. Early rehabilitation goals often focus on mobility, as walking is strongly correlated with independence [53]. However up to 80% of survivors have upper limb problems in the immediate post-stroke period[11] with studies reporting significant rates of persisting impairment ranging from 30%[11] up to as high as 75%[12].

Recovery of upper limb dexterity and function is reported in the range of 30%[13] with as few as 5-20% achieving full functional recovery[14].

Many stroke survivors have somatosensory deficits but a large proportion of these may be missed in assessment. A prospective observational study of 70 stroke survivors identified 53% as having impaired tactile sensation, 89% with impaired stereognosis, and 63% with deficits in proprioception[54]. Other foci for intervention include coordination deficits, apraxia and complications of upper extremity involvement. Negative features of upper motor neuron syndrome such as weakness can lead to subluxation whilst positive features such as spasticity can lead to pain and contracture. The multifactorial aetiology of hemiplegic shoulder pain[55]with or without the presence of subluxation[34] has made it resistant to most treatment approaches.

Using the World Health Organization International Classification of Functioning, Disability and Health (ICF) framework the burden of upper limb impairment after a stroke can be seen in terms of its impact on the potential activity and participation domains of a stroke survivor's future life (Figure 1). The lack of autonomy in daily tasks following stroke can influence an individual's self-image, willingness to go out and quality of life. Multiple interventions are often needed to address the shifting nature of problems over an acute, subacute and chronic period. Gains in motor recovery measures do not necessarily translate to equivalent improvements in functional upper limb use so there is a need to focus on both impairment and activity measures to guide intervention options[56].

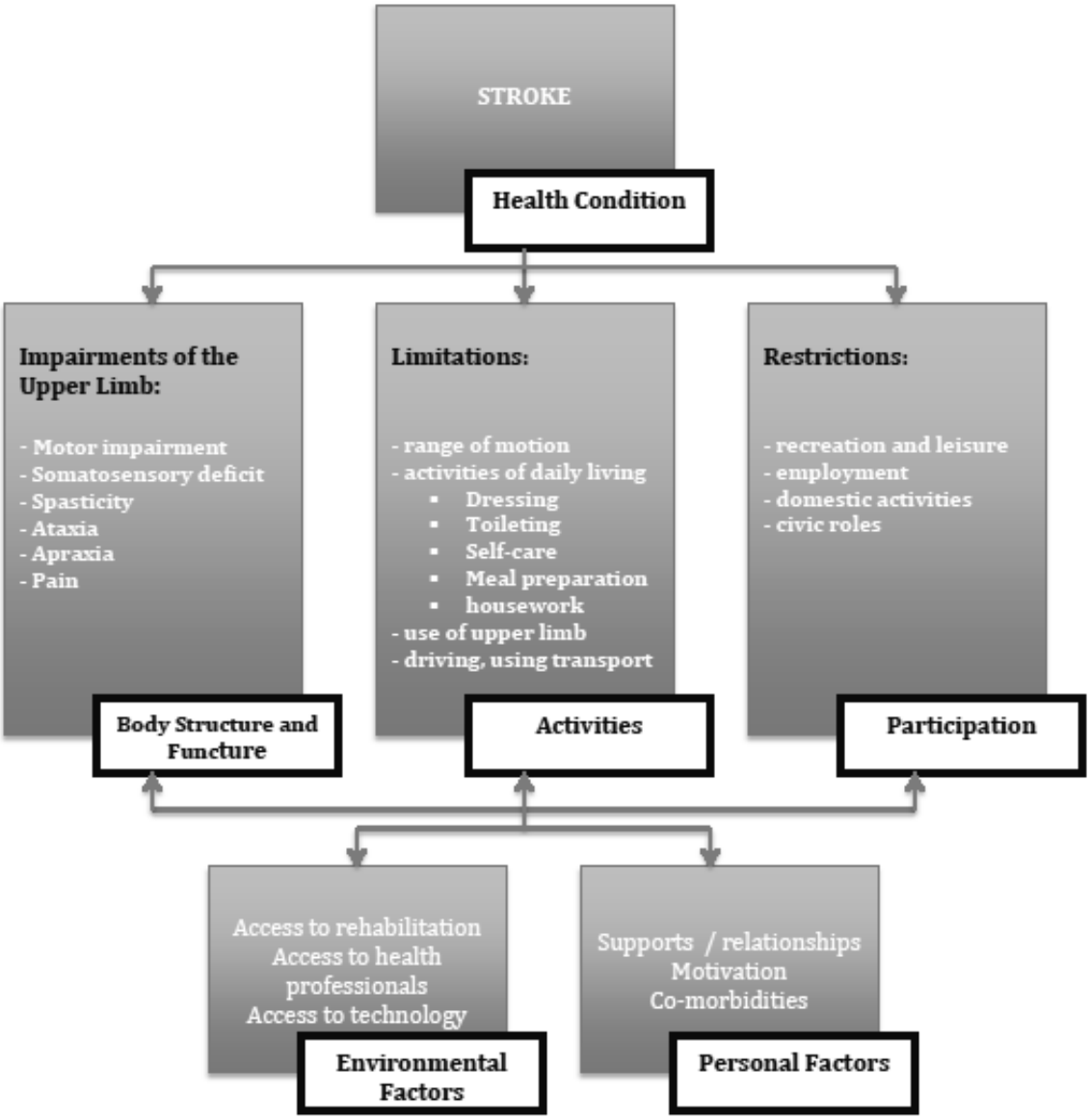


Figure 1. Schematic representation of the World Health Organization International Classification of Functioning, Disability and Health (ICF) – Upper Limb post Stroke

What does the evidence say about upper limb recovery after stroke?

Understanding patterns of upper limb recovery following stroke could potentially allow the application of targeted and appropriate interventions to stratified patient groups, resulting in a more efficient allocation of resources[57]. Rehabilitation can focus on compensatory strategies, and / or restorative approaches but decisions about who should receive which approach often vary. The Canadian Evidence-Based Review of Stroke Rehabilitation (EBRSR)[3] advises that restorative goals are appropriate for those patients who are expected to achieve greater upper limb motor recovery, whilst compensatory goals are more appropriate when poor motor recovery is anticipated[3]. In the absence of any recovery, prevention of secondary complications such as spasticity or shoulder instability might be the most suitable focus of treatment[57]. In practice, decisions on the therapy approach are often based on a combination of the therapist's experience and the patient's response to therapy. Prognostication can be valuable in setting realistic goals, as well as in the selection of most appropriate and beneficial rehabilitation interventions. For example the severity of early motor impairment is an important factor associated with recovery potential[13, 58], but it can also assist in identifying a client cohort who may respond more positively to robot-assisted training[59, 60]

A recent systematic review summarized evidence-based clinical and neurophysiological factors associated with upper limb recovery (Figure 2).

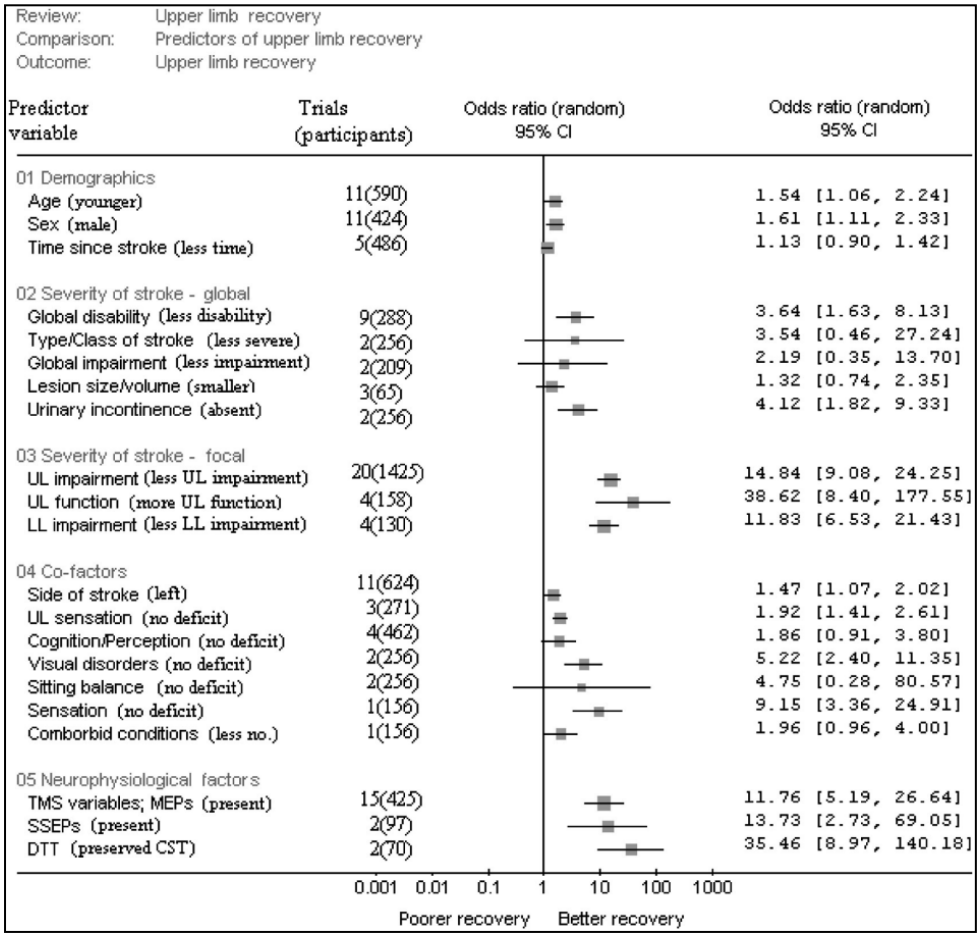


Figure 2. The association of baseline variables (odds ratio ≥95% CI) with Upper Limb Recovery. Reproduced with authors' permission[57]

Combining the strongly predictive factors outlined above, the Predicting Recovery Potential (PREP) algorithm has been proposed to assist the clinician in prognostication and treatment selection. The algorithm[57] uses the following three components (activity of shoulder abduction and finger extension, Transcranial Magnetic Stimulation, and Magnetic Resonance Imaging) to stratify acute stroke survivors of mean age 70 into categories of complete, notable, limited or no recovery of the upper limb at 12 weeks.

A prospective observational study of 299 stroke survivors[61] assessed upper limb capacity at the beginning and at the completion of rehabilitation in subjects with a mean age of 60 (11.1). With the use of the Stroke Upper Limb Capacity Scale (SULCS), a ten item clinical assessment of arm and hand capacity, this study also concluded that absence of early proximal arm control bodes a poorer prognosis for future hand capacity.

Neuroanatomical imaging may enhance clinical assessments, with increasing evidence that neurophysiological measures obtained from TMS may produce useful information[58]. Information regarding lesion size and lateralization can help to establish anticipated deficits and recovery patterns. Pure cortical involvement predicts recovery of up to 75% of patients with hemiplegic upper limb, as opposed to the significant decline in motor recovery to rates less than 5% when lesion location involves the corona radiata or posterior limb of the internal capsule[62]. In particular, evidence of integrity of descending motor tracts is closely correlated to functional recovery outcomes[63].

Decisions on the likelihood of recovery made in the acute post stroke period require ongoing evaluation to allow for false negatives, assess motivation and share information with the patient and family. Patient perspectives, education and individualized goal-setting are important considerations

in stroke rehabilitation. The impact of personal and environmental factors (see Figure 2) should never be underestimated. Secondary analysis of a multisite randomized controlled trial described the involvement of caregivers as a more significant determinant of upper limb improvement than initial motor impairment or therapy intensity[64].

What are the current and emerging rehabilitation strategies for treating upper limb impairments after stroke?

The current clinical approach framework

It is widely accepted that optimal care for the stroke survivor is achieved in an acute stroke unit followed by either treatment in a stroke rehabilitation unit, early supported home rehabilitation program or a dedicated outpatient unit. There is no evidence to support excluding stroke patients from stroke units based on age. Mortality and dependency rates are reduced with this model, with best outcomes achieved with integrated acute and rehabilitation care[65]. There is increasing evidence suggesting that intense rehabilitation should commence early after stroke to facilitate task-specific repetition, with evidence that this has a positive impact on both physical recovery and quality of life measures[66, 67].

The National Stroke Foundation (NSF)[36] provides the clinical guidelines for evidence-based stroke care in Australia. The guidelines stipulate high-grade evidence supporting the structure of rehabilitation to enable maximal practice for the patient within the first 6 months post stroke (Level A, NSF). Research supports the key elements driving upper limb rehabilitation to be intensity, specificity and repetition. Practice dose can be maximized with task-specific circuit class training or video self-modelling (Level B, NSF). Circuit class therapy has been established as a safe and

effective rehabilitation technique [68] and achieves comparable results to those achieved in one on one therapy sessions[69].

In general there is a demand for increased dose and task-specificity[70, 71] within the established framework of rehabilitation to maximize recovery through restoration of function, adaptation to impairment, and reduction of secondary complications. However, skilled staff are scarce and rehabilitation units are limited. The future of stroke rehabilitation increasingly includes technological approaches[72]. In approaching the application of new technologies, a collaborative approach is required between researchers and clinicians[71]. Key elements for success are outlined [71] as encompassing understanding of the pathophysiology of brain disease and appropriate hypotheses to guide treatment, as well as the need for ongoing clinical assessments of efficacy and systematic approaches with which therapists can apply new technologies. Focus must necessarily remain on the individual, with an understanding that purpose-driven goals impacting patient attention and motivation are vital parameters in motor relearning[73].

The type, timing and intensity of interventions are the focus of ongoing research. Technological and conceptual therapeutic advances advocate early focus on motor relearning, but extend beyond the acute period with evidence additionally supporting the important impact of interventions in the chronic post stroke period. Advances in rehabilitation applications enable stroke survivors with severe hemiparesis to participate in restorative therapies[74], rather than be limited to compensatory strategies. Intervention targeting restitution goals centre on the established concepts of neuroplasticity. Neuroplasticity is the 'inherent capacity for cortical reorganization or development of new functional connections in response to learning and experience'[75]. Functional brain imaging techniques, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) corroborate the model of neuroplasticity as a contributor to motor recovery

following stroke[76, 77]. Importantly, functional imaging supports the ability of post-stroke therapies to influence and be influenced by neuroplastic changes[78, 79]. Rehabilitative training enhances cortical representation.

Langhorne et al[80] conducted a systematic review of interventions to promote upper limb motor recovery following stroke summarized in Figure 3.

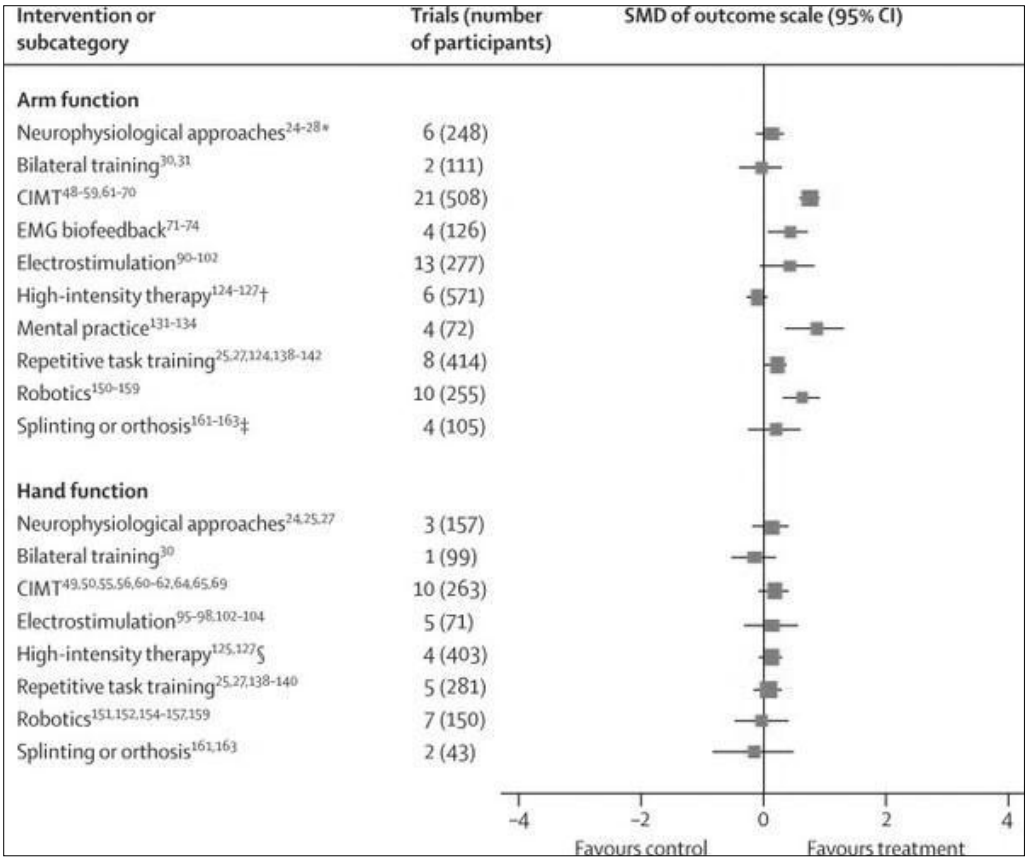


Figure 3. Interventions to improve upper-limb motor recovery after stroke. Reproduced with permission of authors[80]

This figure summarizes the results for upper-limb interventions targeting the recovery of arm or hand function, and shows the intervention category, number of trials (participants recruited) plus the SMD and 95% CI for the effect of the intervention on the outcome measure.

Established concepts in upper limb rehabilitation post stroke

Repetitive, task-specific training

Hubbard et al[81] outline the development of repetitive task-specific training in rehabilitation, with origins in basic science and psychological theories of motor development. From the 1990s onward, there has been a growing body of research, with robust evidence to support[3] repetitive task-specific training as an approach for improving measure of upper limb function. Task-specific training involves repetitive part and whole task practice of tasks that are meaningful to an individual patient. The neuroscientific premise for task-specific training as a portal to motor learning are based on the experience- and learning-dependent aspects of neuroplasticity[81].

A randomized controlled trial of 103 stroke survivors compared task-specific training with the standard neurodevelopmental technique of Bobath therapy over 4 weeks and demonstrated superior and maintained outcomes for the task specific group[82]. Maximum benefit from task-orientated training is achieved with intensive and early post-stroke application[83]. The 5 key elements for successful implementation of task-specific training[81] include:

i. Tasks which are relevant to the patient and context
ii. Random and changing tasks
iii. Repetitive tasks with massed practice

iv. Part and whole task practice

v. Reinforced with positive and timely feedback

The clinical application of number of repetitions supported by evidence is often a limiting factor, and adoption of new technologies assists in enhancing training opportunities. Task-specific training is easy to implement in a variety of clinical settings and is a meaningful and motivating therapy approach for individuals. As a result, there is widespread uptake of this approach. Stroke management guidelines generally recommend this intervention, though the American Veterans Affairs / Department of Defence Clinical Practice Guidelines specifically states not to use repetitive practice in rehabilitation of the upper limb. This viewpoint is not elaborated on in the document, but may reflect results of the 2010 Cochrane review[84] which supported use of repetitive training in the lower limb, but not in the upper limb.

Bimanual training

The evidence base for bimanual training is less secure. The approach is based on theoretical models[85] in which bilateral simultaneous movement may result in interhemispheric disinhibition and sharing of 'normal' movement commands[86] from the contralesional hemisphere to the symmetrically organized upper limb motor representation in the ipsilesional hemisphere . The concept of bilateral transfer in stroke rehabilitation refers to the transfer of a learned motor control program from the practiced limb to the hemiparetic limb. A 2011 randomized controlled trial[87] supported the role of bilateral transfer in enhancing upper limb motor skills post stroke.

Originally investigated by Mudie and Matyas[88], there is conflicting and inconclusive evidence regarding the treatment effect of bilateral upper limb training.[89 90, 91]. A 2010 systematic review[92] reported BATRAC (Bimanual Arm Training with Rhythmic Auditory Cueing) as the most common

and consistent bimanual training approach. Evidence supports this intervention in upper limb therapy in chronic phase of recovery, though the review calls for further randomized controlled trials. However a comparison of functional gains subsequent to bilateral and unilateral training did not indicate any advantage from bimanual interventions[93], with the observation that bilateral training is specific for bilateral tasks, whilst unilateral training offers specificity for unilateral tasks[93]. It must be considered, however, that bilateral training might offer a more functional training opportunity in comparison to unilateral limb use.

Constraint-induced movement therapy

Constraint-induced movement therapy (CIMT) was first proposed by Taub in 1994[94] and involves constraint of the unaffected limb for 90% of waking hours, combined with forced use of the affected limb and massed practice, in a cohort of chronic post-stroke patients with sufficient finger flexion and wrist extension to allow use of hemiparetic upper limb. Sunderland and Tuke[95] outline the theory on which CIMT is based, with the hypothesis that impairment and subsequent reduction in function are exacerbated by acquired learned non-use of the affected upper limb, and subsequent reduction of upper limb cortical representation. Despite this, compensatory strategies, as opposed to reductions in impairment, are favoured as the mechanism of CIMT[96].

CIMT is effective in improving spontaneous use of the hand in a select group of sub-acute and chronic stroke patients[80]. Patient selection is made on basis of motor impairment[10] and on ability to tolerate and adhere to constraint impacts the applicability of this intervention[80]. Due to inclusion criteria, it has been estimated that less than 30% of potential candidates are able or eligible to participate in trial settings[97]. Compliance, fatigue and the time consuming nature and practicality of associated therapy are additional potential limitations[80, 97]. The EXCITE trial[98] assessed CIMT as compared to standard therapy, with a mean age of 61 (standard deviation 13.5) in the intervention

group. Increasing age may well reduce the impact of traditional CIMT. At this stage, CIMT is less likely to be used in acute or even subacute inpatient settings than in an outpatient setting. However modified CIMT (mCIMT) protocols for use in acute and subacute stroke rehabilitation are being assessed[99], with the goal of early restoration of function and prevention of the development of compensatory strategies. Modifications to the original CIMT protocol include earlier application of the intervention, reduced hours of constraint and reduced overall number of consecutive weeks of therapy. Evidence supports mCIMT in a subacute stroke population[82], and the EXPLICIT-stroke trial[100] will further assess mCIMT in an acute cohort. mCIMT may widen the applicability, implementation and acceptability of this therapeutic approach.

Neuromuscular electrical stimulation

The growing range of applications of neuromuscular electrical stimulation (NMES) stems from initial work by Liberson, a medical researcher and specialist in physical rehabilitation, in the 1960s[101]. NMES involves application of low-dose electrical current over motor nerves of affected muscles. Stimulation of peripheral nerves can improve motor performance and cortical excitability following stroke [102]. NMES can be applied to promote functional tasks (functional electrical stimulation; FES), with or without active participation by the patient. A 2006 Cochrane review[103] on the effectiveness of electrical stimulation in upper limb functional recovery stated that there is insufficient evidence to guide clinical practice. National guidelines reflect the current level of evidence, with the National Institute for Healthcare and Excellence (NICE) Guidelines recommending against routine use of electrical stimulation for the arm and hand[50], whilst the Canadian Best Practice Recommendations for Stroke Care promotes use of FES to reduce impairment and improve function[104] (see Table 2).

A systematic review of 19 clinical trials[105] concluded that stimulation triggered by voluntary effort was consistently more effective that passive stimulation of a paretic limb. This concept was further explored and supported by results of a recent small study in which electrical stimulation was able to be systematically reduced as upper limb voluntary effort and motor performance improved[106]. In exploring the role of electrical stimulation in the non-functional hemiplegic upper limb, a 2012 single blind randomized controlled trial[107] of 90 subjects demonstrated a positive effect on distal motor performance, but did not show a significant effect on function. Importantly, this study involved a more representative sample with mean age of 74.6 (standard deviation 11.0). NMES has also been shown to reduce post-stroke spasticity[108] and hemiplegic shoulder pain[109].

One of the potential advantages of this approach is that families can be taught to deliver the treatment and it can be delivered at home, and newer implantable devices may further improve options for its use. Disadvantages of the current application techniques include potential patient hypersensitivity to stimulation sensation, skin reactions and skills required for effective application. As with repetitive practice, the dose delivered in real-world therapy scenarios is often much less than that proposed by the literature. Additionally, NMES is contraindicated in patients with cardiac pacemakers, epilepsy, pregnancy, and in the presence of underlying dermatological conditions.

Emerging interventions in upper limb rehabilitation post stroke

Robotics

Robotic / device-driven rehabilitation systems offer the promise of providing an efficient approach to delivering an increased dose of therapy and providing practice which includes specificity of movement pattern generation, feedback and repetition[110] . The explosion of research on robotic systems as therapy heralds a new era in rehabilitation. Initial robotics utilized in rehabilitation settings focused on augmentative and compensatory strategies, with more recent evidence moving towards restorative approaches.

A Cochrane review concluded that[111] that robotics may improve function and activities of daily living post stroke, but do not improve upper limb strength. An earlier systematic review[112] also reported trends towards greater functional improvement with robotic use, but raised the question regarding whether gains were due to the treatment type, or the increased treatment dose and intensity. A 2012 systematic review[113] comparing dose equivalence between robotics and standard therapy, did not demonstrate better outcomes in motor recovery or function. There is some evidence for robotics use with the upper limb treatment across the spectrum of recovery phases, from acute[111] to subacute and chronic stages of recovery[114, 115]. One problem confronting clinicians is that while the evidence suggests robotic approaches are useful in improving functional and motor outcomes at the shoulder and elbow[3] there is little evidence for their use at the wrist and hand where gains are most functional. Patient satisfaction and adherence appear good with this approach possibly because many robotics include high quality gaming approaches which engage and motivate patients[116]. In summary, whilst evidence continues to emerge, at present robotics appear to be a useful complement to conventional approaches mainly because they offer a way of achieving higher "doses" of therapy.

Virtual reality and gaming strategies

Virtual reality for rehabilitation purposes first gained attention in the 1990s. As acceptance and technology have exponentially increased, this intervention is playing an ever-increasing role in the rehabilitation setting. Henderson et al[117] describe virtual reality "as a computer-based, interactive, multisensory simulation environment that occurs in real time". Virtual reality offers goal-directed and reward-based task training[118], with an immersive virtual environment potentially aiding task-specificity and patient motivation[117]. Feedback is predominantly visual, but can also be provided through other sensory modalities and interfaces. Multisensory feedback has an established role in promoting motor learning[119].

Using virtual reality in neurorehabilitation is based on the hypothesis that activation of neural motor areas occurs both as a result of motor execution and imagery of that same task[120]. The correlations between observation of computer generated imagery and generated actions are hypothesized to engage bilateral motor cortices. As with robotics, one of the principle contributions of virtual reality may be its potential for providing increased therapy dose. A 2011 Cochrane Review of the evidence for virtual reality approaches in stroke rehabilitation[121] reviewed 19 trials with a total of 565 participants, surmising that overall there is still limited evidence for virtual reality when compared to the same dose of conventional treatment. However there is promising evidence that virtual reality approaches improve upper limb recovery and impact positively on activities of daily living. Problems were noted in generalizing the findings to older people as most trials included younger people in the chronic phase. Only 34% of screened patients were recruited to studies suggesting there are significant barriers to the uptake of this approach. This raises concern about the generalizability of this intervention to an older population with no experience of gaming systems[122].

Studies evaluating patient perspectives have reported positively on acceptability[123], enjoyment, purpose and challenge[124]. However most of these studies continue to focus on younger stroke

survivors while patient reports from a Discrete Choice Experiment of older patients in a geriatric rehabilitation ward[122] found older patients preferred traditional therapy over video-game based therapy. It is important to note that video game therapy does not involve 'immersion' as such is not strictly within the definition of virtual reality[72].

Non-Invasive Brain Stimulation

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS), both non-invasive brain stimulation techniques, are postulated to have an adjuvant role in priming neural structures for maximizing therapeutic outcomes[79, 125]. The mechanism for improving responsiveness to therapy is hypothesized to stem from achieving greater balance of excitability between ipsilesional and contralesional motor corticies[125], hence optimizing enhanced plasticity secondary to motor practice[126].

A double-blind study[127] compared rTMS priming by inhibition of the unaffected motor cortex with sham priming prior to motor retraining in a cohort of chronic stroke patients. The authors demonstrated an induced increase in motor cortex excitability with positive influence of motor retraining hand task sustained to one week. A recent review article of 15 studies assessing tDCS in stroke therapy[128] concluded a consistent positive effect in promoting motor recovery in chronic stroke populations, and more so in those with milder degrees of impairment. This is in keeping with evidence for tDCS as a well tolerated and effective intervention for motor impairment[129], though there is conflicting evidence with some studies not supporting enhanced outcomes[130] and others cautioning regarding the lack of long-term data[131]. A 2013 randomized controlled trial[78] demonstrated the benefit of cathodal tDCS in reducing upper limb muscle tone, with flow-over impact on function and activities of daily living. While more work is needed to establish protocols

and identify those most likely to benefit[132, 133], it seems likely that priming the cortex with application of activity-dependent brain stimulation will enter practice in the next decade.

Telerehabilitation

Telerehabilitation is an important emerging method for increasing access to assessment and therapy, including motor rehabilitation. Telerehabilitation is a subset of telemedicine and describes that application of telecommunications and health information technologies to improve access to rehabilitation and services, and to support independent living. The term is used to include assessment, monitoring, prevention, intervention, supervision, education, consultation, and counselling[50]. As countries improve their communication technologies, it is becoming a realistic option for delivering rehabilitation to those who live in remote areas and to those who find it difficult to leave home. Many studies attempt to combine regular visits by therapists and nurses with remote contact (phone or videoconferencing) to support stroke survivors in risk factor management[134] or with psychosocial issues[135]. Several studies have assessed telehealth approaches to improving upper limb function using customised computer based training programs[136-138] but the trials are small and the results have been mixed. If the results are similar, the important outcomes will be costs, which are still high. Forducey (2012) assessed independence in activities of daily living following a telerehabilitation intervention (12 occupational and physio therapy sessions focused on education, retraining of self-care, functional mobility and posture, therapy to improve function in impaired limbs) delivered via video phone compared with delivered in person. Both groups improved but there were no significant differences in outcomes between the groups post intervention[139]. While the potential advantages are obvious, systematic reviews are inconclusive focusing on the highly selected populations, the absence of older people with cognitive impairment in the studies and the lack of information on cost effectiveness[140, 141].

Table 1. Summary of Principles, Advantages and Disadvantages of Upper limb Interventions

Intervention	Origin	Principles	Application	Advantages	Disadvantages
Repetitive Task-Specific Training	Origins in basic science and psychology research	Targets learning-dependent neuroplasticity	Repetitive part and whole task practice of meaningful tasks	Easy to apply Individualised Motivating	Repetitions required in evidence frequently not achieved in clinical setting
Bimanual Training	Mudie and Matyas 1996	Bilateral symmetrical movement activates bilateral motor cortices Bilateral transfer	Symmetrical or alternating use of bilateral upper limbs to complete task	Potentially more functional than unilateral training	Most evidence only in chronic phase Only task specific if for bilateral tasks
CIMT	Taub 1994	Prevent learned non-use and subsequent reduction in cortical representation	Constraint of unaffected upper limb for 90% of waking hours, coupled with massed practice with affected upper limb	High grade evidence for traditional CIMT Modified CIMT protocols emerging for acute / subacute	Select group of patients meet inclusion criteria Limited by adherence, fatigue and compliance Limited evidence in acute setting
NMES	Liberson 1961	Electrical stimulation to peripheral motor nerves to improve motor performance and cortical excitability	Applied by trained therapist; training provided to patient / family Newer implantable options more invasive but may provide superior application	More effective if triggered by voluntary effort Can improve motor performance and reduce spasticity and shoulder pain Can be applied in home setting	Limited evidence of effect on function Application needs training Surface NMES can be uncomfortable; Potential skin reaction Contraindicated in

					epilepsy, pregnancy, pacemakers Time required in evidence often not matched in clinical setting
Robotics	1990s -	Move towards restorative approaches	Multiple applications; Active assisted therapy with specificity of movement patterns, feedback and repetition	Method of increasing repetition / dose of therapy Provides feedback Evidence supports functional gains Applicability to acute, subacute and chronic phases of recovery Good adherence and motivation	Equity of access to robotic technologies Not superior to standard therapy in equivalent dose Less effective on distal motor upper limb motor impairment
Virtual reality and Gaming	1990s -	Activation and engagement of bilateral neural motor areas occurs as result of motor execution and imagery of that task	Computer based, Interactive, immersive, multisensory simulation environment	Goal-directed; motivating with feedback Carry over into ADL function Method for increasing therapy dose Generally well accepted and challenging	Potentially less acceptable to older patient group Not superior to standard therapy in equivalent dose Equity of access

Non-invasive brain stimulation	Recent clinical applications founded on decades of research	Changes in neural excitability (excitation / inhibition) secondary to stimulation	TMS: Rapidly changing magnetic fields via coil over head to induce small electrical currents over motor cortices tDCS: application of constant low current stimulation via electrodes	Cortical changes persists after stimulation Considered safe if follow established protocols	Careful placement of electrodes important for effective application May experience skin irritation, dizziness, nausea, headache May lower seizure threshold in susceptible patients

Prevention and treatment of secondary upper limb complications

Rehabilitation of motor deficits post stroke must additionally aim to prevent and treat secondary complications affecting the upper limb. Commonly identified upper limb secondary complications include spasticity and contracture, subluxation, hemiplegic shoulder pain and distal oedema [142]. The NSF guidelines[36] summarize the evidence in recommending prevention and management options for these complications. Level of evidence is graded from A-D, or as a Good Practice Point (GPP) based on experience and opinion. The highest grade of evidence for management of upper limb complications is level B, defined as "a body of evidence that can be trusted to guide practice in most situations", and is only recorded for one treatment and two preventative strategies in total. The remainder of evidence is level C, D and GPP, reflecting limited new preventative or interventional opportunities for upper limb complications. The paucity of evidence to support the clinician in best prevention and management of common upper limb complications is an area in great need of future focus. Complications can contribute to pain, depression, and poorer ability to participate in specific neurorehabilitation. The impact of such factors on functional outcome is significant.

Spasticity and Contracture

Incidence of focal upper limb spasticity post-stroke is estimated at approximately 20%[143, 144], with approximately 4% with disabling levels of spasticity[144]. Increasing tone is associated with poorer outcomes in terms of pain and dependence[145]. It is generally accepted that early comprehensive physical and occupational therapy may reduce development of spasticity. Evidence does not support hand splinting[3] or stretching regimes[146] to reduce spasticity or prevent contracture nor is intervention recommended in mild to moderate spasticity that does not impair function (good practice point)[36]. Botulinum toxin A, in combination with targeted therapy, has been demonstrated to reduce upper

limb spasticity[147]. Research has previously reported low-on effect to functional outcomes measures[148], though a 2013 systematic review and meta-analysis of ten randomized controlled trials[149] has importantly concluded improvements in both activity and performance. A Cochrane review published this year outlines need for ongoing research to establish optimal types and intensities of multidisciplinary rehabilitation to improve impairment and activity following Botulinum toxin treatment[150].

Subluxation

Rates of subluxation have been variably reported in the literature, with incidence ranging from 17-64%[35]. Correlation between subluxation and development of hemiplegic shoulder pain remains controversial, with reviews of literature not concluding a causative association[29]. Not all patients with subluxation have pain, and not all patients with pain have subluxation. Even though a causal link has not been definitively established, it remains prudent practice to protect the shoulder with careful positioning, supportive devices and education. Supportive devices have not been demonstrated to prevent subluxation, though remain recommended in treatment of established subluxation[36]. Electrical stimulation is advocated in prevention, but has not been demonstrated to reduce actual measures of subluxation[35].

Hemiplegic Shoulder Pain

Hemiplegic shoulder pain is a common complication of, with overall rates affecting approximately 30% of stroke survivors[16]. A paper assessing correlations between upper limb function and the ICF model found shoulder pain to be the variable most associated with limitations in participation[28, 29]. This area is an important focus of future research as up to 20-30% of patients experience pain refractory to current treatment modalities[35].

The paucity of high-grade evidence for treatment options is reflected in current Australian and United Kingdom guidelines, which do not cite any evidence-based therapeutic options specific to a stroke population[36, 37]. Older research outlined careful handling, electrical stimulation, movement with elevation, strapping and avoidance of overhead pulleys as potentially effective interventions to reduce or prevent hemiplegic shoulder pain[40]. There is limited evidence for Botulinum toxin for shoulder pain[41], and evidence against use of intra-articular corticosteroids[34]. A 2001 Cochrane review found inconclusive evidence regarding electrical stimulation, though a systematic review and meta-analysis completed since this time demonstrated long term benefits of intramuscular electrical stimulation[34]. Developing implantable electrical stimulation techniques are reporting high success rates in treatment of previously refractory subluxation associated shoulder pain[35]. A recent randomized controlled trial has provided evidence for the use of suprascapular nerve block in treatment of hemiplegic shoulder pain[151].

Distal Oedema

Hand oedema following stroke occurs in at least 1/3 of survivors[152]. There is limited evidence that dynamic pressure garments, electrical stimulation, and elevation may assist in prevention of oedema[3, 36], whilst pneumatic compression has not been shown to treat established oedema[3].

Guidelines

The World Stroke Organization[153] has compiled an Inventory of International Stroke-Related Best Practice Guidelines 2012. Many countries have national foundations and societies, providing a spectrum from summaries of evidence to specific evidence-based guidelines. Whilst the European Stroke Organization[154] , Belgian Stroke Council[155], The National Stroke Association of Japan[156] and Stroke Society of the Philippines[157] all provide an overview of rehabilitation evidence. Many other national documents often focus on acute medical management, not pertaining specifically to rehabilitation of stroke. Table 2 outlines current national guidelines on upper limb rehabilitation from the United Kingdom[50] , Canada[104], Australia[36] and the United States of America[158]. These guidelines have been selected due to inclusion of detailed guidelines regarding multiple and specific upper limb rehabilitation therapies. The summarized guidelines were easy and free to access, clearly written and recently updated – all factors important for clinician relevance.

Table 2. Summary of Guidelines for Upper Limb Rehabilitation Post Stroke: National Stroke Foundation (Australia), Canadian Best Practice Recommendations for Stroke Care (Canada), Department of Veterans Affairs / Department of Defence Clinical Practice Guidelines (United States of America), and National Institute for Healthcare and Excellence Guidelines (United Kingdom).

SUMMARY OF CURRENT GUIDELINES: Rehabilitation Therapy for Upper Limb Recovery and Function Post Stroke				
	Australia: **National Stroke Foundation (NSF) Guidelines** 2010	Canada: **Canadian Best Practice Recommendations for Stroke Care** 2013	United States of America: **Department of Veterans Affairs / Department of Defence Clinical Practice Guidelines** 2010	United Kingdom: **National Institute for Healthcare and Excellence (NICE) Guidelines** 2013
Virtual Reality	-	Where available, immersive and non-immersive virtual reality techniques can be used as an adjunct therapy to provide additional repetition, intensity and task-oriented training [B]	Consider virtual reality as practice context [C]	-
Repetitive Task-Specific Training	Interventions which can be used routinely include repetitive task-specific training [B]	Patients should engage in meaningful, engaging, progressive and task-specific goal-orientated training [A] Recommend supplementary training programs to improve active movement and function, e.g. GRASP (Graded Repetitive Arm Supplementary Program) Functional dynamic orthoses	Do NOT use repetitive practice of movements in rehabilitation of upper extremity	Offer people repetitive task training after stroke on a range of tasks for upper limb weakness (such as reaching, grasping, pointing, moving and manipulating objects in functional tasks)

		may be offered to patients to facilitate repetitive task-specific training [C]		
Bilateral Training	Bilateral training may be used in addition to routinely offered interventions [C]	-	Recommend bilateral practice to improve upper extremity function [B]	-
Imagery or mental practice	Mental practice may be used in addition to routinely offered interventions [B]	Suitable patients should be encouraged to engage in mental imagery to enhance upper limb sensorimotor recovery [Early A; Late B]	-	-
Splinting	-	Routine use of splints is not recommended for range of motion and spasticity of the upper limb [early A; late B]	-	Do not routinely offer wrist and hand splints to people with upper limb weakness after stroke Consider wrist and hand splints in people at risk after stroke Where used, splints should be assessed and fitted by trained healthcare professionals and training provided to patient and family / carer
Electro-mechanical or robot-assisted training	Interventions which can be used routinely include mechanical assisted training [B]	-	Recommend robot-assisted movement therapy as an adjunct to conventional therapy in patients with deficits in arm function to improve motor skill at the joints trained [B]	-

Botulinum Toxin	In stroke survivors who have persistent moderate to severe spasticity, botulinum toxin A should be trialled in conjunction with rehabilitation therapy which includes clear goals [B]	Botulinum toxin can be used to increase range of motion and decrease pain for patients with focal and /or symptomatically distressing spasticity [early C; late A]	-	-
Electrical Stimulation	Electrical stimulation may be used in addition to routinely offered interventions for upper limb activity [C] In stroke survivors who have persistent moderate to severe spasticity, electrical stimulation and / or EMG biofeedback can be used [C] For people with severe weakness who are at risk of subluxation, management should include one or more interventions, including electrical stimulation [B]	Functional Electrical Stimulation (FES) targeted at the wrist and forearm muscles should be used to reduce motor impairment and improve function [A] For patients with flaccid arm, electrical stimulation should be considered [B]	Recommend treatment with FES for patients who have impaired upper extremity muscle contraction, specifically with patients with elbow/wrist motor impairment [B] Recommend FES for patients who have shoulder subluxation [B] Consider FES and mental practice combined with repetitive and intense motor practice of functional tasks [B]	Do not routinely offer people with stroke electrical stimulation for their hand and arm. Consider a trial of electrical stimulation in people who have evidence of muscle contraction after stroke but cannot move their arm against resistance. Ensure that therapy is guided by a qualified rehabilitation professional. The aim of electrical stimulation should be to improve strength while practicing functional tasks in the context of a comprehensive stroke rehabilitation program Continue electrical stimulation if progress towards clear functional goals has been demonstrated

Constraint-induced Movement Therapy (CIMT)	Interventions which can be used routinely include constraint-induced movement therapy in selected people [A]	CIMT or mCIMT should be used for a select group of patients who demonstrate at least 20° of active wrist extension and 10° of active finger extension with minimal sensory or cognitive deficits Traditional CIMT, (therapy >2 hours / day) should not be used within the first month post stroke [A] Modified CIMT may be initiated in the first month following stroke in appropriate patients [A]	Recommend CIMT for individuals with at least 10 degrees of extension in two fingers, the thumb and the wrist [A]	Consider constraint-induced movement therapy for people with stroke who have movement of 20 degrees of wrist extension and 10 degrees of finger extension. Be aware of potential adverse events
Strength Training	-	The GRASP program is a recommended supplementary program which involves strength training	Consider strengthening exercises in addition to functional task practice [C]	Consider strength training for people with muscle weakness after stroke.
Hemiplegic Shoulder Pain	For people with severe weakness who are at risk of developing shoulder pain, management may include: - Shoulder strapping [B] - Interventions to educate staff, carers and patient [GPP] For people who develop shoulder pain, management should be based on evidence-based interventions for acute	Prevention by Joint protection strategies: - Positioning at rest [B] and during functional mobility [C] - Supporting during wheelchair use with hemi-tray [C] - Slings in flaccid stage only [C] Overhead pulleys should not be used [A]	-	Provide information for people with stroke and their families and carers on how to prevent pain or trauma to the shoulder if they are at risk of developing shoulder pain Manage shoulder pain after stroke using appropriate positioning and other treatments according to each person's need.

	musculoskeletal pain [GPP] The routine use of the following is NOT recommended for established shoulder pain: - Corticosteroid injections [C] - Ultrasound [C]	Arm should not be moved beyond 90’ shoulder flexion or abduction, unless scapular upwardly rotated and humerus laterally rotated [A] Education [A] Avoid traction in assisted movements [C] Management of Pain: - Gentle stretching [B] with gradual increased in range - Analgesics if no contra-indications [C] - Botulinum toxin injection into subscapularis and pectoralis muscles if pain related to spasticity [A] - Subacromial corticosteroid injection s can be used in patients when pain related to injury or inflammation of subacromial region [A] - In a subset of patients who experience pain related to both injury / inflammation and spasticity, dual therapy should be used (BTX and steroid injections) [C]	For guidance on managing neuropathic pain follow Neuropathic pain (NICE clinical guideline 96).

NSF Levels of Evidence: A - body of evidence can be trusted to guide practice; B - body of evidence can be trusted to guide practice in most situations; C - body of evidence provides some support for recommendations but care should be taken in its application; D - body of evidence is weak and recommendation must be applied with caution; GPP - Good practice point; recommended best practice based on clinical experience and expert opinion

Canadian Best Practice Recommendations: A - Strong recommendation. Evidence from randomized controlled trials or meta-analyses of randomized controlled; B - Single randomized controlled trial or well-designed observational study with strong evidence; or well-designed cohort or case–control analytic study; or multiple time series or dramatic results of uncontrolled experiment. Desirable effects closely balanced with undesirable effects; C - At least one well-designed, nonexperimental descriptive study (e.g., comparative studies, correlation studies, case studies) or expert committee reports, opinions and/or experience of respected authorities, including consensus from development and/or reviewer groups trials. Desirable effects clearly outweigh undesirable effects, or vice versa.

VA/DoD Levels of Evidence: A – a strong recommendation that the clinician provide the intervention to eligible patients; B – a recommendation that clinicians provide (the service) to eligible patients; C – no recommendation for or against the routine provision of the intervention is made; D – recommendation is made against routinely providing the intervention to asymptomatic patients; I – The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention

The challenge of implementing evidence based practice in clinical settings

The quantity of stroke rehabilitation research continues to increase, providing an expanding breadth of evidence on which to base clinical management. Decisions on therapy interventions have historically been predominantly based on clinical experience but while the shift towards practice grounded on research has occurred there is need for more evidence on which types of strokes will respond to particular interventions. A key problem remains in ensuring that current evidence is implemented.

Sackett et al[159] defines evidence-based practice as involving "the integration of best external evidence with clinical expertise and patient values". Evidence-based guidelines are designed to improve patient outcomes but national audits reveal uptake is inconsistent. The Australian National Stroke Foundation (NSF) audit of 2012 revealed that whilst 90% of strokes were admitted to hospital, only one third were accessing rehabilitation[160]. In patients accessing rehabilitation, there are missed therapeutic opportunities, with the majority of patient time still spent inactive[161]. Canadian research[162, 163] reflecting on the challenges of transferring evidence into practice identified the following problems: poor generalizability of research finding to the 'average' patient, limitations in the strength of evidence available, and difficulties with the practicalities of adhering closely to evidence based guidelines[162].

The Australian NSF case note audit in 2012[160] included an assessment of the level of implementation of evidence-based guidelines for upper limb impairment management post stroke. This case series audit was conducted across 101 hospitals with a total of 2801 patients. Data collected indicated that of 69% stroke survivors with upper limb impairment, 93% received at least one treatment

recommended in the guidelines, and 14% received none of the guideline interventions. Higher rates were reported for 'repetitive task specific training' and 'other therapy', 83% and 50% respectively. CIMT and mechanically assisted therapies were used less often with reports of 6% and 9% respectively. The lower rates reported for these items may well reflect a more acute patient population than currently indicated for CIMT, and limited access to equipment for newer mechanically-assisted therapies. Disappointingly, these figures demonstrate little improvement in incorporation of evidence into practice when compared to earlier audits[142]. Implementation of technology in clinical practice similarly remains low[70]. Therapist experience[164] and the practical issue of therapist time constraints in accessing, understanding and implementing evidence also affect the implementation of evidence.

Increasing the amount of therapy has been a focus in many centres and dedicated stroke rehabilitation units are trending towards additional weekend therapy, benchmarking hours of therapy per day and providing more task-specific therapies[160]. Other potential methods for increasing dose and augmenting conventional therapies lie in the adoption of novel methods of service delivery, including technology-assisted options.

Identifying the research to practice gap, a five-phase tool for successful implementation of technology in upper limb stroke rehabilitation has been proposed[70]. The five phases are designed to motivate and enable therapists to employ new practices[70], and include:

i. Orientation: establishing awareness of new technology to therapists
ii. Insight: providing information and understanding of potential of new therapies
iii. Acceptance: therapist and patient motivation to incorporate new therapies
iv. Change: introducing new therapies with opportunities for training, and implementation of an easy-to-use system
v. Retention of change: incorporation into existing practices and protocols

The practicalities of funding and resource allocation are likely to continue to limit access and older people are at risk of being excluded. New technologies such as telehealth offer the opportunity for more equitable access to clinical expertise. For example, a case series reviewing a combination of CIMT with remote video-linked technology reported gains in function, with good adherence and patient satisfaction[165].

Conclusion

Stroke rehabilitation of the upper limb is an exciting and evolving area of specialty interest. Therapeutic and technological advances are enabling greater access to the benefits of neuroplasticity and focused individualized therapy frameworks. Research is establishing treatment options across all phases of rehabilitation, and identifying potential treatments for previously refractory complications. A focus on technologies acceptable to all age groups is vital to ensure applicability of available treatment options, and clinician and therapist support must be central in attempts to successfully maintain an implementation of change that is relevant to the client population.

Future Perspective

Rehabilitation of the upper limb in older stroke survivors continues to be a research frontier which has been energized by new technologies but which is grounded in the basic need to find ways to allow older people to recover independence. The growth of online stroke survivor communities providing peer support, information and advice is increasing the demand for therapy and recovery.

The enduring foci of rehabilitation involve: providing patients and families with goal focused therapy which they feel they have input to, improving access to rehabilitation, increasing the proportion of active therapy time during rehabilitation, and providing a range of settings in addition

to the standard inpatient hospital rehabilitation ward. New technologies such as robotics, gaming, telehealth and telerehabilitation are likely to allow remote provision of therapy and exercise therapy, though attention to acceptability and support in older populations is crucial.

Once the cost effectiveness of telerehabilitation approaches has been established, clinicians require more information on acceptance patterns of older adults and modifying factors before widespread uptake is likely. It has been suggested that technology acceptance in older adults may be lower because they weigh the time required to learn the technology against the perceived usefulness[166]. As a result new skills are needed from therapists delivering rehabilitation using technologies and in particular providing older stroke survivors with a motivating context related benefit is likely to be important[167]. Older people are heterogeneous and many are familiar with technologies but it seems likely that older people with minimal exposure to technologies will require longer training times than younger patients. Fear of failure is known to be a greater problem in older populations compared to younger patient groups so identifying prior experience with technologies should influence the amount of time allocated for training[167]. Overall, the effective introduction of technologies to deliver rehabilitation requires highly usable designs which are appropriate for people with impairments (vision, dexterity, cognition) and adequate training.

Finally despite the emergence of novel technological therapies there has been little progress with key secondary complications of the upper limb post stroke which are more common in older stroke survivors [168] and may significantly impact on quality of life. Complications such as shoulder pain and spasticity are extremely common and warrant particular focus of research. In fact, prevention or effective management of these complications in turn will allow the stroke survivor to more successfully access emerging technologies.

Table 3. Executive Summary

Prognostication of Upper Limb Recovery Post Stroke
▪ Early, accurate assessment of the likelihood of an upper limb recovering motor function would assist in targeting / stratifying appropriate interventions, ▪ Predictors of potential motor recovery include initial severity of motor impairment, location and size of lesion, and integrity of descending motor tracts; caregiver support is also predictive. ▪ Age alone is not a strong predictor of rehabilitation or recovery potential
Rehabilitation Strategies for Upper Limb Restitution and / or Compensation
▪ Repetitive task specific training is supported by evidence and offers meaningful context to patients; evidence for bimanual training is less robust. ▪ Virtual reality and gaming strategies may offer an adjunct to therapies, though applicability in an older population needs further research. ▪ Constraint-induced movement therapy is an effective treatment option in a select group of compliant patients with sufficient motor activity. ▪ Neuromuscular electrical stimulation may reduce shoulder pain and spasticity, but evidence is conflicting regarding effect on motor recovery.
Implementation of Evidence into Practice
▪ Audits of the implementation of National Guidelines on Stroke Rehabilitation for upper limb continue to reveal uneven implementation of best practice e.g. constraint therapy protocols are rarely implemented. ▪ There is consensus on many effective therapies for upper limb rehabilitation which should

start early and be provided in an adequate "dose". However, when resources are rationed older people may be excluded from accessing stroke rehabilitation therapies. While older people and carers have direct access to information on best practice rehabilitation via national stroke organization websites they have little input into decision making on program priorities. New funding models which include consumers and carers in decision making are needed.

Future Perspectives

- Rehabilitation for the upper limb is evolving but simple treatments for secondary complications of the upper limb post stroke (e.g. shoulder pain) are lacking.
- One strategy to deal with the increasing demand for rehabilitation is earlier decision making around whether therapy is focused on compensatory or restorative goals. New protocols combining early TMS and repeated standardized clinical assessments in the first weeks are being tested and seem likely to change clinical practice.

Chapter Three

Literature Review

Hemiplegic Shoulder Pain

Suprascapular Nerve Block

3.1 Literature Review – Hemiplegic Shoulder Pain

Overview

The previous chapter provides an overview of the impact of stroke on the upper limb. Frequent upper limb deficits have been described and evidence for treatment options summarised.

The need for greater research focus on the common complications of upper limb impairment narrows the focus of the literature review presented in this chapter.

Hemiplegic shoulder pain is the central theme of this thesis. In order to provide a strong clinical context, this chapter will review the current evidence regarding the following pertinent aspects of:

- Epidemiology of hemiplegic shoulder pain
- Aetiology of hemiplegic shoulder pain
- Impact of hemiplegic shoulder pain
- Prophylaxis and treatment of hemiplegic shoulder pain

3.1.1 Epidemiology of Hemiplegic Shoulder Pain

Hemiplegic shoulder pain is one of the four most common complications of stroke[15], second only to depression[169]. Kalichman and Ratmansky (2011) summarise 22 studies on the prevalence of hemiplegic shoulder pain from 1971-2009[55]. Studies vary in sample size from 20-1000 participants, and report gross variations in prevalence between 5-84%. The summary table (**Table 1)** from this article has been modified to reflect only those studies of prevalence conducted in the last two decades, as well as to add more recent studies and details of study design which may account for outcome disparities.

Disparities in rates likely reflect inconsistent definitions of HSP, inclusion / exclusion criteria, timing of assessment, and study populations[32, 39, 55]. It is worth noting, however, that studies of selected rehabilitation inpatient populations report higher rates of HSP, reflecting a subset of stroke survivors admitted. The higher rate of HSP in inpatient rehabilitation adds further weight to the need for greater focus on this at-risk population.

Recent population based studies from New Zealand[170] Sweden[22] and Denmark[171] have reported more conservative prevalence rates of 23%, 30%, and 15% respectively (highlighted in Table 1). Ratnasabapathy et al[170] conducted a populated-based study in New Zealand in 2003, with analysis of self-reported shoulder pain on survivors from a total of 1761 stroke events. They concluded an increasing rate of pain during follow up, 17% at one week, 20% at one month, and 23% at six months. No objective measures were included in the data collection. In comparison to this, the more recent Swedish study by Lindgren et al 2007[16] included both subjective and objective measures of 327 patients stroke survivors from initial number of 416. Objective measures included supination in 90° of upper limb elevation (graded as 1 – loss of motor function, 2 - reduced motor function, 3 –

normal motor function), presence or absence of sensory deficit, and measure of subluxation. All measures were taken at baseline, 4 months and 16 months. Overall prevalence of 30% within the follow up period is reported, with rates of 22% and 24% (new and persistent pain) noted at 4 and 16 months respectively. The Danish population-based follow up study achieved a 63% response rate to a pain questionnaire sent 2 years following stroke onset; 608 responders from 964 stroke survivors identified from a National Database. New onset of hemiplegic shoulder pain within 2 years from stroke onset was reported by 15% of responders.

No Australian population-based studies have reported on the incidence or prevalence of hemiplegic shoulder pain for comparison. Australian population-based studies focussing on stroke outcomes, such as the The North East Melbourne Stroke Incidence Study (NEMESIS)[25] and the Perth Community Stroke Study[172] have focused on other factors such as quality of life and stroke incidence respectively.

Table 1. Prevalence of Hemiplegic Shoulder Pain (modified from Kalichman and Ratmansky[55])

Author	**Year**	**Origin**	**Setting**	**Study Population**	**Length of follow up**	**Prevalence of HSP, *n (%)***
Jespersen et al[173]	1995	Denmark	Rehabilitation Hospital	Retrospective review of 173 consecutive patients admitted to rehabilitation unit with stroke	6 months	38 (22)
Wanklyn et al[18]	1996	England	Cohort study	108 inpatients with stroke; mean age 71	6 months	69 (63.8)
Zorowitz et al[174]	1996	United States	Rehabilitation Hospital	26 inpatients with stroke and subluxation	Single assessment	9 (45)
Gamble et al[175]	2002	England	Cohort study	123 consecutive patients with acute stroke	6 months	49 (40)
Ratnasabapathy et al[170]	2003	New Zealand	Population-based study	All cases of stroke over 12 month period n=1201 at 6 months	6 months	284 (23)
Aras et al[19]	2004	Turkey	Rehabilitation Hospital	85 consecutive patients with stroke and hemiplegia	Single assessment	54 (63.5)
Lindgren et al[16]	2007	Sweden	Population-based study	416 consecutive first ever stroke; n = 327 at 4 months n= 305 at 16 months	16 months	 71 (22) at 4 months 74 (24) at 16 months (new and recurrent) 99 (30) overall
Dromerick et al[176]	2008	United States	Rehabilitation Hospital	46 consecutive admissions to stroke rehabilitation unit	Single assessment	17 (37)
Sackley et al[177]	2008	United Kingdom	Multicentre cohort study	122 participants with stroke diagnosis identified via Stroke Register	12 months	67 (55) – any pain 64 (52) – HSP

Suethanapornkul et al[178]	2008	Thailand	Multicentre cohort study	327 patients from 9 rehabilitation centres across 9 months	Duration of rehabilitation admission	62 (19)
Barlak et al[179]	2009	Turkey	Rehabilitation Hospital	187 consecutive patients with first unilateral stroke	Single assessment	114 (61)
Klit et al[171]	2011	Denmark	Population-based follow up design	964 stroke survivors identified via National Stroke Database: 608 stroke survivors responding to questionnaire sent 2 years post-stroke	Single questionnaire	92 (15.1) with shoulder pain within 2 years of stroke onset
Hansen et al[180]	2012	Denmark	Hospital: Stroke Unit	299 consecutive inpatients with stroke; 275 assessed at 6 months	6 months	45 (16.4)
Joy et al[181]	2012	India	Rehabilitation Hospital	Prospective study of 140 hemiplegic patients aged 40-80 years admitted over 2 year period	6 months	52 (48)
Fabunmi et al[182] *Conference proceedings*	2014	Nigeria	Multicentre descriptive cohort study	102 patients with stroke across 6 hospitals	12 months	75 (73.5)

3.1.2 Aetiology of Hemiplegic Shoulder Pain

There are multiple possible causes of hemiplegic shoulder pain, including nociceptive pain, peripheral neuropathic pain, central neuropathic pain, or a combination of these[183]. In fact, more than thirty causes of acute hemiplegic shoulder pain have been identified[184]. Combined causative factors may exist independently of each other, or one might trigger the development of another[185]. An estimated one third of patients have multiple contributing aetiologies[30].

Wilson et al (2011) propose a model where acute and chronic hemiplegic shoulder pain may be explained by differing aetiologies[184]. The authors postulate that direct causes of acute HSP may be distinct from maladaptive central nervous system sensitisation associated with chronic or persistent pain presentations[184]. This theory was further explored by Roosink et al (2011)[186] with a small sample assessment comparing cortical somatosensory processing between chronic stroke rehabilitation patients (greater than 6 months post stroke) with and without pain, and healthy controls. This study[186] observed reduction in cortical processing across all stroke patients, more marked in those with chronic hemiplegic shoulder pain.

Kalichman and Ratmansky[185] suggest delineating underlying pathologies into 3 main groups:

1. Soft-tissue lesions
2. Impaired motor control
3. Altered peripheral and central nervous system activity

Soft tissue lesions

The most common soft tissue injuries affecting the shoulder following stroke include rotator cuff pathologies[55], biceps tendonitis[55], adhesive capsulitis[55], myofascial pain[55], bursitis[39] and impingement[39]. Nociceptive soft tissue injuries can result from the two other aetiological categories of impaired motor control and altered peripheral and central nervous system activity[55, 187]. Additionally, repetitive trauma and improper manual handling may contribute[39, 187]. Soft tissue pathologies such as adhesive capsulitis (frozen shoulder) can be either a cause or effect of hemiplegic shoulder pain[17, 39]. Yi et al[188] compared properties of the glenohumeral joint capsule between controls, patients with adhesive capsulitis and patients with HSP. They observed that capsular stiffness was increased in patients with HSP, but not to the same extent as in adhesive capsulitis.

Biomechanical and kinematic changes around the shoulder joint can typically present with lateral scapular rotation and reduction in glenohumeral range[189]. A 2008 study of MRI findings in patients with hemiplegic shoulder pain demonstrated that 35% had MRI findings of at least one rotator cuff, bicep or deltoid muscle impairment, and 53% had MRI findings of tendinopathy[190]. Over-interpretation of imaging findings is cautioned, however, with a later study[23] performing enhanced MRI and ultrasounds on 41 stroke patients (25 with hemiplegic shoulder pain, 16 without hemiplegic shoulder pain) concluding that only capsulitis was independently associated with pain. Pompa et al (2011)[191] performed a pilot study using enhanced-MRI to evaluate hemiplegic shoulder pain. In a sample of 41 patients (average one month post stroke onset), the authors concluded that capsulitis was the most common aetiology identified in those with hemiplegic shoulder pain[191]. The routine use of MRI poses a cost / benefit question that needs to be assessed with larger samples and compared with clinical assessment outcomes. Dogun et al[192, 193] compared ultrasonography and MRI findings in a cohort of 68 patients with hemiplegic shoulder pain, describing common

musculoskeletal injuries. The authors observed inconsistencies between the findings using each modality, and recommended MRI as the evaluation of choice in HSP.

Impaired motor control

Upper motor neuron lesions can cause typical changes with loss of motor control / reduced motor function and changes in muscle tone. Early deficits tend to reflect flaccidity in tone, whereas spasticity changes develop with time. With the stability of the shoulder significantly dependent on muscle function, hypotonia of muscles of the shoulder girdle can lead to significant instability[55], postural malalignment[33] and potentially glenohumeral subluxation. These elements can be identified as risk factors for subsequent soft tissue injury[194]. Subluxation may itself be a cause of shoulder pain, but evidence is conflicting and correlations remain controversial[7, 55]. Not all patients with subluxation have pain, and not all patients with pain have subluxation[32, 178, 195].

Altered peripheral and central nervous system activity

Neuropathic pain elements can include peripheral nerve entrapment associated with impaired motor control[55], though there may be central mechanisms at play in the development of complex neuropathic pain presentations[187, 196].

Benlidayi[187] further categorises central nervous system related presentations into 3 categories:

i. Neglect and sensory impairment
ii. Central Post Stroke Pain (CPSP) - disruption of spinothalamocortical system
iii. Central Sensitisation

The understanding of the more complex central nervous system contributions to pain is a growth area in current research. Somatosensory deficits, predominant in right hemisphere lesions, can complicate pain presentations[22]. Inconclusive theories[39] regarding central sensitisation postulate impaired neural control of the sympathetic system[33, 194], enhanced neuronal excitability[55 197], and involvement of multiple levels of the somatosensory neural-axis[196].

Multiple and often overlapping contributing factors make definitive aetiological diagnosis of hemiplegic shoulder pain a clinically difficult problem[185]. Further to this, difficulty in precise assessment of aetiology makes treatment selection even more problematic[39]. Current treatment strategies largely target the better understood biomechanical contributors to pain, without significant attention to central pain components. This approach frequently does not provide adequate relief of symptoms[183].

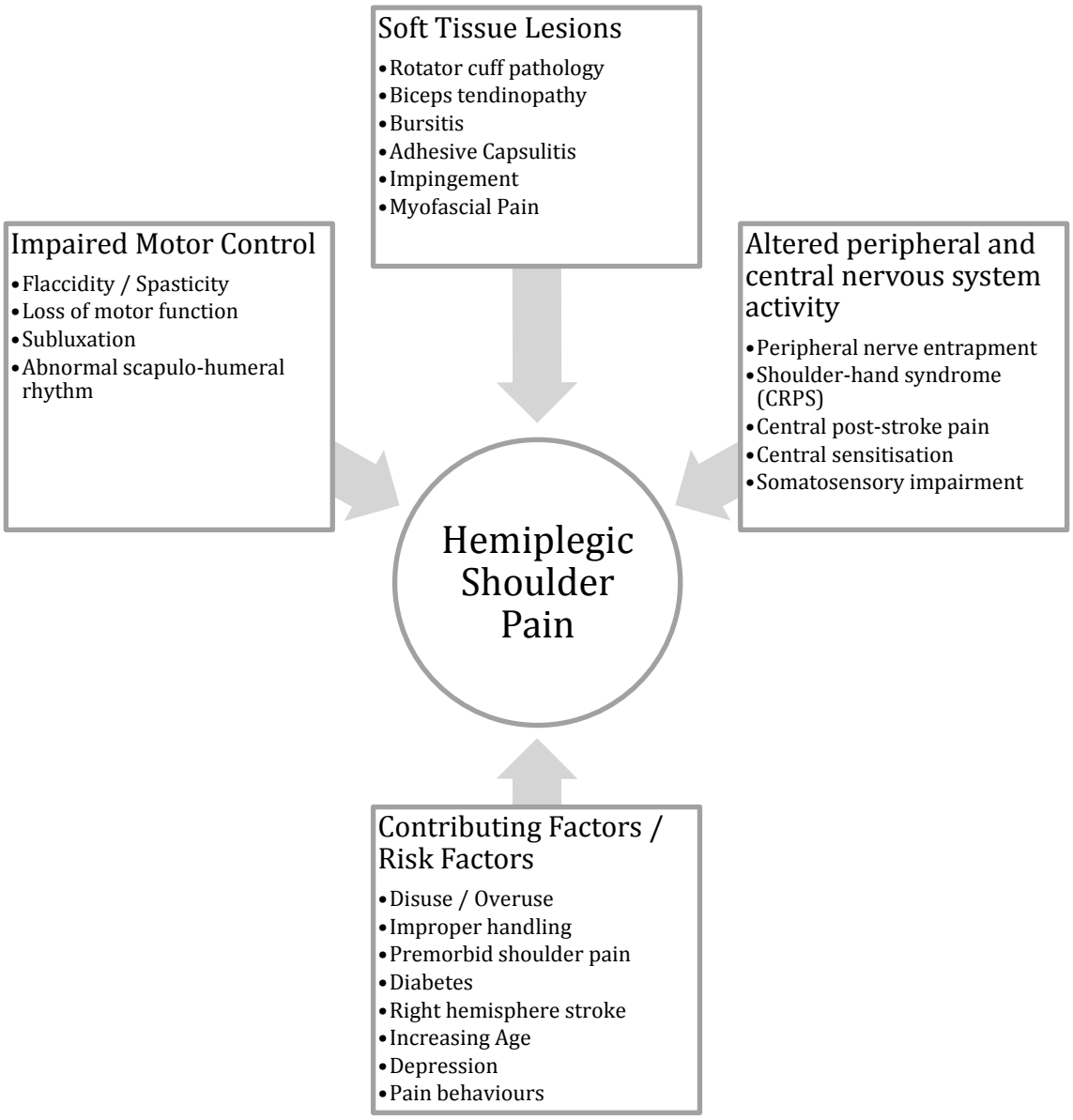


Figure 1. Potential Contributors to Hemiplegic Shoulder Pain

Adapted from Kalichman and Ratmansky[31, 55], Roosink et al[183], Demirci et al[198], Benlidayi[187] and Lindgren et al[199]

3.1.3 Impact of Hemiplegic Shoulder Pain

Hemiplegic shoulder pain is a common complication of stroke. Its prevalence alone, however, is not the primary motivation to improve its management. From a rehabilitation perspective, and in the context of the previously discussed ICF model, proximal upper limb pain can be seen to contribute to activity level impairments of distal function, postural alignment and balance. Reduced autonomy can impact an individual's body image and sense of self. Activities of daily living, successful transfers, and subsequent level of dependence, stem from functional limitations. Upper limb pain is the most common stroke-related cause of reduced participation[200]. Review of the literature reveals the multiple and significant areas of impact associated with the presence of hemiplegic shoulder pain.

Table 2. The Impact of Hemiplegic Shoulder Pain

Evidence of the Impact of Hemiplegic Shoulder Pain	
	Worsens global outcome [23]
	Reduces functional recovery[39, 55 201]
	Leads to serious disability[39]
	Reduces sleep quality[55]
	Depression [22 55, 201]
	Increases length of hospitalisation[18, 20, 21, 55, 201]
	Interferes with rehabilitation process [20, 21, 201]
	Lowers rate of discharge home[21]
	Limits access to developing technological upper-limb rehabilitation techniques[176]
	Impacts pain related quality of life[202]

Most studies regarding the impact of pain on quality of life following stroke are confined to selected series and limited outcome measures (see Table 3). In 2007, Chae et al[202] conducted a study on 61 volunteer participants with post-stroke shoulder pain. They concluded that hemiplegic shoulder pain affected pain-related quality of life, but they were unable to draw conclusions about the impact of pain on motor impairment of activity limitation. Other studies, including the large population-based North East Melbourne Stroke Incidence Study (NEMESIS)[25], have explored variables associated with health-related quality of life following stroke, though not specifically HSP. There have been no previous Australian population-based studies that have specifically reviewed the impact of hemiplegic shoulder pain on quality of life (QoL).

Evidence is lacking regarding the explicit impact of specific hemiplegic shoulder pain on health-related quality of life (HR-QoL) in an unselected population.

Table 3. Studies Examining Pain and Quality of Life in Stroke Populations

Author and Year	Sample (n)	Study Design	Quality of Life Outcome Measure	Outcome
SELECTED CLINICAL SAMPLES:				
Chae et al 2007[202] United States of America	61 volunteer outpatients with hemiplegic shoulder pain (HSP)	Cross-sectional, secondary analysis of baseline data from a multisite clinical trial	Brief Pain Inventory (BPI) Question 23 to assess pain-related QoL	HSP impacts QoL
Kong et al 2004[203] Singapore	177 outpatients with stroke diagnosis	Cross-sectional survey	Short-form health survey (SF-36)	High pain report (any) Pain not associated with reduced QoL
Naess et al 2012[204] Norway	328 patients with stroke diagnosis	Questionnaire sent to all surviving stroke patients admitted over 2 year period	HRQoL measures by 15D and EuroQol, EuroQol VAS	Pain, fatigue, and depression associated with QoL
Widar et al 2004[205] Sweden	43 patients with stroke diagnosis and chronic pain	Interview and questionnaires	Short-form health survey (SF-36)	Chronic pain associated with reduced QoL Concluded need for population based studies
UNSELECTED POPULATION SAMPLES:				
Hackett et al 2000[206] New Zealand	639 patients at 6 year follow up post stroke (of 1761 initial participants in Auckland Stroke Study 1991-1992)	Population-based case-control study with an age- and sex-matched control population	Short-form health survey (SF-36)	HR-QoL relatively good at for survivors of stroke at 6 year follow up

Appelros 2006[207] Sweden	377 consecutive patients in population-based study	Baseline and 1 year follow-up.	Nil specific QoL measure	11% with stroke-associated pain Pain associated with depression Comment on impact on QoL but no specific measure reported
Sturm et al 2006[25] North East Melbourne Stroke Incidence Study (NEMESIS)[25] Australia	Patients with first ever strokes over one year period:381 strokes in 353 people	Population-based study	Assessment of quality of life tool (AQoL)	Reported on factors impacting HR-QoL 2 years following stroke (not inclusive of HSP)

3.1.4 Prophylaxis and Treatment of Hemiplegic Shoulder Pain

Review articles into the management of hemiplegic shoulder pain have demonstrated a lack of robust evidence for best practice, and highlight the need for further research[34, 194]. Whilst there are complexities in the specific identification of pain which has multiple aetiologies, there is a lack of high quality or definitive outcome studies[201]. The National Stroke Foundation guidelines reflect the lack of high grade evidence specific to hemiplegic shoulder pain, with the main management recommendation to use interventions for 'acute musculoskeletal pain'.

Table 4. National Stroke Foundation Guidelines

Section 7.6 NSF: PAIN (7.6.1 Shoulder Pain)[36]

National Stroke Foundation Guidelines: Shoulder Pain	**Evidence Grade**
For people with severe weakness who are at risk of developing shoulder pain, management may include: • Shoulder strapping • Education of staff, carers and people with stroke	 B Good practice point
For people who develop shoulder pain, management should be based on evidence-based interventions for acute musculoskeletal pain	Good practice point
The routine use of the following interventions is NOT recommended for people with shoulder pain • Intra-articular steroid injection • Ultrasound	 C C

Pertinent results of reviews and research on individual therapy options are summarised below.

Prophylaxis

The idiom that 'prevention is better than a cure' resonates in a population where there is little evidence to support treatment of established pain. Education, positioning and protection of the 'at-risk' upper limb make good clinical sense, though evidence for these prophylactic strategies is limited[39]. These measures remain 'good practice points' in recommendations[187] and guidelines[36]. A 2005 Cochrane review[208] concluded that there was insufficient evidence that supportive devices (slings, orthoses) are effective in the prevention or treatment of subluxation of the shoulder or subsequent development of shoulder pain. In 2006, a randomised controlled trial of placebo strapping compared to therapeutic strapping in 33 participants over a 4 week period in stroke rehabilitation showed shoulder pain could be prevented in 9 out of 10 patients considered at risk of developing pain[209]. The authors postulated that earlier therapeutic strapping may offer superior protection, in keeping with risk of soft tissue injuries during the early flaccidity phase[194]. Positioning in conventional protective slings might promote synergist postures[17] or distal disuse. Newer sling designs provide vertical glenohumeral support via a proximal humeral cuff and figure of eight strapping across the back, hence leaving the upper limb in a functional position for balance and use of the distal arm. These newer slings are anecdotally well tolerated, and in current use in rehabilitation settings, though an evidence base is yet to be established.

Manual Physiotherapy Interventions

Literature exists describing the individualisation of therapy interventions based on patient need, as well as clinician experience and preference. The variables associated with therapy selection are difficult to control for in research trials, resulting in a paucity of high grade evidence. Physiotherapy techniques such as Bobath therapy are commonly practiced, with the target of reducing tone and promoting normal movement patterns in the recovering limb. There is Level 1b evidence that Bobath techniques reduce HSP more than passive cryotherapy. It is now widely accepted that aggressive mobilisation with forceful overhead pulleys should not be recommended[194], with gentle range and exercise as a preferred approach[210]. Static positional stretches are also out of favour, with Level 1b evidence that both of these previously endorsed interventions may actually increase shoulder pain.

Functional Electrical Stimulation

Functional Electrical Stimulation (FES) is a form of Neuromuscular Electrical Stimulation (NMES) as described in Chapter 2 (page 29). The use of FES in the post-stroke upper limb has predominantly focussed on functional recovery, reduction of subluxation, and reduction of spasticity [39]. In 2008, a Cochrane review of 4 trials with small patient numbers concluded that there was insufficient evidence to guide the use of FES to treat or prevent hemiplegic shoulder pain[211], which reflects conflicting evidence in both acute and chronic hemiplegic shoulder pain over recent years. A randomised trial[212] published in 2013 assessed the impact of combined static stretching with electrical stimulation, with no reduction in shoulder pain, range or function demonstrated. The ideal intensity of FES treatment is thought to be 6 hours per day, 5 days per week for a total of 6 weeks. This presents logistical barriers in the context of appropriate application, as well as FES unit

availability both within and external to inpatient rehabilitation settings. These observations have led to the growing interest in experimental and potentially more efficacious[39] implantable percutaneous or intramuscular stimulation devices. Intramuscular electrical stimulation showed significantly better long term effects compared to hemisling[195], and more importantly early pilot and case studies are showing promising results with improved patient tolerance and significant reduction in pain with the use of single lead implanted devices[184, 213, 214].

Botulinum Toxin A

Kong 2007[215] conducted a randomised controlled trial comparing intramuscular Botulinum Toxin-A (BoNT-A) to placebo in 17 participants with hemiplegic shoulder pain associated with spasticity. This trial demonstrated reduction in spasticity measures, but not reduction in pain in the intervention group. A systematic review in 2010 [195] similarly demonstrated no significant difference in outcome of pain between intramuscular BoNT-A and placebo. Pooled analysis of 5 randomised controlled trials in a 2011 Cochrane review by Singh and Fitzgerald[41] provided judicious support for the use of intramuscular BoNT-A in hemiplegic shoulder pain specifically deemed to be secondary to an aetiology of spasticity. Further exploring the effectiveness of BoNT-A in pain associated with spastic hemiplegia, a randomised controlled study published in 2012 (n=21) failed to demonstrate a reduction in hemiplegic shoulder pain by group allocation[216].

A novel pilot study[42] of intra-articular BoNT-A in 5 patients with refractory hemiplegic shoulder pain demonstrated promising reduction of pain, with randomised controlled trials recommended. Nevertheless, at this stage no convincing evidence exists for the routine use of Botulinum Toxin in hemiplegic shoulder pain.

Intra-articular and Subacromial steroid injection

Intra-articular steroid injection is not recommended as a routine treatment option in hemiplegic shoulder pain[36]. Randomised controlled trials have not demonstrated a statistically significant reduction in HSP following intra-articular injection[195 217]. Trials which have targeted known soft tissue pathologies (impingement, tendonitis, bursitis) have demonstrated more promising results for the use of corticosteroid injection (intra-articular or subacromial)[43]. Viana et al 2012[218] reviewed interventions for chronic HSP and concluded there was a role for intra-articular injections in patients with pain persisting greater than 6 months.

Subacromial injections appear to be an effective treatment for appropriately selected patients with HSP. This is supported by a randomised controlled trial[219] of 58 participants with HSP and evidence of a rotator cuff disorder where a superior reduction in pain and disability was demonstrated in the group receiving injection as compared to placebo. The sub-population in this trial was narrowly selected, with exclusion of any patients with CRPS, biceps tendon disorders, severe spasticity, shoulder subluxation, severe motor weakness, primary osteoarthritis, or presence of another obvious cause of pain.

Table 5. Summary of Evidence for Prophylaxis and Treatment of Hemiplegic Shoulder Pain

Intervention	**Summary of Evidence**	**Key Studies**				
		Author and Year	Study Design	Sample (n)	Outcome Measures	Conclusion
Prophylactic Stretching	Good practice point (clinical experience /expert opinion)[39, 194] Limited evidence specific to pain in individual studies[212, 220]	Gustafsson and McKenna 2006[220]	Randomised controlled trial (RCT) Positional stretching programme compared to upper limb support only	n = 32 Patients with first ever stroke admitted to rehabilitation hospital	Pain-free range of motion (external rotation) Pain score (rest and on movement) Motor recovery Functional independence	No significant difference in hemiplegic shoulder pain by group allocation
		De Jong et al 2013[212]	Multicentre randomised controlled trial 8 week program of arm stretching combined with electrical stimulation compared to sham control	n = 46 Patients with subacute stroke and severe upper limb motor deficit	Passive range of motion Presence and severity of hemiplegic shoulder pain Restrictions in daily living Tone Motor control and subluxation	Combined arm stretch and electrical stimulation does not improve range of motion, pain or function in patients after stroke
Prophylactic supportive devices (e.g. sling)	Insufficient evidence to support routine use[221]	Ada et al 2005[221]	Cochrane review	4 trials Total of 142 participants	Trials reported on the following outcomes: Subluxation Shoulder range Shoulder pain Upper limb function Contracture	Insufficient evidence to conclude whether supportive devices prevent pain or subluxation, improve function or impact contracture development

Prophylactic Strapping	May offer superior protection for those at risk of HSP[209] Level B evidence[36]	Griffin and Bernhardt 2006[209]	Randomised controlled trial	n = 33 Patients with stroke and low /; no muscle function at shoulder; considered 'at risk' of developing HSP 4 weeks of therapeutic strapping compared to placebo strapping	Number of pain-free days Range of movement Tone	Therapeutic strapping limited development of hemiplegic shoulder pain during rehabilitation in at risk stroke patients
Therapeutic strapping for established pain	Low level evidence that may reduce HSP (but not improve function)[32]	Pandian et al 2013[222]	Multicentre randomised controlled trial	n = 162 First ever stroke Shoulder taping compared to sham taping	Pain Function	Trend towards pain reduction and functional improvement, but did not reach significance
Education (patient and staff)	Good practice point [36]	-	-	-	-	-
Manual handling guidelines	Good practice point[30, 39]	-	-	-	-	-
Mobilisation / Manual therapies	Strong evidence that aggressive range of motion therapy likely to increase HSP[194, 223] Gentle passive range to maintain range of motion is supported[194]	Kumar et al 1990[224]	Randomised trial	28 patients with hemiplegia Allocated to one of 3 interventions groups: Range by therapist Board assisted range Overhead pulley	Pain incidence	Overhead pulley significantly associated with development of pain (62% as compared to 8% and 12% in other treatment groups)
Functional Electrical Stimulation (FES) as prophylaxis	Insufficient evidence that FES prevents HSP[211]	Price et al 2008[211]	Cochrane review	4 trials Total of 172 participants	Pain incidence Pain severity	No significant change in pain incidence or intensity; insufficient evidence

Functional Electrical Stimulation (FES) as treatment	Limited evidence that may reduce pain if used at ideal dosage/ intensity[211] Promising pilot studies evaluating implantable neuromuscular stimulation[184, 213, 214] but further studies needed	Price et al 2008[211]	Cochrane review	4 trials Total of 172 participants	Pain incidence Pain severity	No significant change in pain incidence or intensity; insufficient evidence
		Snels et al 2002[225]	Literature review of interventions for hemiplegic shoulder pain	14 studies identified	Pain	Poor-moderate methodological quality of selected trials – unable to make definitive conclusions. FES one of the most promising interventions
		Wilson et al 2010[184]	Case report	n = 1 59 year old male with chronic refractory HSP Single lead percutaneous peripheral nerve stimulation (6 hours day for 3 weeks)	Pain Pain interference Quality of life Pain-free external rotation range	Case study demonstrates effectiveness and feasibility of intervention.
		Yu et al 2010[213]	Case report	n = 1 58 year old male with chronic HSP Electrical stimulation with fully implanted microstimulator (6 hours / day for 12 weeks)	Pain Passive range of motion Motor function Sensation Subluxation Quality of life	50% reduction in HSP at 3 months Improve range and motor function Other outcome measures unchanged. Device well tolerated
		Nguyen et al 2015[214]	Case report	n = 1 Patient with refractory HSP	Pain Quality of life	75% reduction in HSP during trial phase. Complete resolution of pain whilst implanted device active.

Interferential current stimulation	Small sample RCT evidence supports interferential superior to placebo treatment[192]	Suriya-Amarit et al 2014[192]	Randomised controlled trial	n = 30 Patients with hemiplegic shoulder pain randomised to receive either interferential or placebo	Shoulder Pain Pain-free passive range of motion	Interferential reduces pain during movement and increases pain-free range of motion
Analgesia	Level 2 evidence that oral non-steroidal anti-inflammatories can reduce HSP in patients during therapy session Gabapentin effective and well tolerated[226]	Kesiktas et al[226]	Randomised controlled trial	n = 100 patients with hemiplegia randomised to receive gabapentin 800mg or paracetamol 1500mg daily	Range of external rotation Shoulder pain Spasticity Function	Some improvement in both groups Gabapentin statistically superior for pain reduction. Well tolerated in study

Intra-articular and Subacromial Steroid Injections	Routine use not recommended[36, 194] Limited evidence supports use of steroid injection in selected patients[43, 219]	Snels et al 2000[225]	Randomised controlled trial	n = 37 Patients with hemiplegic shoulder pain randomised to receive either 3 x intra-articular triamcinolone acetonide injections or placebo	Pain Arm function Passive external rotation of shoulder	Reduction in hemiplegic pain scores in the intervention group were greater than placebo, but did not reach statistical significance
		Lakse et al 2009[43]	Randomised controlled trial	n = 38 Participants with hemiplegic shoulder pain randomised to receive active injection (intra-articular OR subacromial) versus placebo	Passive range of motion Pain	Reduction of pain in intervention group Recommend use of injections in appropriately selected patients
		Rah et al 2012[219]	Randomised controlled trial	n = 58 Participants with hemiplegic shoulder pain and evidence of rotator cuff pathology Randomised to receive subacromial triamcinolone injection or lidocaine (placebo)	Pain Function Shoulder disability Active range of motion	Subacromial injection showed improvement in pain, disability and range up to 8 weeks post injection in a group of selected patients with evidence of rotator cuff disorder.

Botulinum Toxin	Conflicting evidence that intramuscular Botulinum A (BoNT-A) can reduce HSP associated with spasticity[41, 215, 216] Preliminary studies indicating intra-articular BoNT-A could be an effective treatment for refractory HSP[42]	Singh and Fitzgerald 2011[41]	Cochrane review	6 trials (all RCT) Total of 164 participants 5 trials included population with post-stroke shoulder pain; 1 trial with non-stroke pain Intramuscular BoNT-A compared to placebo	Pain Disability Abduction range	Small sample sizes Demonstrated that single BoNT-A injection reduced pain, reduced and disability and improved abduction range (chronic pain associated with spastic hemiplegia)
		Kong et al 2007[215]	Randomised controlled trial	n = 17 Randomised to receive single injection BoNT-A (biceps and pectoralis major) or placebo	Pain Tone	No significant difference in pain outcome by group allocation. BoNT-A injection reduced spasticity
		Marciniak et al 2012[216]	Randomised controlled trial	n = 21 Participants with significant post-stroke shoulder spasticity BoNT-A (pectoralis +/- teres major) versus placebo	Pain Disability Upper limb function Range of motion Spasticity	Pain reduction at 4 weeks was independent of group allocation Selected disability measures improved in intervention group
		Castiglione et al 2011[42]	Pilot study	n = 5 Patients with severe refractory HSP at rest Intra-articular BoNT-A injection	Pain at rest and on passive movement	Significant pain reduction at 2 and 8 weeks post injection RCT study required

3.2 Literature Review – Suprascapular Nerve Block

Overview

Following on from the preceding review of the current status of evidence in management of hemiplegic shoulder pain, this section further explores the suprascapular nerve block as a potential treatment option in a post stroke population. An emerging therapy option, Suprascapular nerve block has not yet been included in the systematic reviews regarding management strategies in hemiplegic shoulder pain.

The anatomy of the Suprascapular Nerve and the mechanism of blockade are outlined. Building on this basic procedural understanding, the evidence of this technique is then critically reviewed.

The Suprascapular nerve block is supported as an effective treatment of shoulder pain in non-stroke populations, but there is a lack of robust evidence for the use of this technique specifically for hemiplegic shoulder pain in populations of stroke survivors.

3.2.1 Anatomy of the Suprascapular nerve

The suprascapular nerve is a mixed motor and sensory peripheral nerve which provides the main sensory supply to the shoulder. An understanding of the origin, location and innervation of this nerve (Table 5) provides the framework for the procedural components of nerve blockade.

Table 6. Suprascapular Nerve: Origin, Location and Innervation

Origin
Peripheral nerve arising from the upper trunk of the brachial plexus (ventral rami of (C4),C5, C6) See Figure 2
Location[227]
Anatomic cadaveric study to measure location of Suprascapular Nerve: "Passes posterolaterally from its origin, through the suprascapular foramen, to reach the posterior scapular region, where it lies in the plane between bone and muscle" See Figure 3
Innervation[7, 228]
Motor and sensory components. Innervates Supraspinatus muscle and Infraspinatus muscle Branches to Glenohumeral and Acromioclavicular joints Branches to Trapezoid and Coracoacromial ligaments Subacromial bursa Sympathetic innervation to joint capsule (superior and posterior components) *Provides 70% of the sensation to the shoulder articulation*[228]

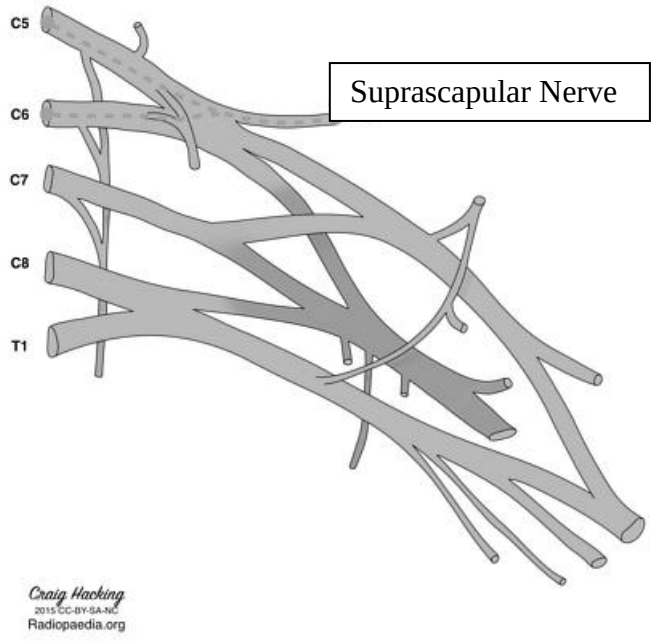


Figure 2. Brachial Plexus as Origin of Suprascapular Nerve
http://radiopaedia.org/images/13728351

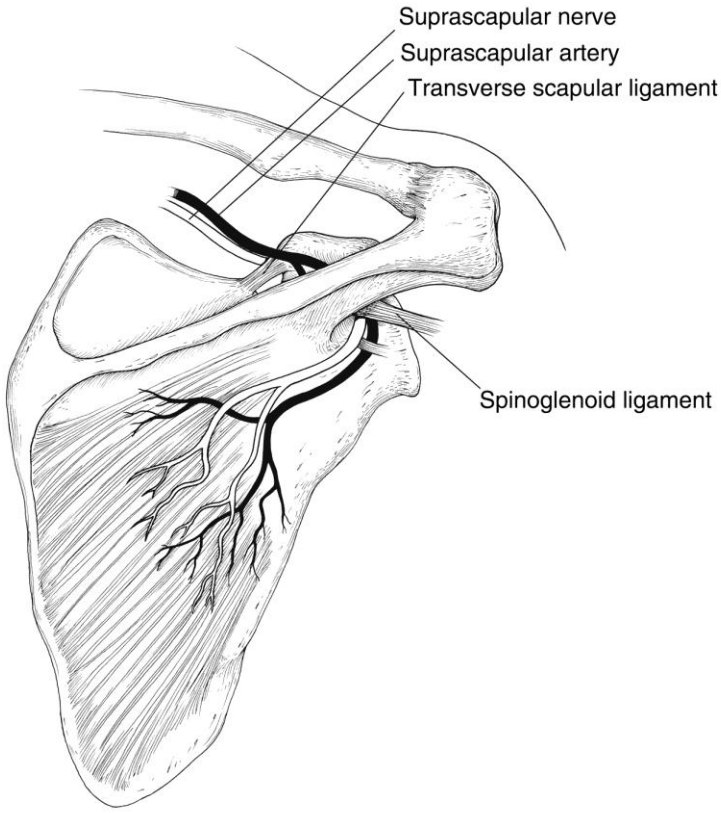


Figure 3. Anatomical Location of the Suprascapular Nerve (posterior view)
https://www.jaaos.org/content/17/11/665/F1.large.jpg

3.2.2 Suprascapular Nerve Block: Procedural Technique

Introduction to the Suprascapular Nerve Block

Suprascapular nerve block (SSNB) is not a new technique for chronic shoulder pain in non-stroke populations, having been first described in 1941[229]. Di Lorenzo and Domenico[7] describe SSNB as a technique "to help alleviate acute or chronic pain, help maintain treatment participation, reduce need for analgesia and potentially 'reset' the pain generators". It has been observed that the duration of effect of SSNB can outlast its anticipated pharmacological effects[230], with postulation that this may reflect an interruption in feedback amplification of pain response[231].

SSNB involves local administration of injection agents (long acting local anaesthetic and corticosteroid) to block the nerve. There are several techniques outlined in the literature, which have developed over time. The indirect technique described by Dangoisse et al[232] has been commonly adopted in non-surgical pain research[46], and proven effective in blocking the accessible sensory innervation to the shoulder[47]. This technique is deemed to reduce the risks of complications, including brachial plexus injury, pneumothorax and suprascapular vessel or nerve injury[228].

Research has explored the potential benefits of imaging guided SSNB, including fluoroscopy[233], ultrasound[234] and CT scan[235] guidance. These techniques allow smaller volumes of local anaesthetic due to more precise needle location, and potential for reduction in side effect profile. Comparison of CT guided injection with land-mark based SSNB did not demonstrate an improvement in clinical outcome or patient acceptability[235]. In contrast, ultrasound guided SSNB technique resulted in reduced complications and potentially longer duration analgesic effect[236].

Table 7. Suprascapular Nerve Block: Procedural Technique

Indirect Suprascapular Nerve Block Technique *(adapted from description by Dangoisse et al[232])*
Anatomical landmarks are used to identify injection location into supraspinous fossa • The examiner marks out each end of the spine of the scapula, as well as the angle of the scapula. • The point where a perpendicular line from the angle of the scapula intersects the spine of the scapula is identified • A further mark is identified approximately 2cm superior and lateral to the point of intersection Aseptic technique; antiseptic preparation of the skin is completed following identified of anatomical landmarks Injection preparation • 10ml 0.5% bupivacaine and 1ml 40mg/ml methylprednisolone are drawn up into a 10ml syringe Injection administration • Performed from posterior approach • Needle is introduced at point identified above, parallel to blade of scapula • bony floor of the supraspinous fossa provides feedback to injection position • draw back slightly off of floor of fossa, and ensure nil blood on syringe drawback • Full 11ml infiltrated slowly into supraspinous fossa

3.2.3 Suprascapular nerve block in non-stroke populations

Suprascapular nerve block has an established role as a safe and efficacious[45] treatment of non-stroke shoulder pain. Factors prompting further research in post stroke populations include the proven value in non-stroke shoulder pain, the large sensory innervation of the suprascapular nerve, and the potential benefits of feedback inhibition in the management of chronic pain.

Table 8. Evidence for Suprascapular Nerve Block in Chronic Non-Stroke Shoulder Conditions

Evidence Supports use of SSNB in the following Non-Stroke Populations **Acute and Chronic Conditions**
Post-operative pain / regional anaesthesia[47] Degenerative shoulder conditions[46] • Rheumatoid Arthritis[46 227, 231] • Osteoarthritis of Glenohumeral joint[237] Rotator cuff pathology[228, 238] Adhesive capsulitis / frozen shoulder[228, 239 227] Calcific tendinitis[228] Cancer[228, 237]

3.2.4 Suprascapular nerve block in stroke populations

With sensory innervation to approximately 70% of the shoulder, suprascapular nerve block is an emerging area of research as a potential treatment option in hemiplegic shoulder pain. Suprascapular nerve block is considered a safe, simple, and inexpensive treatment modality [240].

The protocol paper and randomised controlled study presented in this thesis represent the first adequately powered, randomised, placebo-controlled trial of suprascapular nerve block for hemiplegic shoulder pain. Chapter 5 details the rationalisation, methods and results. Other studies both prior and subsequent to the author's trial (highlighted) have been summarised in the Table 9. An early study by Lee and Khunadorn[241] hypothesised that a suprascapular nerve lesion may have aetiological significance in the development of hemiplegic shoulder pain. Results did not confirm this theory, and suprascapular nerve block was reported as a poor treatment option.

Two more recent trials have investigated suprascapular nerve block as compared to alternative treatments of therapeutic ultrasound[230] and intra-articular steroid injection[242] respectively. The small sample sizes and lack of placebo control make it difficult to draw conclusions from the results. Additionally, the exclusion criteria outlined by Yasar[242] limit the generalisability of results. Exclusions criteria comprised any patients with neglect, distal upper limb pain, neuropathic pain, pressure sores or infection, MMSE <24, language limitation, or degenerative changes on x-ray, or patients on oral analgesics. An interesting prospective open label cohort study by Di Lorenzo and Domenico[7] assessed repetitive suprascapular nerve blocks (every 3-4 days for 30 days). Pain reduction over 6 weeks follow up was greater in the intervention group (n=24 randomised to SSNB group from 47 enrolled participants), suggesting that repetitive nerve blocks may be an appropriate treatment option for refractory hemiplegic shoulder pain.

Table 9. Trials of Suprascapular Nerve Block for Hemiplegic Shoulder Pain (HSP)

Author and Year	Sample (n)	Study Design	Outcome Measure	Outcome
Lee and Khunadorn 1986[241]	30 male patients with HSP, mean time since stroke 30 months	SSNB to all participants	Suprascapular Nerve latencies (ms) Pain (VAS)[38, 243]	SSNB poor and failed to provide complete relief
Boonsong 2009[230]	10 Rehabilitation inpatients with HSP	Randomised to receive either SSNB or therapeutic ultrasound	Pain (VAS) Range of motion	Pain score reduction in both groups
Yasar 2011[242]	26 Rehabilitation inpatients with HSP	Randomised to receive either SSNB or intra-articular steroid	Pain (VAS) Range of motion	Both treatments effective
Adey-Wakeling et al 2013[151]	64 inpatients (Acute stroke and Rehabilitation wards) with HSP	Randomised Controlled Trial: SSNB compared to placebo	Pain (VAS) Disability (Croft)[244] Dependence (mRS)[245] QoL (EuroQoL)[246]	Safe and effective Statistically and clinically superior to placebo
Di Lorenzo & Domenico 2013[7]	47 Rehabilitation patients (inpatient and ambulatory) with HSP	Prospective cohort study	Pain (VAS) Rate of pain improvement	Effective pain relief via neural modulation with repetitive SSNB
Jeon et al 2014[247]	30 Rehabilitation inpatients with HSP	Randomised to one of 3 groups: SSNB alone, intra-articular steroid alone, or both	Pain (VAS) Range of motion	Reduction in pain over time, but no significant difference by allocation

HSP – hemiplegic shoulder pain
SSNB – suprascapular nerve block
VAS – visual analogue scale
ms – milliseconds
Croft – Croft Disability Index
mRS – modified Rankin scale
QoL – quality of life

Chapter Four

Epidemiology of Hemiplegic Shoulder Pain

4.1 Introduction to Publication

Publication 2: Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain After Stroke: A prospective population based study. *Archives of Physical Medicine and Rehabilitation* 2015; 96: 241-7

Purpose

The purpose of this study was to provide local incidence of hemiplegic shoulder pain within a defined metropolitan population in Adelaide, South Australia. Additionally, association and patterns of pain presentation were assessed to provide clinically relevant information regarding risk factors and potential treatment targets.

Published in

Archives of Physical Medicine and Rehabilitation

Impact factor 2.565

Contribution from primary author

This study was performed on data made available from an NH&MRC funded project (#565402). The candidate was not an investigator on the grant. The candidate was involved prior to the commencement of data collection, and worked with the investigators to specify the data items on shoulder pain to be included in the study.

The candidate was then responsible for direct training of the nursing staff that collected the data, and the development of a training video for shoulder assessment (see photos 1 and 2) used for further

training and refresher training of data collectors. Involvement in data collection at Southern Adelaide hospital sites was also the responsibility of the primary author.

The manuscript was written by the primary author, with consultation and review provided by the listed co-authors. The candidate conceived the research questions and completed the initial data analysis on shoulder pain following consultation with the statistician. Final analyses reported in the paper were run by the study statistician.

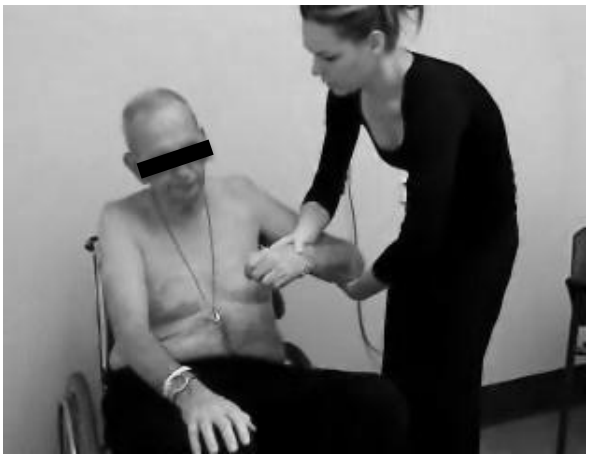


Photo 1 Image from Education Video: Objective Assessment of the Hemiplegic Shoulder *(participant provided consent of use of image)*

Photo 2 Image from Education Video: Objective Assessment of the Hemiplegic Shoulder *(participant provided consent of use of image)*

4.2 Publication 2

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain After Stroke: A prospective population based study. *Archives of Physical Medicine and Rehabilitation* 2015; 96: 241-7

Incidence and Associations of Hemiplegic Shoulder Pain After Stroke: A prospective population based study.

Abstract

Objective: To provide an epidemiological perspective of the clinical profile, frequency and determinants of post stroke hemiplegic shoulder pain.

Design: A prospective population-based study of an inception cohort of participants with 12 months follow up period.

Participants: Multiple ascertainment techniques were used to identify 318 confirmed stroke events in 301 individuals. Among 301 adults with stroke, data on shoulder pain were available for 198 (83% of survivors) at baseline, and 156 and 148 at 4 and 12 months, respectively.

Setting: Participants were recruited within a geographically defined metropolitan region with estimated population of 148,000 in Adelaide, Australia. Ascertainment and follow up included both general community and hospital settings.

Interventions: not applicable

Main Outcome Measures: Subjective reports of onset, severity and aggravating factors for pain, and three passive range of motion measures were collected at baseline, and follow-up at 4 and 12 months.

Results: 10% of participants reported shoulder pain at baseline, whilst 21% reported pain at each follow-up assessment. Overall, 29% of all assessed participants reported shoulder pain during 12 months follow up, with the median pain score (VAS = 40) highest at 4 months and more often associated with movement at later time points. Objective passive range of motion tests elicited higher frequencies of pain than self-report, and predicted later subjective shoulder pain (crude relative risk of 3.22 (95%CI 1.01-10.27).

Conclusions: The frequency of post-stroke shoulder pain is almost 30%. Peak onset and severity of hemiplegic shoulder pain in this study was at 4 months, outside of rehabilitation admission timeframes. Systematic use of objective assessment tools may aid in early identification and management of stroke survivors at risk of this common complication of stroke.

Key Words (3-7)

Stroke, epidemiology, hemiplegia, shoulder, pain

Introduction

Hemiplegic shoulder pain has been described as one of the four most common medical complications following stroke[15], with others including depression, falls and urinary tract infections[1]. Earlier studies have reported the frequency of shoulder pain following stroke to be as high at 65-70%[17-19]. A more recent prospective Swedish study of 416 consecutive stroke patients reported that almost a third of stroke survivors developed shoulder pain, the majority of whom reported moderate to severe pain[16]. Contributions to pain development are often multifactorial; biomechanical factors are significant[176], and may occur in isolation or in addition to changes in tone[248] or neuropathic mechanisms[249]. Hemiplegic shoulder pain is associated with a reduction in functional use of the arm[225], interference with rehabilitation[225], increased length of stay[225] and higher rates of depression[250]. Complexities in aetiology and subsequent diagnosis mean that treatment of shoulder pain is difficult and reviews have found little evidence to guide clinicians on effective prophylactic and treatment options[34]. Understanding the pattern of presentation, and establishing tools to support early identification of those likely to develop pain would assist clinicians and patients.

The primary aim of this study was to determine the frequency, characteristics over time, and associations of hemiplegic shoulder pain in a defined metropolitan population of South Australia. The secondary aim was to evaluate the predictive use of three standardised passive objective measures of shoulder range as screening tools for development of shoulder pain. Objective assessment is necessary in conjunction with subjective questioning, as self-report alone has been shown to be a poor predictor of examination findings[176], and accurate clinical assessment and diagnosis is vital in establishing targeted management plans. A case control study suggested that a simple set of clinical assessments (three passive range of motion tests) conferred a 98% probability of predicting early hemiplegic shoulder pain at rest[251]. The generalizability of this finding is limited

due to its small sample with multiple exclusion criteria (thalamic infarcts, upper limb sensory deficit, previous shoulder injury, complex regional pain syndrome, dysphasia). We evaluated this same set of assessments on all participants in a stroke incidence study, based on the principles of complete ascertainment[252], to test their application as a predictor of development of hemiplegic shoulder pain.

Methods

Overview

The Adelaide stroke incidence study (ASCEND) was a prospective population-based stroke incidence study conducted in a defined region of the western suburbs of Adelaide, South Australia, with a census projected population of over 148,000. During the period from 15 July 2009 to 15 July 2010, multiple ascertainment methods were used to identify all occurrences of stroke. Ethics approval was obtained from every tertiary hospital in Adelaide and University of Adelaide and all participants provided consent prior to enrolment in the study. Detailed methodology has been previously described[253], including specific information regarding the study population and ascertainment techniques.

Following informed consent, participants were assessed at baseline, at 4 months and at 12 months. All data were collected as part of the larger ASCEND study and entered into a custom-designed online database. The data set specific to this study was extracted via an automated database query and then manually checked against the raw database. Only data that were truly prospective were included for analyses, as retrospective report of subjective pain measures was not deemed reliable and retrospective case note data would not include the objective tests.

Definitions

Stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin"[1]. Hemiplegic shoulder pain was defined as any subjective complaint of pain in the contralesional, or affected hemiplegic shoulder following stroke. Hemiplegic shoulder pain encompasses all aetiologies and we did not exclude patients on the basis of premorbid shoulder pathology. Pain was measured using a Visual Analogue Scale (VAS range 0-100) with severity classified into mild (10-30) and moderate-severe (40-100) in line with previous publications[254, 255]. Upper limb motor function was determined using question 5 from the NIHSS – motor arm score of 3 or above was classified as 'no motor function' (score 3 = no effort against gravity; score 4 = no movement), and reduced motor function was score 1-2 (score 1 = drift; score 2 = limited effort against gravity).

Demographic Data, Subjective and Objective Assessments

The subset of data of interest in the study included record of demographic data, and baseline and follow up subjective and objective measures pertaining specifically to shoulder pain.

Demographic and clinical characteristics were recorded to characterise the subsets within the study population and to explore any associations with risk of development of shoulder pain. Data included age, gender, significant medical history, stroke subtype and aetiology, affected hemisphere, and motor arm component of the National Institute of Health Stroke Scale (NIHSS).

Subjective information included history of shoulder pain prior to stroke and presence of shoulder pain on affected side. If pain was reported, further questions regarding time of onset, severity of pain,

and aggravating factors were asked. Patients were asked if pain was worse at rest, on movement (active or passive), or at night. Pain severity was scored using a vertical VAS. Each consented participant was assessed by a trained study nurse.

A rehabilitation physician taught all data collectors a standardised approach to objective tests, and a video support package was made and provided for ongoing reference.

Objective measures of the participants' affected upper limb included[251]:

- the modified Neer test (forced passive forward flexion) tested in a seated position
- passive Hand-Behind-Neck test (passive abduction, external rotation) tested in a seated position, and
- passive external rotation as compared to unaffected limb. Passive external rotation was measured with the patient in a seated position. Range was measured using a goniometer.

Any pain on modified Neer or passive hand-behind-neck was scored as a positive result. Affected limb passive external rotation range of more than 10º less than the unaffected limb was scored as positive limitation of range of movement.

Statistical Analysis

Comparisons were made of baseline demographics for participants with and without shoulder pain using Wilcoxon tests for continuous variables or chi-squared tests for categorical variables. Non-parametric tests (i.e. Wilcoxon or Kruskal-Wallis tests) were selected in the context of analysis of continuous variables because some variables (such as VAS and NIHSS) had skewed distribution. The primary outcome was onset of shoulder pain within the first year of stroke onset. Measures of shoulder function (subjective report of pain, pain severity, aggravating factors, and objective assessments) at each visit were compared using Kruskal-Wallis or chi-squared tests. Associations between baseline demographic subsets and development of shoulder pain were assessed using logistic regression models and statistically significant predictors were included into multivariable logistic regression models. Data are reported with the standard level of significance ($P < 0.05$) and with 95% confidence intervals (CI). All analyses were performed using SAS software version 9.2 (Cary, NC, USA).

Results

As some participants had more than one stroke event, a total of 318 strokes were confirmed in 301 people in the study population. Excluded were 103 people without a shoulder assessment due to death (60%), retrospective ascertainment (12%), or non-consent to participation (28%) (See Figure 1). For baseline assessments, 73% of all recruited patients were assessed within one week of symptoms onset[253] (average 8.7 days post onset). At baseline, a shoulder assessment was completed on 198 (83%) of 239 survivors, 156 (75%) at 4 months, and 148 (77%) at 12 months. A total of 226 shoulder assessments were performed at any assessment point within the follow-up period, with complete data from all 3 time points available for 105 participants surviving to 12 month follow-up.

Among survivors, baseline characteristics were comparable between participants with and without pain, except severity of upper limb deficits and history of premorbid shoulder pain which were significantly greater in those participants reporting subjective pain (Table 1).

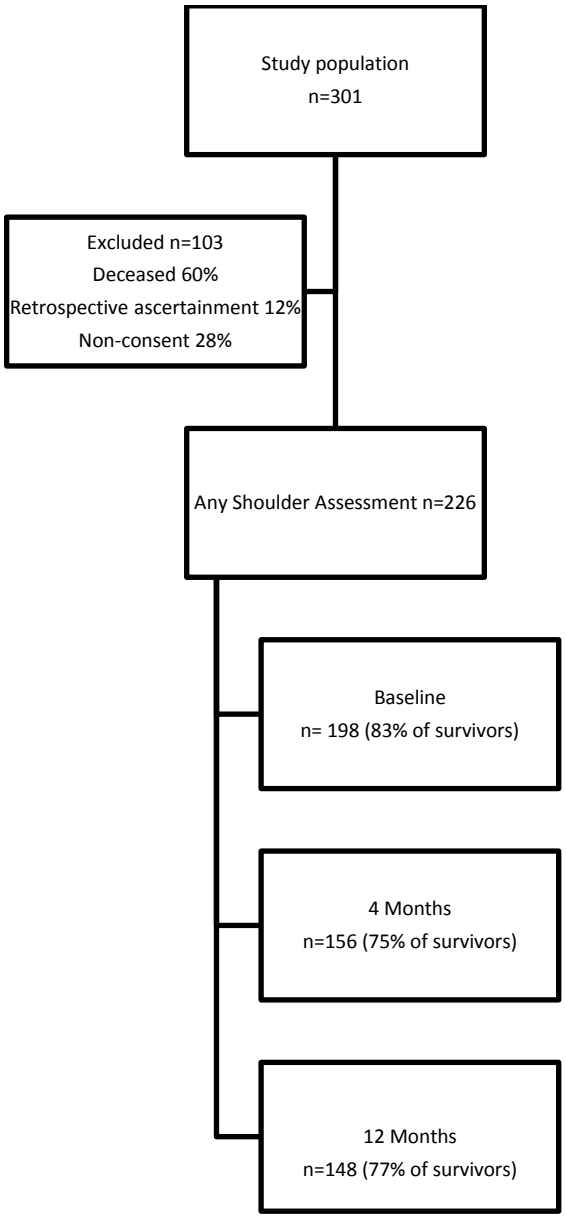


Figure 1. Patient Flow

Table 1. Baseline characteristics of participants with and without shoulder pain			
	No pain (n=161)	**Pain (n=65)**	**p value**
Mean age (SD)	73 (15)	72 (14)	0.501
Female	72 (45%)	30 (46%)	0.845
Medical history			
Previous stroke	37 (23%)	8 (12%)	0.069
Previous MI	24 (15%)	11 (17%)	0.705
Hypertension	104 (72%)	45 (71%)	0.907
Diabetes	39 (24%)	18 (28%)	0.587
History of shoulder pain	7 (4%)	17 (27%)	**<0.0001**
Stroke subtype			
Total ischaemic	142 (88%)	58 (89%)	0.888
Large artery	24 (15%)	9 (14%)	
Cardioembolic	57 (35%)	22 (34%)	
Lacunar	20 (12%)	6 (9%)	
Other/unknown ischaemic	41 (25%)	21 (32%)	
Haemorrhagic	14 (9%)	6 (9%)	
Unknown	5 (3%)	1 (2%)	
Oxfordshire subtype			
LACS	35 (22%)	19 (30%)	0.410
TACS	26 (17%)	14 (22%)	
PACS	67 (43%)	22 (34%)	
POCS	28 (18%)	9 (14%)	
Left Hemisphere	89 (59%)	33 (52%)	0.349
Median NIHSS* (IQR)	5 (1 to 10)	5 (2 to 12)	0.202
Motor arm			
Reduced function	42 (26%)	24 (38%)	**0.0002**
No function	22 (14%)	20 (31%)	**0.0002**

The demographic and clinical variables of participants receiving shoulder assessment as compared to those not receiving any assessment are summarised in Supplementary data Table I. In the group who did not receive a shoulder assessment, there were significantly more haemorrhagic strokes (25% versus 9%) and Total Anterior Circulation Syndrome (TACS) strokes (67% versus 18%), reflecting higher mortality from more severe strokes. Data from patients who did not receive shoulder assessment were excluded from further analysis.

Table 2 summarises the incidence of shoulder pain over 12 months. Comparison of participants receiving any assessment (n=226) to participants receiving assessments at all time points (n=105) demonstrated similar frequencies at each follow up, with a clear pattern of increasing frequency of pain over 12 months. Of stroke survivors receiving any assessment, 10% reported pain at baseline and 21% at each follow up period. Overall, approximately one third (65/226=29%) of individual participants reported onset of shoulder pain within the 12 months following their stroke. In the cohort of participants receiving shoulder assessment at all three time points (n=105), Figure 2 shows that shoulder pain increased in frequency over time: 8% at baseline, 18% at 4 months, and 21% at 12 months A relatively low rate of pain resolution at each time point is demonstrated (6% at 4 months and 14% at 12 months respectively).

Table 2. Incidence of shoulder pain				
	Pain / Subjects (%)			
226 subjects with any assessments				
Baseline	19	/	198	**(10%)**
4 months	32	/	156	**(21%)**
12 months	31	/	148	**(21%)**
Total Incidence of any shoulder pain in individual participants over 12 months	65	/	226	**(29%)**
105 subjects with all assessments				
Baseline				
Incidence	08	/	105	**(8%)**
4 months				
New onset pain	17	/	105	(16%)
Persistent pain	02	/	105	(2%)
Total	19	/	105	**(18%)**
12 months				
New onset pain	12	/	105	(11%)
Persistent pain	10	/	105	(10%)
Total	22	/	105	**(21%)**

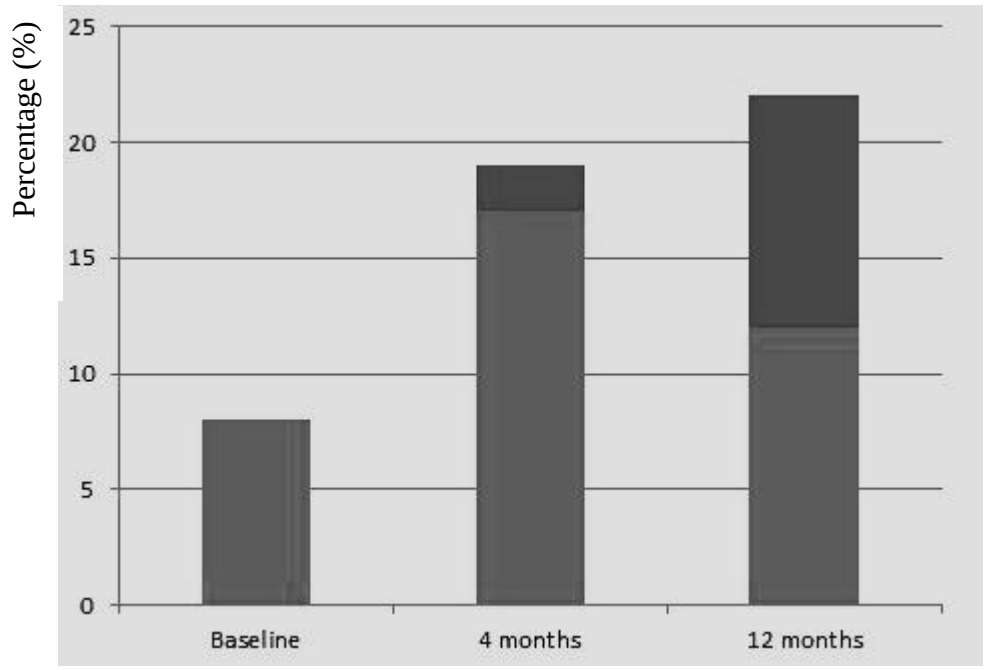


Figure 2. Frequency of Hemiplegic Shoulder Pain

N= 105 (subjects with all assessments)

Subjective reports of severity and factors aggravating hemiplegic shoulder pain amongst participants receiving any assessment are summarised in Table 3. The median pain score (VAS = 40) was highest at 4 months. Pain characteristics in the early weeks demonstrated milder pain (median VAS = 15) which was more prominent at rest (including night). At follow up, pain was shown to be more associated with limited active and passive range of movement and significantly fewer participants reported pain which was worse at rest or at night (Figure 3).

Table 3. Severity and Factors aggravating shoulder pain in participants receiving any assessment			
	Baseline (n=198)	4 month (n=156)	12 month (n=148)
Any shoulder pain*	19 (10%)	32 (21%)	31 (21%)
Median VAS (IQR)†	15 (0 to 40)	40 (15 to 71)	10 (0 to 40)
Aggravating factors†			
At rest	3 (18%)	1 (3%)	2 (7%)
With range of movement	9 (53%)	19 (64%)	23 (77%)
At night	5 (29%)	10 (33%)	5 (17%)
Positive modified Neer	14 (7%)	35 (23%)	26 (18%)
Positive passive hand behind neck	6 (3%)	22 (16%)	18 (13%)
Positive passive external rotation	21 (11%)	38 (25%)	33 (22%)
Values are n(%) or median (IQR) *Patients receiving any assessment within 12 months (n=226) †Amongst patients with shoulder pain			

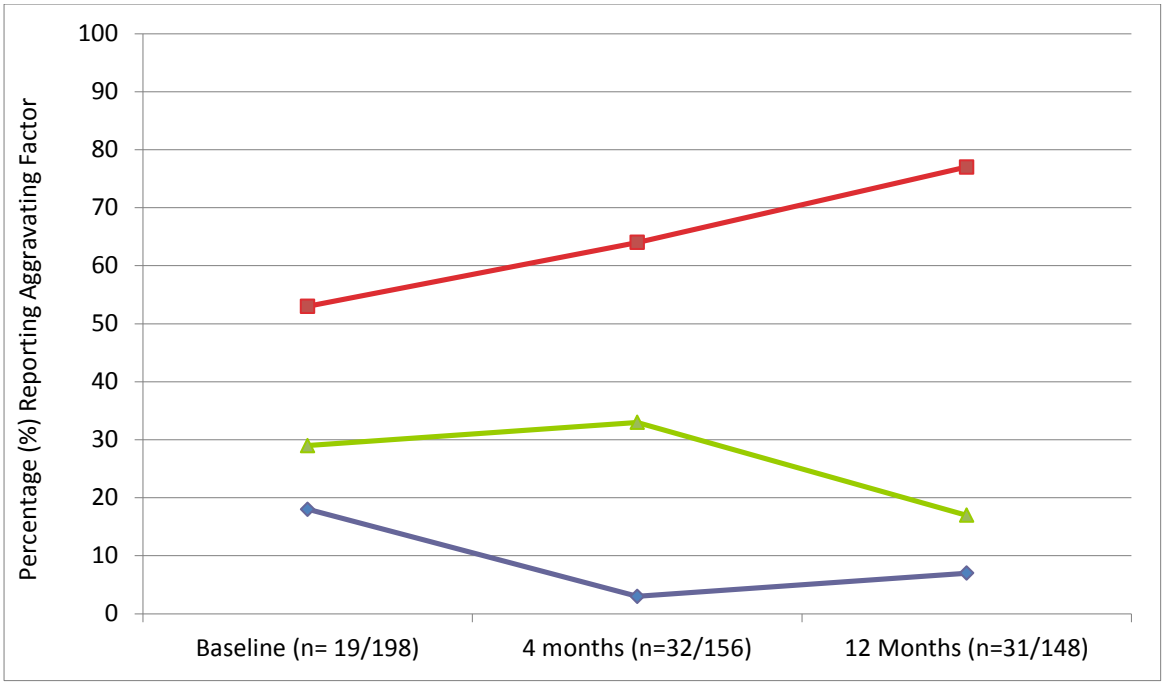


Figure 3. Factors aggravating shoulder pain over 12 months

Crude and multivariable analysis found a strong association between premorbid shoulder pain and post-stroke hemiplegic shoulder pain (Table 4). Additionally, an absence of upper limb motor function was strongly associated with risk of shoulder pain (OR 3.19 (1.77-6.9) p=0.0003). The odds ratio (CI 95%) for pain associated with reduced arm function was 1.24 (0.7-2.17) p=0.458. A large proportion (86%) of participants with TACS strokes died before the baseline assessment. There was no association of shoulder pain and basic demographics, stroke syndrome, affected hemisphere, or stroke severity.

Table 4. Determinants of Hemiplegic Shoulder Pain (n=226)

	Crude OR (95%CI)	p value	Multivariate-adjusted OR (95%CI)	p value
Mean age (SD)	0.96 (0.79 to 1.17)	0.690		
Female	1.03 (0.77 to 1.37)	0.845		
Medical history				
Previous stroke	0.47 (0.21 to 1.07)	0.074		
Previous MI	1.16 (0.53 to 2.54)	0.705		
Hypertension	0.96 (0.50 to 1.85)	0.907		
Diabetes	1.20 (0.62 to 2.30)	0.587		
History of shoulder pain	**8.09 (3.16 to 20.75)**	**<0.0001**	**7.43 (2.64 to 20.89)**	**0.0001**
Stroke subtype				
Total ischaemic				
Large artery	Reference			
Cardioembolic	1.10 (0.60 to 2.01)	0.767		

In stroke survivors who reported pain at baseline, baseline passive range of motion tests were not consistently positive (not all patients reporting pain had positive objective tests). Follow-up assessments demonstrated increasing frequency of positive objective tests in those with reported pain, and objective passive range of motion tests were associated with higher frequencies of pain than were elicited by self-report alone. Further evaluation revealed that positive baseline objective assessments, despite the absence of subjectively reported pain, conferred a statistically significant

crude relative risk of 3.22 (95% CI 1.01 to 10.27) for future development of hemiplegic shoulder pain within a 12 month period. Multivariate analysis, adjusting for high NIHSS score (>5 above median) and significant motor upper limb deficit, demonstrated an odds ratio of 2.13 (CI 0.54 to 8.35) although this was not significant (Table 5).

Table 5. Associations of shoulder pain and 12 month outcome

	n of pain/patients (%)					
	positive findings*	negative findings	Crude OR (95% CI)	p value	multivariable-adjusted OR (95% CI) †	p value
Shoulder pain	7/13 (54%)	33/124 (27%)	3.22 (1.01 to 10.27)	0.049	2.13 (0.54 to 8.35)	0.2773
Dependency	25/52 (48%)	34/108 (31%)	2.02 (1.02 to 3.97)	0.043	1.80 (0.67 to 4.88)	0.2453

*Positive modified Neer, positive passive hand behind neck or positive passive external rotation.

†Adjusted for significant risk factors in this subgroup (high NIHSS score [>=median (5)] and motor arm)

Discussion

In a field in need of greater research focus, this study contributes data on early incidence of pain and pain characteristics in the first year post stroke. Additionally, the study supports the predictive value of easily reproducible objective screening tests.

This study found that approximately one third of stroke survivors experienced shoulder pain at some stage in the 12 months post stroke, with peak incidence of pain at 4 months. Congruous data in studies of comparable methodology[16, 17, 33] lend weight to this finding regarding rate of shoulder pain (previous papers reported rates as high as 70%)[17, 31, 175]. A pertinent issue to consider, in the context of persistently significant rates of hemiplegic shoulder pain, is the possibility that this may reflect a lack of improved prevention measures regarding education and shoulder care over more recent years. Thus, despite previous studies highlighting the amplitude of this issue, it is postulated that minimal gains in evidence-based treatment and prevention options, or translation of the same into practice, are indicated.

A novel finding of our study is the comparatively low frequency of very early (average 8.7 days) hemiplegic shoulder pain (10%). Lindgren et al[5] followed up 416 people from a Stroke Register, with specific study pain questions and assessment at 4 and 16 months; at follow up I (4 months), almost 40% of participants reported that their pain begun between 0-2 weeks post stroke. In the current study, prospective data regarding baseline pain were collected. Interestingly, patients who reported pain within the first few days following stroke were not necessarily those who went on to have persistent pain complaints. There was a much higher rate of new onset pain at 4 month follow-up compared to pain persisting from baseline assessment, highlighting the need for ongoing monitoring after hospital discharge. A relatively low rate of pain resolution at each time point was

demonstrated (6% at 4 months and 14% at 12 months respectively), further indicating the need to establish an increased pool of effective evidence-based treatment options. The increasing association of pain with range of movement (active and passive) over time may represent cumulative musculoskeletal contributors and adaptive mechanisms, with pain on movement recognised as one of the cardinal features of musculoskeletal pain[256]. Mechanisms of pain may differ and additional research exploring evidence-based treatment options that address early versus later onset hemiplegic shoulder pain are needed.

The predominant associations between clinical profile and risk of shoulder pain were in participants with premorbid pain and those with more marked upper limb motor deficit. Whilst previous population-based studies[5] have found motor deficit to be predictive, they have not demonstrated premorbid shoulder pain as a risk factor for developing pain. In this study, history of shoulder pain was reported in 27% of participants with hemiplegic shoulder pain, compared to only 4% of those who did not report pain. This differs from Lindgren et al[5], who found similar rates of premorbid shoulder pain reported by those who subsequently developed pain and those who did not (23% versus 22% respectively). Pain history is a simple question easily added to clinical screening assessment battery and further helps identify an at-risk cohort.

The association of compromised range of motion with persistent pain is supported by recent studies. Research supports that persistent pain is more likely in patients with left sided weakness[199], and in those who demonstrate reduced passive abduction range[196, 199], as well as patients with reduced external rotation range, impaired voluntary motor control and spasticity[196, 199]. We did not find an association between affected hemisphere and pain development, but our data does support the previous findings that pain is associated with reduced passive abduction and external rotation

(passive hand-behind-neck and external rotation tests respectively), and impaired motor function. Testing of passive range is often impacted by increasing tone, though formal spasticity assessment was not included in this study.

With the three passive range of motion tests used, it was possible to identify those likely to develop pain. Those patients who demonstrated a positive response on an objective passive range of movement test at baseline trended to be at increased risk of later pain, suggesting that these tests may serve a useful screen among at-risk patients, namely those with more severe upper limb paresis. Rajaratnam[251] proposed use of all three tests to identify those at risk of early pain at rest. Results from this study support use of these tests as a screening tool beyond the early phase, with evidence that positive objective results double a patient's probability of developing future hemiplegic shoulder pain. At both follow up points, the passive external rotation test and modified Neer test recorded greater number of positive results than the passive hand-behind-neck. Passive external rotation findings on follow up were greater than subjective report of pain alone (21% reported pain at 4 months, 25% recorded positive external rotation test; 21% reported pain at 12 months, 22% recorded positive passive external rotation test). Remaining objective tests did not provide results higher than subjective pain result, but it must be considered that the variety of movements covered by the use of all three of these tests provides a more thorough screening tool. The tests used are simple to perform, easy to teach in a reproducible manner, and time and cost efficient in the context of incorporation into standardised protocols. Whilst it is well established that transfer of evidence into clinical practice is significantly delayed, the use of such a simple screening assessment can be hoped to be easily implemented within a field of medicine at ease with joint assessment and manual handling.

The use of screening assessments should not replace more in-depth diagnostic assessments of patients with verified hemiplegic shoulder pain. The increasing body of research exploring the contribution and overlap of neuropathic as well as nociceptive pain mechanisms[196, 249, 257] highlights the importance of careful assessment beyond the musculoskeletal paradigm covered by the outlined objective measures. As such, the assessment outlined is supported as a screening tool, rather than a diagnostic tool. More in depth assessment is required to ascertain potential contributors to active pain, and should consider specific spasticity measures and comprehensive pain history. Screening in this study is perhaps of more utility to identify those not subjectively reporting pain at rest but potentially experiencing pain with range of movements beyond their active range. The data supports that positive objective tests double the risk of future development of pain. It must also be highlighted that the paucity of evidence-based treatment options currently available means that successful screening does not yet yield significant benefit to the patient group. A focus on effective treatment options is required in order to make best use of screening within an assessment and management protocol.

Study Limitations

The study was limited by some loss of patient data due to early death or delay in ascertainment which reduced the ability to achieve timely or prospective assessment. As highlighted in the parent study[253], ascertainment may have been incomplete despite intensive efforts. In addition, there was variable loss of data at the follow up assessments. Finally, we did not account for spasticity in our assessments, which could have affected passive range and pain reports.

Strengths of our study include the use of 'ideal' methodology[252] to avoid selection bias and the prospective assessments available for analyses.

Conclusion

Close to 30% of people develop pain in the first year after stroke, with peak incidence at 4 months. Comparison with an earlier population study[5] shows that, despite increased focus on evidence-based treatments in stroke, over 7 years no reduction in frequency of this common complication stroke has been shown. Systematic use of clinical assessments is useful in identifying people at risk of shoulder pain. As the disorder is most common and severe after hospital discharge, targeted protocols including predictive objective measures may facilitate improved identification and management. Further research is required to elucidate a practical range of preventative and treatment options for this condition.

Sources of Funding

The ASCEND study was funded by a Project Grant (565402) from the National Health and Medical Research Council of Australia.

Conflicts / Disclosures

None to declare

Chapter Five

Suprascapular Nerve Block for the Treatment of Hemiplegic Shoulder Pain

5.1 Introduction to Publication

Publication 3: Allen ZA, Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83

Purpose

This protocol paper was written to outline the research plan for the randomised controlled trial. Preparation of the paper required thorough justification of the methods, including sample size calculation and outcome assessments. Clinical trials registration and publication of the protocol is presented to demonstrate the robust planning and adherence to the trial protocol.

Published in

BMC Neurology

Impact Factor 2.04

Contribution from primary author

Primary Author – Dr Zoe Allen (ZA) **previous surname**

With supervision from Professor Maria Crotty and Associate Professor E Michael Shanahan, ZA developed the project proposal. Preparation of the manuscript was led by the primary author with input from co-authors.

5.2 Publication 3

Allen ZA, Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83

Does suprascapular nerve block reduce shoulder pain following stroke: a double-blind randomised controlled trial with masked outcome assessment

Abstract

Background: Shoulder pain is a common complication of a stroke which can impede participation in rehabilitation programs and has been associated with poorer outcomes. The evidence base for current medical and therapeutic management options of hemiplegic shoulder pain is limited. This study will evaluate the use of suprascapular nerve block injection as part of an interdisciplinary approach to the treatment of shoulder pain following stroke. The technique has previously been proven safe and effective in the treatment of shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions but its usefulness in a stroke population is unclear.

Methods / Design: A double blind randomised placebo controlled trial will assess the effect of a suprascapular nerve block compared with placebo in a population of 66 stroke patients. The trial will measure effect of injection on the primary outcome of pain, and secondary outcomes of function and quality of life. Measurements will take place a baseline, and 1, 4 and 12 weeks post intervention. Both groups will continue to receive routine physiotherapy and standard ward care.

Discussion: The results of this study could reduce pain symptoms in persons with mechanical shoulder pain post stroke and provide improvement in upper limb function.

Trial Registration: This trial is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR) - ACTRN12609000621213

Background

In any year, there are approximately 48,000 stroke events amongst Australians. Shoulder pain is a distressing complication of hemiplegia[33] and is reported as one of the 4 most common medical complications of stroke[15]. The prevalence of shoulder pain following stroke has reported to be as high as 70%[17]. A more recent prospective population study of 327 consecutive stroke patients concluded that almost a third of this population developed moderate-severe shoulder pain after stroke onset[22]. This more moderate figure reflects the 2006 paper by the same investigators, which focused on patient's perspectives on pain[250]. Each of these studies highlights a correlation between pain and reduced functional ability, as well as higher incidence of depression.

Hemiplegic shoulder pain is associated with reduction in functional use of the arm, interference with rehabilitation and increased length of hospitalisation[217]. A further complication of hemiplegic shoulder pain is identified as a limitation to patient access to developing technological upper-extremity rehabilitation techniques[176].

Investigation into the cause of hemiplegic shoulder pain has revealed a multifactorial aetiology[30]. Note is made of the dependence on musculotendinous integrity to provide stability of the shoulder complex. The most common non-central, musculoskeletal aetiologies of hemiplegic shoulder pain include adhesive capsulitis, subluxation and rotation cuff pathologies, with up to one-third of patients having multiple contributing factors[30]. Biomechanical changes result from a combination of paralysis, fluctuation in muscle tone and prolonged shoulder immobility which lead to postural malalignment [33]. Dromerick et al[176] investigated the characteristics of hemiplegic shoulder pain, demonstrating that approximately 50% of the sample population experienced pain in the vertical stabilisers of the shoulder (biceps and supraspinatus). A 2006 evidence-based medicine review concluded that subluxation may be a cause of shoulder pain[32], though literature is inconsistent

regarding this association. It should be noted that not all shoulder pain is associated with the complication s of limb flaccidity, and may be attributable to spasticity or central-pain concepts.

There is lack of evidence to support the development of clear clinical guidelines, as identified in an overview of the challenges of managed shoulder pain after stroke[38]. This paper concludes that further efforts are required to examine intervention options. There have been positive research results of the use of Functional Electrical Stimulation[32], though a Cochrane Systematic Review[211] of this topic did not support electrical stimulation as an effective pain treatment. There is a lack of Level 1 evidence for surgical interventions, motor blocks and intra-articular corticosteroid injection.

Suprascapular nerve block is a safe and efficacious treatment of shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions[46]. The objective of this study is to evaluate the use of Suprascapular nerve block as part of an interdisciplinary approach to the treatment of shoulder pain following stroke. There is anecdotal report of successful use of suprascapular nerve block in threating intractable hemiplegia shoulder pain[33], though to date no clinical trials have been completed to form an evidence base.

Methods and Design

The study design is a double blind randomised placebo controlled trial which will assess the effect of a suprascapular nerve block compared with placebo in a population of 66 stroke patients (Figure 1). The trial will measure effect of injection on the primary outcome of pain, and secondary outcomes of function and quality of life. Measurements will take place at baselines, and 1,4, and 12 weeks post intervention. Both groups will continue to receive routine physiotherapy and standard ward care.

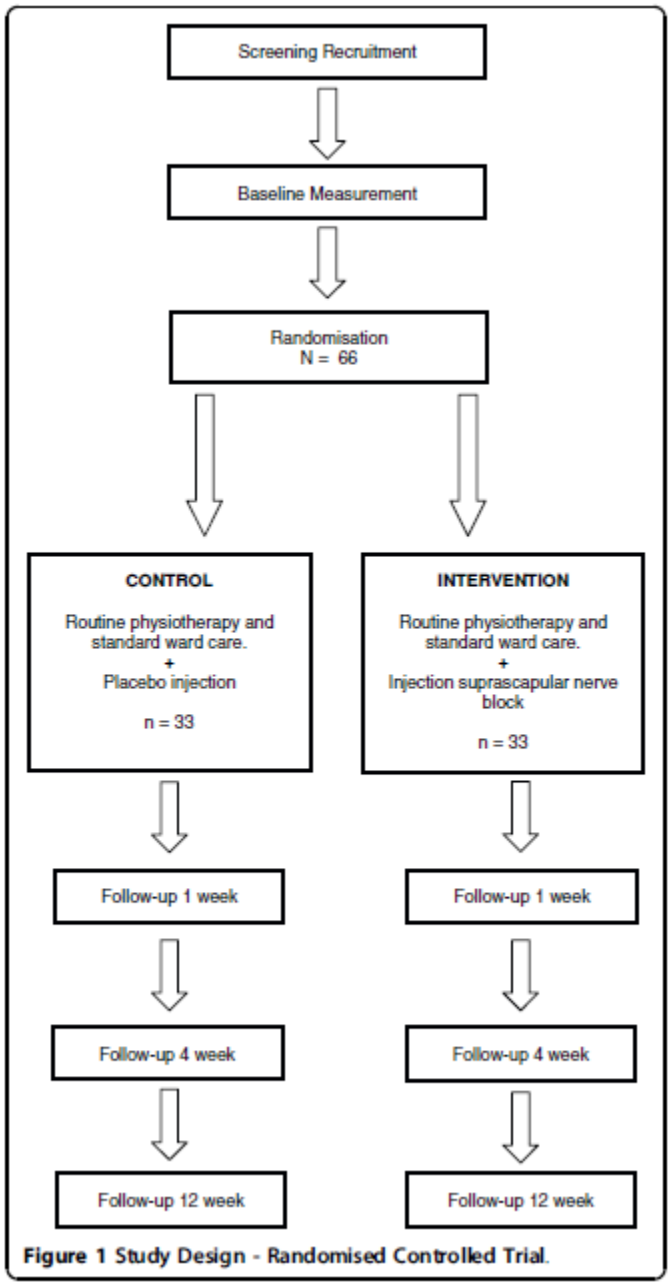


Figure 1 Study Design - Randomised Controlled Trial.

Figure 1. Study Design - Flow Chart

Randomised Controlled Trial

Participants

Participants will be willing patients aged over 18 years with a diagnosis of acute stroke within the previous 12 months and onset of hemiplegia shoulder pain post stroke with a visual analogue scale (VAS) score of >30mm (100mm scale). Exclusion criteria will include the following:

- cognitive deficit that precludes patients from reliably using subjective outcomes measures (Mini-Mental State Examination (MMSE) < 23)
- language deficits (inability to follow 2-stage command) or limited English language that preclude patients from reliably using subjective outcome measure scales
- allergy to proposed injection agents (depo-medrol 40mg and 0.5% bupivacaine hydrochloride)

Setting/Locations

Participants invited to participate in the study will be recruited via the acute stroke and rehabilitation wards at multiple hospital sites across Adelaide, South Australia, including: Repatriation General Hospital, Flinders Medical Centre, The Queen Elizabeth Hospital, Hampstead Rehabilitation Hospital (Royal Adelaide Hospital), and Griffith Rehabilitation Hospital. Ethics approval for the study has been granted by the Human Research Ethics Committees of Flinders Medical Centre (61/09), Royal Adelaide Hospital (09235), Repatriation General Hospital (09/09) and Queen Elizabeth Hospital (2009031).

Procedures

Participants will be assessed at baseline (following recruitment) and then at 1, 4 and 12 weeks following injection. In addition to demographics and classification of stroke, these four assessments will include the following measures:

i. AbilityQ and ShoulderQ[258]
ii. Modified Rankin Scale [245]
iii. Croft Disability Questionnaire[244]
iv. Euroqol[246]
v. Visual Analogue Scale [246, 259]
vi. Application of 3 clinical tests shown to be predictive (98% probability) of hemiplegic shoulder pain[251]

Following consent and baseline measures, participants will be randomised to receive suprascapular nerve block or placebo injection. Allocation will be managed by a pharmacist external to the project.

Randomisation

Participants will be assessed for eligibility, provided with information about the study, provide informed consent, be enrolled into the study and complete the baseline assessment prior to allocation into the control or intervention group. Participants will be assigned to the control or intervention groups by a pharmacist external to the project by simple randomisation generated by a computer software system.

Intervention

Intervention Group: The intervention group will receive a suprascapular nerve block injection to the back of the affected shoulder (using depo-medrol 40mg and 0.5% bupivacaine hydrochloride). The technique proposed for suprascapular nerve block[46] involves approaching the patient from posterior aspect of the shoulder, which will ensure the patient is unable to visualise syringe contents. The doctor administering the injections will not be blinded for safety reasons. This approach has been used in a prior trial examining suprascapular nerve blocks[46]. Intervention participants will continue to receive routine ward care of positioning of limb, careful manual handling and physiotherapy / occupational therapy suitable for the individual. The treating team will remain blinded to the randomisation.

Control Group: The control group will receive an injection to the back of the shoulder of 5mL normal saline infiltrated subcutaneously after the 2mL subcutaneous 1% lidocaine infiltration. Control participants will continue to receive routine ward care of positioning of limb, careful manual handling and physiotherapy / occupational therapy suitable for the individual. This project does not involve the withholding of standard treatment to any participant. The treating team will remain blinded to the randomisation.

Outcomes

Outcomes will be assessed at 1 week, 4 weeks and 12 weeks by a physiotherapist blind to allocation. Proposed primary outcome measure involves use of a 100-point modified visual analogue scale (VAS) to assess pain[259]. This measure involves a 100mm vertical line with periodic demarcations, anchored with the written extremes of subjective pain. Patients are asked to mark the severity of their current self-perceived pain on the scale, and this is then recorded in millimetre readings. Research suggests that a minimum changes of 20mm on the VAS is required to demonstrate

clinically significant lessening of pain (initial reports >60mm)[259]. Whilst a lesser minimum change is accepted for lower initial pain scores, we have chosen the stronger difference in the context of best evidence in a population who is predicted to reported higher pain scores.

Secondary outcomes of disability and quality of life will be measured using the Modified Rankin Scale[245], Croft Disability Questionnaire[244], and the EuroQol Health Questionnaire[246]. The Croft Disability Questionnaire[244] includes 22 questions regarding disability associated specifically with shoulder pain. This measure is validated and chosen for this study as it more applicable in a more dependant sample population. Minimal level of detectable change (90% confidence) will be 3 points. Secondary outcome of spasticity will be measured using the Modified Ashworth Scale (MAS). MAS scores spasticity from 0-5.

Validity data will be collected for the AbilityQ and ShoulderQ measures[258]. These tools were developed by Lynn Turner-Stokes in 2006 to provide a sensitive measure of shoulder pain which is responsive to change in pain experience in a stroke population.

Sample Size

Based on the data in Table 1[46], the standard deviation of the change scores are assumed to be in the range of 18-25. The attached table includes the estimated required sample size for a range of standard deviations and the tree different clinically interesting changes above.

Hence using a conservative estimate, it is expected that a sample size of 26 participants per group (treatment and placebo) will achieve a statistically and clinically significant difference between the two groups (power 80%, alpha 0.05). To allow for deaths and withdrawals with a total attrition rate of 20%, a minimum total of 66 participants will be recruited, 33 per group. It is anticipated that

recruitment of 66 participants (33 treatment, 33 placebo) will take approximately 12 months and that each patient will be followed for 12 weeks.

Table 1. Sample Size Calculation

Standard Deviation (change)	Treatment Change	N per group	N total
18	20	14	28
	28	8	16
	30	7	14
20	20	17	34
	28	9	18
	30	8	16
22	20	20	40
	28	11	22
	30	10	20
25	20	26	52
	28	14	28
	30	12	24

Statistical Analysis

Data will be exported into SPSS software for subsequent analyses. A statistical analysis plan will be carried out after masking allocation.

The research questions will be assessed using an intention to treat approach. Independent sample t-tests, Mann-Whitney U tests and Chi-square test of association will be used as appropriate to compare groups at baseline. To determine differences between the groups at the primary end-point, ANOVA or logistic regression will be used with models adjusted according to potential confounders.

Discussion

The protocol has been carefully designed with the aim of achieving measureable, replicable and important results. The methodological strength of the study focuses around the use of placebo control, though the contributors acknowledge that this may pose a recruitment challenge. Considering that eligible patients have pain score of >3 (30mm), it is anticipated that patients may decline participation on the grounds of not wanting to risk 50/50 chance of randomisation to placebo group. Taking this into account, greater time allowance has been given for recruiting. Careful provision of information prior to consent is vital in ensuring patients are fully aware of implication of the randomisation. All patients will be informed of their randomisation group at the end of their trial participation and offered active suprascapular nerve block if desired.

Another uncertainty is in establishing methodology to catch probable timing of hemiplegic shoulder pain. Lindgren's 2007 population-based study on hemiplegic shoulder pain found that the majority of the incidence of pain occurred within the first 4 months post stroke[22]. Our inclusion criteria allow for patients to be up to twelve months post stroke, allowing for later incidences of pain occurrence. Difficulty may arise, however, in that ethics approval required injection in inpatient facilities only. It is anticipated that many otherwise eligible participants may be unidentified by inpatient recruitment strategies.

Despite the realistic uncertainties outlined above, this study will provide useful information pertaining to an important topic. Shoulder pain is a common and debilitating symptoms for a large number of people following stroke, and currently there is poor evidence regarding effective treatments. If the study shows that the suprascapular nerve block is efficacious in management of hemiplegic shoulder pain, it could potentially provide a new treatment options for stroke patients.

5.3 Introduction to Publication

Publication 4: Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial. *Stroke*. 2013; 44:3136-3141

Purpose

This manuscript describes a randomised controlled trial. Prior to undertaking the trial, the protocol was registered (ACTRN12609000621213) and published (Chapter 5.1-5.2).

The trial is the first placebo-controlled trial of suprascapular nerve block for hemiplegic shoulder pain, and demonstrates that single suprascapular nerve block is a valuable treatment for this population. In a field with little high-level evidence to guide treatment options, this study represents an important step forward.

Published in

Stroke

Impact Factor 6.018

Contribution from primary author

Primary Author – Dr Zoe Adey-Wakeling (ZAW)

ZAW, with supervision from Professor Maria Crotty and Associate Professor Michael Shanahan, was the lead investigator in this randomised controlled trial. Following development of the protocol,

ZAW conducted all of the recruitment and baseline data assessments for the trial. All injections (both suprascapular nerve block and placebo) were conducted by ZAW. Primary data was collected by ZAW, with follow up data collected by a research assistant blinded to group allocation. ZAW ran the initial data analysis, after consultation with a statistician (Pawel Skuza). Final analyses presented in the paper were checked and re-run by a statistician. The manuscript was written by ZAW, with review by co-authors.

5.4 Publication 4

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial. *Stroke*. 2013; 44:3136-3141

Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial

Abstract

Background: Shoulder pain is a common complication after stroke which can impede participation in rehabilitation and has been associated with poorer outcomes. Evidence based treatments for hemiplegic shoulder pain are limited. Suprascapular nerve block (SSNB) is a safe and effective treatment of shoulder pain associated with arthritic shoulder conditions, but its usefulness in a stroke population is unclear.

Methods: We undertook a randomised controlled trial assessing the effectiveness of SSNB in a population of 64 stroke patients (onset < 1 year) with hemiplegic shoulder pain. The primary outcome was pain measured on a visual analogue scale (VAS). Secondary outcomes were disability (Modified Rankin Scale, Croft Disability Index) and quality of life (EuroQol Health Questionnaire). All participants were assessed prior to randomisation, and at 1, 4 and 12 weeks post intervention. Both groups continued with routine therapy.

Results: Whilst both intervention and control groups demonstrated reduction in pain score, participants who received SSNB consistently demonstrated superior, statistically significant pain reduction compared to placebo. Mean VAS reduction in the SSNB group was over 18mm greater

than participants receiving placebo injection. The number needed to treat with SSNB to reduce one stroke survivor's pain by 50% at four weeks is 4. No significant differences in function or quality of life were observed. No adverse events were reported.

Conclusion: Suprascapular nerve block is a safe and effective treatment for patients with hemiplegic shoulder pain.

Trial Registration: This trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) - ACTRN12609000621213.

Introduction

Shoulder pain is a distressing complication of hemiplegia[33] and is one of the four most commonly reported medical complications of stroke[15]. The aetiology of hemiplegic shoulder pain is multifactorial[30, 55] and contributions have been described from biomechanical changes[33, 176], spasticity[248, 260] and central-pain mechanisms[196, 249].

Population based studies suggest that approximately one quarter of stroke survivors develop hemiplegic shoulder pain[22, 170], though higher rates of 52-54% have been reported in large studies using retrospective[198], prospective[177] and literature review[240] methodologies. Hemiplegic shoulder pain is associated with reduced functional ability[250], a higher incidence of depression[250], interference with rehabilitation and an increased length of hospitalisation[217].

Despite the high incidence and significant impact of shoulder pain post stroke, there is little robust evidence to inform clinical practice[34, 201] with reviews examining the management of hemiplegic shoulder pain concluding that further efforts are required to examine intervention options[33, 34, 201].

Published systematic reviews have not included information on the use of suprascapular nerve block (SSNB) as an intervention type due to the emerging nature of this procedure in stroke populations and a lack of robust trials. Since commencement of this trial, two small trials have been published in this field[230, 242]. Comparison of SSNB with intra-articular steroid injection[242] did not demonstrate either treatment to be superior, whilst in a preliminary study[230] of ten people, comparison of SSNB with ultrasound treatment trended toward greater improvement in the SSNB group. Conclusions regarding the efficacy of SSNB are unable to be drawn from these studies due to small numbers, absence of power analysis and absence of placebo control.

Suprascapular nerve block has been shown to be a safe[45] and efficacious treatment for shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions[46-48]. It is unclear whether the results of these trials can be generalised to people with non-arthritic shoulder pain. The objective of our study was to compare the effect of SSNB to placebo on shoulder pain in a population of stroke survivors in the first year after stroke. The secondary objective was to examine the effects on function and quality of life.

Methods

The study design is a parallel group, randomised, placebo controlled trial. Sixty four participants gave written informed consent and were randomly assigned to an experimental group (suprascapular nerve block) or placebo group (normal saline injection). A protocol paper was published at commencement[261].

Setting

Participants were recruited from acute stroke and rehabilitation wards across Adelaide, South Australia between 2009 and 2012. Ethics approval was granted for all sites, including Repatriation General Hospital, Flinders Medical Centre, The Queen Elizabeth Hospital, Hampstead Rehabilitation Centre, Griffith Rehabilitation Hospital and Calvary Rehabilitation Hospital. Participants were recruited following education sessions and provision brochures to each facility.

Participants and Eligibility Criteria

Participants were required to be aged over 18 years with a diagnosis of acute stroke within the previous 12 months, and to report hemiplegic shoulder pain with a minimum VAS of 30 mm (100 mm scale). Minimum pain score was selected in the clinical context that invasive interventions are not routine for mild pain. Exclusion criteria included significant cognitive impairment (Mini-Mental State Examination < 23) or language deficits (inability to follow 2-stage command, limited English) that might affect the reliability of responses to outcome measures scales. Hypersensitivity to injection agents excluded participation. Following protocol publication and trial commencement, authors decided to exclude palliative patients, as it was deemed unethical to knowingly offer placebo during palliation.

Randomisation, Treatment Allocation and Blinding

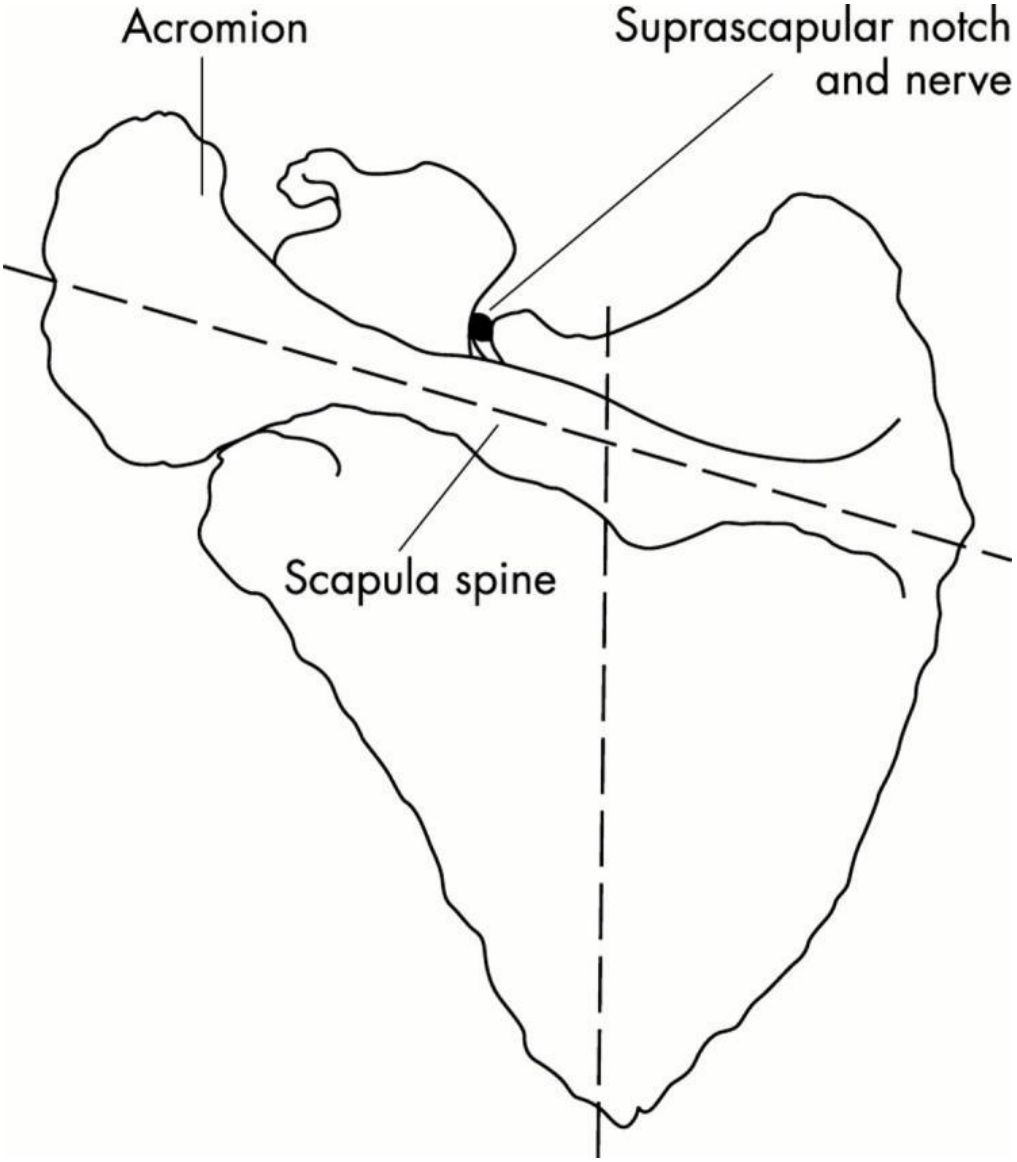
A computer generated randomised number sequence allocated participants to either the intervention or the control group. Randomisation was managed by a Clinical Trials Pharmacist external to the study. Allocation was assigned after baseline assessment. The principal investigator (ZA) was responsible for eligibility assessment, consent, baseline assessment and injection of all participants. Where she was involved in treating the participant, consent was obtained by another investigator. All outcome assessments were completed by one physiotherapist who was masked to treatment allocation. Participants and treating staff remained masked to allocation.

Interventions

Participants were randomly assigned to receive either a suprascapular nerve block or a placebo subcutaneous normal saline injection. The principal investigator (ZA) was responsible for syringe

preparation, and was aware of the allocation as the injection technique and appearance of syringe contents varied between groups. Both groups continued to receive routine therapy Syringe size and needle gauge (10ml syringe and a 21 gauge 38mm needle) were consistent across both groups. Blinding of participants was maintained by consistent preparation and positioning of all patients; all received a 2ml subcutaneous infiltration of 1% lidocaine prior to injection.

The experimental group received a suprascapular nerve block injection with 1ml of 40mg/ml methylprednisolone and 10ml 0.5% bupivacaine hydrochloride. The technique used for SSNB has been used in a prior trial[46]. Anatomical landmarks were used to determine injection site into the supraspinous fossa. The needle was introduced parallel to the scapula blade and the syringe contents slowly injected into the enclosed space of the supraspinous fossa. (See figure below) The placebo group received an injection of 5 ml normal saline infiltrated subcutaneously to the same region of the shoulder.



Supplemental Figure I. Landmarks for suprascapular nerve block

Outcomes

Participants were assessed prior to randomisation and at 1, 4, and 12 weeks following injection. Demographic data collected included age, gender, dominance, duration since stroke, stroke type and location. The primary outcome of pain was measured using a vertical Visual Analogue Scale (VAS). This measure involves a 100mm vertical line anchored with the extremes of subjective pain. Self-perceived pain severity is rated and recorded in millimetre readings[259]. The VAS is easy to use, readily reproducible[243], validated in a stroke population[38] and a commonly used in prior research. A minimum VAS change of 20mm is reportedly required to achieve clinically significant pain reduction for patients with initial pain scores >60 mm[259]. Secondary outcomes of disability and quality of life were measured using the Modified Rankin Scale[245], Croft Disability Questionnaire[244], and the EuroQol Health Questionnaire[246]. The Croft Disability Questionnaire includes twenty-two questions regarding disability associated with shoulder pain. This validated measure was chosen due to applicability in a more dependent population. The minimal level of detectable change (90% confidence) is defined as 3 points.

Sample Size and Statistical Analysis

A prospective sample size calculation, previously described in protocol paper[261], calculated that a sample size of 26 participants per group was required to achieve a statistically and clinically significant difference between the two groups (power 80%, alpha 0.05). Minimally significant clinical change in VAS was set at 20mm. Allowing for an attrition rate of 20% accommodating deaths and withdrawals, we aimed to recruit a total of 66 participants, 33 per group.

Research into the efficacy of SSNB in shoulder pain associated with rheumatoid arthritis[46] demonstrated a mean VAS difference of 22.9mm at one week, with the intervention superior to

placebo. This study was used to assist in the development of the power calculation, with the hypothesis that treatment with SSNB would reduce hemiplegic shoulder pain by the minimally important clinical change of 20mm when compared to placebo injection.

All data entry was completed by a research assistant masked to allocation. Data was exported into IBM SPSS (version 20) for statistical analyses on an intention to treat basis. Independent samples t-tests, Mann-Whitney U tests and Chi-square test of association were used to compare groups at baseline. Repeated measures were analysed using a generalized linear mixed model due to advantage in dealing with missing values (maximum likelihood analysis)[262] and the robust approach to calculation of effect. Results of primary outcomes are expressed as means with 95% confidence intervals. The level for statistical significance for hypothesis tests was set at 0.05. Linear regression analysis was performed to assess potential associations in responding patients. EQ-5D weights were derived using the Australian general population algorithm[263].

Results

Of 129 persons assessed for eligibility, 64 were enrolled and randomised into two groups (Figure 1). Reasons for exclusion are tabulated in online supplement (please see Data Supplement I). The mean time from stroke onset to trial referral was 12 weeks; 11(SD 8) weeks for control group and 13(SD 9) weeks for intervention group. The mean difference between scheduled and actual follow up was less than one day for all time points.

Supplemental Table I. Reasons for Non-Enrolment

Excluded from Randomisation (n=65)	
Did not meet Eligibility Criteria (n=42)	
VAS < 3/10	24
Insufficient Cognition / Language	9
Pain in Other Region (non-shoulder)	4
Palliative Patient	3
Stroke > 12 months ago	2
Declined to Participate (n=18)	
Unwilling for Randomisation to Placebo	6
Needle Phobia	5
No reason given	5
Risk of adverse reaction	2
Referred but Unable to be Contacted (n=5)	

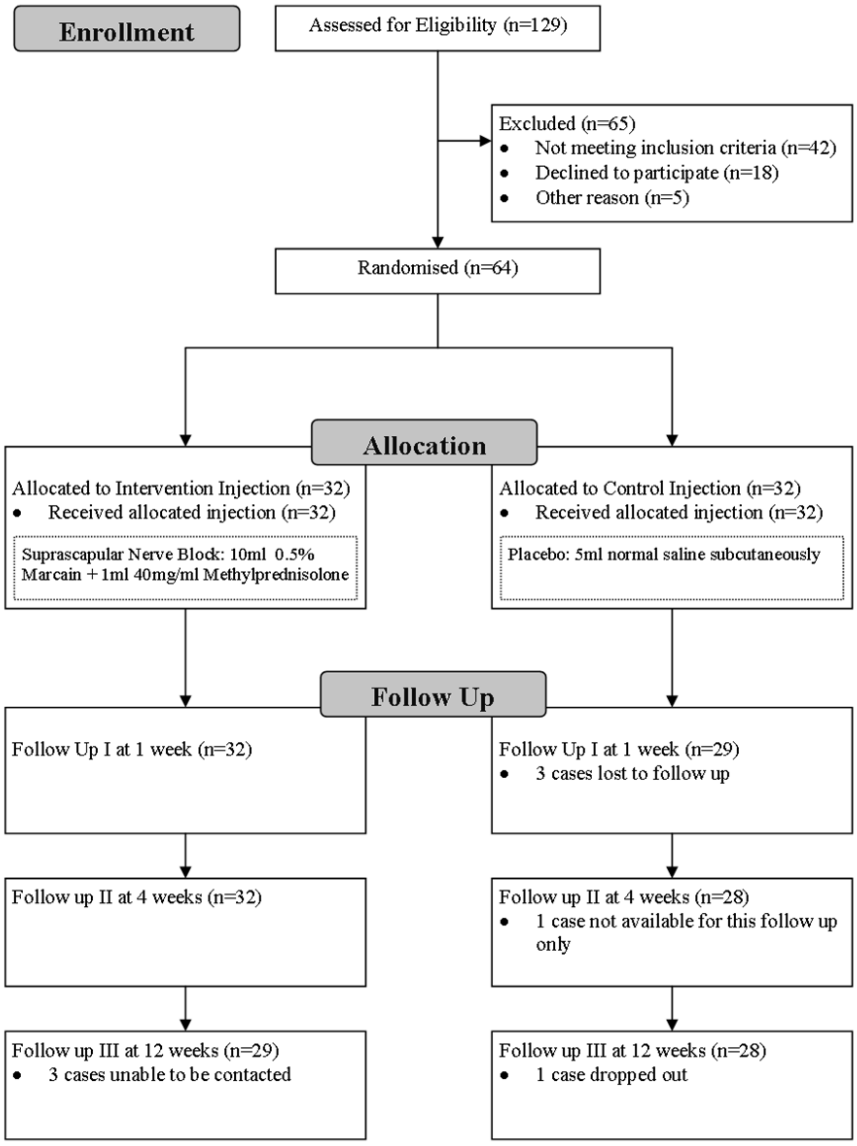


Figure 1. Flow of Participants Through Study

Three participants in the control group were lost to follow up. One further control participant was not available for follow up at four weeks, but was available at subsequent time points. One participant from the control group and three from the intervention group were unable to be contacted at 12 weeks. A total of 29 participants in the intervention group and 28 in the control group completed the trial with an overall attrition rate of 11%.

The demographic characteristics of participants at baseline were similar across groups (Table 1). The groups were well matched on stroke severity (NIHSS), motor weakness of the affected upper limb, and pain severity (VAS). Percentages of infarct versus haemorrhage were comparable, and Oxfordshire stroke classification demonstrated equivalent numbers of anterior and posterior circulation strokes. Potentially confounding factors such as spasticity and subluxation were also similar. No gender-based differences were detected.

Table 1. Baseline characteristics of participants with hemiplegic shoulder pain		
Baseline Variable	**Control (n=32)**	**Intervention (n=32)**
Age in years		
0-65	16 (50%)	15 (46.9%)
66-79	13 (40.6%)	19 (28.1%)
80+	3 (9.4%)	8 (25%)
Number (%) male	15 (46.9%)	21 (65.6%)
Number (%) right hemisphere stroke	21 (65.6%)	23 (71.9%)
Number (%) right hand dominant	26 (81.3%)	29 (90.6%)
Duration post stroke in weeks *mean (SD)*	11 (8)	13 (9)
NIHSS* *mean (SD)*		
Total† NIHSS	8 (4)	7 (3)
Motor score‡ affected arm	2 (1)	2 (1)
Stroke Type		
Number (%) Infarct	29 (90.6%)	27 (84.4%)
Number (%) Haemorrhage	3 (9.4%)	5 (15.6%)
Oxfordshire classification§		
TACS	10 (31.3%)	6 (18.8%)
PACS	16 (50.0%)	21 (65.6%)
LACS	4 (12.5%)	2 (6.3%)
POCS	1 (3.1%)	2 (6.3%)
Other	1 (3.1%)	1 (3.1%)
Number with subluxation (%)	10 (31.3%)	10 (31.3%)
Modified Rankin Scale *mean (SD)*	4 (1)	4 (1)
Croft Disability Q *mean (SD)*	12 (5)	12 (4)
Modified Ashworth Scale		
0	16 (50%)	16 (50%)
1	11 (34.4%)	11 (34.4%)
2	5 (15.6%)	2 (6.5%)
3	0 (0%)	2 (6.5%)

Values are number (%) unless otherwise stated

*NIHSS = National Institute of Health Stroke Scale

†NIHSS total score 5-15 = moderate severity stroke

‡NIHSS motor score upper limb of 2 = some effort against gravity, limb cannot get to or be maintained at 90°

§Oxfordshire Classification: TACS = total anterior circulation syndrome; PACS = partial anterior circulation syndrome; LACS = lacunar syndrome; POCS = posterior circulation syndrome

Primary Outcomes

Results for the primary outcome of pain (VAS) are summarised in Table 2 and Figure 2. Mean pain scores at baseline were comparable across the groups (p=0.379). Pairwise contrasts between groups were statistically significant at all follow up time points, with the SSNB group consistently demonstrating greater mean VAS reduction when compared to placebo (p=0.02 at Week 1, p=0.01 at Week 4, p=0.02 at Week 12). Linear regression analyses were performed to assess associations and predictors of responders. There were no statistically significant associations between any of the variables assessed; namely age, gender, spasticity (Modified Ashworth Scale), stroke severity (baseline NIHSS) or disability (Croft Disability Index).

Table 2. VAS pain scores between groups by treatment allocation

Time point	Control Mean (95% CI)	Intervention Mean (95% CI)	Pairwise Contrast Control-intervention	P value
Baseline	73.03 (66.10-79.99)	68.91 (62.25-75.56)	04.12	0.379
1 week	47.90 (36.58-59.21)	29.78 (19.29-40.23)	18.12	**0.02***
4 weeks	49.73 (40.62-58.83)	31.69 (21.40-41.97)	18.04	**0.01***
12 weeks	46.20 (34.63-57.78)	28.14 (17.81-38.46)	18.06	**0.02***

* Statistically significant

Sequential Bonferroni adjusted significance level is 0.05

Confidence interval bounds are approximate

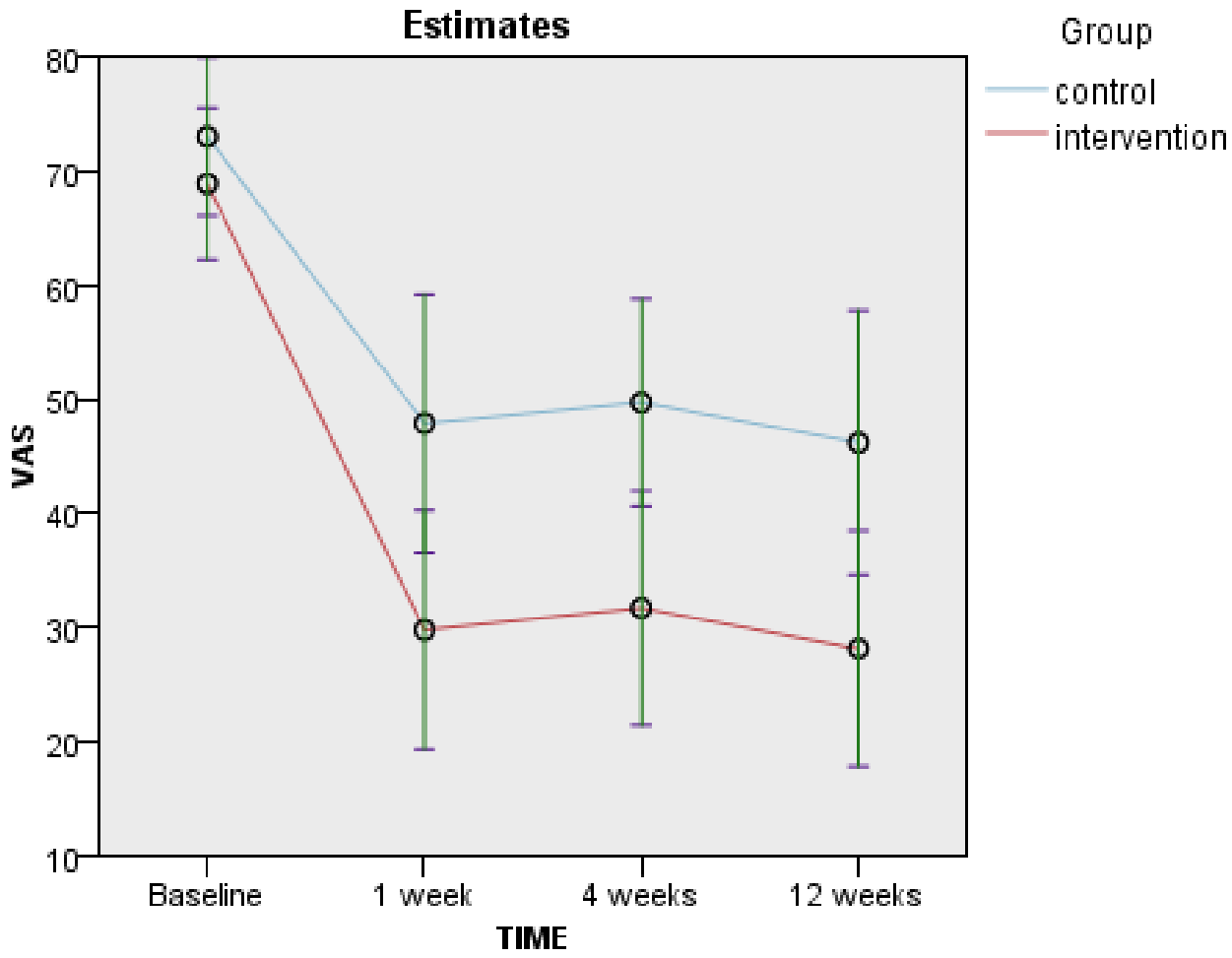


Figure 2. VAS pain scores between groups by treatment allocation

Secondary Outcomes

There were no differences between groups at any follow up time point in the secondary outcomes of disability and quality of life which were assessed with Modified Rankin Scale (mRS), Croft Disability Scale and EuroQol Health Questionnaire (EQ-5D). Both the intervention and control groups recorded a mean mRS score of 4(SD 1) at baseline. The majority of participants in both groups had a mRS of 3 or 4 (moderate – moderately severe disability) at all time points. The mean change in Croft Disability Index was non-significant between groups and at each follow up time point. EQ-5D weights for both groups reflected improved health-related quality of life over time, independent of effect from group allocation.

No adverse effects were reported.

Discussion

Comparable clinically important variables at baseline reflected successful randomisation. Whilst there were a higher proportion of total anterior circulation strokes (TACS) in the control group, the composite of total and partial anterior syndromes (TACS and PACS) was evenly distributed (81.3% in control group, 84.4% in intervention group). It is possible that subjective pain report in participants with TACS may have been influenced by higher cortical dysfunction, though the authors accounted for this in exclusion criteria. Whilst the difference of 4.12mm in baseline VAS between groups did not reach clinical or statistical significance, it could indicate a potential confounding factor. The mean time between stroke onset and enrolment was similar between groups, in keeping with the typical nadir of hemiplegic shoulder pain at the 2-3 month mark[264].

A single SSNB injection provides superior reduction in hemiplegic shoulder pain in comparison to placebo injection. The SSNB group demonstrated a mean VAS reduction of approximately 37mm, with a 18mm difference between intervention and control groups, maintained at each assessment. The definition of a minimal clinically important change on the 100mm VAS has been debated; papers report clinical importance from as little as 12mm[254]-15mm[265], up to 30mm[266, 267]. In our pre-trial protocol we aimed for a VAS change of 20mm to reach a robust level of clinical importance[259]. In order to consider our results in a clinically relevant context, data were subsequently reviewed to assess the percentage of responders who achieved criteria for patient defined successful[266] pain reduction of 50% and 30mm. The 4 week time point was taken to be of highest clinical interest, given the known pharmacodynamics of the active injection agent. At 4 weeks, 78% of all participants receiving SSNB reported any improvement in symptoms, with 80% of these responders demonstrating $\geq$ 20mm VAS pain reduction. The number needed to treat with SSNB to achieve a clinically significant pain reduction of 50% in one person was 4 (95%CI 3-29) at four weeks and 4 at twelve weeks (95%CI 2-25).

The marked placebo response (mean change of 25mm) is expected[268] in a subjective outcome trial utilising a sham injection, and is consistent with other studies of SSNB[46]. A degradation of this effect over follow up might have been expected[22] and we hypothesize that the maintained placebo response over time may reflect the natural history of hemiplegic shoulder pain as compared to degenerative shoulder conditions.

Despite significant pain reduction, there was no impact on the secondary outcomes of function and quality of life. The self report of health-related quality of life following stroke is affected by multiple factors, and improvement in a single variable of pain was insufficient to improve overall quality of life. Pain reduction may allow for more intensive therapies that could affect future independence.

Suprascapular nerve block is not a new intervention[232]. There has been an increasing body of literature in non-stroke populations, describing the SSNB as a simple, successful and reproducible intervention. As evidenced by results of this trial, the breadth of application of this intervention continues to expand. The suprascapular nerve involves a high proportion of sympathetic fibres, and supplies 70% of pain fibres to the shoulder. The mechanism of initial pain reduction is attributed to blocking these sensory fibres[47] and reducing nociceptive input to the central nervous system[242]. Lack of degradation of treatment effect by 3 months, suggests an additional potential mechanism in this population. It has been postulated[46] that there may be a reduction in central sensitisation secondary to diminished nociceptive stimulus as a potential effect of SSNB. This is in keeping with more recent studies which have identified features consistent with somatosensory sensitisation in patients with HSP, suggesting both nociceptive and neuropathic components of pain[196].

Strengths and Limitations

This is the first randomised controlled study to investigate SSNB as a treatment for hemiplegic shoulder pain. We recruited from stroke and rehabilitation settings across the city and believe our findings are generalisable to clinical practice. A single injector and single outcome assessor throughout this study reduced the risk of variations in technique and assessments. In future studies, alternatives to the Croft Disability Index could be considered. In practice, this questionnaire did not clearly delineate between disability secondary to hemiplegia and limitations secondary to pain.

The major limitation of this trial is that it is a small study with a comparatively short follow up period of 3 months. Estimation of treatment effect may be greater in this current study given the influence of a smaller sample size[269]. Further work is required with larger sample size, with the aim

of identifying characteristics of clinical responders and clarifying the mechanism of therapy effect in this population.

Summary / Conclusion

Suprascapular nerve block is a safe and effective treatment option for patients with hemiplegic shoulder pain in the first year after stroke. The intervention is easily reproducible in the clinical setting, offering a practical and important advance for this patient population.

Acknowledgements

Kelly Pinkney; outcome assessment

Maayken van den Berg; data analysis, statistical analysis

Pawel Skuza; statistical advice

Sources of Funding

This study was supported by a grant from Foundation Daw Park, Research Management Committee, Repatriation General Hospital.

Conflict of interest statement / disclosures

All authors state that there are no conflicts of interest to declare.

5.5 Introduction to Publication

Publication 5: Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal Physical Rehabilitation Medicine* 2015. 1(2):009

Purpose

A subgroup analysis was conducted to assess the clinically relevant variables associated with pain reduction in the randomised controlled trial previously presented. Responder data was reviewed across both allocation groups. The purpose of this post hoc analysis was to guide clinical practice by highlighting patient groups who may or may not respond to the intervention. The results suggest that patients under 80 and with high baseline pain levels are most likely to respond to the suprascapular nerve block injection.

Published in

Jacobs Journal of Physical Rehabilitation Medicine

Contribution from Primary Author

Primary Author – Dr Zoe Adey-Wakeling (ZAW)

ZAW reviewed the dataset from the original randomised controlled trial, and consulted with statistician about the most robust way to proceed with analysis. SPSS and SAS statistical packages were used to run analyses. The analyses presented in the final paper were re-run by the statistician. The manuscript was written by ZAW with supervision from co-authors as listed.

5.6 Publication 5

Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal Physical Rehabilitation Medicine* 2015. 1(2):009

Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response

Abstract

Background and aims: Suprascapular nerve block is an effective intervention for hemiplegic shoulder pain post stroke. This study aims to ascertain baseline variables associated with significant shoulder pain reduction in a post-stroke population receiving suprascapular nerve block versus placebo.

Methods: Post hoc subgroup analysis of data from a randomised controlled trial. Participants included 64 patients with hemiplegic shoulder pain (mean onset 12 weeks post stroke); 32 received suprascapular nerve block and 32 received placebo subcutaneous normal saline injection.

Results: Greater rates of pain reduction were found in participants with severe baseline pain ($p=0.0454$) and participants aged under eighty ($p=0.0417$). Persons aged over eighty demonstrated poor response to intervention. Heterogeneity of sex interaction was associated with reduced placebo effect in females ($p=0.036$).

Conclusions: Participants with severe baseline pain or aged <80 years were more likely to have reduced pain following injection. Patients >80 warrant further investigations prior to consideration of this intervention. Stroke subtype and level of spasticity were not associated with response.

Keywords:

Stroke; hemiplegia; pain; nerve block; treatment; age

Introduction

Hemiplegic shoulder pain occurs in approximately 25-30% of the post-stroke population[22, 26], but there is a paucity of evidence-based treatments. Multiple aetiologies can contribute to the development of hemiplegic shoulder pain, including soft tissue injuries, changes in motor control, and central nervous system alterations[31]. The impact of varying aetiologies contributes to the clinician's dilemma in selection of appropriate, evidence-based interventions. Prophylaxis includes positioning and safe manual handling techniques, though there is no causative association demonstrated[39]. Treatment options with increasing evidence base include Botulinum toxin A[41] and functional electrical stimulation[34], whilst there is conflicting evidence regarding the use of intra-articular steroid injections[34, 43].

The authors' recent randomised controlled study[151] demonstrated statistically and clinically significant benefits of suprascapular nerve block (SSNB) in a post-stroke population. This safe and effective treatment[45] warrants further studies in larger populations to provide greater understanding of characteristics of clinical responders and the impact of effective pain management on independence and quality of life.

Whilst larger scale studies are awaited, it is clinically relevant to consider which patients are the best candidates for the intervention. Reviewing the original trial data, this paper aims to explore the clinical variables associated with greatest reduction in reported pain.

Methods

A 'within study' post hoc subgroup analysis was performed on the data from *Suprascapular nerve block for shoulder pain in the first year after stroke: a randomised controlled trial*

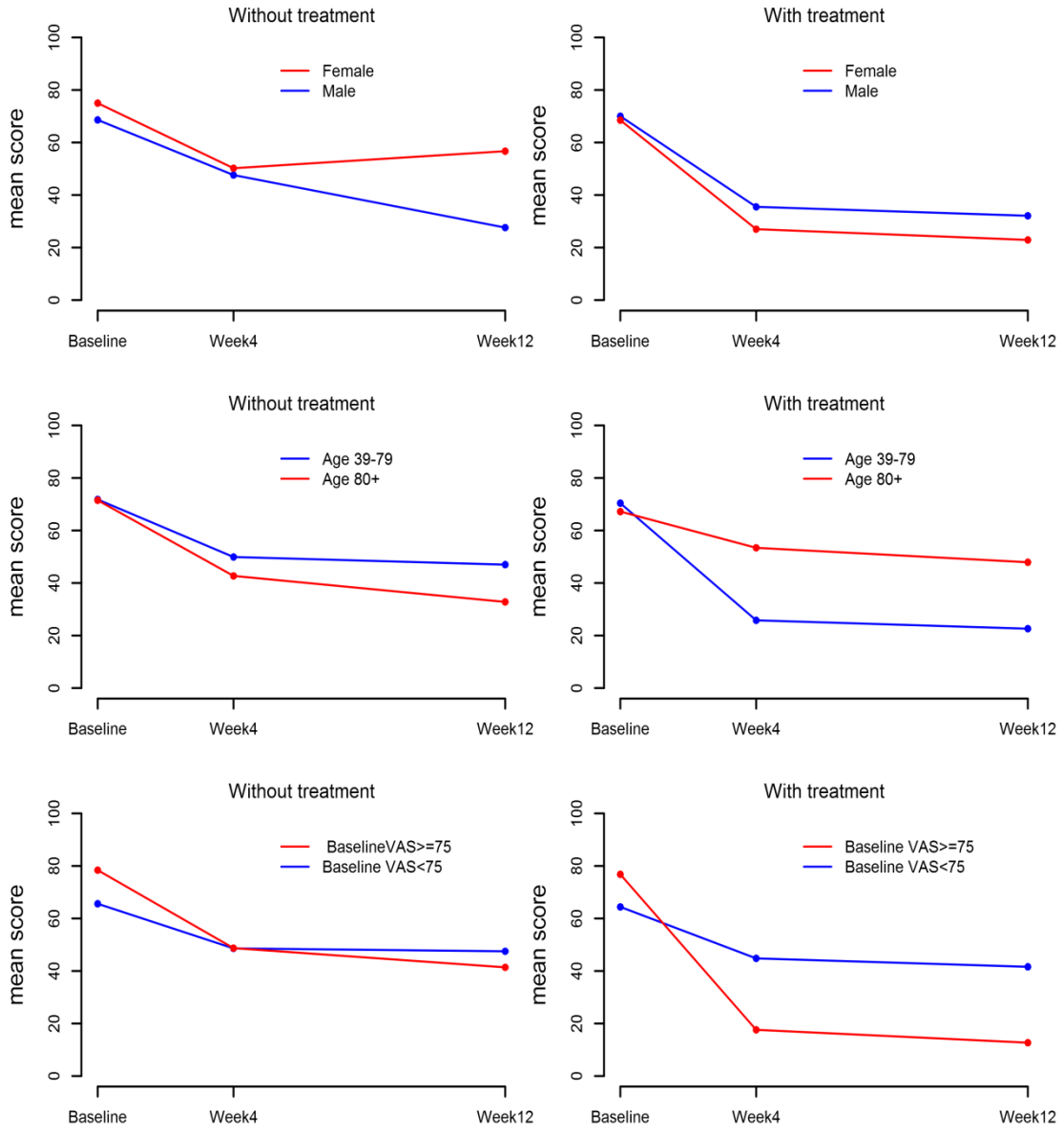
(ACTRN12609000621213)[3]. This randomised controlled trial assessed the effectiveness of SSNB on primary outcome of pain (100mm visual analogue scale, VAS) in a population of 64 stroke survivors with hemiplegic shoulder pain >30mm. The original paper[151, 261] outlines the ethics approval, informed consent, full methodology and outcomes. Patients were randomised to receive intervention (SSNB) or placebo injection. Suprascapular nerve block (10ml 0.5% bupivacaine hydrochloride and 1mL of 40mg/mL methylprednisolone) was performed via posterior approach, with use of anatomic landmarks to inject into the supraspinous fossa[46]. The placebo group received 5mL normal saline subcutaneous injection to the same region of the shoulder. Baseline demographics showed that the intervention group consisted of 65.6% males, whilst the placebo group was 46.9% males. The majority of participants suffered ischaemic stroke (84.4% in intervention group, 90.6% in control group). There were a greater proportion of elderly participants in the intervention group (25% aged 80 years and over) versus placebo (9.4% aged over 80). Patients were assessed at baseline, and followed up at one week, one month and three months. The intervention group demonstrated a statistically and clinically significant pain reduction when compared to control.

Subgroup analyses were performed to assess the interaction of treatment allocation with seven key baseline variables including age, gender, stroke subtype (infarct vs haemorrhage), upper limb motor deficit on National Institute of Health Stroke Scale (NIHSS) upper limb motor subscale, pain type (movement vs rest / night), spasticity, and VAS. Continuous baseline variables were dichotomised into clinically relevant binary outcomes for the analyses: NIHSS upper limb score definitions were split into 'able to maintain antigravity' (0-2) vs 'unable to maintain antigravity' (3+); severe pain was defined as VAS $\geq$75mm and mild-moderate pain as <75mm[6]; spasticity (Modified Ashworth Scale, MAS) was dichotomised as 'none' (MAS 0) or 'any' (MAS 1+).

Subgroup analyses were conducted by incorporating interaction terms into linear mixed models. The overall treatment effect for the subgroup were calculated by lsmens statement with a 2-way interaction term subgroup*treatment with cl and diff option by SAS linear mixed models. Means, mean difference, confidence intervals and p values at different time points were calculated by lsmeans statement with a 3-way interaction term subgroup*treatment*time with cl and diff option by SAS linear mixed models. All p values were two sided. Analyses were performed in SAS 9.3 (SAS Institute, Cary NC).

Results

Age under 80 and higher baseline pain scores are associated with more significant response to suprascapular nerve block intervention in hemiplegic shoulder pain. No significant interactions were found between treatment group and stroke type (ischaemic vs haemorrhagic), or baseline level of spasticity, pain type, or upper limb motor deficit, illustrating that treatment effect was not likely to be influenced by these factors. Subgroup analysis (Figures 1 and 2) suggests overall heterogeneity of treatment interactions for sex (p=0.036), age (p=0.0417) and severity of baseline pain (p=0.0454), indicative of impact on response to intervention. Figure 2 outlines p values for separated time points. P values reported test the hypothesis that mean differences (control-intervention) are zero.



VAS Visual Analogue Scale

Figure 1. Subgroup analysis - treatment and time effects

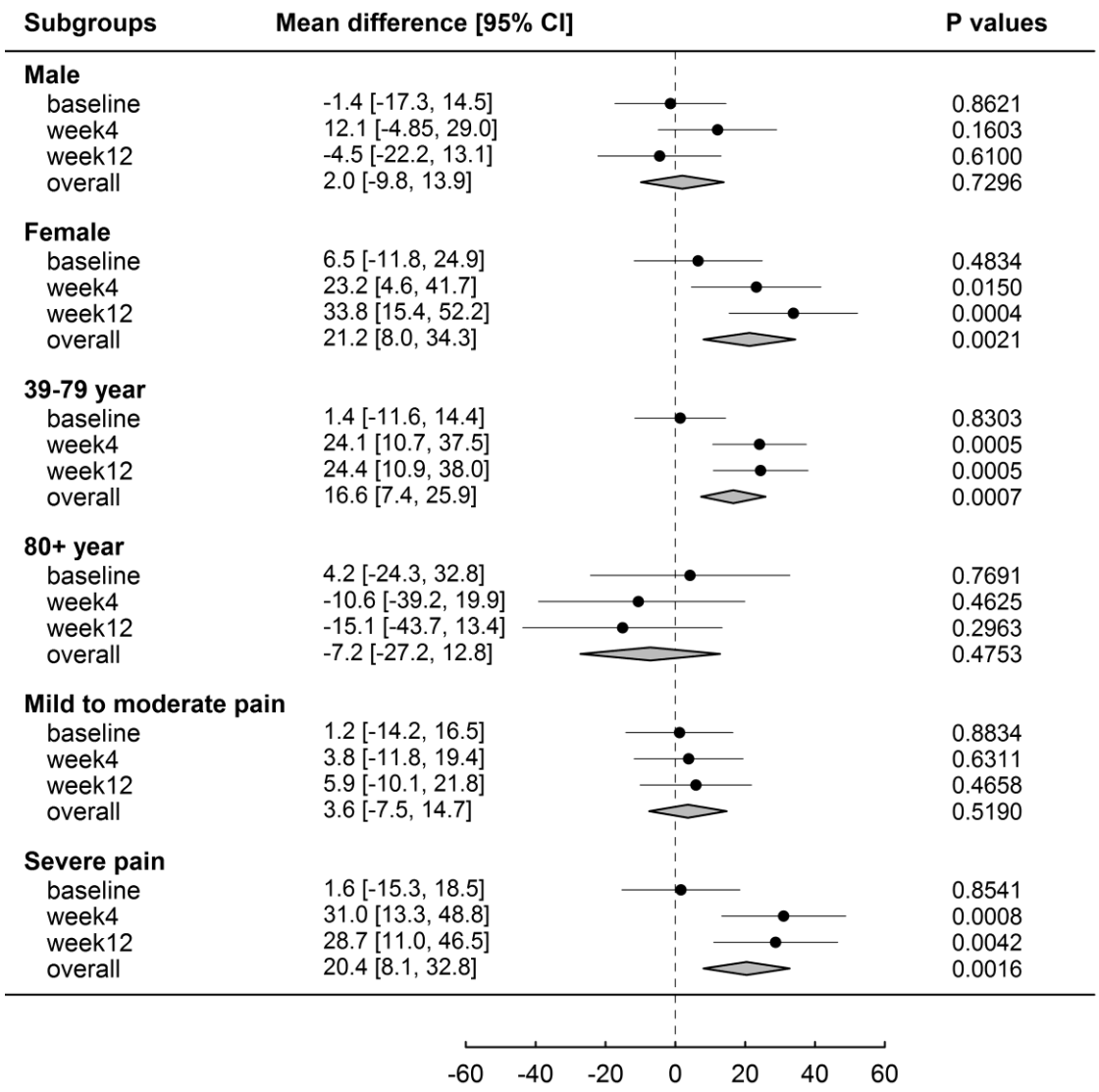


Figure 2. Subgroup analysis treatment effects

Whilst participants aged under 80 had significant response to intervention, those aged over 80 demonstrated poor response. The interaction between treatment and sex appears related to the reduced impact of placebo on females (Figure 1), with equivalent effect of active intervention in both males and females.

Discussion

The author's randomised controlled trial[151] concluded that SSNB is an effective intervention for hemiplegic shoulder pain. Subgroup analyses suggests that this intervention is most effective in patients aged <80 or with severe baseline pain.

There have been no previous published placebo-controlled randomised controlled trials of SSNB in a stroke population. As such, this subgroup analysis provides a first suggestion of participant variables which may increase the likelihood of a positive response. Similar analyses in non-stroke populations were not found, but subgroup analyses on stroke patients with hemiplegic shoulder pain have been reported in the context of intra-articular steroid injection[217]. The authors[217] reported that subgroup analyses supported the hypothesis that patients with neglect, visual field deficit and sensory deficits had higher risk of shoulder injury and subsequent capsulitis, and thus less likely to respond to intra-articular injection. Comparison to this study is not possible, as SSNB is effective in adhesive capsulitis[270] and the studies do not use comparable exclusion criteria or outcome measures.

It is important to consider these findings in context of clinical plausibility. Subgroup variables were selected within a clinical framework where interactions were conceivable. Statistically significant interactions were suggested for females, those aged <80, and patients with severe baseline pain. Whilst there is evidence suggesting sex differences in pain experience and analgesic response[271], the

finding in the current paper reflects reduced placebo response in females (Figure 1). Previous research has observed reduced placebo responses in females[272, 273], with hypothesised explanations including biochemical differences and absence of stress relief in females receiving placebo. Whilst this sex difference is biologically plausible in a placebo controlled trial, this finding should not influence the decision for administration of an active intervention. Age >80 was associated with poor intervention response, whilst participants aged <80 demonstrated increased likelihood of favourable response. Additional underlying pathologies may affect response in older people, and shoulder imaging may play a more important role in guiding treatment in a more complex presentation of hemiplegic shoulder pain. Greater response in those with severe baseline pain is consistent with previously documented effectiveness of SSNB in severe pain[228], and supports the role of this intervention in cases non-responsive to simple analgesics and conservative therapies.

Not all subgroups analysed demonstrated significant interactions, including spasticity and degree of motor deficit. P values on separated analyses of spasticity data indicated interaction, but overall interaction analysis suggests lack of heterogeneity of treatment effect. It has been postulated that patients with significant spasticity may achieve optimal response if the spasticity is treated[248] but we were unable to find any suggestion that the level of spasticity was associated with pain or response to treatment.

Findings of subgroup analyses are observational and have inherent limitations. The post hoc nature of our analyses impacts on the reliability of results. This is a small trial and we performed only seven 'within study' analyses.

Summary and Conclusion

Shoulder pain following stroke is a common problem with limited treatment options. SSNB is a promising treatment and our findings suggest its effects are not confined to one stroke subtype. Greatest response occurs in patients aged <80 and those with high reported baseline pain. Whilst no definitive conclusions should be drawn from this analysis, the results generate interesting hypotheses for consideration in larger powered future studies.

Acknowledgements

The randomised controlled trial was supported by a grant from Foundation Daw Park, Repatriation General Hospital.

Chapter Six

Impact of Hemiplegic Shoulder Pain on Health-Related Quality of Life

6.1 Introduction to Publication

Publication 6: Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based stud. *American Journal of Physical Medicine and Rehabilitation, Accepted January 2016*

Purpose

Health-related quality of life is a vital focus on patient-centred rehabilitation.

As outlined in the literature review, there have been no previous population studies assessing the association between health-related quality of life and hemiplegic shoulder pain. The only paper identified involved a selected volunteer sample of 61, demonstrating impact of HSP on the pain domain of quality of life. Given the high prevalence of HSP, it is important to establish impact of health-related quality of life to add impetus to heightening the clinical focus. This is the first methodologically robust study in an unselected population to demonstrate that shoulder pain at any time in the first year following stroke is an independent predictor of 12 month health-related quality of life.

American Journal of Physical Medicine and Rehabilitation – **accepted January 2016**

Contribution from Primary Author

Primary Author – Dr Zoe Adey-Wakeling (ZAW)

ZAW was granted access to the original dataset of the population-based study, with thanks to the ASCEND NH&MRC investigators. ZAW condensed multiple spreadsheets into SPSS, and converted to a format for analysis. The initial analyses were run by ZAW after consultation with the statistician. Final analyses presented in the paper were re-run by the statistician. The statistician performed all imputation and sensitivity analyses.

The manuscript was authored by ZAW, with review and input from the listed co-authors.

6.2 Publication 6

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation – accepted January 2016*

Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study

Abstract

Background and Purpose: Hemiplegic shoulder pain occurs commonly after stroke but most studies are confined to selected series and limited outcome measures. The aim of this study was to determine factors associated with health-related quality of life at 12-months after first stroke in a population-based registry.

Methods: A prospective population-based study in a geographically defined region of Adelaide, South Australia. Multiple ascertainment methods were used to identify all cases of stroke within a 12 month period, with objective and subjective measures undertaken at baseline and at 4 and 12 months of follow-up. Multiple regression analyses were used to identify independent variables among those demographic, clinical and process (exposure to shoulder pain and depression, 12-month dependence, access to formal rehabilitation) with health-related quality of life, defined by the summary index score derived from EuroQol-5D-3L at 12 months post-stroke.

Results: Hemiplegic shoulder pain, depression, increased dependency, stroke severity, and absence of initial rehabilitation were each significant negatively associated with health-related quality of life.

Age, sex, stroke type (ischaemic vs haemorrhagic), Oxfordshire classification and discharge destination were not related to health-related quality of life.

Conclusion: Hemiplegic shoulder pain impacts on health-related quality of life at 12 months. More effort should be directed towards screening and treating this frequent and manageable complication of stroke.

Introduction

The World Health Organisation[2] defines rehabilitation as "a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments". In this context, the maximisation of health-related quality of life (HRQoL) is identified as a pivotal goal of an individualised and coordinated rehabilitation approach. Previous studies have demonstrated reduced quality of life after acute stroke,[25, 274, 275] with lower HRQoL outcomes associated with disability,[25, 175, 276-278] functional status,[205, 275, 279, 280] depression,[25, 175, 276, 280, 281] female sex,[25, 276, 277] coping strategies,[276] social support,[205, 274, 276, 277, 281] reduced upper extremity function,[175] baseline stroke severity,[25, 277] baseline neglect,[25] institutionalisation,[25] increasing age,[25, 280] dementia,[25] education level[275] and low socioeconomic status.[25, 205, 278] The relationship between pain and HRQoL post-stroke has received far less attention. A recent systematic review[24] reported post-stroke upper limb interventions can impact on HRQoL, but information specifically regarding the quantitative impact of Hemiplegic Shoulder Pain (HSP) is lacking. With frequency of approximately 25%,[26] we hypothesize that HSP would adversely impact on HRQoL as measured at 12 months post-stroke.

Methods

Study population

This paper represents a secondary analysis of data from the Adelaide stroke incidence study (ASCEND), a prospective population-based study within a geographically defined region of metropolitan Adelaide, with a census-projected population of 148,000. ASCEND received formal institutional ethics approval and ensured informed consent of all participants. Multiple methods of case ascertainment were utilised to identify all occurrences of confirmed stroke within a 12 month

period. The methodology has been previously described[253], including detailed information regarding ascertainment techniques, participant characteristics, data collection and storage. Following ascertainment and consent, participants were assessed at baseline, and then at 4 and 12 months later. Data collected included demographics, medical and radiological details of the incident stroke, medical history, shoulder pain assessment and admissions history. Multiple outcome measures were collected at each time point. HSP was identified as an area of interest in the study and attention was paid to accurate measurement at each time point. Subjective measures of HSP included severity, aggravating features, time of onset and pre-morbid shoulder history. Objective measures included presence / absence of pain on 3 manoeuvres: modified Neers test, passive hand-behind-neck, and passive external rotation.

Outcome measures

The current analysis focuses on the factors assessed as potential determinants of 12-month HRQoL as measured by the summary index score derived from the descriptive system of EuroQol-5D-3L (EQ). The EQ-5D-3L compromises a visual analogue scale and a 5-dimension descriptive system (dimensions include mobility, self-care, usual activities, pain / discomfort and anxiety / depression).[282] Australian weight EQ-5D-3L summary index (EQindex) score ranges from -0.217 to 1, with death represented by 0, with negative values represented worse than death and full health represented by 1.[2, 263]

Baseline variables included age, sex, stroke type (ischaemic vs haemorrhagic, Oxfordshire stroke clinical classification, and baseline stroke severity as measured by the National Institute of Health stroke scale (NIHSS). HSP (visual analogue scale; VAS) and depression (Geriatric Depression Scale; GDS) scores were calculated as quantitative exposure values and averaged over all follow-up periods.[247]. Measures of the level of dependency (modified Rankin scale: mRS), institutionalisation

(movement into nursing home) and access to inpatient rehabilitation were reviewed at 12-months follow up.

Continuous variables of mRS and NIHSS were divided into clinically meaningful categories: mRS was dichotomized into 'independent 0-2', and 'dependent 3-6', where a mRS score of 0 is fully independent, and a score of 6 is given for death;[283] NIHSS was divided into 3 categories; mild <7, moderate 7-22, and severe >22[283]. Pain (VAS) and depression (GDS) scores were aggregated as exposure calculations over all follow up assessments.

Statistical analysis

The outcome variable for the study was EQ index score. The association between each predictor variable with the outcome variable were assessed by two sample student t test (sex, stroke type, any HSP, inpatient rehabilitation and whether GDS>5) and one-way ANOVA (age, NIHSS).

With the assumption that data were missing at random, we used multiple imputations to impute missing values in the database. The variables used to impute the missing values were age, gender, stroke type, Oxfordshire classification, baseline NIHSS, HSP score, GDS score and EQ index score. The EQ index was assigned zero in participants who had died by 12 months. 20 databases were imputed. Multiple linear regression analysis based on imputed databases was performed to test the association between HSP and HRQoL, controlling all other considered confounders. Sensitivity analyses for the multiple linear regressions were performed by using complete cases in the database and were compared with imputed results. All data analyses were conducted using SPSS 21 and SAS 9.3.

Results

The dataset of urban participants in ASCEND included 318 cases of stroke among 301 people. Only first-ever cases of stroke within the follow-up period was analysed for this study (n=300 with the exclusion of single duplicate case). Flowchart 1 outlines the sample and available follow up data. Completeness of data collection varied between follow-up periods and individual cases.

There were 12 month HRQoL data available for 263 participants (87.7%), inclusive of 105 people who died prior to 12-month follow-up (in these cases the index score was attributed as 0). The mean 12 months EQ index score was 0.463 (SD 0.435). Table 1 summarises association between EQ index scores and each predictor variable. Comparison of the mean EQ index between participants with / without any HSP over the follow-up period demonstrated lower mean scores in the group reporting HSP compared to those with no pain: 0.572 (0.357) versus 0.725 (0.369), p=0.017.

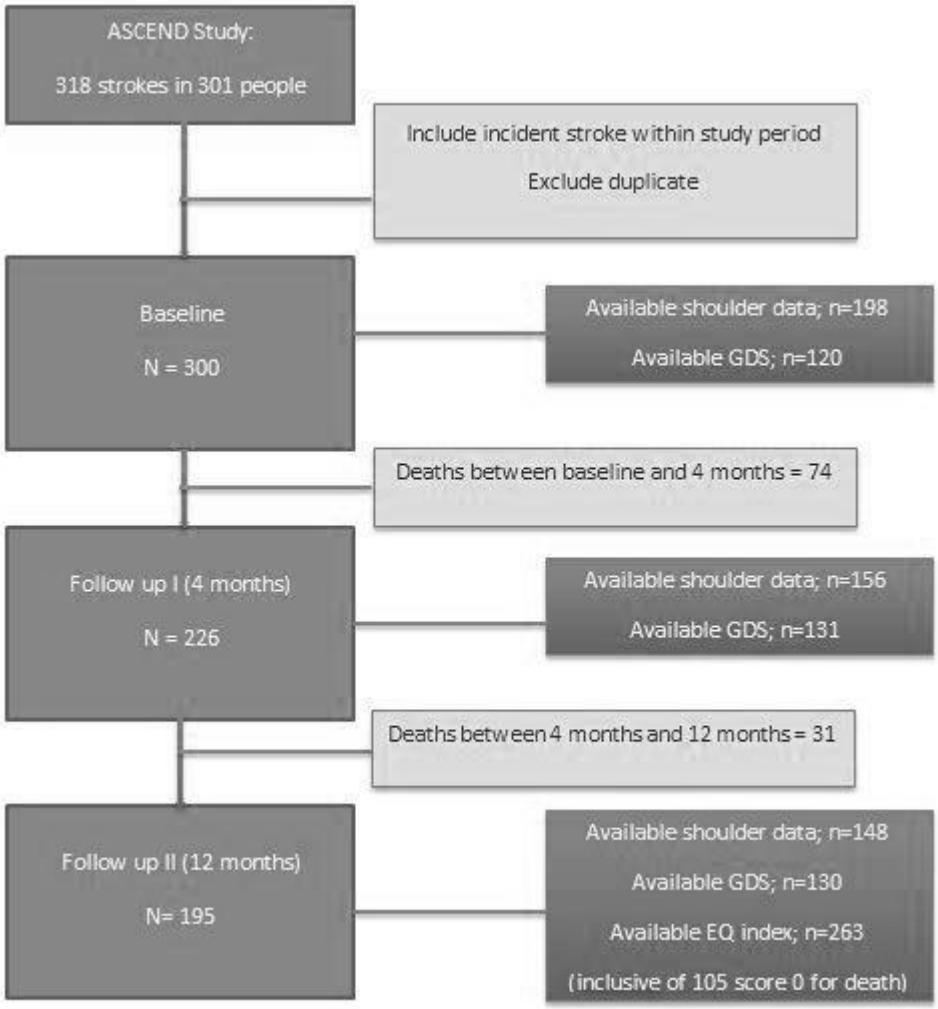


Figure 1. Flowchart of sample

Table 1. Baselines Variables and Mean EQ index at 12 months

Variable		**n**[*]	**EQ Index**[†] **Mean (SD)**[‡]	**Univariable p**
Sex	Male	133	0.531 (0.442)	0.024
	Female	125	0.410 (0.420)	
Age	<34	3	0.930 (0.121)	<0.001
	35-44	5	0.826 (0.389)	
	45-54	18	0.664 (0.399)	
	55-64	31	0.742 (0.366)	
	65-74	36	0.719 (0.336)	
	75-84	87	0.398 (0.435)	
	≥85	78	0.250 (0.365)	
Stroke Type	Ischaemic	219	0.515 (0.431)	0.013
	Haemorrhagic	29	0.303 (0.415)	
NIHSS[§]	Mild <7	120	0.715 (0.373)	<0.001
	Mod 7-22	84	0.359 (0.386)	
	Severe >22	32	0.068 (0.206)	
Any HSP[‖]	Yes	58	0.572 (0.357)	0.017
	No	77	0.725 (0.369)	
Inpatient rehabilitation	Yes	74	0.671 (0.344)	0.005
	No	141	0.505 (0.441)	
Pre-stroke institutionalisation	Yes	37	0.158 (0.305)	<0.001
	No	213	0.541 (0.428)	
GDS[#] >5	Yes	26	0.516 (0.384)	0.002
	No	86	0.763 (0.339)	

[*]n number with available data

[†]EQ EuroQol-5D-3L

[‡]SD standard deviation

[§]NIHSS National Institute of Health Stroke Scale

[‖]HSP Hemiplegic shoulder pain

[#]GDS Geriatric depression scale

Multivariable linear regression analysis demonstrated that increasing exposure scores for HSP (VAS) and depression (GDS), together with stroke severity (NIHSS) and 12 month dependence (mRS) were each independently and significantly associated with lowered HRQoL utility scores at 12 months (Table 2). Absence of access to inpatient rehabilitation after stroke was also associated with lower EQ index scores. Age, sex, stroke type (ischaemic vs haemorrhagic), Oxfordshire classification and institutionalisation at 12 months were not associated with reduced HR-QoL.

Sensitivity analysis by comparing results for complete cases and imputed cases of multiple linear regression showed that the association between HSP and EQ index score, association between depression (GDS) and EQ index score, and association between mRS and EQindex score were consistent (see appendix).

Table 2. Multiple linear regression of pooled analysis- Independent variables associated with reduced EQ utility score at 12 months (dependent variable EQindex)

Variable		**β (95% C.I.[†])**	**p value**
Age		-0.002 (-0.005- 0.000)	0.066
Sex	Male	0.005(-0.054-0.065)	0.867
	Female	0[a]*	
Stroke Type	Ischaemic	0.034 (-0.069-0.137)	0.517
	Haemorrhagic	0[a]*	
NIHSS[‡] (baseline)	Mild	0.239 (0.090-0.388)	**0.002**
	Moderate	0.204 (0.063-0.345)	**0.004**
	Severe	0[a]*	
Oxfordshire	PACS	-0.069 (-0.323-0.186)	0.598
	TACS	-0.091 (-0.357-0.175)	0.503
	LACS	-0.078 (-0.334-0.179)	0.553
	POCS	-0.085 (-0.342-0.179)	0.514
	Unknown	0[a]*	
HSP[§] VAS[‖]		-0.011 (-0.013- -0.008)	<**0.001**
GDS[#]		-0.037(-0.049- -0.025)	<**0.001**
mRS[**] (12 month)	Independent	0.214 (0.133-0.295)	<**0.001**
	Dependent	0[a]*	
Institutionalisation (12 months)	No	0.043 (-0.049-0.135)	0.359
	Yes	0[a]*	
Inpatient Rehabilitation	No	-0.084 (-0.147- -0.022)	**0.008**
	Yes	0[a]*	

*0[a] set to zero because parameter redundant
[†]CI confidence interval
[‡]NIHSS National Institute of Health Stroke Scale
[§]HSP Hemiplegic shoulder pain
[‖]VAS Visual analogue scale
[#] GDS Geriatric depression scale
* *mRS Modified Rankin scale

Discussion

Our analysis of the ASCEND dataset has shown that HSP reported at any time in the first year after the onset of acute stroke is associated with lower HRQoL. Koog et al's cross-sectional survey of 177 rehabilitation stroke outpatients[203] reported high rates of any pain (42%) but pain was not associated with lower HRQoL. However, Widar et al[205] reviewed 43 selected stroke patients with chronic pain, but not specific to the shoulder, and showed a lower HRQoL score as compared to previous studies, implying that population based studies were need to further evaluate the impact of pain on HRQoL. One small cross-sectional study[202] outlines specific assessment of HSP and its impact on HRQoL. Chae et al[202] concluded a statistically significant association between shoulder pain and quality of life, but not between pain and motor impairment or activity limitation, without any adjustment for depression being made. To the best of our knowledge, this is the first ideal[252] population-based stroke incidence study to include a comprehensive assessment of HSP and showed it to be an independent determinant of subsequent HRQoL.

The HRQoL results reveal significant reduction in mean utility scores in a stroke population, in keeping with previously observations.[25, 274, 275] Australian normative HRQoL benchmark data is now available for comparison, with recent research[2] establishing a general population HRQoL mean of 0.87 with a minimal clinically important difference (MCID) of 0.05. This contextualised the current results as a 50% reduction in HRQoL in a stroke population. Mean HRQoL was lower in participants who reported HSP during the follow-up period (participants with HSP: 0.572 (0.357) versus participants without HSP 0.725 (0.369), p=0.017). The means are observed to be higher than the imputed mean, likely reflecting that completeness of shoulder assessments may have been impacted by overall morbidity.

A comparable Australian population-based study, which was undertaken 10 years ago,[25] used a similar methodology but did not specifically report on the impact of pain on HRQoL. This study used the Assessment of Quality of Life instrument (AQoL)[241] and found a mean utility score of 0.47, while the mean utility score reported in the current study using the EQ-5D-3L was 0.463. Whilst indirect comparison of mean HRQoL scores across populations and time is not valid with different assessment measures, and which reflect differing constructs of quality of life,[282] independent determinants of HRQoL are consistent across studies. Both found that higher levels of NIHSS, depression and disability, along with demographic factors of age and sex, all predicted reduced HRQoL.

A strength of our study is use of a prospective population-based methodology. Moreover, we made adjustment for depression in the statistical analysis model, in order to exclude the expression of pain as a proxy for depression ratings. Limitations are recognised in variable missing data over follow up, which was overcome to some extent by the use of multiple imputations. The association of pain, depression and dependence with HRQoL are seen as being highly significant (pooled data $p<0.001$ for each). Robustness of this result is demonstrated by comparable significance on sensitivity analysis (see appendix table).

Summary

In summary, HSP appears to adversely impact on HRQoL over 12 months after acute stroke. This finding is important in the context of HSP being a potentially preventable (or reversible) factor. More effort should be directed towards screening and treating this high incidence complication of stroke.

Sources of Funding

The ASCEND population based study was funded by a Project Grant (565402) from the National Health and Medical Research Council of Australia

Disclosures

CSA reports holding a Senior Principle Research Fellowship of the National Health and Medical Research Council of Australia

Online Appendix

Supplemental Table I. Sensitivity Analysis; dependent variable EQ index 12 months

Variable		Imputed cases		Completed Cases	
		β (95% C.I.)	p value	β (95% C.I.)	p value
Age		-0.002 (-0.005-0.000)	0.066	-0.001 (-0.004-0.002)	0.540
Sex	Male Female	0.005(-0.054-0.065) 0[a]	0.867	0.039 (0.048-0.125) 0[a]	0.385
Stroke Type	Ischaemic Haemorrhagic	0.034 (-0.069-0.137) 0[a]	0.517	0.079 (-0.124-0.282) 0[a]	0.447
NIHSS (baseline)	Mild Moderate Severe	0.239 (0.090-0.388) 0.204 (0.063-0.345) 0[a]	**0.002** **0.004**	0.047 (-0.186-0.280) -0.021 (-0.233-0.192) 0[a]	0.692 0.849
Oxfordshire	PACS TACS LACS POCS Unknown	-0.069 (-0.323-0.186) -0.091 (-0.357-0.175) -0.078 (-0.334-0.179) -0.085 (-0.342-0.179) 0[a]	0.598 0.503 0.553 0.514		
HSP VAS		-0.011 (-0.013- -0.008)	**0.000**	-0.004 (-0.008- -0.001)	**0.024**
GDS		-0.037(-0.049- -0.025)	**0.000**	-0.047 (-0.067- -0.026)	**<0.001**
mRS (12 month)	Independent Dependent	0.214 (0.133-0.295) 0[a]	**0.000**	0.139 (0.022-0.256)	**0.020**
Institutional living (12 months)	No Yes	0.043 (-0.049-0.135) 0[a]	0.359	0.041 (-0.119-0.201) 0[a]	0.616
Inpatient Rehabilitation	No Yes	-0.084 (-0.147- -0.022) 0[a]	**0.008**	0.001 (-0.092-0.094) 0[a]	0.984

Chapter Seven

Research Findings in Context of Research Objectives

Clinical Modelling and Future Practice

Future Research Directions

Conclusion

This chapter summarises and synthesises the principal findings of the research presented in this thesis, with reference to the initial research objectives outlined in Chapter One. Novel findings are highlighted. Recommendations for changes in clinical practice models, and future research objectives are identified. The limitations of each study have been discussed in each paper previously presented in this thesis, but gaps in the synthesis of the findings will be outlined.

Review of Initial Research Objectives outlined in Chapter One

I. To describe hemiplegic shoulder pain within the broader context of upper limb dysfunction following stroke

II. To characterise the epidemiology, aetiology and clinical approaches to hemiplegic shoulder pain via a review of the literature

III. To determine the current evidence for the use of suprascapular nerve block, including anatomy and description of the procedure, and to summarise the search in both non-stroke and stroke populations

IV. To report the epidemiological patterns of hemiplegic shoulder pain incidence and associations within an Australian stroke population

V. To investigate suprascapular nerve block as a treatment option for hemiplegic shoulder pain compared to placebo; and to characterise patient subtypes more likely to have a positive response to this treatment

VI. To investigate the impact of hemiplegic shoulder pain on health-related quality of life

VII. To synthesise the research findings into clinical recommendations

7.1 Summary of Research Findings in Context of Research Objectives

Objective I

To describe hemiplegic shoulder pain within the broader context of upper limb dysfunction following stroke

Stroke remains a leading cause of disability worldwide. With increasing rates of survival, greater numbers of people are living with disability secondary to their stroke event. Despite increasing research including the emergence of novel therapy options such as robotics for upper limb deficits post stroke, there needs to be greater focus on the common complications such as hemiplegic shoulder pain. Hemiplegic shoulder pain is one of the four most common complications of stroke[284]. A paper assessing correlations between upper limb function and the ICF model found shoulder pain to be the variable most associated with limitations in participation[28, 29]. Participation restriction refers to limitation in an individual's ability to actively participate in all areas of personal and societal life[27], and as such must be recognised as a pivotal rehabilitation focus. Prevention or effective management of these complications may facilitate greater access to emerging technologies and therapy which may in turn further improve outcomes.

Objective II

To characterise the epidemiology, aetiology and clinical approaches to hemiplegic shoulder pain via a review of the literature

Objective III

To describe suprascapular nerve block via a review of the literature; overview of anatomy, nerve block and use as a therapy in both non-stroke and stroke populations

A summary of the literature regarding hemiplegic shoulder pain is presented in Chapter 3.1. The significant variability in reported rates of hemiplegic shoulder pain reflect heterogeneous pain definitions and study designs over many decades. More recent population-based studies from Sweden[16] and New Zealand[170] report more conservative prevalence rates of 23-30%. Whilst these figures are much lower than earlier reports, the incidence is still significantly high and warrants evidence-based interventions to help guide clinical practice. A review of the literature reveals a paucity of high-level evidence regarding interventions for hemiplegic shoulder pain. Commonly, it is noted that interventions do not accommodate the multi-factorial aetiological presentations of this condition. The Australian National Stroke Foundation guidelines[36] for prevention and management of hemiplegic shoulder pain largely refer to 'good practice points' and evidence for musculoskeletal conditions. This is a clear reflection on the lack of quality evidence and the need to expand the understanding of this common complication of stroke.

Chapter 3.2 details the anatomy of the suprascapular nerve the suprascapular nerve block procedure. An overview of the evidence pertaining to suprascapular nerve block in non-stroke populations is presented, with the evidence gap for stroke populations outlined. The need for larger sample,

placebo-controlled randomised studies is established, and supported by international reviews on therapy options for hemiplegic shoulder pain[3].

Objective IV

To report the epidemiological patterns of hemiplegic shoulder pain incidence and associations within an Australian stroke population

Results from the population-based study presented in this thesis confirm that more than 25% of people develop pain in the first year after stroke, with peak incidence at 4 months. This is the first report of incidence rates in a representative Australian population. Comparison with an earlier European population study[5] indicates that an increased focus on evidence-based treatments in stroke has not resulted in a reduction in the frequency of this common complication of stroke. Importantly, when comparing studies of equivalent methodology, it has now been demonstrated that the Australian prevalence rates are consistent with those found in international population-based studies.

Table 1. Comparison of Population-Based Studies: Prevalence of Hemiplegic Shoulder Pain

Author	**Year**	**Origin**	**Setting**	**Number of participants**	**Prevalence HSP *(%)***
Ratnasabapathy et al	2003	New Zealand	Population-based study	1201	23%
Lindgren et al	2007	Sweden	Population-based study	327	30%
Adey-Wakeling et al	2014	Australia	Population-based study	301	29%

Other clinically relevant findings from the Adelaide population-based study include the patterns of pain presentation, with assessment of aggravating factors and relationships over time. A novel finding was the surprisingly high baseline prevalence of hemiplegic shoulder pain in 10% of the study population. Many other studies have described convenience samples of rehabilitation inpatients. In these selected populations there were much higher overall rates of pain reported but when all strokes are looked at, including those who do not reach rehabilitation units, one in ten survivors will suffer with shoulder pain.. This is an important differentiation to make, as consideration of follow up needs to be given to all stroke survivors at risk of pain, not only those accessing inpatient rehabilitation programmes.

Additionally, both peak onset and severity is at 4 months, and this is a time frame frequently beyond an inpatient admission. This has important implications for the identification of patients at risk of developing later hemiplegic shoulder pain, and for implementing appropriate education and follow up plans. The change in pain presentation also assists in identifying potential aetiological changes over time, and hence decision-making regarding appropriate treatment targets.

The study demonstrated that there was an increasing association between pain and range of motion over time, potentially indicating accumulative musculoskeletal injuries with greater time post stroke. Rest pain and night pain were greatest in the early weeks post stroke. Baseline objective passive range of motion tests elicited higher frequencies of pain than self-report, and predicted later subjective shoulder pain (crude relative risk of 3.22 (95%CI 1.01-10.27). This finding supports the role of both subjective and objective measures, even when the patient does not voluntarily report pain.

Objective V

To investigate the role of suprascapular nerve block as a treatment option for hemiplegic shoulder pain, and to characterise patient subtypes more likely to have positive response to this treatment

This thesis has presented research supporting a role for suprascapular nerve block (SSNB) in the treatment of hemiplegic shoulder pain. This thesis includes the first randomised placebo-controlled trial to provide evidence of the statistically and clinically important role of SSNB in a post-stroke population. This intervention is easy to perform, safe and effective, and has the potential to help the 20-30% of patients who experience pain refractory to current treatment modalities[35].

Methodological strengths of the trial included a published protocol paper, blinded outcome assessment and the use of specific and validated outcome measures. Unlike many rehabilitation trials, the intervention was specific and was compared to a placebo, as opposed to 'usual care' or no treatment[285, 286]. Outcome measure considered multiple domains of the ICF[27] model. The primary outcome of pain (VAS) was focussed at the impairment level. Secondary outcomes of function and quality of life were also measured. All outcome measures were validated and are commonly used in rehabilitation research, enabling meaningful comparison to previous studies.

The exclusion criteria were deliberately limited, with the goal to make findings applicable to the larger post-stroke population. Exclusion of patients with significant cognitive and language deficits was applied to enhance reliability of outcome measures, though it should be noted that this would impact generalisability as cognitive[287] and language deficits are common in this cohort, more marked in the early months[288]. The sample size is a limitation of the trial, and the findings should ideally be replicated in a larger trial with longer follow up period.

With a goal of making the research findings as clinically transferrable as possible, further analysis was able to provide insight into those patients who were most likely to show a significant response to this intervention. SSNB is a promising treatment and the findings suggest its effects are not confined to one stroke subtype. A response was more likely to occur in patients aged under eighty, and those with high reported baseline pain. On the basis of these findings and until further evidence emerges, caution should be shown in using these injections for people aged over 80.

Objective VI

To investigate the impact of hemiplegic shoulder pain on health-related quality of life

The final paper presented in this thesis reports on long-term effects of shoulder pain. Using prospective population data of patients in the first year following stroke, the hypothesis that hemiplegic shoulder pain is an independent predictor of reduced health-related quality of life was tested. Analysis demonstrated a highly significant association of hemiplegic shoulder pain with health-related quality of life, with adverse impact of HSP comparable to depression and dependence associations. This finding is important in the context of rehabilitation strategies in hemiplegic shoulder pain; shoulder pain is potentially preventable and / or reversible and more efforts should be directed towards screening and treating this high incidence complication of stroke. Given the impact of these important consequences of HSP, consideration should be given to more comprehensive follow up of stroke survivors. The correlation between hemiplegic shoulder pain and participation[28, 29], and participation and quality of life[25] emphasises the need to focus therapy on the painful hemiplegic shoulder.

Objective VII

To synthesise the research findings into clinical recommendations

The research findings summarised above can be synthesised to help guide clinical practice and recommendations in the Australian context. To make an appropriate assessment of gaps in current frameworks, consideration was given to several factors:

- Review of the literature (Chapter Three)
- Current guidelines and practice recommendations
- New knowledge as presented, and
- The fundamental ideology that rehabilitation is an individualised process.

7.2 Clinical Modelling and Future Practice

7.2.1 Critical Appraisal of Current Clinical Guidelines

The lack of high-quality studies available to inform treatment options for hemiplegic shoulder pain is reflected in current Australian and United Kingdom NICE guidelines, which do not cite any evidence-based therapeutic options specific to a stroke population[36, 37]. The American Department of Veterans Affairs / Department of Defence Clinical Practice Guidelines[158] 2010 (Stroke) do not list any specific recommendations for the management of hemiplegic shoulder pain. The Canadian Best Practice Guidelines 2013[104] and UK Royal College Physicians National Clinical Guidelines for Stroke 2012[289] provide more comprehensive recommendations, and are summarised in the Table 2. The emphasis of the recommendations is on prevention, with only the Canadian guidelines making specific interventional recommendations (Botulinum toxin and steroid injections in selected patients). There are limited recommendations on screening for pain, follow up of the patient with established pain, or monitoring for future pain.

On the basis of a single small randomised controlled trial, routine use of suprascapular nerve block injection cannot be advised. Similarly, robust evidence on screening tools is lacking. However, on the basis of the work in this thesis, recommendations for a systematic approach for clinical teams are put forward and should be tested.

Table 2. Current Guidelines / Recommendations for Hemiplegic Shoulder Pain

Australia: National Stroke Foundation (NSF) Guidelines 2010[36]
For people with severe weakness who are at risk of developing shoulder pain, management may include: • Shoulder strapping [B] • Interventions to educate staff, carers and patient [GPP] For people who develop shoulder pain, management should be based on evidence-based interventions for acute musculoskeletal pain [GPP] The routine use of the following is NOT recommended for established shoulder pain: • Corticosteroid injections [C] • Ultrasound [C] **NSF Levels of Evidence:** A - body of evidence can be trusted to guide practice; B - body of evidence can be trusted to guide practice in most situations; C - body of evidence provides some support for recommendations but care should be taken in its application; D - body of evidence is weak and recommendation must be applied with caution; GPP - Good practice point; recommended best practice based on clinical experience and expert opinion
United Kingdom: National Institute for Healthcare and Excellence (NICE) Guidelines 2013[50]
• Provide information for people with stroke and their families and carers on how to prevent pain or trauma to the shoulder if they are at risk of developing shoulder pain • Manage shoulder pain after stroke using appropriate positioning and other treatments according to each person's need. • For guidance on managing neuropathic pain follow Neuropathic pain (NICE clinical guideline 96).
Canadian Best Practice Recommendations for Stroke Care 2013[104]
<u>Prevention by:</u> Joint protection strategies: • Positioning at rest [B] and during functional mobility [C] • Supporting during wheelchair use with hemi-tray [C] • Slings in flaccid stage only [C] Overhead pulleys should not be used [A] Arm should not be moved beyond 90’ shoulder flexion or abduction, unless scapular upwardly rotated and humerus laterally rotated [A] Education [A] Avoid traction in assisted movements [C]

Management of Pain:

- Gentle stretching [B] with gradual increased in range
- Analgesics if no contra-indications [C]
- Botulinum toxin injection into subscapularis and pectoralis muscles if pain related to spasticity [A]
- Subacromial corticosteroid injections can be used in patients when pain related to injury or inflammation of subacromial region [A]
- In a subset of patients who experience pain related to both injury / inflammation and spasticity, dual therapy should be used (BTX and steroid injections) [C]

A - Strong recommendation. Evidence from randomized controlled trials or meta-analyses of randomized controlled;
B - Single randomized controlled trial or well-designed observational study with strong evidence; or well-designed cohort or case–control analytic study; or multiple time series or dramatic results of uncontrolled experiment. Desirable effects closely balanced with undesirable effects;
C - At least one well-designed, non-experimental descriptive study (e.g., comparative studies, correlation studies, case studies) or expert committee reports, opinions and/or experience of respected authorities, including consensus from development and/or reviewer groups trials. Desirable effects clearly outweigh undesirable effects, or vice versa.

United Kingdom: Royal College Physicians National Clinical Guidelines for Stroke 2012[289]

Every patient with functional loss in their arm should have the risk of developing shoulder pain reduced by:

- Ensuring that everybody handles the weak arm correctly, avoiding mechanical stress and excessive range of movement
- Avoiding use of overhead slings
- Careful positioning of arm

Every patient with arm weakness should be regularly asked about shoulder pain

Every patient who develops shoulder pain should:

- Have its severity assessed, recorded and monitored regularly
- Have preventative measures put in place
- Be offered regular simple analgesia

Any patient who has developed, or is developing, shoulder subluxation should be considered for functional electrical stimulation of the supraspinatus and deltoid muscles

In the absence of inflammatory disorders, intra-articular steroid injections should not be used for post-stroke shoulder pain

United States: Department of Defence Clinical Practice Guidelines 2010

No guidelines for hemiplegic shoulder pain

7.2.2 Developing a ward guideline for assessment and management: practical considerations

Only one prior stroke shoulder pain protocol has been developed and formally tested. Extensive work has been completed by Jackson and Turner-Stokes et al 2002[33] in the development of an Integrated Care Pathway (ICP) for use in the rehabilitation unit of Northwick Park Hospital, United Kingdom. Turner-Stokes et al 2002[194] performed a comprehensive literature review on which to base the development of the ICP, and thorough audit processes have been completed to review the outcome of the pathway implementation[290]. With acknowledgment of the diversity of their target population, the authors' collaborative multidisciplinary approach aimed to develop a pathway to improve the clinical management via co-ordinated practices, timely intervention and appropriate recording processes[33]. The care pathway outlines interventions (assessments, management plans, consideration of specific interventions) with recommended timeframes and standards against which the process could be audited[33]. Early barriers identified included the significant time and effort in implementation, variable documentation standards and the need for regular education / re-education in the context of staff turnover[33]; concerns common to many change knowledge translation projects.

Even though this ICP was developed more than a decade ago, the process followed is in line with recommendations described by Bosch et al 2013[291]. Bosch et al outline a process by which to develop "locally applicable, actionable best practice recommendations", based on prerequisite attention to preliminary steps[291]:

Step 1: extract recommendations from current, high-quality clinical guidelines

Step 2: select strong recommendations in key clinical areas

Step 3: review and update the applicable evidence

Step 4: produce agreed ‘evidence statements’

Step 5: discuss evidence with local stakeholders

Considering the successes and challenges which resulted from the thorough process adopted in the development of the ICP by Jackson et al[33], it is important to recognise that translation of evidence into clinical care is not a straight-forward undertaking.

Knowledge Transfer

As discussed in the first paper (Chapter One), evidenced-based care is the gold standard, but it is reported that translation of evidence into practice lags significantly behind the established science[292]. Canadian research[162, 163] reflecting on the challenges of transferring evidence into practice identified the issues such as poor generalizability of research finding to the ‘average’ patient, limitations in the strength of evidence available, and difficulties with the practicalities of adhering closely to evidence based guidelines[162]. The research presented in this thesis has aimed to adopt methodological approaches to maximise the generalisability of the findings and the strength of the evidence reported; examples including population data sets and broad inclusion criteria.

The use of guidelines aims to target both the individual and organisational levels of implementation[292]. Additionally, maintaining momentum following implementation of pathways or guideline approaches is often cited as a barrier. Education is the pivotal factor in the success of the recommendations to follow.

7.2.3 Contribution of Current Evidence to Clinical Practice

7.2.3.1 Local ward practices

Engagement with local stroke wards has been a focus from the early development of the research presented in this thesis. Small multidisciplinary working groups were established in both the acute Comprehensive Stroke Unit at Flinders Medical Centre, and the Neurological Rehabilitation Ward at Repatriation General Hospital. Audited observations by Occupational Therapist, Heather Block, at Flinders Medical Centre, outlined inconsistencies in positioning and care of the hemiplegic upper limb. The Comprehensive Stroke Unit then implemented alert posters, slings for transfers and formalised positioning recommendations. Whist this was not a formal research project, enthusiasm and awareness regarding this common issue became a focus on these wards. It is important to consider the assessment of baseline ward practices to help identify the actual and perceived 'gaps' in current processes.

7.2.3.2 Recommendations stemming from novel research presented in this thesis

It is not the aim of this thesis to produce a comprehensive guideline, but rather to add the current recommendations to the established guidelines and pathways outlined above. The Australian National Stroke Foundation guidelines[36] would better inform clinician choice if greater focus was made on the appropriate assessment of hemiplegic shoulder pain, as well as specific intervention guidelines for a stroke population. The Integrated Care Pathway (ICP) and documentation proforma recommended by Jackson and Turner-Stokes et al[33] provide a strong basis on which local wards can expand and develop enhanced awareness and more rigorous practices in line with current evidence.

Rehabilitation represents a client-centred approach to improving outcomes, and as such a strong focus on factors such as hemiplegic shoulder pain, now demonstrably known to impact health-related quality of life, are core to this approach.

Expansion of application of ICP[33] as a ward based guideline

Jackson and Turner-Stokes et al[33] proposed that "all rehabilitation centres should have an agreed written protocol for the prevention and treatment of HSP". The ICP discussed was designed for use in a Rehabilitation setting, though immediate implementation in an acute stroke setting would support current opinion for earliest intervention[7] with the view that prophylaxis is potentially the best management principle. With high rates of non-response to HSP treatment interventions, prevention is considered the optimal goal. Systematic use of subjective and objective clinical assessments is useful in identifying people at risk of hemiplegic shoulder pain. A minimum assessment standard would include comprehensive multidisciplinary assessment of the hemiplegic shoulder at both admission and discharge from both acute and subacute settings. Guidelines should also require the clear documentation of such assessments, with consideration to the use of proformas to both promote and reinforce complete documentation. If guidelines and documentation standards are integrated into a single proforms, ease of implementation may be enhanced.

The inherent variability of hemiplegic shoulder pain presentation over time makes stringent protocolisation very difficult, and as such the outlined application should be considered as a pathway guideline. A stepwise approach must be able to be individualised to each patient's presenetation.

Comprehensive assessment and periodic reassessment of presentation throughout admission

The ICP outlined by Jackson and Turner-Stokes et al[33] prescribes initial assessment as including pain history, use of a pain rating scale for subjective report of pain, and evaluation of physical presentation of tone and subluxation[33]. Earliest application of the ICP, inclusive of earliest comprehensive admission assessment by each discipline, represents an ideal standard. Early flaccidity can predispose to greater risk of soft tissue injury so timely assessment and global awareness can be predicted to reduce incident or accumulative injuries.

Identification and documentation of risk factors is an important part of initial assessment, as it ensures comprehensive consideration has been given to all potential aspects impacting current and future presentation. Whilst there remain conflicting opinions in the evidence, the following are the more commonly accepted risk factors for inclusion in a proforma checklist:

- History of premorbid shoulder pain
- Increasing Age
- Increasing severity of motor deficit
- Depression
- Right hemisphere stroke – spectrum of inattention-neglect
- Diabetes

Pain history includes a simple set of questions easily added to a clinical screening assessment battery and further helps identify an at-risk cohort. In the population-based study reported in this thesis, a history of shoulder pain was reported in 27% of participants with hemiplegic shoulder pain, compared to only 4% of those who did not report pain. Subjective pain report needs to be quantified to allow comparison measures throughout admission and following intervention(s).

A vertical visual analogue scale (VAS) is a simple tool that is applicable in the majority of stroke patients. Understanding of the tool and reliability of results could be gauged by use of the AbilityQ[258] prior to administration of the ShoulderQ as developed by Turner-Stokes et al. The AbilityQ uses generic vertical visual analogue scales with instructions for the patient to mark set points. This can be an indicator of 'ability' to reliably use a VAS for pain scoring. The ShoulderQ has a reported positive predictive value of 93.3%, inclusive of stroke participants with cognitive and communication deficits. ShoulderQ importantly incorporates questions about pain history, pain severity and aggravating factors. Identification and documentation of type of pain and aggravating factors are important to assist in identification of potential aetiological factors and establishment of an individualised treatment plan:

- Timing of Pain: Pain worse on movement / At rest / At night
- Specific activities that aggravate pain: Personal care / Dressing / Lifting device / Therapy

The ShoulderQ is a quick and easily reproducible tool[258] which adds structure and documentation standards in assessment. This tool was used in the randomised controlled trial reported in this thesis, with high level pre-trial inter-rater reliability testing between baseline assessor and outcome assessor.

The inclusion of three simple objective screening tests is recommended, even in the absence of subjective pain report. These tests (Modified Neers test, Passive Hand-Behind-Neck, and Passive External Rotation) were proposed by Rajaratnam et al[251] as conferring a 98% probability of development of hemiplegic shoulder pain. The analysis of the population-based dataset, as presented in Chapter 3, demonstrates that baseline objective passive range of motion tests elicited higher frequencies of pain than self-report, and predicted later subjective shoulder pain (crude relative risk of 3.22 (95%CI 1.01-10.27). These results suggest that inclusion of both routine subjective and objective measures is required. This observation is supported by Dromerick[176] , who concludes that questions alone are insufficient in the assessment of hemiplegic shoulder pain presentation.

Focus on aetiological differentials

Consideration of inclusion of Kalichman's[31] summary flowchart of three often overlapping pathological streams of hemiplegic shoulder pain (impaired motor control, soft-tissue lesions, altered peripheral and central nervous system activity) is recommended as an appendix to updated clinical guidelines. Easy reference is important to prompt staff less familiar with the complex pain aetiologies in hemiplegic shoulder pain. Nociceptive, neuropathic and somatosensory assessments need to be included[197]; both subjective and objective assessments should be performed to help the team differentiate between potential contributors to pain. Targeted assessments will guide the clinical decisions regarding the role of imaging.

Limited role for imaging unless clinical suspicion of specific musculoskeletal injury

Complex and often multifactorial aetiology means that not all hemiplegic shoulder pain stems from local soft tissue or joint structures[7] . The literature supports judicial use of imaging, reserving radiological assessment to cases in which there is high clinical suspicion of specific musculoskeletal pathology. Note is made that findings on imaging in fact have a low association with the presence of HSP[184].

Specific intervention recommendations

Suprascapular nerve block was listed in the ICP proposed by Jackson and Turner-Stokes et al[33] as a consideration for intractable pain, based on anecdotal reports only. Suprascapular nerve block can now be included as a specific intervention recommendation in this population, with randomised controlled trial data[151] supporting it as an effective treatment for hemiplegic shoulder pain. Suprascapular nerve block is likely to be most effective in patients with age < 80, and those with higher baseline subjective pain scores. Adherence to evidence-based approaches and good practice point recommendations is promoted. Other therapies and interventions should be considered in the context of each individual presentation.

Education of Patient, Family / Carers, and Ward Staff

It is imperative to impart awareness of hemiplegic shoulder pain as a common complication of stroke. Knowledge translation to all involved in the patient's care, including the patient, should be a focus of the rehabilitation team. The patient who has an understanding of factors that have potential to increase risk of developing pain has an internal locus of control, with ability to improve self-management and guidance of carers. Similarly, family and staff carers are able to better provide prophylaxis and appropriate handling techniques following basic education.

Rehabilitation Trainees need to have specific orientation to the issue of HSP on commencement of neurological ward and outpatient practice. Education sessions, online learning tools, and clinical exposure should aim to provide opportunities to master skills in comprehensive assessment, patient education, and suprascapular nerve block as indicated. The use of guideline approach will assist in standardising the clinical care of patient with HSP.

To disseminate knowledge broadly, and to maintain access to education tools for ongoing learning, online "E-Learning" tools can be used[293]. The option of development of online tools would need to suit the needs and abilities of the relevant stakeholders. Levac et al[293] promote interactive, multimedia design, with a focus on active self-directed learning and varying formats which can appeal to differing learning styles. An on-line portal could include pathways for each of the key target populations, e.g. patient, carers, ward staff, rehabilitation trainees, and general practitioners.

Routine post-discharge follow to target peak severity and onset of hemiplegic shoulder pain at 4 months

The National Stroke Foundation recommends routine post-discharge follow up of patients who have suffered a stroke. Reassessment of the hemiplegic shoulder should be a routine part of this follow-up. Research presented in the thesis has demonstrated that the peak onset and severity of hemiplegic shoulder pain is at 4 months post stroke onset, typically outside of standard admission timeframes. As the disorder is most common and severe after hospital discharge, targeted protocols including predictive objective measures may facilitate improved identification and management.

Discharge correspondence should include information for patient, family / carers, and primary healthcare providers regarding potential development of hemiplegic shoulder pain. Implementation of a Hemiplegic Shoulder Pain Information Package could be considered for inclusion into the "My Stroke Journey" Package (National Stroke Foundation)[36] with information for discussion with a Stroke Liaison Nurse during inpatient stay, and as a resource for post-discharge reference. Additionally, creation of an online portal for General Practitioner education and advice would be beneficial.

Table 3. Summary of Thesis Recommendations

Use of systematic adapted guidelines in both Acute Subacute settings Earliest possible assessment and initiation of management Documentation standards incorporated into guidelines
Comprehensive assessment and re-assessment of presentation - At admission and discharge at minimum - Assessment of risk factors: e.g. Premorbid shoulder pain, Depression, Right hemisphere stroke - Subjective pain severity scoring (vertical VAS) , pain characteristics and aggravating factors as incorporated in ShoulderQ tool - 3 Objective screening tests (even if no subjective complaint of pain) - Assessment of tone and subluxation
Awareness of aetiological differentials and potential for multiple aetiological contributors - impaired motor control - soft-tissue lesions - altered peripheral and central nervous system activity
Limited role for imaging unless clinical suspicion of specific musculoskeletal injury
Specific Intervention Recommendations - Suprascapular nerve block can be considered as an evidence-based treatment modality - May be most effective in patients aged <80 and with high baseline pain score
Education to patient, family and ward staff about protection of the hemiplegic arm - Incorporate best practice recommendations regarding knowledge translation
Explicit discharge correspondence Post discharge follow up as peak severity and peak incidence at 4 months post stroke onset

Table 4. Sample Combined Guideline and Documentation Proforma

NAME	**Admission Assessment DATE**	**Discharge Assessment DATE**
Assessment of Risk Factors:		
Premorbid shoulder pain Right hemisphere stroke Diabetes Depression Other (specify)	□ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □	□ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □
Subjective Assessment:		
Subjective pain severity ShoulderQ VAS for each of: • Pain on movement • Pain at rest • Pain at night	 /10 /10 /10	 /10 /10 /10
Aggravating factors: • Personal care • Dressing • Lifting device • Therapy	 □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No	 □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No
Objective Tests:		
Pain reproduced with • modified Neers test • passive hand-behind-neck >10° less passive shoulder external rotation on hemiplegic side	 □ Yes □ No □ Yes □ No □ Yes □ No	 □ Yes □ No □ Yes □ No □ Yes □ No
Tone • Flaccid UL • Spasticity present	 □ Yes □ No □ Yes □ No Details:	 □ Yes □ No □ Yes □ No Details:
Subluxation	□ Yes □ No Details:	□ Yes □ No Details:
Objective evidence of soft tissue lesions	□ Yes □ No Details:	□ Yes □ No Details:

ASSESSMENT:		
Evidence of contributing aetiologies (circle all that apply) • Impaired motor control • Soft tissue lesion • Altered PNS and / or CNS activity	 □ Yes □ No □ Yes □ No □ Yes □ No Comment:	 □ Yes □ No □ Yes □ No □ Yes □ No Comment:
PLAN		
Any role for imaging?	□ Yes □ No If Yes, Indication:	□ Yes □ No If Yes, Indication:
Prophylactic Strategies recommended (tick all that apply) <u>For all hemiplegic patients:</u> • Upper limb alert arm band • Upper limb alert above bed • Upper limb alert on clinical handover • Careful manual handling • Careful positioning at rest • No aggressive ROM <u>Individual Consideration to:</u> • Shoulder strapping • Sling	 □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Yes □ No □ Yes □ No	 □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Tick to confirm □ Yes □ No □ Yes □ No
Active therapies indicated (tick all that apply) • Functional Electrical Stimulation • Interferential Current Stimulation • Analgesia • Intra-articular steroid (selected cases) • Subacromial injection (selected cases) • Botulinum toxin (selected cases) • Suprascapular nerve block (selected cases)	 □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No	 □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No □ Yes □ No
Education to patient Education to family / carer	□ Yes □ No □ Yes □ No	□ Yes □ No □ Yes □ No
ON DISCHARGE:		
Information re HSP in summary Surveillance guidelines provided to GP Follow up options provided to GP		□ Yes □ No □ Yes □ No □ Yes □ No

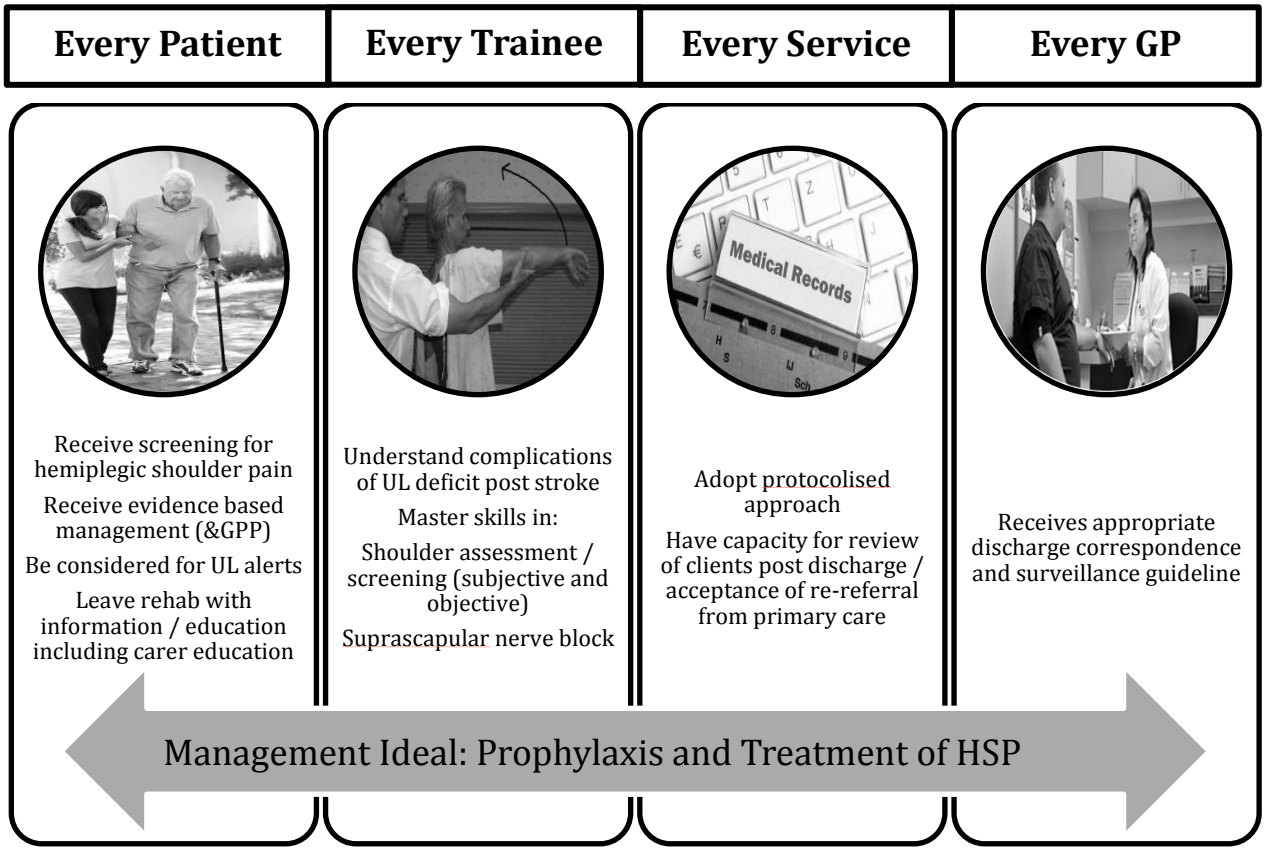


Figure 1. Management Ideal: Prophylaxis and Treatment of HSP

7.3 Future Research Directions

7.3.1 Further research stemming from studies in this thesis

Research compiled in this thesis has added to the depth of clinical knowledge relating to hemiplegic shoulder pain and provides a platform from which further research objectives can be developed.

Feasibility of clinician led trials

The randomised controlled study demonstrated the feasibility of recruiting patients for a clinical trial across Adelaide (two acute Stroke Units and 5 Rehabilitation Units). For a placebo-controlled trial, achievement of both high consent rate (86% of eligible participants consented) and high retention rates (attrition rate 11%) has been demonstrated. This confirms that pragmatic trials are possible within rehabilitation units. Emphasis on cooperation across units is key, and this can be fostered by incorporation of training sessions, in-services and involvement of staff across sites. Staff enthusiasm for trial involvement on topics relevant to their daily practice was observed, and is an important factor to consider in planning of future studies.

Success of this approach suggests that future studies on treatment for chronic complications following stroke can be undertaken. Examples of future clinical-led studies could include intramuscular and intra-articular Botulinum Toxin A for hemiplegic shoulder pain.

Epidemiology of hemiplegic shoulder pain – incidence, patterns and associations

Persistently high prevalence rates of hemiplegic shoulder pain, in the order of 29%[26], may reflect a lack of improved implementation of prevention and treatment measures over more recent years. Barriers to translation of evidence into practice are outlined in Publication 1. It is hoped that the importance of research design incorporating generalisable populations and easy to follow protocols will improve as more clinicians adopt research interests. Incorporation of research findings into local practice is dependent on ongoing championing of the cause, with regular education and review of processes on the ward. Collaboration with key stakeholders, pre and post protocol implementation audits, and assessment of reasons for protocol variation are vital in the successful implementation of change.

The bimodal distribution of pain and the changes in typical pain characteristics at varying time points have implications for future research design. In population studies, careful selection of follow up design will assist in ensuring that representative prevalence data is collected. The pattern of baseline, 4 month and 12 month distributions has been established. Longer term follow-up would provide further understanding of the behaviour and persistence of hemiplegic shoulder pain. The 6 year follow up described in the Auckland Stroke Study[206] revealed good quality of life results in long term stroke survivors. Whilst not specifically addressing the issue of hemiplegic shoulder pain, this may imply that significant resolution of, or adaptation to, post stroke complications may occur with time.

For studies in selected population research, establishment of time since stroke onset will impact both pain severity and pain characteristics. The hypothesis that greater association with accumulative musculoskeletal injuries occurs over time was based on the observation that pain was more commonly associated with range of movement at later follow up points (4 months and 12 months).

Baseline pain was more commonly reported at rest and at night. Comparison of pain characteristics at differing times since stroke onset may not provide an accurate picture of pain patterns over time.

Suprascapular nerve block for hemiplegic shoulder pain

Opportunities for future research are outlined in papers 3 and 4. Spasticity has a known impact on passive range of motion, particularly external rotation. Evidence remains conflicting, but Botulinum toxin A is likely to improve hemiplegic shoulder pain associated with spasticity. Further research is required to investigate associations between persistent hemiplegic shoulder pain and typical changes in tone presentation over time. Additionally, the impact of spasticity on pain report or response to suprascapular nerve block was not a focus in the randomised controlled trial.

The SSNB trial should be repeated using different populations and in different settings. Repeated randomised controlled trials with larger samples would reduce the chance of over-estimation of treatment as seen in smaller samples. Additionally, larger sample size could allow power for more in-depth assessment of characteristics of clinical responders.

The mechanism of suprascapular nerve block (SSNB) therapy effect in the current population also warrants further exploration with extended follow up periods to incorporate 6 month and 12 month review. The randomised controlled trial reported in this thesis only provided follow up to 12 weeks. The lack of degradation of effect at 3 months is beyond the expected pharmacological profile of the injection agents. The mechanism of initial pain reduction is attributed to blocking sensory nerve fibres[47] and reducing nociceptive input to the central nervous system[242]. It has been postulated[46] that there may be a reduction in central sensitisation secondary to diminished nociceptive stimulus as a potential effect of SSNB. This is in keeping with more recent studies which have identified features

consistent with somatosensory sensitisation in patients with HSP, suggesting both nociceptive and neuropathic components of pain[196]. Recent research has demonstrated a positive impact of repeated suprascapular nerve block. Thorough investigation of the length of treatment effect beyond 3 months will help to establish recommendations regarding potential frequency of repeated injections. Additionally, aetiological mechanisms of hemiplegic shoulder pain differ over time, and additional research exploring evidence-based treatment options that address early versus later onset hemiplegic shoulder pain are needed. A 2015 study by Bradnam et al[294] has identified neurophysiological changes in patients with chronic shoulder pain, and indicates potential for normalisation of intracortical inhibition following suprascapular nerve block. Larger studies of this type, and focussed particularly on post-stroke shoulder pain, would enhance current models of understanding.

Evaluation of optimal timing of SSNB administration post stroke is an important focus of further study. Individual pain presentations require flexibility in the timing of this intervention, though there remains the potential that optimising the timing of the nerve block may improve response rates.

Hemiplegic shoulder pain and health-related quality of life

Given the population-based data supporting the negative impact of hemiplegic shoulder pain on health-related quality of life, longer follow up of the suprascapular nerve block effect would also provide an opportunity to explore whether pain reduction can improve quality of life status. The current randomised controlled trial did not demonstrate any impact on secondary outcome of quality of life, but three month follow up is likely too short a period to impact this variable.

Development and Evaluation of an E-Learning Tool specific to HSP

E-Learning is identified as a potential tool to maximise education. Further work in establishing a successful online portal could work to target the primary stakeholders in the field of HSP: the patient and carers, the ward staff, the Rehabilitation Trainee, and the General Practitioner. Tools relevant to each group could be populated to include appropriate depth of Tools should include basic information (written and diagrammatic), key risk factors, treatment options and follow up recommendations. Teaching tools should include videos, checklists of achievement, and continuing medical education opportunities. On-line tools need to be developed in line with patient values, staff values and needs analysis.

Evaluation of impact of ward based protocol – pre and post implementation

The use of a protocolised guideline lends itself to pre- and post-implementation auditing. French et al[295] highlight measuring behaviour change as the final step of a 4 stage approach to change behaviour in order to implement evidence into practice. The review process should focus on change in behaviour and attitudes, patient outcomes and practitioner outcomes[295]. Whilst the auditing process is time consuming, it is vital to the potential long-term success of protocolisation tools. If there is no demonstrable change in stakeholder outcomes, efforts to establish routine use of the protocol may be better spent on other endeavours. On the other hand, if improvements are noted in patient and staff awareness of HSP, frequency of HSP, and skills in management of HSP, then this approach needs to be adopted into routine practice.

7.3.2 Future research opportunities to complement studies presented in this thesis

Several current practices are based on limited evidence, though are accepted as 'good practice point' recommendations. Greater implementation of prophylactic measures might be achieved if stronger evidence were available.

The first knowledge gap is in the acceptability and efficacy of the newer sling designs in the prevention of hemiplegic shoulder pain. Slings are easier to don compared to therapeutic strapping, but traditional designs have had negative impacts on balance, muscle tone and available distal arm use. Newer designs provide proximal support without limitation of range or position.

The second gap is patient and staff understanding, and methods by which to improve these via education need to be explored. Some wards are adopting alert bracelets to remind both the patient and staff of the need to take care with handling of the limb. The concept of E-Learning tools has been discussed, and development of a freely and easily accessible online tool could be trialled. Behaviour change and outcome change should be assessed[295] to compare standards before and after education efforts; auditing, education efforts, and second round auditing of impact should be considered for patients, hospital staff, pre-hospital care providers, and primary care providers.

Emerging approaches with promising initial studies encompass the third area of interest; these include intra-articular botulinum toxin A for pain not associated with spasticity[184], as well as implantable neuromuscular electrical stimulation devices[213, 214].

7.4 Conclusion

Hemiplegic shoulder pain is a common and important complication of stroke. The increasing survival rates following stroke implicate potential extrapolation of hemiplegic shoulder pain as an issue of rising prevalence.

With an impact on all facets of functioning, including body structure and function, activity and participation, hemiplegic shoulder pain has a negative bearing on an individual's functional outcome. A greater understanding and focus on hemiplegic shoulder pain is vital in optimising care, and developing a heightened research focus to develop greater understanding of aetiological contributors and therapeutic options.

Research presented in this thesis demonstrates that hemiplegic shoulder pain occurs in >25% of all stroke survivors, and negatively impacts health-related quality of life. Suprascapular nerve block has been identified as an evidence-based treatment option, with potential responder profiles hypothesised. Translation of findings into clinical practice remains a primary focus for future care models. Systematic approaches to both assessment and management need to be implemented to ensure appropriate and timely care is provided to each individual.

Appendix A **Ethics Approved Patient Information Sheet, Consent and Data Forms From ASSIST Trial (Publication 4)**

ASSIST - Adelaide Suprascapular Intervention in Stroke Trial

Does Nerve Block Reduce Shoulder Pain Following Stroke?

Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with measured outcome assessment

PARTICIPANT INFORMATION SHEET

We would like to invite you to participate in this trial.

Participation in any research project is voluntary. If you do not wish to take part, you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage without providing a reason. Your decision to take part, not to take part or to withdraw will not affect your routine treatment, your relationship with those treating you, or your relationship with The Queen Elizabeth Hospital.

Shoulder pain is a common and debilitating symptom for a large number of people following a stroke. The cause of shoulder pain is usually related to several factors, including trauma, inflammation and positioning. In cases when shoulder pain is unable to be prevented, current treatment options include arm supports, physiotherapy techniques, and simple analgesic medication.

It is commonly observed that shoulder pain persists or is inadequately controlled by these interventions. This research aims to study the effect of an injection that numbs the nerve (Suprascapular Nerve) that supplies pain fibres to the shoulder. The technique has previously been proven safe and effective in the treatment of shoulder pain associated with rheumatoid arthritis and degenerative shoulder conditions.

Repatriation General Hospital Department of Rehabilitation and Aged Care is studying this treatment to see if it is helpful in the treatment of post-stroke shoulder pain.

What happens before I agree to participate?
A rehabilitation doctor will discuss the study with you and will determine whether you are eligible to participate. This written information sheet provides details of the study.

What should you expect if you take part in the study?
In order to conduct this study, we are performing a trial where we compare the standard therapy (physiotherapy, positioning, analgesia) to standard therapy plus the nerve blocking injection. Doctors will use a proven technique to inject either normal saline (non-treatment/control group) or a mixture of local anaesthetic and anti-inflammatory steroid (treatment group). All patients will

receive an injection to the back of the shoulder but only half of these will be with active injection material. You have a 50% chance of receiving the treatment injection.

All participants will be followed up over time to evaluate the effectiveness of the treatment. Baseline information will be gathered before the injection. This will include a pain rating scale, a questionnaire and a brief clinical examination. This is expected to take approximately an hour. Follow-up will be undertaken by a research assistant at 1, 4, and 12 weeks. Assessment will include a rating of your pain, two short questionnaires regarding pain and function, and a brief examination of range of shoulder movement. Each follow up session will take approximately one hour.

What are the benefits of participating in this study?
The potential benefit to you is a decrease in your shoulder pain and possible improved function. It is important to note that your shoulder pain may not improve. The benefit to the community is the possible development of a new treatment options for shoulder pain following stroke.

What are the risks of participating in the study?

The risks of problems from the injection are small and readily treatable. Minor complications include local bleeding and local infection. Infrequent side-effects of steroid injection include headache, flushing, rashes, acute post-injection flare reactions, injection site irritation, joint discomfort (brief) and increased blood glucose concentration (temporary). Rare side-effects of intramuscular steroid injection include muscle wasting, skin and subcutaneous tissue wasting, skin pigmentation changes and sterile abscess formation.

More serious but very rare risks of the nerve block include nerve damage and air leak around the lung (pneumothorax, less than 0.1%). In the event of any complication, you would be treated by the hospital with no cost to you. The hospital carriers insurance should there be any complication from your involvement in this study.

If you become injure during this study, and your injury is a direct result of the effects of study procedures, The Queen Elizabeth Hospital will provide reasonable medical treatment. Your participation in this study shall not affect any other right to compensation you may have under common law.

Confidentiality:
All records containing personal information will remain confidential and no information which could lead to the identification of any individual will be released.

Should you require further details about the study, please contact local investigator, Dr Nigel Quadros, on 8222 7322.

This study has been approved by the Research and Ethics Committees at the Repatriation General Hospital, Flinders Medical Centre, The Queen Elizabeth Hospital, and Royal Adelaide Hospitals. Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, information about the conduct of the study, or your rights as a participant, you may contact the Executive Officer at The Ethics of Human Research Committee at The Queen Elizabeth Hospital, on 8222 6841.

CONSENT TO RESEARCH STUDIES AND PROCEDURES

Name:		
MRN:	**Gender:**	**Age:**
Phone:	**Address:**	
NOK:	**Relationship to patient:**	
NOK Ph:	**NOK Address:**	
Inpatient Site:		**Study ID:**

I,_____
(First/or Given names) (Surname)

have had explained to me by the investigator _____ (or his/her representative) the nature and effects of the Research Study:

ASSIST - Adelaide Suprascapular Intervention in Stroke Trial

Does Nerve Block Reduce Shoulder Pain Following Stroke?

Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with measured outcome assessment

I have been provided with a Patient Information Sheet about the study which I have read and understood.

I understand that the study involves the following procedures:

1. Initial visit (approximately one hour) which will include:
    - Questionnaires (x2)
    - Physcial Examination, and
    - An injection of either:
        i. 10ml bupivacaine and 1ml methylprednisolone under local anaesthetic into the suprascapular fossa (above the shoulder blade) or
        ii. Placebo (5ml normal saline) under local anaesthetic subcutaneously into the same area.

2. Follow up by three reviews, at one week, four weeks and twelve weeks. These reviews are anticipated to take approximately one hour each. Review will include:
    - Questionnaires (x2)
    - Physical examination

- I have understood and am satisfied with the explanations that I have been given and hereby consent to the participation in the above study.

- I understand that the results of these studies may be published, but my identity will be kept confidential.

- I understand that the procedure may not be of any benefit to myself, and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the investigator in any respect.

- I understand that representatives from the Hospital Research and Ethics Committee, from the sponsoring organisation for this study and/or from Government Drug Regulatory Authorities may need to access my medical record for information related to the study for the purpose of audit. I authorise access to my medical record for this purpose.

- I declare that I am over the age of 18 years.

Signature:_____
Date:_____

Signature of Witness: _____
Date:_____

Printed Name of Witness: _____

ASSIST - Adelaide Suprascapular Intervention in Stroke Trial

Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with measured outcome assessment

Assessment of Eligibility

Name:		
MRN:	**Gender:**	**Age:**
Phone:	**Address:**	
NOK:	**Relationship to patient:**	
NOK Ph:	**NOK Address:**	
Inpatient Site:		

	Actual	**Meets Criteria**	**Doesn't Meet Criteria**
Age > 18			
Date of Stroke Within previous 12 months			
Presence of Post-Stroke Shoulder Pain on hemiplegic side VAS ≥ 3 (?4)*			
Cognitive Screen: MMSE score*: > 23			
Language Screen: Follows 2-stage command:			
Sufficient English:			
No Allergy to depo-medrol, bupivacaine hydrocholoride or 1% lignocaine			
Willing to Participate:			
ELIGIBLE?			

ASSIST - Adelaide Suprascapular Intervention in Stroke Trial

Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with measured outcome assessment
Baseline Data Collection

Today's Date:

Study ID:	
Inpatient Site:	

* See attached scales

STROKE HISTORY:

Stroke Date:					
Stroke Type:	Infarct		Haemorrhage		
Oxfordshire Subtype*	TACS	PACS	LACS	POCS	Other
Mobility:	Aided:		Unaided:		
	Home	Community		Unlimited	

HEMIPLEGIC SHOULDER PAIN:

Handedness:			
Affected hemisphere:			
Time of onset of shoulder pain post stroke:			
Relevant history associated with shoulder pain:			
Current Medications:			
Previous Treatment for shoulder pain (including medications):			
ShoulderQ*:	**4a:**	**4b:**	**4c:**
Subluxation of Hemiplegic Shoulder: Present / Absent			
Neer Test: Positive / Negative			
Passive HBN Test: Positive / Negative			
Passive ER >10' difference			
Modified Ashworth Scale	**Sh Abd:**	**Elb F:**	**Wrist F:**

DISABILITY:

NIHSS*:	
Rankin*:	
Croft Disability Index*:	

Appendix B Publications

1. **Adey-Wakeling Z,** Crotty M. Upper Limb rehabilitation following stroke: current evidence and future perspectives. *Aging Health* 2013; 9(6):629-648 http://www.futuremedicine.com/loi/ahe: DOI:10.2217/ahe.13.67

2. **Allen ZA,** Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83-88; DOI: 10.1186/1471-2377-10-83

3. **Adey-Wakeling Z,** Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial. *Stroke* 2013; 44: 3136-3141; DOI: 10.1161/STROKEAHA.113.002471

4. **Adey-Wakeling Z,** Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal of Physical Medicine and Rehabilitation* 2015; 1(2):009; http://www.jacobspublishers.com/images/Physical_Rehab/J_J_Physical_Rehab_Med_1_2_009.pdf

5. **Adey-Wakeling Z,** Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7*;* DOI: 10.1016/j.apmr.2014.09.007

6. **Adey-Wakeling Z,** Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study. *American Journal of Physical Medicine and Rehabilitation – 2016;* DOI: 10.1097/PHM.0000000000000496

Appendix C Summary Notes on Primary Author Contribution

Proposal Development

Under the supervision of Professor Maria Crotty and Associate Professor E Michael Shanahan, the candidate developed the project proposals and made all methodological decisions.

Ethics Approval

Ethics applications for Publications #3 and #4 (randomised controlled trial) were written and submitted by the candidate. For the purpose of the multi-centre RCT, ethics approval submissions were made and approved by three separate Human Research and Ethics Committees (see Appendix B). Ethics approval for analyses of the population data set was confirmed to be included in the NH&MRC fund approvals.

Literature Review

The candidate was responsible for all reviews of the literature, with additional guidance from Prof Maria Crotty (Papers 1-4), Assoc Prof E Michael Shanahan (Papers 2-4), and Professor Jonathon Newbury (Papers 2 and 6).

Data Collection

The candidate designed and managed all data collection for Paper #4 (randomised controlled trial). A pharmacist external to the study conducted the blinded randomisation. The candidate performed

all recruitment (unless participant directly under her care), baseline data collection, and injections. Foundation Daw Park grant funding assisted in the employment of a blinded outcome assessor for follow up assessments.

Data from the NH&MRC funded ASCEND population-based study was made available to the candidate. The candidate was not an investigator on the grant. The candidate was involved prior to the commencement of data collection, and worked with the investigators to specify the data items on shoulder pain to be collected. This included involvement in decisions regarding inclusion of specific shoulder subjective and objective questions / items in the protocol. Additionally, the candidate was directly involved in training nursing staff in the technique for completing objective measures, including the creation of a video-training module.

The candidate was involved in data collection for participants admitted within the Southern Adelaide Local Health Network. Research team members were involved in recruitment and assessment of participants outside of this region (Central and Northern LHN)

Data Analysis

The candidate conducted the literature review prepared for Paper #1.

Data analysis techniques were enhanced by completion of Flinders University Research Higher Degree training days in SPSS Statistics (basic and intermediate courses). For each paper, the candidate completed first run data analysis independently, prior to consultation with Statistician. Final statistical analysis in the published articles was run by the study statistician.

Preparation and Writing of Manuscripts for Submission

The candidate was the primary author on all published manuscripts. Primary authorship reflects that the candidate was responsible for the majority of writing work for these papers.

*Please note that the Candidate's Surname changed from **ALLEN to ADEY-WAKELING** during her candidature, as is reflected in Primary Author Name on Publication #3, and some of the original ethics approvals in Appendix B*

Appendix D Permissions for inclusion of material from published papers in thesis

Professor Maria Crotty

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Crotty M. Upper Limb rehabilitation following stroke: current evidence and future perspectives. *Aging Health* 2013; 9(6):629-648

Allen ZA, Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83-88

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial.
Stroke 2013; 44: 3136-3141

Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal of Physical Medicine and Rehabilitation* 2015; 1(2):009

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending*

Signature

Associate Professor Michael Shanahan

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Allen ZA, Shanahan EM, Crotty M. Study Protocol: Does Suprascapular Nerve Block Reduce Shoulder Pain Following Stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology* 2010; 10:83-88

Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular Nerve Block For Shoulder Pain In the First Year After Stroke: A Randomised Controlled Trial. *Stroke* 2013; 44: 3136-3141

Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal of Physical Medicine and Rehabilitation* 2015; 1(2):00

Signature

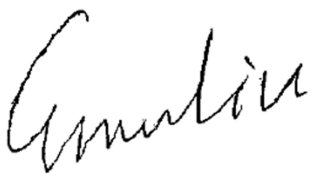
Enwu Liu

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Crotty M, Liu E, Shanahan M. Suprascapular Nerve Block for Hemiplegic Shoulder Pain Post Stroke: Subgroup Analysis of Pain Response. *Jacobs Journal of Physical Medicine and Rehabilitation* 2015; 1(2):009

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending*

Signature

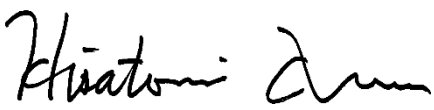


Hisatomi Arima

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Signature



Dr James Leyden

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending*

Siganture

Associate Professor Timothy Kleinig

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending*

Yours Sincerely,

Signature

Professor Craig Anderson

I have given permission for the work undertaken and published as part of co-authored papers listed below to be included in the candidate's thesis:

Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Incidence and Associations of Hemiplegic Shoulder Pain Post Stroke: Prospective population based study. *Archives of Physical Medicine and* Rehabilitation 2015; 96: 241-7

Adey-Wakeling Z, Liu E, Crotty M, Leyden J, Kleinig T, Anderson C, Newbury J. Hemiplegic shoulder pain impacts on quality of life after acute stroke: a prospective population-based study *American Journal of Physical Medicine and Rehabilitation; accepted Jan 2016; publication pending*

4 February 2016

Signature

Appendix E Grant Approval

FOUNDATION DAW PARK INCORPORATED

Supporting medical research at Repatriation General Hospital

Foundation Daw Park Inc.
C/- Repatriation General Hospital
Daws Road, Daw Park
South Australia 5041

T (08) 8275 1029
F (08) 8277 5401
www.foundationdawpark.org.au

ABN 46 079 696 857

15th December, 2009

Dr Zoe Allen
Division of Rehabilitation, Aged Care and Allied Health
Repatriation General Hospital
Daws Road
DAW PARK SA 5041

Dear Zoe

FOUNDATION DAW PARK 2009/2010 GRANT SUBMISSION:
Does Nerve Block Reduce Shoulder Pain Following Stroke?

Further to the deliberations of the Research Management Committee of the Repatriation General Hospital and approval by the Board of Directors, Foundation Daw Park, I am delighted to advise that the above project will be funded to the value of $9,090.91 as per your submission. The funds will be transferred to the Repatriation General Hospital bank account in January 2009.

An invitation is extended for you to join our Chairman, Board of Directors and invited VIP guests along with other successful grant recipients for morning tea on Thursday, 18th February, 2010. A formal invitation with venue details will be with you in late January.

We are currently implementing a web based program for regular six monthly reporting on your project's progress. Once implementation is finalised, we will contact you in relation to training and access.

Congratulations on your successful application.

Yours sincerely,

Chris Jenner
Executive Director

Appendix F Awards Associated with this Thesis

Flinders University, Vice Chancellor's Best Student Research Paper Award 2014

Clinician's Special Purpose Fund Prize for Clinical Research in Medicine 2013

Flinders University and Flinders Medical Centre

Flinders University
inspiring achievement

Flinders University
Office of the Deputy Vice-Chancellor (Research)

2014 Best Student Research Paper

THIS IS TO CERTIFY THAT

Zoe Adey-Wakeling

WAS AWARDED THE FLINDERS UNIVERSITY BEST STUDENT RESEARCH PAPER FOR:

Suprascapular Nerve Block for Shoulder Pain in the First Year After Stroke: A randomized Control Trial

January 2015

Professor David Day
Deputy Vice-Chancellor (Research)
Flinders University

CRICOS No. 00114A

Department of Medicine

Flinders University
Flinders Medical Centre

"Clinician's Special Purpose Fund Prize for Clinical Research in Medicine 2013"

DR ZOE ADEY-WAKELING

Congratulations on being awarded the Clinician's Special Purpose Fund Prize for Clinical Research in Medicine 2013

Professor Philip Aylward
Regional Clinical Director (Medicine)
Medicine, Cardiac & Critical Care

Dr David Wattchow
Chairperson
Clinicians Special Purpose Fund Committee

Bibliography / Reference List

REFERENCES

1. Investigators WMP. The world health organisation monica project (monitoring trends and determinants in cardiovascular disease). *J Clin Epidemiol*. 1988;41:105-114
2. Organisation WH. World report on disability. 2011:96
3. Foley N, Teasell R, Jutai J, Bhogal S, Kruger E. Evidence-based review of stroke rehabilitation: Upper extremity interventions. 2012
4. International association for the study of pain. 2015;August 2014
5. Klit H FN, Overad K, Andersen G, Jensen TS. Pain following stroke: A population-based follow-up study. *PLos ONE*. 2011;6
6. Roosink M GA, Ijzerman MJ. Defining post-stroke pain: Diagnostic challenges. *Lancet Neurology*. 2010;9:344
7. Di Lorenzo L, Domenico S. Neural modulation of hemiparetic shoulder pain by repetitive ultrasound-guided suprascapularis nerve block. *Open Journal of Anesthesiology*. 2013;3:126-132
8. Taskaynatan MA, Yilmaz B, Ozgul A, Yazicioglu K, Kalyon TA. Suprascapular nerve block versus steroid injection for non-specific shoulder pain. *Tohoku Journal of experiemental medicine*. 2005;205:19-25
9. Lawrence E, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalance of acute stroke impairments and disability in a multiethnic population. *Stroke*. 2001;32:1279-1284
10. Stoykov ME, Corcos DM. A review of bilateral training for upper extremity hemiparesis. *Occup Ther Int*. 2009;16:190-203

11. van Delden AL, Peper CL, Harlaar J, Daffertshofer A, Zijp NI, Nienhuys K, et al. Comparing unilateral and bilateral upper limb training: The ultra stroke program design. *BMC Neurol*. 2009;9:57

12. Verbunt JA, Seelen HA, Ramos FP, Michielsen JH, Wetzelaer WL, Moennekens M. Mental practice-based rehabiliation training to improve arm function and daily activity performance in stroke patients: A randomised controlled trial. *BMC Neurology*. 2008;8:7

13. Kong KH, Chua KS, Lee J. Recovery of upper limb dexterity in patients more than 1 year after stroke: Frequency, clinical correlates and predictors. *Neurorehabilitation*. 2011;28:105-111

14. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb. *Stroke*. 2003;34:2181-2186

15. McLean. Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. *Archives of Physical Medicine and Rehabilitation*. 2004;2004

16. Lindgren I, Jonsson AC, Norrving B, Lindgren A. Shoulder pain after stroke: A population based study. *Stroke*. 2007;38:343-348

17. Bender L, McKenna K. Hemiplegic shoulder pain: Defining the problem and its management. *Disability and Rehabilitation*. 2001;23:698-705

18. Wanklyn P, Forster A, Young J. Hemiplegic shoulder pain - natural history and investigation of associated features. *Disability and Rehabilitation*. 1996;18:497-501

19. Aras M, Gokkaya N, Comert D, Cakci A. Shoulder pain in hemiplegia - results from a national rehabilitation hospital in turkey. *American Journal of Physical Medicine and Rehabilitation*. 2004;83:713-719

20. Wanklyn P FA, Young J. Hemiplegic shoulder pain (hsp): Natural history and investigation of associated features. *Disability and Rehabilitation*. 1996;18:497-501

21. Roy CW SM, Hill LD, Harrison A, Marshall S. The effect of shoulder pian on outcome of acute hemiplegia. *Clinical Rehabilitation*. 1995;9:21-27

22. Lindgren I JA, Norrving B, Lindgren A. Shoulder pain after stroke: A prospective population-based study. *Stroke*. 2007;38:343-348

23. Pompa A CA, Troisi E, Di Mario M, Tonini A, Pace L, Casillo P, Cuccaro A, Grasso MG. Enhanced-mri and ultrasound evaluation of painful shoulder in patients after stroke: A pilot study. *European Neurology*. 2011;66:175-181

24. Pulman J, Buckley E. Assessing the efficacy of different upper limb hemiparesis interventions on improving health-related quality of life in stroke patients: A systematic review. *Topics in Stroke Rehabilitation*. 2013;20:171-188

25. Sturm JW, Donnan GA, Dewey HM, Macdonnell RAL, Gilligan AK, Srikanth V, et al. Quality of life after stroke: The north east melbourne stroke incidence study (nemesis). *Stroke*. 2004;35

26. Adey-Wakeling Z, Arima H, Crotty M, Leyden J, Kleinig T, Anderson CS, et al. Incidence and associations of hemiplegic shoulder pain post stroke: A prospective population based study. *Arch Phys Med Rehabil*. 2014;38:343-348

27. Organisation WH. International classification of functioning, disability and health. 2001;2015

28. Faria-Fortini MS, Cassiano JG, Teixeira-Salmela LF. Upper extremity function in stroke subjects: Relationships between the international classification of functioning, disability and health domains. *J Hand Ther*. 2011;24:257-264

29. Murie-Fernandez M, Iragui MC, Gnanakumar V, Meyer M, Foley N, Teasell R. Painful hemiplegic shoulder in stroke patients: Causes and management. *Neurologia*. 2012;27:234-244

30. Lo SF, Chen SY, Lin HC, Jim YF, Meng NH, Kao MJ. Arthrographic and clinical findings in patients with hemiplegic shoulder pain. *Arch Phys Med Rehabil*. 2003;84:1786-1791

31. Kalichman L, Ratmansky M. Underlying pathology and associated features of hemiplegic shoulder pain. *American Journal of Physical Medicine and Rehabilitation*. 2011;90:768-780

32. Teasell R, Foley N, Bhogal S. Evidence-based review of stroke rehabilitation: Painful hemiplegic shoulder. *Evidence based review of stroke rehabilitation*. 2006;2009

33. Jackson D, Turner-Stokes L, Khatoon A, Stern H, Knight L, O'Connell A. Development of an integrated care pathway for the management of hemiplegic shoulder pain. *Disability and Rehabilitation*. 2002;24:390-398

34. Koog YH, Jin SS, Yoon K, Min BI. Interventions for hemiplegic shoulder pain: A systematic review of randomised controlled trials. *Disability and Rehabilitation*. 2010;32:282-291

35. Stolzenberg D, Siu G, Cruz E. Current and future interventions for glenohumeral subluxation in hemiplegica secondary to stroke. *Top Stroke Rehabil*. 2012;19:444-456

36. Foundation NS. Clinical guidelines stroke management.

37. American T, Association,. Practice standards guidelines. 2013;September 2013

38. Price CI, Curless RH, Rodgers H. Can stroke patients use visual analgoue scales? *Stroke*. 1999;30:1357-1361

39. Maxwell AM, Nguyen VQ. Management of the hemiplegic shoulder. *Curr Phys Med Rehabil Rep*. 2013;1:1-8

40. Barreca S, Wolf SL, Fasoli S, Bohannon R. Treatment interventions for the paretic upper limb of stroke survivors: A critical review. *Neurorehabilitation and Neural Repair*. 2003;17:220-226

41. Singh JA, Fitzgerald PM. Botulinum toxin for shoulder pain. *Cochrane Database of Systematic Reviews*. 2011;1

42. Castiglione A, Bagnato S, Boccagni C, Romano MC, Galardi G. Efficacy of intra-articular injection of botulinum toxin type a in refractory hemiplegic shoulder pain. *Archives of Physical Medicine and Rehabilitation*. 2011;92:1034-1037

43. Lakse E, Gunduz B, Erhan B, Celik EC. The effect of local injections in hemiplegic shoulder pain: A prospective, randomised, controlled study. *Am J Phys Med Rehabil*. 2009;88:805-811

44. Ritchie ED, Tong D, Chung F, Norris AM, Miniaci A, Vairavanathan SD. Suprascapular nerve block for postoperative pain relief in arthroscopic shoulder surgery: A new modality? *Anesth Analg*. 1997;84:1306-1312

45. Shanahan EM, Shanahan KR, Hill CL, Ahern MJ, Smith MD. Safety and acceptability of suprascapular nerve block in rheumatology patients. *Clin Rheumatol*. 2012;31:145-149

46. Shanahan EM, Ahern MJ, Smith MD, Wetherall M, Bresnihan B, Fitzgerald O. Supracapular nerve block (using bupivacaine and methylprednisolone acetate) in chronic shoulder pain. *Ann Rheum Dis*. 2003;62:400-406

47. Nam YS, Jeong JJ, Han SH, Park SE, Lee SM, Kwon MJ, et al. An anatomic and clinical study of the suprascauplar and axillary nerve blocks for shoulder arthroscopy. *J Shoulder Elbow Surg*. 2011;20:1061-1068

48. Dahan TH, Fortin L, Pelletier M, Petit M, Vadeboncoeur R, Suissa S. Double blind randomised clinical trial examining the efficacy of bupivacaine supracapular nerve blocks in frozen shoulder. *J Rheumatol*. 2000;27:1464-1469

49. National clinical guidelines for stroke, 4th edition. 2012:25

50. Excellence NIfHC. Stroke rehabilitation: Long-term rehabilitation after stroke (clinical guideline 162). 2013

51. Pinter MM, Brainin M. Rehabilitation after stroke in older people. *Maturitas*. 2012;71:104-108

52. Tarkka IM, Kononen M. Methods to improve constraint-induced movement therapy. *NeuroRehabilitation*. 2009;25:59-68

53. Paolucci S, Bragoni M, Coiro P, De Angelis D, Fusco FR, Morelli D, et al. Quantification of the probability of reaching mobility independence at discharge from a rehabilitation hospital

in nonwalking early ischemic stroke patients: A multivariate study. *Cerebrovascular Disease*. 2008;26:16-22

54. Connell LA, Lincoln NB, Radford KA. Somatosensory impairment after stroke: Frequency of different deficits and their recovery. *Clin Rehab*. 2008;22:758-767

55. Kalichman L, Ratmansky M. Underlying pathology and associated factors in hemiplegic shoulder pain. *American Journal of Physical Medicine and Rehabilitation*. 2011;90:768-780

56. Burridge JH, Tuk R, Notley SV, Pickering RM, Simpson DM. The relationship between upper limb activity and impairment in post-stroke hemiplegia. *Disability and Rehabilitation*. 2009;31:109-117

57. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The prep algorithm predicts potential for upper limb recovery after stroke. *Brain*. 2012;135:2527-2535

58. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: A systematic review and meta-analysis. *Clinical Rehabilitation*. 2012;26:291-313

59. Morone G, Bragoni M, Iosa M, De Angelis D, Venturiero V, Coiro P, et al. Who may benefit from robotic-assisted gait training? A randomised clinical trial in patients with subacute stroke. *Neurorehabil Neural Repair*. 2011;25:636-644

60. Pignolo L. Robotics in neuro-rehabilitation. *J Rehab Med*. 2009;41:955-960

61. Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: Who regains hand capacity? *Archives of Physical Medicine and Rehabilitation*. 2013;94:839-844

62. Shelton F, Reding M. Effect of lesion location on upper limb recovery after stroke. *Stroke*. 2001;32:107-112

63. Radlinksa B, Ghinani S, Leppert IR, Minuk J, Pike GB, Thiel A. Diffusion tensor imaging, permanent pyramidal tract damage, and outcome in subcortical stroke. *Neurology*. 2010;75:1048-1054

64. Harris JE, Eng JJ, Miller WC, Dawson AS. The role of caregiver involvement in upper-limb treatment in individuals with subacute stroke. *Physical Therapy*. 2010;90:1302-1310

65. Foley N, Salter K, Teasell R. Specialised stroke services: A meta-analysis comparing three models of care. *Cerebrovascular Disease*. 2007;23:194-202

66. Bernhardt J, Thuy MNT, Collier JM, Legg LA. Very early versus delayed mobilisation after stroke. *Cochrane Database of Systematic Reviews*. 2009;1

67. Schweickert W, Pohlman M, Pohlman A, Nigos C, Pawlik A, Esbrook C, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet*. 2009;373:1874-1882

68. English C, Hillier S. Circuit class therapy for improving mobility after stroke. *Cochrane Database of Systematic Reviews*. 2010

69. Hillier SL, Stiller KR, Warden-Flood A. Cicuit class therapy versus individual physiotherapy sessions during inpatient stroke rehabilitation: A controlled trial. *Archives of Physical Medicine and Rehabilitation*. 2007;88:955-963

70. Hochstenbach-Waelen A, Seelen HA. Embracing change: Practical and theoretical considerations for successful implementation of technology assisting upper limb training in stroke. *J Neuroeng Rehabil*. 2012;9:52

71. Siekierka E, Eng K, Bassetti C, Blickenstorfer A, Cameirao M, Dietz V, et al. New technologies and concepts for rehabilitation in the acute phase of stroke: A collaborative matrix. *Neurodegener Dis*. 2007;4:57-69

72. Iosa M, Morone G, Fusco A, Bragoni M, Coiro P, Multari M, et al. Seven capital devices for the future of stroke rehabilitation. *Stroke Research and Treatment*. 2012

73. Yekutiel M. *Sensory re-education of the hand after stroke*. London: Whurr publishers; 2000.

74. Eng K, Siekierka E, Pyk P, Chevrier E, Hauser Y, Cameirao M, et al. Interactice visuo-motor therapy system for stroke rehabilitation. *Med Biol Eng Comput*. 2007;45:901-907

75. Teasell R, Bayona N, Salter K, Hellings C, Bitensky J. Progress in clinical neurosciences: Stroke recovery and rehabilitation. *The Canadian Journal of Neurological Sciences*. 2006;33:357-364

76. Schaechter JD, Connell BD, Stason WB, Kaptchuk TD, Krebs DE, Macklin EA, et al. Correlated change in upper limb function and motor cortex activation after verum and sham acupuncture in patients with chronic stroke. *J Altern Complement Med*. 2007;13:527-532

77. Takeuchi N, Izumi SI. Rehabilitation with poststroke motor recovery: A review with focus on neural plasticity. *Stroke Research and Treatment*. 2013

78. Wu D, Qian L, Zorowitz RD, Zhang L, Qu Y, Yuan Y. Effects of decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: A randomised sham-controlled study. *Arch Phys Med Rehab*. 2013;94:1-8

79. Harvey RL, Stinear JW. Cortical stimulation as an adjunct to upper limb rehabilitation after stroke. *The Journal of Injury, Function and Rehabilitation*. 2010;2:S269-278

80. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: A systematic review. *Lancet Neurology*. 2009;8:741-754

81. Hubbard IJ, Parsons MW, Neilson C, Carey LM. Task-specific training: Evidence for and translation to clinical practice. *Occup Ther Int*. 2009;16:175-189

82. Arya KN, Berma R, Garg RK, Sharma VP, Agarwal M, Aggarwal GG. Meaningful task-specific training for stroke rehabilitation: A randomised controlled trial. *Topics in Stroke Rehabilitation*. 2012;19:193-211

83. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: What's the evidence? *Clin Rehabil*. 2004;18:833-862

84. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database of Systematic Reviews*. 2009;4

85. Sleimen-Malkoun R, Temprado JJ, Thefenne L, Berton E. Bimanual training in stroke: How do coupling and symmetry-breaking matter? *BMC Neurol*. 2011;11:11

86. Mudie MH, Matyas TA. Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? *Disabil Rehabil*. 2000;22:23-37

87. Ausenda C, Carnovali M. Transfer of motor skill learning from the healthy hand to the paretic hand in stroke patients: A randomised controlled trial. *European Journal of Physical and Rehabilitation Medicine*. 2011;47:417-425

88. Mudie MH, Matyas TA. Upper extremity retraining following stroke: Effects of bilateral practice. *J Neural Rehabil*. 1996;10:167-184

89. Cauraugh JH, Lodha N, Naik SK, Summers JJ. Bilateral movmement training and stroke motor recovery progress: A structured review and meta-analysis. *Hum Movt Sci*. 2010;29:853-870

90. Coupar F, Pollock A, van Wijck F, Morris J, Langhorne P. Simultaneous bilateral training for improving arm function after stroke. *Cochrane Database of Systematic Reviews*. 2010;4

91. Van Delden AE, Peper CE, Beek PJ, Kwakkel G. Unilateral versus bilateral upper limb exercise therapy after stroke: A systematic review. *J Rehab Med*. 2012;44:106-117

92. Latimer CP, Keeling J, Lin B, Henderson M, Hale LA. The impact of bilateral therapy on upper limb function after chronic stroke: A systematic review. *Disabil Rehabil*. 2010;32:1221-1231

93. McCombe-Waller S, Whitall J. Bilateral arm training: Why and who benefits? *NeuroRehabilitation*. 2008;23:29-41

94. Taub E, Miller NE, Novack RA, Cook EW. Technique to improve chronic motor deficit after stroke. *Archives of Physical Medicine and Rehabilitation*. 1994;74:347-354

95. Sunderland A, Tuke A. Neuroplasticity, learning and recovery after stroke: A critical evaluation of constraint-induced therapy. *Neuropsychol Rehabil*. 2005;15:81-96

96. Kitago T, Liang J, Huang VS, Simon P, Tenteromano L, Lazar RM, et al. Improvement after constraint-induced movement therapy: Recovery of normal motor control or task-specific compensation? *Neurorehabilitation and Neural Repair*. 2013;27:99-109

97. Wolf S. Revisiting constraint-induced movement threapy: Are we too smitten with the mitten? Is all nonuse "learned" and other quandries. *Physical Therapy*. 2007;87:1212-1223

98. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris DM, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The excite randomised clinical trial. *JAMA*. 2006;296:2095-2104

99. van Wegen NR, van der Krogt H, Bakker C, Buma F, Klomp A, van Kordelaar J, et al. Characterising the protocol for early modified constraint-induced movement therapy in the explicit-stroke trial. *Physiotherapy Research International*. 2013;18:1-15

100. Nijland R, van Wegen E, van der Krogt H, Bakker C, Buma F, Klomp A, et al. Characterising the protocol for early modified constraint-induced movement therapy in the explicit-stroke trial. *Physiotherapy Research International*. 2013;18:1-15

101. Liberson W, Holmquest H, Scott M. Functional electrotherapy: Stimulation of the common peroneal nerve synchronised with the swing phase of gait of hemiplegic subjects. *Arch Phys Med Rehabil*. 1961;42:202-205

102. Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey LL, Lojovich JM, Carey JR. Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Experimental Brain Research*. 2004;154:450-460

103. Pomeroy VM, King L, Pollock A, Baily-Hallam A, Langhorne P. Electrical stimulation for promoting recovery of movement or functional ability after stroke. *Cochrane Database of Systematic Reviews*. 2006;2

104. Foundation HaS. Canadian best practice guidelines for stroke care.2013

105. Kroon JR, IJzerman MJ, Chae J, Lankhorst GJ, Zilvold G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *J Rehabil Med*. 2005;37:65-74

106. Meadmore KL, Hughes AM, Freeman CT, Zhonglun C, Tong D, Burridge JH, et al. Functional electrical stimulation mediated by iterative learning and 3d robotics reduces motor impairment in chronic stroke. *J Neuroeng Rehabil*. 2012;9:32

107. Rosewilliam S, Malhotra S, Roffe C, Jones P, Pandyan A. Can surface neuromuscular electrical stimulation of the wrist and hand combined with routine therapy facilitate recovery of arm function in patients with stroke? *Arch Phys Med Rehabil*. 2012;93:1715-1721

108. Sahin N, Ugurlu H, Albayrak I. The efficacy of electrical stimulation in reducing the post-stroke spasticity: A randomised controlled trial. *Disabil Rehabil*. 2012;34:151-156

109. Sheffler LR, Chae J. Neuromuscular electrical stimulation in neurorehabilitation. *Muscle and Nerve*. 2007;35:562-590

110. Loureiro RC, Harwin WS, Nagai K, Johnson M. Advances in upper limb stroke rehabilition: A technology push. *Med Biol Eng Comput*. 2011;49:1103-1118

111. Mehrholz J, Hadrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database of Systematic Reviews*. 2012

112. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: A systematic review. *Neurorehabil Neural Repair*. 2008;22:111

113. Norouzi-Gheidari N, Archambault PS, Fung J. Effects of robot-assisted therapy on stroke rehabilitation in upper limbs: Systematic review and meta-analysis of the literature. *J Rehabil Res Dev*. 2012;49:479-496

114. Liao WW, Wu CY, Hsieh YW, Chang WY. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: A randomised controlled trial. *Clin Rehabil*. 2012;26:111-120

115. Frisoli A, Procopio C, Chisari C. Positive effects of robotic exoskeleton training of upper limb reaching movements after stroke. *J Neuroeng Rehabil*. 2012;9:36

116. Bovolenta F, Sale P, Dall'Armi V, Cerici P, Franceschini M. Robot-aided therapy for upper limbs in patients with stroke-related lesions. Brief report of clinical experience. *Journal of Neuroengineering and Rehabilitation*. 2011;8:18

117. Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: A systematic review of effectiveness for upper limb motor recovery. *Topics in Stroke Rehabilitation*. 2007;14:52-61

118. King M, Hale L, Pekkari A, Persson M, Gregorsson M. An affordable, computerised, table-based excercise system for stroke survivors. *Disabil Rehabil Assist TEchnol*. 2010;5:288-293

119. Johansson BB. Current trends in stroke rehabiliation: A review with focus on brain plasticity. *Acta Neurologica Scandinavia*. 2011;123:147-159

120. Holper L, Muehlemann T, Scholkmann F, Eng K, Kiper D, Wolf M. Testing the potential of a virtual reality neurorehabilitation system during performance of observation, imagery and imitation of motor actions recorded by wireless functional near-infrared spectroscopy. *Journal of Neuroengineering and Rehabilitation*. 2010;7:57

121. Laver K, George S, Thomas S, Deutsch JE, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database of Systematic Reviews*. 2011

122. Laver K, Ratcliffe J, George S, Burgess L, Crotty M. Is the nintendo wii fit really acceptable to older people? A discrete choice experiment. *BMC Geriatrics*. 2011;11:64

123. Hale LA, Satherley JA, McMillan NJ, Milosavljevic S, Hijmans JM, King MJ. Participant perceptions of use of cywee z as adjunct to rehabilitation of upper limb function following stroke. *J Rehabil Res Dev*. 2012;49:623-634

124. Lewis GN, Woods C, Rosie JA, McPherson KM. Virtual reality games for rehabilitation of people with stroke: Perspectives from the users. *Disability and Rehabilitation*. 2011;6:453-463

125. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. *Brain*. 2008;131:1381-1390

126. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. *J Neuroengineering Rehabil*. 2009;6

127. Takeuchi N, Tada T, Toshima M, Chuma T, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *Journal of Rehabilitation Medicine*. 2008;40:2988-2303

128. Marquez J, Van Vliet P, McElduff P, Lagopoulos J, Parsons M. Transcranial direct current stimulation (tdcs): Is it effective as a stroke therapy. *Presentated at: Stroke 2013 Conference*. 31 July-2 August 2013

129. Reis J, Fritsch B. Modulation of motor performance and motor learning by transcranial direct current stimulation. *Current Opinion in Neurology*. 2011;24:590-596

130. Hesse S, Waldner A, Mehrholz J, Tomelleri C, Pohl M, Werner C. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: An exploratory, randomised multicenter trial. *Neurorehabil Neural Repair*. 2011;25:838-846

131. Ayache SS, Farhat WH, Zouari HG, Hosseini H, Mylius V, Lefaucheur JP. Stroke rehabilitation using noninvasive cortical stimulation: Motor deficit. *Expert Review of Neurotherapeutics*. 2012;12:949-972

132. Takeuchi N, Tada T, Matsuo Y, Ikoma K. Low-frequency repetitive tms plus anodal transcranial dcs prevents transient decline in bimanual movement induced by contralesional inhibitory rtms after stroke. *Neurorehabil Neural Repair*. 2012;26:988-998

133. Edwardson MA, Lucas TH, Carey JR, Fetz EE. New modalities of brain stimulation for stroke rehabilitation. *Experimental Brain Research*. 2013;224:335-358

134. Adie K, James M. Does telephone follow-up improve blood pressure after minor stroke or tia? *Age and Ageing*. 2010;39:598-603

135. Smith G, Egbert N, Palmieri P, Dellman-Jenkins M, Nanna K. Reducing depression in stroke survivors and their informal caregivers: A randomised clinical trial of a web-based intervention. *Rehabil Psychol*. 2012;57:196-206

136. Huijbregts M, Cameron J, Taylor D, McEwen S, Kagan A, Streiner D. Videoconference delivery of a stroke self-management program: A mixed methods waiting list randomised controlled trial. *Stroke*. 2010;41:e357

137. Piron L, Turolla A, Tonin P, Piccione F, Lain L, Dam M. Satisfaction with care in post-stroke patients undergoing a telerehabilitation programme at home. *Journal of Telemedicine and Telecare*. 2008;14:257-260

138. Piron L, Turolla A, Agostini M, Zucconi C, Cortese F, Zampolini M, et al. Exercises for paretic upper limb after stroke: A combined virtual reality and telemedicine approach. *J Rehab Med*. 2009;41:1016-1020

139. Forducey P, Glueckauf R, Bergquist T, Maheu M, Yutsis M. Telehealth for persons with severe functional disabilities and their caregivers: Facilitating self-care management in the home setting. *Psychological Services*. 2012;9:144-162

140. Kairy D, Lehoux P, Vincent C, Visintin M. A systematic review of clinical outcomes, clinical process, healthcare utilisation and costs associated wtih telerehabilitation. *Disabil Rehabil*. 2009;31:427-447

141. Johansson T, Wild C. Telerehabilitation in stroke care - a systematic review. *Journal of Telemedicine and Telecare*. 2011;17:1-6

142. Gustafsson L, Yates K. Are we applying interventions with research evidence when targeting secondary complications of the stroke-affected upper limb. *Aust Occup Ther J*. 2008;56:428-438

143. Welmer AK, Widen HL, Sommerfeld DK. Location and severity of spasticity in the first 1-2 weeks and at 3 and 18 months after stroke. *Eur J Neurol*. 2010;17:720-725

144. Lundstrom E, Terent A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *European Journal of Neurology*. 2008;15:533-539

145. Wissel J, Schelosky LD, Christie W, Faiss JH, Mueller J. Early development of spasticity following stroke: A prospective, observational trial. *J Neurol*. 2010;257:1067-1072

146. Katalinic OM, Harvery LA, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contractures. *Cochrane Database of Systematic Reviews*. 2010;9

147. Yablon SA, Brin MF, VanDenburgh AM, Zhou J, Garabedian-Ruffalo SM, Abu-Shakra S, et al. Dose response with botulinum toxin a for post-stroke spasticity: A pooled data analysis. *Mov Disord*. 2011;26:209-215

148. Shaw LC, Price CI, van Wijck FM, Shackley P, Steen N, Barnes MP, et al. Botulinum toxin for the upper limb after stroke (botuls) trial: Effect on impairment, activity limitation, and pain. *Stroke*. 2011;42:1371-1379

149. Foley N, Pereira S, Salter K, Fernandez MM, Speechley M, Sequeira K, et al. Treatment with botulinum toxin improves upper-extremity function post stroke: A systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2013;94:977-989

150. Demetrios M, Khan F, Turner-Stokes L, Brand C, McSweeney S. Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for poststroke spasticity. *Cochrane Database of Systematic Reviews*. 2013;6

151. Adey-Wakeling Z, Crotty M, Shanahan EM. Suprascapular nerve block for shoulder pain in the first year after stroke: A randomised controlled trial. *Stroke*. 2013;44:3136-3141

152. Leibovitz A, Baumoehl Y, Roginsky Y, Glick Z, Habot B, Segal R. Edema of the paretic hand in elderly poststroke nursing patients. *Arch Gerontol Geriatr*. 2007;44:37-42

153. Organisation WS. Inventory of international stroke-related best practice guidelines 2012. 2012;September 2013

154. Organisation ES. Stroke guidelines.September 2013

155. Belgian-Stroke-Council, Thijs V, Peeters A, Dewindt D, Hemelsoet D, De Klippel N, et al. Organisation of inhospital acute stroke care and minimum criteria for stroke care units. Recommendations of the belgian stroke council. *Acta Neurol Belg*. 2009;109:247-251

156. Shinohara Y, Yanagihara T, Abe K, Yoshimine T, Fujinaka T, Chuma T, et al. Japanese guidelines for the managemnet of stroke. Vii - rehabilitation. *Journal of Stroke and Cerebrovascular Diseases*. 2011;20:S145-S180

157. Phillipines SSot. Guidelines for the prevention, treatment and rehabilitation of stroke. 2010;September 2013

158. Defense Do. Clincal practice guidelines for management of stroke.August 2013

159. Sackett D, Rosenberg W, Gray J, Haynes R, Richardson W. Evidence based medicine: What is it and what isn't it. *BMJ*. 1996;312:71-72

160. Foundation NS. National stroke audit: Rehabilitation services report 2012

161. Astrand A, Saxin C, Cumming T. Slightly more active, just as alone: A comparative observational study of stroke rehabilitation and acute stroke care in sweden. *Presented at: Stroke 2013 Conference*. 31 July- 2 August 2013

162. Teasell R. Challenges in the implementation of evidence in stroke rehabilitation. *Top Stroke Rehabil*. 2012;19:93-95

163. Bayley MT, Hurdowar A, Richards CL, Korner-Bitensky N, Wood-Dauphinee S, Eng JJ, et al. Barriers to implementation of stroke rehabilitation evidence: Findings from a multisite pilot project. *Disabil Rehabil*. 2012;34:1633-1638

164. Kimberley TJ, Samargia S, Moore LG, Shakya JK, Lang CE. Comparison of amounts and types of practice during rehabilitation for traumatic brain injury and stroke. *J Rehabil Res Dev*. 2010;47:851-862

165. Page SJ, Levine P. Modified constraint-induced therapy extension: Using remote technologies to improve function. *Arch Phys Med Rehabil*. 2007;88:922-927

166. Melenhorst AS, Rogers WA, Bouwhius DG. Older adults motivated choice for technological innovation: Evidence for benefit drive selectivity. *Psychology and Aging*. 2006;21:190-195

167. Wilkowska W, Ziefle M. Which factors form older adults' acceptance of mobile information and communication technologies? *Human-computer interaction for einclusion*. Berline, Heidelberg: Springer-Verlag; 2009:81-101.

168. Divani AA, Majidi S, Barrett AM, Noorbaloochi S, Luft AR. Consequences of stroke in community dwelling elderly. The health and retirement study, 1998 to 2008. *Stroke*. 2011;42:1821-1825

169. Kendall R. Musculoskeletal problems in stroke survivors. *Topics in Stroke Rehabilitation*. 2010;17:173-178

170. Ratnasabapathy Y, Broad J, Baskett J, Pledger M, Marshall J, Bonita R. Shoulder pain in people with a stroke: A population-based study. *Clin Rehabil*. 2003;17:304-311

171. Klit H, Finnerup NB, Overvad K, Anderson G, Jensen TS. Pain following stroke: A population-based follow-up study. *PLoS One*. 2011;6

172. Anderson CS, Stewart-Wynne E, Jamrozik K, Burvill P, Chakera T. Perth community stroke study: Design and preliminary results. *Clin Exp Neurol*. 1990;27:125-129

173. Jespersen HF, Jorgensen HS, Nakayama H, Olsen TS. Shoulder pain after a stroke. *Int J Rehabil Res*. 1995;18:273-276

174. Zorowitz RD, Hughes MB, Idank DT, I., Johnston MV. Shoulder pain and subluxation after stroke: Correlation or coincidence? *American Journal of Occupational Therapy*. 1995;50:194-201

175. Gamble G, Barberan E, Laasch HU, Bowsher D, Tyrrell PJ, Jones AK. Poststroke shoulder pain: A prospective study of the association and risk factors in 152 patients from a consecutive cohort of 205 patients presenting with stroke. *European Journal of Pain*. 2002;6:467-474

176. Dromerick AW, Edwards DF, Kumar A. Hemiplegic shoulder pain syndrome: Frequency and characteristics during inpatient stroke rehabilitation. *Arch Phys Med Rehab*. 2008;89:1589-1593

177. Sackley C, Brittle N, Patel S, Ellins J, Scott M, Wright C, et al. The prevalence of joint contracutres, pressure sores, painful shoulder, other pain, falls, and depression in the year after a severely disabling stroke. *Stroke*. 2008;39:3329-3334

178. Suethanapornkul lS, Kuptniratsaikul PS, Kuptniratsaikul V, Uthensut P, Dajpratha P, Wongwisethkarn J. Post stroke shoulder subluxation and shoulder pain: A cohort multicenter study. *J Med Assoc Thai*. 2008;91:1885-1892

179. Barlak A, Unsal S, Kaya K, Sahin-Onat S, Ozel S. Poststroke shoulder pain in turkish stroke patients: Relationship with clinical factors and functional outcomes. *Int J Rehabil Res*. 2009;32:309-315

180. Hansen AP, Marcussen NS, Klit H, Kasch H, Jensen TS, Finnerup NB. Pain following stroke: A prospective study. *Scandanavian Journal of Pain*. 2012;3:194

181. Joy AK, Ozukum I, Nilachandra L, Khelendro T, Nandabir Y, Kunjabasi W. Prevalence of hemiplegic shoulder pain in post-stroke patients - a hospital based study. *IJPMR*. 2012;23:15-19

182. Fabunmi A, Awolola E, Fowodu O, Amusat S. Shoulder pain among stroke survivors: Prevalence and pattern. *33rd Annual Scientific Meeting of the Merican Pain Society*. 2014;15(Suppl 1):S37

183. Roosink M RG, Geurts ACH, IJzerman MJ. Towards a mechanism-based view on post-stroke shoulder pain: Theoretical considerations and clinical implications. *Neurorehabilitation*. 2012;30:153-165

184. Wilson RD, Gunzler DD, Bennett ME, Chae J. Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: Ra randomised controlled trial. *Am J Phys Med Rehabil*. 2014;93:17-28

185. Kalichman L RM. Underlying pathology and associated factors of hemiplegic shoulder pain. *American Journal of Physical Medicine and Rehabilitation*. 2011;90:768-780

186. Roosink M, Buitenweg JR, Renzenbrink GJ, Geurts AC, IJzerman MJ. Altered cortical somatosensory processing in chronic stroke: A relationship with post-stroke shoulder pain. *NeuroRehabilitation*. 2011;28:331-344

187. Benlidayi IC, Basaran S. Hemiplegic shoulder pain: A common clinical consequence of stroke. *Pract Neurol*. 2014;14:88-91

188. Yi Y, Lee KJ, Kim W, Oh BM, Chung SG. Biomechanical properties of the glenohumeral joint capsule in hemiplegic shoulder pain. *Clinical Biomechanics*. 2013;28:873-878

189. Niessen M JT, Meskers C, Koppe P, Konijnenbelt M, Veeger D. Kinematics of the contralateral and ipsilateral shoulder: A possible relationship with post-stroke shoulder pain. *Journal of Rehabilitation Medicine*. 2008;40:482-486

190. Shah RR HS, Elovic EP et al. Mri findings in the painful poststroke shoulder. *Stroke*. 2008;39:1808-1813

191. Pompa A, Clemenzi A, Troisi E, Di Mario M, Tonini A, Pace L, et al. Enhanced-mri and ultrasound evaluation of painful shoulder in patients after stroke: A pilot study. *Eur Neurol*. 2011;66:175-181

192. Suriya-Amarit D, Gaogasigam C, Siriphorn A, Boonsong S. Effect of interferential current stimulation in management of hemiplegic shoulder pain. *Archives of Physical Medicine and Rehabilitation*. 2014;95:1441-1446

193. Dogun A, Karabay I, Hatipoglu C, Ozgirgin N. Ultrasound and magnetic resonance findings and correlation in hemiplegic patients with shoulder pain. *Topics in Stroke Rehabilitation*. 2014;21:S1-7

194. Turner-Stokes L, Jackson D. Shoulder pain after stroke: A review of the evidence base to inform the development of a an integrated care pathway. *Clin Rehabil*. 2002;16:276-298

195. Koog YH JS, Yoon K, Min BI. Interventions for hemiplegic shoulder pain: Systematic review of randomised controlled trials. *Disability and Rehabilitation*. 2010;32:282-291

196. Roosink M, Rensenbrink GJ, Geurts AC, Ijzerman MJ. Towards a mechanism-based view on post-stroke shoulder pain: Theroetical considerations and clinical implications. *NeuroRehabilitation*. 2012;30:153-165

197. Roosink M vDR. Classifying post-stroke shoulder pain: Can the dn4 be helpful? *European Journal of Pain*. 2011;15:99-102

198. Demirci A, Ocek B, Coseoglu F. Shoulder pain in hemiplegic patients. *J Phys Med Rehabil Sci*. 2007;1:25-30

199. Lindgren I, Lexell J, Jonsson AC, Brogardh C. Left-sided hemiparesis, pain frequency, and decreased passive shoulder range of abduction are predictors of long-lasting poststroke shoulder pain. *PM R*. 2012;4:561-568

200. Faria-Fortini I MS, Cassiano JG, Teixeira-Salmela LF. Upper extremity function in stroke subjects: Relationships between the international classification of functioning, disability and health domains. *Journal of Hand Therapy*. 2011;24:257-264

201. Snels IA DJ, van der Lee JH, Lankhorst GJ, Beckerman H, Bouter LM. Treating patients with hemiplegic shoulder pain. *American Journal of Physical Medicine and Rehabilitation*. 2002;81:150

202. Chae J, Mascarenhas D, Yu D, Kirsteins A, Elovic EP, Flanagan SR, et al. Poststroke shoulder pain: Its relationship to motor impairment, activity limitation and quality of life. *Archives of Physical Medicine and Rehabilitation*. 2007;88:298-301

203. Kong KH, Woon VC, Yang SY. Prevalence of chronic pain and its impact on health-related quality of life in stroke survivors. *Arch Phys Med Rehabil*. 2004;85:35-40

204. Naess H, Lunde L, Brogger J. The effects of fatigue, pain and depression on quality of life in ischemic stroke patients: The bergen stroke study. *Vascular Health and Risk Management*. 2012;8:407-413

205. Widar M, Ahlstrom G, Ek AC. Health-related quality of life in persons with long-term pain after a stroke. . *J Clin Nurs*. 2004;14:497-505

206. Hackett ML, Duncan JR, Anderson CS, Broad JB, Bonita R. Health-related quality of life among long-term survivors of stroke: Results from the auckland stroke study, 1991-1992. *Stroke*. 2000;31:440-447

207. Appelros P. Prevalence and predictors of pain and fatigue after stroke: A population-based study. *International Journal of Rehabilitation Research*. 2006;29:329-333

208. Ada L FA, Canning CG. Supportic devices for preventing and treating subluxation of the shoulder after stroke. *Cochrane Database of Systematic Reviews*. 2005

209. Griffin A, Bernhardt J. Strapping the hemiplegic shoulder prevents development of pain during rehabilitation: A randomised controlled trial. *Clinical Rehabilitation*. 2006;20:287-295

210. Page T, Lockwood C. The prevention and management of shoulder pain in the hemiplegic patient. *JBI Reports*. 2003;1:149-165

211. Price CIM, Pandyan AD. Electrical stimulation for preventing and treating post-stroke shoulder pain. *Cochrane Database of Systematic Reviews*. 2008

212. de Jong LD, Dijkstra PU, Gerritsen J, Geurts ACH, Postema K. Combined arm stretch positioning and neuromuscular electrical stimulation during rehabilitation doesnot improve range of motion, shoulder pain or function in patients after stroke: A randomised trial. *Journal of Physiotherapy*. 2013;59:245-254

213. Yu DT, Friedman AS, Rosenfeld EL. Electrical stimulation for treating chronic poststroke shoulder pain using a fully implanted microstimulator with internal battery. *Am J Phys Med Rehabil*. 2010;89:423-428

214. Nguyen VQ, Bock WC, Groves CC, Whitney M, Bennett ME, Lechman TE, et al. Fully implantable peripheral nerve stimulation for the treatment of hemiplegic shoulder pain: A case report. *Am J Phys Med Rehabil*. 2015;94:146-153

215. Kong KH, Neo JJ, Chua KS. A randomised controlled trial of botulinum toxin a in the treatment of hemiplegic shoulder pain associated with spasticity. *Clinical Rehabilitation*. 2007;21:28-35

216. Marciniak CM, Harvey RL, Gagnon CM, Duraski SA, Denby FA, McCarty S, et al. Does botulinum toxin type a decrease pain and lessen disability in hemiplegic survivors of stroke with shoulde rpain and spasticity?: A randomised, double-blind, placebo-controlled trial. *Am J Phys Med Rehabil*. 2012;91:1007-1019

217. Snels IA BH, Twisk JW, Dekker JH, de Koning P, Koppe PA, Lankhorst GJ, Bouter LM. Effect of triamcinolone acetonide injections on hemiplegic shoulder pain: A randomised clinical trial. *Stroke*. 2000;31:2396-2401

218. Viana R, Pereira S, Mehta S, Miller T, Teasell R. Evidence for therapeutic interventions for hemiplegic shoulder pain during the chronic stage of stroke: A review. *Topics in Stroke Rehabilitation*. 2012;19:514-522

219. Rah UW, Yoon SH, Moon DJ, Kwack KS, Hong JY, Lim YC, et al. Subacromial corticosteroid injection on poststroke hemiplegic shoulder pain: A randomised, triple-blind, placebo-controlled trial. *Arch Phys Med Rehabil*. 2012;93:949-956

220. Gustafsson L, McKenna K. A programme of static positional stretches does not reduce hemiplegic shoulder pain or maintain shoulder range of motion - a randomised controlled trial. *Clin Rehabil*. 2006;20:277-286

221. Ada L, Foongchomcheay A, Canning CG. Supportive devices for preventing and treating subluxation of the shoulder after stroke. *Stroke*. 2005;36:1818-1819

222. Pandian JD, Kaur P, Arora R, Vishwambaran DK, Toor G, Mathanqi S, et al. Shoulder taping reduces injury and pain in stroke patients: Randomised controlled trial. *Neurology*. 2013;5:528-532

223. Snels IA, Beckerman H, Lankhorst GJ, Bouter LM. Risk factors for hemiplegic shoulder pain: A systematic review. *Critical Reviews in Physical Medicine and Rehabilitation*. 2002;14:223-233

224. Kumar R, Metter EJ, Mehta AJ, Chew T. Shoulder pain in hemiplegia: The role of exercise. *American Journal of Physical Medicine and Rehabilitation*. 1990;69:205-208

225. Snels IA, Dekker JH, van der Lee JH, Lankhorst GJ, Beckerman H, Bouter LM. Treating patients with hemiplegic shoulder pain. *American Journal of Physical Medicine and Rehabilitation*. 2002;8:150-160

226. Kesiktas N, Ketenci A, Sindel D, Ozarslan M. The treatment of shoulder pain after stroke. *8th World Congress of the International Society of Physical Medicine and Rehabilitation*. 2014;6(Supp 2):S128-S129

227. Nam YS JJ, Han SH, Park SE, Lee SM, Kwon MJ, Ji JH, Kim KS. An anatomic and clinical study of the suprascapular and axilarry nerve blocks for shoulder arthroplasty *Journal of Shoulder and Elbow Surgery*. 2011

228. Fernandes MR, Barbosa AM, Sousa AL, Ramos GC. Suprascapular nerve block: Important procedure in clinical practice. *Rev Bras Anestesiol*. 2012;62:1

229. Wertheim HM, Rovenstein EA. Suprascapular nerve block. *Anesthesiology*. 1941;2:541-545

230. Boonsong P, Jaroenarpornwatana A, Boonhong J. Preliminary study of suprascapular nerve block (ssnb) in hemiplegic shoulder pain. *J Med Assoc Thai*. 2009;92:150-160

231. Gado K, Emery P. Modified suprascapular nerve block with bupivaine alone effectively controls chronic shoulder pain in patients wtih rheumatoid arthritis. *Ann Rheum Dis*. 1993;52:215-218

232. Dangiosse MJ, Wilson DJ, Glynn CJ. Mri and clinical study of a easy and safe technique of suprascapular nerve blockade. *Acta Anaesthesiol Belg*. 1994;45:49-54

233. Kang SS, Jung JW, Song CK, Yoon YJ, Shin KM. A new anterior approach for fluoroscopy guided suprascapular nerve block - a preliminary report. *Korean Journal of Pain*. 2012;25:168-172

234. Sigenthaler A, Moriggl B, Mlekusch S, Schliessbach J, Haug M, Curatolo M. Ultrasound guided suprascapular nerve block, description of a novel supraclavicular approach. *Reg Anesth Pain Med*. 2012;37:325-328

235. Shanahan EM, Smith MD, Wetherall M. Suprascapular nerve block in chronic shoulder pain: Are the radiologists better? *Ann Rheum Dis*. 2004;63:1035-1040

236. Gorthi V, Moon YL, Kang JH. The effectiveness of ultrasonography-guided suprascapular nerve bock for perishoulder pain. *Orthopedics*. 2010;16:238-241

237. Chan C-W, Peng PWH. Suprascapular nerve block: A narrative review. *Regional Anaesthesia and Pain Medicine*. 2011;36:358-373

238. Vecchio PC, Adebajo AO, Hazleman BL. Suprascapular nerve block for persistent rotator cuff lesions. *J Rheumatol*. 1993;20:453-455

239. Favejee MM, Huisstede BMA, Koes VW. Frozen shoulder: The effectiveness of conservative and surgical interventions - systematic review. *Br J Sports Med*. 2011;45:49-56

240. Turner-Stokes L JD. Shoulder pain after stroke: A review of the evidence base to inform the development of an integrated care pathway. *Clinical Rehabilitation*. 2002;16:276-298

241. Lee KH, Khundadorn F. Painful shoulder in hemiplegic patients: A study of the suprascapular nerve. *Arch Phys Med Rehab*. 1986;67:818-820

242. Yasar E, Vural D, Safaz I, Balaban B, Yilmaz B, Goktepe AS, et al. Which treatment approach is better for hemiplegic shoulder pain in stroke patients: Intra-articular steroid or suprascapular nerve block? A randomised controlled trial. *Clin Rehabil*. 2011;25:60-68

243. Todd KH. Clinical versus statistical significance in the assessment of pain relief. *Ann Emerg Med*. 1996;27:439-441

244. Croft P, Pope D, Zonca M, O'Neill T, Silman A. Measurement of shoulder related disability: Results of a validation study. *Ann Rheum Dis*. 1994;53:525-528

245. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: Implication for stroke clinical trial: A literature review and synthesis. *Stroke*. 2007;38:1091-1096

246. Dorman P, J, Waddell F, Slattery J, Dennis M, Sandercock P. Is the euroqol a valid measure of health-related quality of life after stroke? *Stroke*. 1997;28:1876-1882

247. Jeon WH, Park GW, Jeong HJ, Sim YJ. The comparison of effects of suprascapular nerve block, intra-articular steroid injection, and a combination therapy on hemiplegic shoulder pain: Pilot study. *Ann Rehabil Med*. 2014;38:167-173

248. Yelnik AP, Colle FM, Bonan IV, Vicaut E. Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: A randomised, double-blind, placebo controlled study of botulinum toxin a. *J Neurol Neurosurg Psychiatry*. 2007;78:845-848

249. Zeilig G, Rivel M, Weingarden H, Gaidoukov E, Defrin R. Hemiplegic shoulder pain: Evidence of a neuropathic origin. *Pain*. 2013;154:263-271

250. Jonsson A, Lindgren I, Hallstrom B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: A population-based study focusing on patients' perspectives. *Journal of Neurology, Neurosurgery and Psychiatry*. 2006:590-595

251. Rajaratnam B, Kumar P, Goh J, Chan Y. Predictability of simple clinical tests to identify shoulder pain after stroke. *Archives of Physical Medicine and Rehabilitation*. 2007;88:1016-1021

252. Sudlow CLM, Warlow CP. Comparing stroke incidence worldwide - what makes studies comparable? *Stroke*. 1996;27:550-558

253. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study: Declining stroke rates but many preventable cardioembolic strokes. *Stroke*. 2013;44:1226-1231

254. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J*. 2001;18:205-207

255. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: What is moderate pain in millimetres? *Pain*. 1997;72:95-97

256. Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: A discussion of the realtionship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol*. 1991;69:683-694

257. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: Clinical characteristics, pathophysiology and management. *The Lancet Neurol*. 2009;8:857-868

258. Turner-Stokes L, Jackson D. Assessment of shoulder pain in hemiplegia: Sensitivity of the shoulderq. *Disabil Rehabil*. 2006;28:389-395

259. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med*. 2001;38:633-638

260. Van Ouwenaller C, Laplace PM, Chantraine A. Painful shoulder in hemiplegia. *Arch Phys Med Rehabil*. 1986;67:23-26

261. Allen ZA, Shanahan EM, Crotty M. Does suprascapular nerve block reduce shoulder pain after stroke: A double-blind randomised controlled trial with masked outcome assessment. *BMC Neurology*. 2010;10:83-88

262. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med*. 1997;16:2349-2380

263. Viney R, Norman R, King MT, Cronin P, Street DJ, Knox S, et al. Time trade-off derived eq-5d weights for australia. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2011;14:928-936

264. Podhuri KR. Shoulder pain in stroke patients and its effect on rehabilitation. *J Stroke Cerebrovasc Dis*. 1993;3:261-266

265. Busse JW, Guyatt GH. Optimising the use of patient data to improve outcomes for patients: Narcotics for chornic noncancer pain. *Expert Rev Pharmacoecon Outcomes Res*. 2009;9:171-179

266. Forouzanfar T, Weber WE, Kemler M, van Kleef M. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin J Pain*. 2003;19:281-285

267. Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after adequate pain control. *Acad Emerg Med*. 2003;10:1128-1130

268. Hoffman GA, Harrington A, Fields HL. Pain and the placebo: What we have learned. *Perpect Biol Med*. 2005;48:248-265

269. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: Meta-epidemiological study. *BMJ*. 2013;346:f2304

270. Jones DS, Cattopadhyay C. Suprascapular nerve block for the treatment of frozen shoulder in primary care: A randomised trial. *Brit J Gen Pract*. 1999;49:39-41

271. Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, et al. Studying sex and gender differences in pain and analgesia: A consensus report. *Pain*. 2007;32:S26-S45

272. Lyby PS, Aslakesen PM, Flaten MA. Variability in placebo analgesia and the role of fear of pain - an erp study. *Pain*. 2011;152:2405-2412

273. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron*. 2008;59:195-206

274. Haley WE, Roth DL, Kissela B, Perkins M, Howard G. Quality of life after stroke: A prospective longitudinal study. *Qual Life Res*. 2011;20:799-806

275. Ones K, Yilmaz E, Cetinkaya B, Caglar N. Quality of life for patients poststroke and the factors affecting it. *Journal of Stroke and Cerebrovascular Diseases*. 2005;14:261-266

276. Carod-Artal FJ, Egido JA. Quality of life after stroke: The importance of a good recovery. *Cerebrovasc Dis*. 2009;27:204-214

277. Lopez-Espuela F, Zamorano JD, Ramirez-Moreno JM, Jimenez-Caballero PE, Portilla-Cuenca JC, Lavado-Garcia JM, et al. Determinants of quality of life in stroke survivors after 6 months, from a comprehensive stroke unit: A longitudinal study. *Biol Res Nurs*. 2014;Oct 6

278. Delcourt C, Hackett M, Wu Y, Huang Y, Wang J, Heeley E, et al. Determinants of quality of life after stroke in china; the chinaquest (quality evaluation of stroke care and treatment) study. *Stroke*. 2011;42:433-438

279. King RB. Quality of life after stroke. *Stroke*. 1996;27:1467-1472

280. Jonsson AC, Lindgre I, Hallstrom B, Norrving B, Lindgren A. Determinants of quality of life in stroke survivors and their informal caregivers. *Stroke*. 2005;36::803-808

281. Alguren B, Fridlund B, Cieza A, Sunnerhagen KS, Christensson L. Factors associated with health-related quality of life after stroke: A 1-year prospective cohort study. *Neurorehabilitation and Neural Repair*. 2012;26:266-274

282. Group E. Euroqol - a new facility for the measurement of health-related quality of life. *Health Policity*. 1990;16:199-208

283. Savitz SI, Lew R, Bluhmk E, Hacke W, Fisher M. Shift analysis versus dichotomisation of the modified rankin scale outcome scores in ninds and ecass-ii trials. *Stroke*. 2007;38:3205-3212

284. McLean DE. Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. *Arch Phys Med Rehabil*. 2004;85:466-469

285. Wade DT. Outcome measures for clinical rehabilitation trials: Impairment, function, quality of life, or value? *Am J Phys Med Rehabil*. 2003;82:S26-S31

286. Fregni F, Imamura M, Chien HF. Challenges and recommendations for placebo controls in randomized trials in physical and rehabilitation medicine: A report of the international placeblo symposium working group. *Am J Phys Med Rehabil*. 2010;89:160-172

287. Ballard C, Rowan E, Stephens S, Kalaria R, Kenny RA. Prospective follow-up study between 3 and 15 months after stroke: Improvements and decline in cognitive function among dementia-free stroke survivors >75 years of age. *Stroke*. 2003;34:2440-2444

288. Lesniak M, Bak T, Czepiel W, Seniow J, Czlonkowska A. Frequency and prognostic value of cognitive disorders in stroke patients. *Dementia and Geriatric Cognitive Disoders*. 2008;26:356-363

289. Party ISW. *National clinical guidelines for stroke (4th ed)*. London, UK: RACP; 2012.

290. Jackson D, Turner-Stokes L, Williams H, Das-Gupta R. Use of an integrated care pathway: A third round audit of the management of shoulder pain in neurological conditions. *J Rehab Med*. 2003;35

291. Bosch MC, Tavender EJ, Gruen RL, Green SE. How to define 'best practice' for use in knowledge translation research: A practical, stepped and interactive process. *Journal of Evaluation in Clinical Practice*. 2013;19:763-768

292. Di Carlo A, Pezzella FR, Fraser A, Bovis F, Baeza J, McKevitt C, et al. Methods of implementation of evidence-based stroke care in europe: European implementation score collaboration. *Stroke*. 2015;46:2252-2259

293. Levac D, Glegg SMN, Camden C, Rivard LM, Missiuna C. Best practice recommendations for the development, implementation, and evaluation of online knowledge translation resources in rehabilitation. *Physical Therapy*. 2015;95:648-662

294. Bradnam L, Shanahan EM, Hendy K, Reed A, Skipworth T, Visserand A, et al. Afferent inhibition and cortical silent periods in shoulder primary motor cortex and effect of a suprascapular nerve block in people experiencing chronic shoulder pain. *Clinical Neurophysiology*. 2015;In press

295. French SD, Green SE, O'Connor DA, McKenzie JE, Francis JJ, Michie S, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: A systematic approach using the theoretical domains framework. *Implementation Science*. 2012;9:38