A Comparison of Intranasal Fentanyl, Subcutaneous Fentanyl and Intramuscular Pethidine during Childbirth: A Randomised Controlled Trial

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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'If I don't know my options, I don't have any'. ~ Diana Korte

'They always say that time changes things, but you actually have to change them yourself'. ~

Andy Warhol

Dedication to:

My wonderful husband, Adrian.

Without your continuing support I may never have undertaken this venture.

My two beautiful, unique and brilliant children, Jade and Joel.

There is an enormous sense of accomplishment in completing this significant project,

which has posed numerous challenges and rewards and has reshaped my very being.

However, no achievement has ever been as momentous, fulfilling or exceptional

as that of being your mother.

No greater accolade can be awarded than receiving the title

'Mum'

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Declaration

I certify that this thesis does not incorporate without acknowledgment 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.

Signed…………………………………… Date………………………………

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Summary

Administration of intramuscular (i.m.) pethidine is the standard practice in many maternity units for women who request analgesia during labour (Jones et al. 2012). Yet pethidine has a slow onset and has potential adverse effects for both the mother and neonate (Anderson 2011). Other opioids have been used in childbirth with varying success, for example, fentanyl. When compared to intravenous (i.v.) PCA pethidine, i.v. PCA fentanyl produced fewer adverse effects in the mother and baby (Douma et al. 2010; Rayburn et al. 1998), but this route of administration restricts the woman's ability to ambulate and requires additional resources, such as programmable PCA pumps and associated equipment.

In other clinical settings, fentanyl has proved effective when administered by intranasal (i.n.) and subcutaneous (s.c.) routes, but the efficacy of these routes have not been examined during childbirth. This study compared the clinical effectiveness of i.n. fentanyl, s.c. fentanyl and i.m. pethidine in labouring women requesting analgesia.

Methods

This randomised controlled trial, a three-arm parallel group design, was undertaken in two settings: the largest tertiary referral centre for maternal care in South Australia (SA) and a regional maternity unit. Parturients were randomised to receive i.n. fentanyl (n=52), s.c. fentanyl (n=53) or i.m. pethidine (n=51). The sample size calculation was undertaken to address the primary outcome, which was reduction of pain score using the Visual Analogue Scale (VAS) at 30 minutes post-treatment. Other maternal variables examined included: experiences of personal control during childbirth, level of sedation, antiemetic use, vital signs, labour duration and birth outcomes. Intention to use the treatment again and breastfeeding outcomes also were recorded post-birth. Neonatal outcomes examined included: Apgar scores

at 1 and 5 minutes, arterial cord blood pH and nursery admission. The outcomes were analysed by intention-to-treat.

Results

All three groups reported clinically significant reductions in pain scores 30 minutes post-administration (mean reduction: 1.2 i.n. fentanyl, 1.1 s.c. fentanyl, 1.6 i.m. pethidine; $p<0.001$), with no significant differences between groups. While experiences of personal control during childbirth were similar, 82.9% of parturients in the i.n. fentanyl group and 80.6% in the s.c. fentanyl group reported that they would use the treatment again, as compared to only 44.0% of women receiving pethidine ($p<0.001$). In addition, women in both fentanyl groups were observed to have significantly less sedation 30 minutes post-treatment ($p\leq0.03$), and shorter labours by at least 2 hours ($p<0.05$). There were no differences between groups for Apgar scores, but neonates in the pethidine group were more likely to require nursery admission post-birth ($p<0.02$). Women in the pethidine group also were more likely to report difficulty with the establishment of breastfeeding within the first 6 weeks postpartum as compared to women in the fentanyl groups ($p<0.01$).

Conclusion

Fentanyl administered via the i.n. and s.c. routes is as efficacious in relieving labour pain as i.m. pethidine and results in greater satisfaction to use the treatment, less sedation, shorter labour, fewer neonatal admissions to nursery and fewer difficulties in the establishment of breastfeeding. This RCT provided evidence that fentanyl is a suitable alternative to pethidine in providing parenteral pain relief to labouring women.

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Publications

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Abbreviations

AF	Artificially fed
BF	Breastfed
BMI	Body mass index
BFHI	Baby friendly health initiative
CNS	Central nervous system
CTG	Cardiotocography
CTN	Clinical Trial Notification
EDB	Epidural block
FHR	Fetal heart rate
GA	General anaesthesia
LAS	Labour Agentry Scale
LSCS	Lower section caesarean section
i.m.	Intramuscular
i.n.	Intranasal
IQR	Interquartile range
i.v.	Intravenous
MAP	mean arterial pressure
MLE	maximum likelihood estimation
M6G	morphine-6-glucuronide
N_2O+O_2	nitrous oxide and oxygen
NACS	neurologic & adaptive capacity scores
NICU	neonatal intensive care unit
NRS	Numerical Rating Scale
O&G	obstetrics and gynaecology
PCA	patient controlled analgesia

PCINA	patient-controlled intra-nasal analgesia
PRN	As needed
RR	risk ratio/relative risk
RCT	Randomised controlled trial
SD	Standard deviation
SA	South Australia
SCBU	special care baby unit
s.c.	subcutaneous
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization

Glossary

Acidosis: A condition of the blood in which the bicarbonate concentration is below normal. The mean umbilical artery pH after uncomplicated pregnancy and labour ranges from 7.25 to 7.31 (Vandenbussche et al. 1999).

Antiemetic: A drug that is effective against vomiting and nausea.

Apgar score: A scoring system applied after birth (usually at 1 and 5 minutes) to evaluate the condition of the baby, A score of 0, 1, or 2, is given for breathing effort, heart rate, muscle tone, reflexes, skin colour. A score <7 is a sign that the baby needs medical attention.

Assisted birth: A birth where either forceps or ventouse are used to help with the delivery of the neonate.

Baby friendly health initiative: This initiative was developed by the WHO and UNICEF in 1990. In a BFHI facility, breastfeeding is encouraged, supported and promoted. Breastfed babies are not given breast milk substitutes (infant formula), dummies or teats unless medically indicated or it is the parents' informed choice.

Body Mass Index: A standard for recording obesity statistics. BMI = weight (kg) $\div$ height^2 (metres). This is used as <18.5 underweight, 18.5 to <25 normal, 25 to <30 overweight, 30 to <35 obese, 35 to <40 severely obese, 40+ morbidly obese (Scheil et al. 2013).

Cardiotocography: An electronic method of simultaneously recording fetal heart rate (FHR), fetal movements and uterine contractions to identify the probability of fetal hypoxia (Pattison & McCowan 2006).

Caesarean section: Birth of a neonate by an abdominal operation (Scheil et al. 2013).

Clinical effectiveness: The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care (NICE Clinical Guidelines, No. 55).

Established labour: Regular, rhythmic, progressive uterine contractions that produce effacement and dilation of the cervix.

First stage of labour: Regular painful contractions, and resulting in progressive cervical dilatation from 4 cm (NICE Clinical Guidelines, No. 55).

Gestational age: The duration of pregnancy in completed weeks determined by the best obstetric estimate, using ultrasonography and the first day of the last normal menstrual period (Scheil et al. 2013).

Hypoalgesia: A decreased sensitivity to pain.

Induction of labour: An intervention undertaken to stimulate the onset of labour by pharmacological or other means (Scheil et al. 2013).

Multigravida: A woman who has been pregnant more than once (Scheil et al. 2013).

Neurologic & adaptive capacity scores: A screening test to detect CNS depression from drugs and differentiate effects from birth trauma and perinatal asphyxia. The NACS is based on 20 criteria, and scored 0, 1, or 2. The criteria assesses five areas: adaptive capacity, passive tone, active tone, primary reflexes, and alertness including crying, and motor activity (Amiel-Tison et al. 1982).

Numerical rating scale: An 11-, 21- or 101-point scale where the end points are the extremes of "no pain" and "pain as bad as it could be", or "worst pain". The NRS can be graphically or verbally delivered (Williamson & Hoggart 2005).

Parity: The total number of previous pregnancies resulting in live births or stillbirths (Scheil et al. 2013).

Parenteral: Taken into the body or administered in a manner other than through the digestive tract. For the purpose of this thesis parenteral refers to the i.v., i.m., s.c. or the i.n. route.

Preterm: Less than 37 completed weeks' gestation (Scheil et al. 2013).

Primigravida: A woman pregnant for the first time (Scheil et al. 2013).

Primipara: A pregnant woman who has had no previous pregnancy resulting in a live birth or stillbirth (Scheil et al. 2013).

Postpartum: Defined as the six weeks after childbirth.

Postpartum haemorrhage: A blood loss of 600 mL for a normal birth and 750 mL for a caesarean birth.

Second stage of labour: The period between full cervical dilatation to the birth of the neonate.

Visual analogue scale: A 100 mm line with the end points assigned words representing the extremes of the phenomenon being assessed. For pain intensity the descriptive words such as "no pain" and "worst pain imaginable" are written at the end points. The patient is asked to mark the line at the point that represents the perceived pain experienced (Ludington & Dexter 1998).

Verbal rating scale: A pain scale that uses adjectives to represent increasing pain intensities. The most common words used being: "no pain", "mild pain", "moderate pain" and "severe" or "intense pain". For ease of recording these adjectives are assigned numbers (Williamson & Hoggart 2005).

Chapter 1   Background: Parenteral pain relief in childbirth

Pain relief options are one of the major maternity issues women face in labour. Choice may include non-pharmacological and pharmacological forms of analgesia, with pharmacological methods offered as standard care in many countries (Ullman et al. 2010). All available pain relief options offer varying risks and benefits, as well as different levels of effectiveness and availability (Lally et al. 2008). In Australia, the three most common forms of pharmacological pain relief offered for labour pain include: inhalation analgesia (nitrous oxide and oxygen), parenteral opioids (pethidine, fentanyl and remifentanil in controlled settings), and epidural block (SA Perinatal Practice Guidelines 2014). While there is some evidence to suggest these pharmacological methods produce pain relief, they also are associated with adverse effects (Jones et al. 2012).

Currently, epidural analgesia is described as the 'gold standard' for providing effective pain relief for women in labour (Cambic & Wong 2010). This technique however, is invasive and associated with the increased risk of serious adverse effects such as hypotension, motor block, fever, urinary retention, dural tap, infection and increased likelihood of instrumental vaginal birth (Jones et al. 2012). For women unable or unwilling to use an epidural, pethidine (also known as meperidine) is the most common parenterally administered opioid for labour pain (Jones et al. 2012).

Although pethidine is commonly used for pain management in childbirth, it also is reported to produce numerous adverse effects (Bricker & Lavender 2002). These effects include sedation (Fairlie et al. 1999), vomiting (Ullman et al. 2010), prolonged labour (Khooshideh & Shahriari 2009), reduced variability of fetal heart rate (Sekhavat & Behdad 2009; Solt et al. 2002), higher incidence of neonatal acidosis (Sosa et al. 2006), reduced Apgar scores (Sharma et al. 2004) and feeding difficulties for up to 6 weeks postpartum (Belsey et al. 1981; Nissen et al. 1997).

In addition, pethidine has an onset of action up to 20 minute. Its action is then prolonged due partly to the active metabolite, norpethidine. This prolonged action is of concern as norpethidine has been associated with neuronal depression in the neonate up to 60 hours post-birth (Morselli & Rovei 1980). The Australian and New Zealand College of Anaesthetists have recommended that pethidine use should be discouraged in favour of other opioids due to the risk of toxicity from the accumulation of norpethidine and associated neuroexcitatory effects that include nervousness, tremors, twitches, multifocal myoclonus and seizures (Macintyre et al. 2010).

Currently, there are few alternative parenterally administered opioids used for labour pain, with choice limited to what is held at the different hospitals (Ullman et al. 2010). While women report increased satisfaction with the use of opioids compared to non-opioids to control labour pain (Othman et al. 2012), practitioners in the obstetric setting continue to debate which opioid and mode of administration provides the most effective pain relief (Ullman et al. 2010). In South Australia (SA), the majority of women (99.3%) birth in a hospital (Scheil et al. 2013), these hospitals follow the Perinatal Practice Guidelines for normal pregnancy, labour and puerperium management, which lists pethidine, fentanyl or remifentanil (in controlled settings) as options available for pharmacological methods of pain relief (SA Maternal & Neonatal Clinical Network). Despite these options, the standard practice for all South Australian tertiary hospitals is to offer intramuscular (i.m.) pethidine when women request analgesia in labour (P Palm 2014 pers. comm., 15 December; S. Scroggs 2014 pers. comm., 15 December).

Although research on the use of remifentanil and fentanyl in childbirth has focused on the benefits of intravenous (i.v.) patient-controlled analgesia (PCA), this route requires specialised equipment, venous access, additional monitoring and results in higher opioid consumption than intermittent parenteral administration (Macintyre et al. 2010). While i.v. PCA remifentanil has

been shown to provide effective pain relief, a recent systematic review reported that remifentanil had a comparable degree of adverse effects when compared with parenteral pethidine (Schnabel et al. 2012). In addition, caution for use of remifentanil in obstetrics has been suggested with four recent case reports of maternal respiratory and/or cardiac arrest (Muchatuta & Kinsella 2013).

Advances in pain management in non-obstetric settings have led to the use of less-invasive techniques of administering fentanyl (Grape et al. 2010). In particular, research in these areas has shown fentanyl to be efficacious when administered by the intranasal (i.n.) (Panagiotou1 & Mystakidou 2010) and the subcutaneous (s.c.) routes (Dietrich & Tobias 2003). Advantages of fentanyl include rapid onset of pain relief and no active metabolite (Anderson 2011). Until recently, parenterally administered fentanyl has only been studied in the obstetric setting when administered intravenously. When compared to i.v. PCA pethidine, i.v. PCA fentanyl has been shown to produce fewer adverse effects in the mother and baby (Douma et al. 2010; Rayburn et al., 1998), but like the use of i.v. PCA remifentanil, this route of administration restricts the woman's ability to ambulate, requires venous access, availability of anaesthetic staff and specialised equipment that is not always widely available.

The most recent pregnancy outcome data for SA reported 20,248 hospital births occurred in 2011, 80.3% occurred in metropolitan hospitals (teaching and private) and 19.7% in country maternity units (Scheil et al. 2013). In an attempt to reduce resources and offer women additional choice in labour analgesia, a number of country hospitals in SA have been administering s.c. fentanyl to women requesting pain relief in labour, but to date only one study has explored the effects of this method during labour (Fleet et al. 2014). In addition, the only study to examine i.n. fentanyl use in an obstetric population was undertaken following elective caesarean section, where i.n. fentanyl was reported to be safe and effective (Wong et al. 2003).

No studies were found that examined i.n. fentanyl for women during childbirth. Therefore, this study aimed to compare the standard practice of administering pethidine by i.m. injection, with fentanyl administered by the less invasive i.n. and s.c. routes. Results of this study will be interpreted in light of available evidence, and include recommendations for practice and further research.

1.1 The physiology of labour pain and the role of endogenous opioids

In the 1950s, Friedman defined active labour as the progressive effacement and dilatation of the cervix, accompanied by regular painful contractions (Friedman 1954). The experience of labour pain is unique and affected by multiple physiological and psychological factors. As such, some women describe minimal discomfort, while others find the pain extremely distressing (Jones et al. 2012). Although not completely understood, the pain experienced is believed to originate from different sites depending on the phase of labour (Lowe 2002). Physiologically, labour is described as three stages that results in contraction of the myometrium of the uterus to produce downward propulsion of the fetus and ending with expulsion of the placenta. Stage one prepares the uterus for the birth of the fetus, stage two describes the passage of the fetus through the bony canal, and stage three empties the uterus with the birth of the placenta (Pairman et al. 2014).

Pain from uterine contractions, visceral pain, in the first stage of labour stems from the constriction of the utero-placental arteries that results in myometrial ischemia (Lowe 2002). This pain is transmitted via afferent fibres to the spinal cord by sympathetic nerves in the inferior and superior hypogastric plexus and hypogastric nerve that pass through the nerve roots at the level of T10 to L1 (Rowlands & Permezel 1998). Pain from the second stage of labour, somatic pain, results from the distension of the vulva, uterine ligaments, pelvic floor, pressure and displacement of the urethra, bladder, rectum, lumbosacral plexus, fascia. Impulses are

transmitted to the sacral plexus at S2 to S4 through stimulation of the pudendal nerve via fine myelinated A delta fibres (Rowlands & Permezel 1998).

Pregnancy-induced hypoalgesia occurs in the last trimester and during labour due to the increased release of endorphins. This results in an increase in pain threshold, and may be associated with feelings of euphoria and analgesia (Rowlands & Permezel 1998). The β-endorphins are secreted by the pituitary gland in response to pain and excitement and bind to the opiate receptors to produce a morphine-like effect that reduces the labouring woman's perception of pain, and promotes a feeling of coping (Riss & Bieglmayer 1984).

While little is known about the mechanism responsible for the activation of β-endorphins (Riss & Bieglmayer 1984), pain signals during labour are believed to be blocked by β-endorphins, and other endogenous opioids, as they bind to opiate receptors in the central nervous system (CNS) to interfere with the release of neurotransmitters from the afferent nerves (Goebelsmann et al. 1984). This is thought to prevent transmission of the pain signal to the brain via the afferent pathways at the level of the dorsal horns (Blackburn 2013). Stein (1993) reported that there is some evidence that substance P, which is released from the terminals of sensory nerves, is modified during pregnancy. Although the mechanism is not completely understood, it may relate to activation of opioid receptors or progesterone-induced increase in enkephalinase, which degrades both substance P and enkephalin (Stein 1993), to contribute to cervical ripening (Mowa et al. 2003). This also inhibits the primary role of substance P, which is to transmit pain signals to the CNS (Iversen 1998).

In addition to the production of their own endorphins the fetus also may benefit from maternal endorphin release and other stress hormones produced in labour. These hormones cross the placenta and are believed to provide analgesia to the fetus, as well as stimulating the fetal respiratory centre and reducing the stress of labour. These effects result in an alert baby at birth

(Ombra et al. 2007). Postnatally, β-endorphins have been shown to be twice the level in colostrum than in maternal plasma (Zanardo et al. 2001), and may assist the neonate to overcome birth stress, tissue damage and adaptation to extrauterine life. However, unmanaged maternal pain can result in negative effects that increase anxiety, adding to the maternal physiologic responses of muscle tension, hyperventilation, increased cardiac output, increased blood pressure, and decreased oxygen consumption that can result in impaired uterine contractions and prolonged labour (Rowlands & Permezel 1998). These adverse effects may contribute to reduced placental perfusion resulting in altered fetal heart rate in labour, as the exchange of gases, nutrients and waste products is reduced, leading to an increased level of carbon dioxide and lactic acid causing fetal acidosis (Blackburn 2013).

1.2 Women's expectations and experiences of labour pain

Many factors influence a woman's experience of childbirth, including her response to pain in labour. While most women receive analgesia for labour, the pain experienced by each woman is highly variable. This unique experience is believed to be affected by not only physiological factors, such as maternal position in labour and mobility, but also psychosocial factors, levels of fear and anxiety or confidence (Othman et al. 2012).

Levels of fear and anxiety, may range from mild worry to extreme fear, a condition called tokophobia (Stoll & Hall 2013). This fear leads some women to dread and avoid childbirth despite desperately wanting a baby (Hofberg 2000). Previous studies have shown that high levels of anxiety around labour are associated with negative outcomes that include uncontrolled pain, prolonged labour and emergency caesarean section (Leap et al. 2012). These outcomes may result in low satisfaction with the experience of labour and childbirth.

Women's level of fear and anxiety impact on their attitudes towards birth, the birthing choices they make and potentially their experience. For example, Stoll and Hall (2013) reported that

young women with high levels of fear believed medical intervention was a means of managing labour and birth. In contrast, young women with low fear regarded interventions more critically, believing birth to be a natural process. Heinze and Sleigh (2003) also suggested that women who chose to birth using an epidural had high fear of birth, an external locus of control for childbirth, and a preference for a passive role in the birthing process. In contrast, women who laboured without an epidural were more likely to have a low fear of birth, an internal locus of control for childbirth, and a preference to actively participate in the childbirth process. Additionally, women who decided not to have an epidural prior to going into labour scored higher on a scale designed to assess knowledge of risks associated with epidural use (Heinze & Sleigh 2003).

Other factors, such as involvement of care providers, have been associated with improved maternal satisfaction, particularly among women experiencing high levels of anxiety. For example, continuity of midwifery care models, where a relationship develops between the woman and her midwife throughout pregnancy, promotes confidence in the experience of pregnancy, labour, and childbirth. These positive experiences enable women who may have been fearful and anxious about their ability to cope with the pain of labour to do so without using pharmacological pain relief and to develop feelings of empowerment (Leap et al. 2012).

A systematic review undertaken to examine which method of pain relief was most efficacious to women in childbirth concluded suitability of pain relief methods needed to be tailored to each woman's circumstances, experience and expectation of labour pain (Jones et al. 2012). Therefore, some women may choose to use non-pharmacological methods of pain relief, such as water immersion, relaxation, acupuncture and massage which assist them to 'cope' with the pain of labour (Jones et al. 2012). However, other women may wish to have more pharmacological options that assist 'relieve' labour pain (Ullman et al. 2010). Hence, it is

important that a variety of effective pain relief options be available that enable women more choice to individualise their care.

1.3 Assessment of labour pain

Although labour pain is considered to have both a sensory and an emotional component, research tends to predominantly focus on reported pain intensity (Capogna et al. 2010). Pain intensity may be influenced by numerous factors such as, previous pain experiences, education, culture, expectations and anxiety, environmental factors, and support from caregivers (McCool et al. 2004). While childbirth is regarded to be one of the most painful events to be experienced (Niven & Murphy-Black 2000; Lowe 2002), not all women report the pain of labour to be a negative experience (Rowlands & Permezel 1998), and not all women want to be pain free (Ross 1998).

As pain is considered a subjective experience, research strongly supports the need for the assessment of pain intensity to be based upon self-report (Reed & Van Nostran 2014). There are several tools that have been validated for the measurement of pain intensity and these include the numerical rating scale (NRS), the verbal rating scale (VRS) and the visual analogue scale (VAS) (0–10cm) (Reed & Van Nostran 2014). The VAS has been reported as the 'gold standard' for use in research, as well as in clinical practice (Bergh et al. 2012).

Pain scores in labour are known to increase with cervical dilation. Therefore, it may be difficult to interpret pain intensity after the administration of analgesia (Conell-Price et al. 2008; Capogna et al. 2010). This is highlighted by Tsui et al. (2004) compared VAS pain scores pre- and 30 minutes post-administration of i.m. pethidine and a placebo (normal saline), a significant reduction of VAS pain score was observed in the pethidine group (median decrease by 1.1 cm), whereas the placebo group reported an increase in VAS pain scores (median increase of 0.4 cm) at the same time-point. To assist in the interpretation of results, recent

studies have recommended pain scores be considered in conjunction with additional observations that measure need for further analgesia, maintenance of personal control and overall satisfaction with treatment (Carvalho & Cohen 2013; Schwenglenks et al. 2014).

1.4 Opioid use in obstetrics

Methods of pain management for childbirth have been recorded throughout history, with opium described as the first opioid used for labour pain in Ancient Chinese writings (Ryan-Haddad 2006). Later, in the early 18th century, morphine was isolated from crude opium by a German pharmacist, Friedrich Wilhelm Adam Sertürner. However, parenteral administration of morphine did not occur until the French physician, Charles Pravaz, invented the hypodermic needle and syringe in 1853. In the early 19th century various combinations of other drugs and morphine were introduced to produce a "twilight sleep" that often resulted in maternal confusion and forgetfulness of the birth experience. Despite poor analgesic properties and adverse neonatal effects, such as respiratory depression, this treatment remained in use for many years (Bricker & Lavender 2002).

In 1939, the first use of pethidine was described by Eisleb and Schaumann when it was introduced as a synthetic substitute for atropine. Pethidine was reported to not only possess spasmolytic properties similar to those of atropine but also was antagonistic to acetylcholine, inhibited contraction of smooth muscle and produced an analgesic effect. The University College Hospital in London first reported the use of pethidine for pain relief in obstetric settings in 1942 (Barnes 1947). Pethidine became legally available to midwives in the United Kingdom for independent use in the 1950s and has remained popular ever since (Wee et al. 2004). Despite much debate around the efficacy of pethidine it has remained the most commonly used opioid for labour pain relief worldwide (Ullman et al. 2010). However, the search for an ideal analgesic agent for obstetric use has continued and while newer and faster acting derivatives

of pethidine have been identified, their use in obstetrics has remained limited (Ullman et al. 2010).

Fentanyl is a synthetic opioid first synthesised by Janssen Pharmaceutica in Belgium in the 1950s. It is estimated to be approximately 50 to 100 times more potent than morphine. While fentanyl was initially used in the 1960s for i.v. anaesthesia and analgesia (Jaslow et al. 2007), there are few reports of the parenteral administration of fentanyl in obstetrics before the 1980s (Rayburn et al. 1989). The benefits of fentanyl, when compared to other opioids include producing less nausea and pruritus due to its increased lipid solubility (Jordan 2010). Fentanyl has become widely used in epidural analgesia for women in labour, partly due to the lipophilic properties that make it more likely to remain in the spinal cord (Jordan 2010). Apart for epidural administration, few studies have examined the clinical effectiveness of other parenteral routes of fentanyl during childbirth (Othman et al. 2010).

Remifentanil has been introduced for use in obstetrics in the late 1990s as an adjunct to general anaesthesia for caesarean births (Anderson 2011). Known for its rapid onset and short duration of action, remifentanil has been shown to be effective when used by i.v. PCA in labour (Schnabel et al. 2012). Studies are still determining appropriate dosage regimens as many studies report the need for oxygen supplementation due to maternal desaturation during labour and high rates of sedation and nausea (Anderson 2011). Consequently, use of remifentanil is limited to controlled settings where close monitoring can be undertaken for respiratory depression and sedation (Devabhakthuni 2013).

1.4.1 Parenteral administration of opioids in SA maternity units

Pharmacological pain relief in obstetrics is standard practice in all South Australian hospitals. The South Australian Pregnancy Outcome Unit report 17.9% of women in SA used parenteral opioids in labour (Scheil et al. 2013). As previously discussed, in SA the Perinatal Practice

Guidelines for normal pregnancy, labour and puerperium management list pethidine, fentanyl or remifentanil (in controlled settings) as the three available opioids for parenteral administration. Pethidine remains the standard practice for all SA tertiary maternity hospital, with i.v. fentanyl used in some circumstances. In addition, several rural SA settings administer s.c. fentanyl for women requesting analgesia in labour. Although the use of i.v. PCA remifentanil is limited, two of the three tertiary hospitals in SA use this method of analgesia as an alternative to epidural block, on the rare occasion that epidural placement is unsuccessful or contraindicated (P Palm 2014 pers. comm., 15 December; S. Scroggs 2014 pers. comm., 15 December). In other states of Australia, while pethidine administration is still common, some maternity units have returned to the use of administering morphine in an attempt to eradicate the use of pethidine.

1.4.2 Pharmacology of pethidine, morphine, remifentanil and fentanyl

Opioid drugs bind to the opiate receptors, of which there are three different types—mu, kappa, and delta (Trescot et al. 2008). Mu receptors mediate analgesia, sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, decreased gastrointestinal motility, and urinary retention. Kappa receptors promote sedation, dyspnea, dysphoria, spinal analgesia, and dependence. In contrast, delta receptors activation is not well studied but may relate to psychomimetic and dysphoric effects (Trescot et al. 2008). Most clinically relevant opioids are mu agonists and have their primary activity at mu receptors. Morphine and fentanyl have a high affinity for mu receptors and are potent analgesics, whereas pethidine is a relatively weak mu and kappa agonist (Vallejo et al. 2011).

The pharmacokinetic properties of bioavailability, distribution and elimination vary with the different opioid drugs. These parameters are controlled by the physiology of the body, which undergoes numerous adaptations in pregnancy that include increased glomerular filtration rate,

modified hepatic function, and increased volume of distribution as a result of increased blood volume and fat deposition (Blackburn 2013).

Fetal exposure is an inadvertent result of maternal administration of an opioid. While all opioids readily cross the placenta via diffusion, some are trapped in the fetal compartment as a result of ionisation of the drugs (Jones et al. 2012). Additionally, drug action in the fetus may be prolonged due to the immature fetal liver and the formation of active opioid metabolites. This, together with ion trapping, can result in higher drug levels in the fetus than in the mother and delayed clearance. For example, the plasma half-life of pethidine is 3–7 hours in the mother compared with 18–23 hours in the neonate (Anderson 2011). In addition, the half-life of the active metabolite norpethidine is 20 hours in the mother and 60 hours in the neonate (Jordan 2010). Norpethidine in high levels is toxic and has been associated with neuronal depression up to 60 hours post-birth (Morselli & Rovei 1980). Furthermore, there are concerns relating to maternal effects from opioid administration that include respiratory depression, sedation, nausea and/or vomiting, hypoventilation, hypotension, prolonged labour, urine retention, pruritus and the slowing of gastric emptying (Jordan 2010).

Morphine also has an active metabolite, morphine-6-glucuronide (M6G), which contributes to the prolonged action in the neonate (Anderson 2011). Studies comparing morphine with pethidine have identified no significant difference in analgesic effects and similar levels of heavy sedation (Jones et al. 2012).

In contrast, remifentanil is an ultra short-acting synthetic mu opioid receptor agonist that has no active metabolite and a much faster onset and clearance due to rapid metabolism by non-specific blood and tissue esterases. Due to its short duration of action, remifentanil is administered either by intermittent i.v. PCA or with a continuous background infusion (Devabhakthuni 2013). When i.v. PCA remifentanil was compared with pethidine,

significantly decreased oxygen saturation was observed. However, i.v. PCA remifentanil resulted in more sedation than fentanyl or pethidine (Douma et al. 2010).

Fentanyl also has a rapid onset and short duration of action, and similar to remifentanil, it lacks an active metabolite. The half-life of fentanyl in the neonate ranges between 75 and 440 minutes (Anderson 2011). Until recently, all studies that examined the use of fentanyl for pain relief in labour examined the effects of i.v. administration. These studies showed that i.v. fentanyl produces less sedation and nausea in women than pethidine. In addition, no long-term fetal or neonatal effects were identified (Fleet et al. 2011).

Few studies have examined the pharmacokinetics of fentanyl when administered by the s.c. route, and no studies involved women in labour. Capper et al. (2010) studied the pharmacokinetics of a single 200 microgram bolus dose of s.c. fentanyl administered to healthy male volunteers in order to provide guidance on dosage intervals. This study found that after a bolus dose the median maximum concentration of fentanyl was 0.55 ng/mL (range 0.28–0.87 ng/mL), which was reached at a median time of 15 minutes (range 10–30 minutes). The terminal half-life was 10 hours (range 5.48–16.37 hours). Absorption of s.c. fentanyl was relatively rapid and similar to the rate of absorption previously reported for s.c. morphine (Capper et. al. 2010). The only study that investigated the use of s.c. fentanyl for women in labour (Fleet et al. 2014) did not examine the pharmacodynamics; however, it did note that a clinically significant reduction of pain scores was achieved, vital signs were not affected, anti-emetics were not required and all women remained alert with no observable sedation (Fleet et al. 2014).

A review examining the pharmacokinetics of i.n. fentanyl found that the pH of the solution affects the bioavailability of fentanyl (Grape et al. 2010), so different formulations result in its bioavailability ranging between 55% and 89% (Christrup et al. 2008; Lim et al. 2003; Striebel

et al. 1993). These studies have found that i.n. fentanyl was rapidly absorbed through the nasal mucosa and produced therapeutic levels within 2–7 minutes. Table 1.1 provides a summary of the analgesic properties of pethidine, morphine, remifentanil and fentanyl.

Table 1.1   **Analgesic properties of pethidine, morphine, remifentanil and fentanyl**

	Route	Onset (min)	Peak (min)	Elimination half-life
Pethidine	i.m.	10-20	30-60	Adult 3–7h Neonate 18–23h
Morphine	i.m.	10-20	30-60	Adult 2–4h Neonate 13.9h
Remifentanil	i.v. PCA	0.5- 1	2	Adult 9min
Fentanyl	i.v.	1	5	Adult 3–4h Neonate 75–440min
	s.c.*	10	15	Adult 10h
	i.n.#	5	5	Adult 12–48min

Source: Anderson (2011), *Capper et al. (2010), #Lim et al. (2003)

1.5 Significance of the study

In circumstances where women request pain relief in childbirth, but are unable or unwilling to use an epidural, there are few options available. In many maternity units the standard practice is to administer i.m. pethidine (Anderson 2011), yet pethidine is known to produce adverse maternal and neonatal effects (Jones et al. 2012). More recently, faster acting opioids, such as fentanyl and remifentanil administered by i.v. PCA, have been used in some maternity settings (Anderson 2011). However, remifentanil has been found to have an increased potential for respiratory and cardiac arrest so is restricted to controlled settings where specialist services are available (Muchatuta & Kinsella 2013). Administration via i.v. PCA also poses problems as this method requires venous access, specialised equipment, restricts mobility and is known to result in higher opioid consumption (Macintyre et al. 2010). This method, therefore, significantly restricts availability, particularly to women birthing in rural and remote settings where resources and specialist services are often limited.

In an attempt to provide women with an alternative to i.m. pethidine, a number of country hospitals in SA have been offering s.c. fentanyl for labour analgesia. Preliminary data has

suggested s.c. fentanyl provided effective pain relief with few maternal and neonatal adverse effects (Fleet et al. 2014). In non-obstetric settings, the use of i.n. fentanyl has been shown to be as effective as i.v. PCA (Macintyre et al. 2010) and has the benefit of being non-invasive. To date, only one study has examined s.c. fentanyl for women in labour and no studies have been published to determine the effectiveness of i.n. fentanyl during childbirth. Therefore, the intention of this study was to examine alternative techniques of parenteral opioid administration, which have been shown to be clinically effective in non-obstetric settings, requires few resources and is not restricted to use in controlled settings.

1.6 Study aim

The aim of this research was to investigate the analgesic effect of i.n. fentanyl, s.c. fentanyl and i.m. pethidine when administered during childbirth. The primary outcome was to compare the change in pain scores at 30 minutes post-treatment. Key secondary outcomes related to factors associated with the analgesic effect that included feelings of coping and control during childbirth, and maternal satisfaction to use the treatment again. Additional secondary outcomes examined potential maternal and neonatal treatment effects (see Chapter 3.5.1–Secondary outcome measures for further details).

1.6.1 Hypotheses

The following hypotheses were tested:

1.6.1.1 Primary outcome: analgesic effect

- Fentanyl administered i.n. during childbirth will be at least as efficacious as the current practice of administering i.m. pethidine.

- Fentanyl administered s.c. during childbirth will be at least as efficacious as the current practice of administering i.m. pethidine.

1.6.1.2 Key secondary outcome: Feelings of coping and control

- Fentanyl administered i.n. during childbirth will provide women a greater perception of control to cope with the pain of labour than i.m. pethidine.

- Fentanyl administered s.c. during childbirth will provide women a greater perception of control to cope with the pain of labour than i.m. pethidine.

1.6.1.3 Other secondary outcomes: adverse effects

- Fentanyl administered i.n. during childbirth will provide fewer adverse effects for mother and neonate than i.m. pethidine.

- Fentanyl administered s.c. during childbirth will provide fewer adverse effects for mother and neonate than i.m. pethidine.

1.7 Summary

Labour pain is unique and women's experiences vary due to multi-dimensional factors relating to physiological, psychological and social components. While the majority of women use pharmacological forms of pain relief, their options are limited. Pethidine is the most commonly administered opioid for labour pain but results in adverse effects. Fentanyl has been suggested as a suitable alternative, but there is a dearth of research to support its use in obstetrics. Alternative less-invasive methods of administering fentanyl, such as i.n. and s.c., have been

demonstrated to be safe and efficacious in non-pregnant populations when compared to other opioids. These modes of administration have, however, not been studied in the obstetric population to determine analgesic effects.

Chapter 2 provides a review of the literature to explore the obstetric use of pethidine and fentanyl over the past 10 years. Subsequent chapters discuss the research design and methods, results and discussion of this study. In addition, an interpretation of the findings in light of other evidence is presented, along with the strengths and limitations of the design. Finally, implications for clinical practice and further research are proposed.

Chapter 2   Parenteral administration of pethidine and/or fentanyl in childbirth: A review of the past 10 years

Parenteral administration of pethidine is the standard practice for many maternity units worldwide when women request pain relief during labour and are either unable or unwilling to use epidural analgesia (Jones et al. 2012). Much debate has surrounded the use of pethidine and other opioids for pain relief in labour. In particular, the analgesic effect and the potential for adverse maternal and neonatal outcomes have been questioned (Anderson 2011; Bricker & Lavender 2002; Iliadou 2009). While some studies suggest parenteral administration of opioids provides pain relief during childbirth, further research is required to determine which analgesic agent is most effective (Jones et al. 2012; Ullman et al. 2010). In addition, recent Cochrane Reviews have recommended the need for consistency in reporting research outcome measures, such as pain intensity, maternal satisfaction, and longer term neonatal outcomes, including influence on breastfeeding (Jones et al. 2012; Ullman et al. 2010).

In SA, all tertiary maternity units continue to offer pethidine when women request an opioid for pain relief during childbirth. Although several South Australian rural settings have implemented the alternative practice of administering s.c. fentanyl (Fleet et al. 2014), few studies have examined the use of fentanyl in labour when administered by parenteral routes (Fleet et al. 2011). In the past decade, advances in pain management in non-obstetric settings have shown fentanyl to be efficacious when administered by the less-invasive s.c. (Radbruch et al. 2011) and i.n. routes (Hansen et al. 2012).

While several recent systematic reviews have examined literature published between 1988 and 2010 on the use of parenteral administration of opioids during childbirth, no studies were discussed that involved the s.c. or i.n. routes (Bricker & Lavender 2002; Jones et al. 2012; Ullman et al. 2010). Therefore, this literature review sought to identify whether there have been

changes in parenteral pain management in the obstetric setting since the publication of earlier reviews.

2.1 Search strategy

The search for relevant articles was conducted using electronic databases, key journals and reference lists of selected research papers and reviews. Literature obtained was sourced from OVID, CINAHL, Web of Knowledge (ISI), Medline and Cochrane library databases. Key words used were: fentanyl, Sublimaze®, pethidine, meperidine, Demerol®, pain relief, labour, childbirth, efficacy, narcotic, opioid, subcutaneous, intravenous, intramuscular, intranasal, nasal, patient controlled analgesia (PCA).

2.1.1 Selection process

The selection criteria included primary research articles published from 2004 to 2014, that examined maternal and neonatal outcomes based on contemporary obstetric practice and current dosage regimens. In particular, research articles were sought that investigated the use of fentanyl and/or pethidine regimens during childbirth, including maternal effects such as, reported pain scores, requirement for rescue analgesia (cross-over to epidural), sedation, nausea and/or vomiting, duration of labour, mode of birth, postpartum haemorrhage, sense of control in labour, satisfaction with treatment and breastfeeding outcomes at discharge and/or in the postnatal period. Neonatal effects explored included, Apgar score at 1 and 5 minutes, arterial cord blood pH, naloxone administration, admission to neonatal intensive care unit (NICU) or special care baby unit (SCBU) and neurologic and adaptive capacity scores. Articles were excluded if they related to the effects of fentanyl or pethidine when administered via axial (epidural or spinal) routes or combined the drug with other opioids.

Articles identified were quantitative and included RCTs and observational studies that examined the efficacy of fentanyl or pethidine when compared to placebo or other opioids

during childbirth. The majority of studies investigated the use of PCA, i.v. or i.m. administration. Although the author is aware that alternative modes of fentanyl administration, such as s.c. injection (C Goodall 2009, personnel comm., 13 Nov.) and the i.n. route (D Taylor 2013, pers. comm., 27 March), are currently being used in obstetric practice for management of labour pain, the only publication found related to the preliminary findings of this author on the use of s.c. fentanyl in labour (Fleet et al. 2014).

2.1.2 Appraisal of studies

In total, 20 articles met the inclusion criteria, five articles investigated the use of fentanyl and 15 articles examined pethidine administered during labour. Only one article was identified that directly compared fentanyl with pethidine (Douma et al. 2010). All articles examined were considered valuable in providing evidence to answer the review question. To comprehensively analyse the design of each study a level of evidence category was assigned using the National Health and Medical Research Council (NH&MRC) classification system and critiqued using the guidelines recommended for quantitative studies (Schneider et al. 2013). The articles are summarised in Appendices 1a & 1b.

2.2 Identified themes

A thematic analysis was performed, with each article reviewed and the major themes extracted. Three recurrent themes emerged when studies were examined; maternal analgesic effects, maternal physiological effects and neonatal effects. These themes were then grouped into sub-themes (Tables 2.1a,b), data were summarised into tables (Tables 2.2a,b,c–2.6a,b,c) and the evidence synthesised to enable a comparative discussion of the identified research.

Table 2.1a   **Themes identified from the fentanyl studies reviewed (n=5)**

Themes	Sub-themes	No. of studies	Empirical sources
Maternal analgesic effects	Treatment regimen	5	Douma et al. (2010); Fleet et al. (2014); Halpern et al. (2004); Marwah et al. (2012); Shoorab et al. (2013)
	Pain intensity	5	**Douma et al. (2010)***; Fleet et al. (2014); Halpern et al. (2004); **Marwah et al. (2012)***; Shoorab et al. (2013)
	Rescue analgesia/cross-over to epidural	3	Douma et al. (2010); Halpern et al. (2004); Marwah et al. (2012)
	Satisfaction	2	Halpern et al. (2004); Shoorab et al. (2013)
Maternal physiological effects	Sedation levels, emesis and vital signs	5	Douma et al. (2010); Fleet et al. (2014); Halpern et al. (2004); Marwah et al. (2012); Shoorab et al. (2013)
	Labour duration	4	Douma et al. (2010); Fleet et al. (2014); Halpern et al. (2004); **Shoorab et al. (2013)***
	Mode of birth	3	Douma et al. (2010); Fleet et al. (2014); **Halpern et al. (2004)***
Neonatal effects	Fetal heart rate	2	Douma et al.2010; Halpern et al. (2004)
	Apgar scores	5	Douma et al. (2010); Fleet et al. (2014); Halpern et al. (2004); Marwah et al. (2012); Shoorab et al. (2013);
	Arterial cord blood pH	3	Douma et al. (2010); Halpern et al. (2004); Marwah et al. (2012)
	Naloxone use	4	Douma et al. (2010); Fleet et al. (2014); Halpern et al. (2004); Marwah et al. (2012)
	Nursery admission	1	Fleet et al. (2014)
	Neurologic & adaptive capacity scores	1	Douma et al. (2010)
	Breastfeeding	1	Fleet et al. (2014)

*Studies powered to examine theme as the primary outcome.

Table 2.1b   Themes identified from the pethidine studies reviewed (n=15)

Themes	Sub-themes	No. of studies	Empirical sources
Maternal analgesic effects	Treatment regimen	15	Abdollahi et al. (2014); Blair et al. (2005); Elbohoty et al. (2012); El-Refaie et al. (2012); Khooshideh & Sharhriari (2009); Nelson & Eisenach (2005); Sekhavat & Behdad (2009); Shahriari & Khooshideh (2007); Sharma et al. (2004); Sosa et al. (2004; 2006); Tsui et al. (2004); Wee et al. (2014); Weissman et al. (2009); Yilmaz et al. (2009)
	Pain intensity	11	Abdollahi et al. (2014); **Blair et al. (2005)***; **Elbohoty et al. (2012)***; El-Refaie et al. (2012); Khooshideh & Sharhriari (2009); **Nelson & Eisenach (2005)***; **Shahriari & Khooshideh (2007)***; Sosa et al. (2004); **Tsui et al. (2004)***; **Wee et al. (2014)****; **Weissman et al. (2009)****
	Rescue analgesia/ cross-over to epidural	2	Tsui et al. (2004); Wee et al. (2014)
	Satisfaction	5	Blair et al. (2005); Khooshideh & Sharhriari (2009); Shahriari & Khooshideh (2007); Tsui et al. (2004); Wee et al. (2014)
Maternal physiological effects	Sedation levels, emesis and vital signs	10	Blair et al. (2005); Elbohoty et al. (2012); El-Refaie et al. (2012); Khooshideh & Sharhriari (2009); Nelson & Eisenach (2005); Shahriari & Khooshideh (2007); Tsui et al. (2004); Wee et al. (2014); **Weissman et al. (2009)****; Yilmaz et al. (2009)
	Labour duration	11	Abdollahi et al. (2014); Blair et al. (2005); Elbohoty et al. (2012); **El-Refaie et al. (2012)***; **Khooshideh & Sharhriari (2009)***; Sekhavat & Behdad (2009); Shahriari & Khooshideh (2007); Sharma et al. (2004); **Sosa et al. (2004)***; Wee et al. (2014); **Yilmaz et al. (2009)***
	Mode of birth	10	Elbohoty et al. (2012); El-Refaie et al. (2012); Sosa et al. (2004); Sekhavat & Behdad (2009); Khooshideh & Sharhriari (2009); Shahriari & Khooshideh (2007); **Sharma et al. (2004)***; Tsui et al. (2004); Wee et al. (2014); Yilmaz et al. (2009)
Neonatal effects	Fetal heart rate	7	Blair et al. (2005); Elbohoty et al. (2012); Nelson & Eisenach (2005); **Sekhavat & Behdad (2009)***; Tsui et al. (2004); Wee et al. (2014); Yilmaz et al. (2009)
	Apgar scores	13	Abdollahi et al. (2014); Blair et al. (2005); Elbohoty et al. (2012); El-Refaie et al. (2012); Khooshideh & Sharhriari (2009); Nelson & Eisenach (2005); Sekhavat & Behdad (2009); Shahriari & Khooshideh (2007); Sosa et al. (2004); Tsui et al. (2004); **Wee et al. (2014)****; **Weissman et al. (2009)****; Yilmaz et al. (2009)
	Arterial cord blood pH	5	Blair et al. (2005); El-Refaie et al. (2012); Sosa et al. (2006; 2004); Tsui et al. (2004); Wee et al. (2014)
	Naloxone use	6	Blair et al. (2005); Elbohoty et al. (2012); El-Refaie et al. (2012); Sekhavat & Behdad (2009); Sosa et al. (2004); Wee et al. (2014)
	Nursery admission	5	Elbohoty et al. (2012); El-Refaie et al. (2012); Sosa et al. (2004); Tsui et al. (2004); Yilmaz et al. (2009)
Neonatal effect	Neurologic & adaptive capacity scores	2	Blair et al. (2005); Sosa et al. (2004)
	Breastfeeding	1	Wee et al. (2014)

*Studies that examined the theme as the primary outcome. **Studies reported to be powered to examine more than one primary outcome.

2.2.1 Analgesic effects

When maternal analgesic effects were examined, four sub-themes emerged (treatment regimen, pain intensity, cross-over to epidural, and satisfaction with treatment). Only two of the five studies that investigated the use of fentanyl had a primary outcome to examine analgesic effect through the measurement of pain intensity (Table 2.1a). Whereas seven of the 15 studies that examined pethidine had a primary outcome to examine pain intensity (Table 2.1b). All studies that examined analgesic efficacy did so by measuring changes to pain intensity assessed by VAS, VRS or NRS (Tables 2.2a,b,c).

All studies used different parameters for conducting power calculations to assess outcome measures, and sample sizes required ranged from 20 to 2703 participants (Tables 2.3a,b,c report primary outcome and sample size calculations). No studies had primary outcomes that examined maternal satisfaction with treatment or cross-over to epidural. As seen in Tables 2.2a,b,c dosage regimens differed depending on the route of administration and the study aim. These differences in research design may have contributed to the different results that have been summarised in Tables 2.2a.b.c.

2.2.1.1 Treatment regimen

Drug protocols for all 20 studies were examined to identify dosage regimens used. All studies that investigated the use of fentanyl in labour, examined i.v. administration, except for Fleet et al. (2014) that studied the effects of s.c. fentanyl administration. In comparison, six of the 15 studies that examined pethidine use investigated the i.m. route (Table 2.2b), while seven studies looked at i.v. pethidine administration (Table 2.2c). All 20 studies reported different dosage regimens, with respect to initial dose, timing, amount of subsequent dose/s, maximum hourly dose and maximum total dose (Tables

2.2a,b,c). For example, the bolus dose of i.v. fentanyl ranged from 25 to 100μg and timing ranged from 25 μg/ hour to 20–50 μg/ 3–10 minutes through the use of i.v. PCA (Table 2.2a). Similarly, when the effects of pethidine were studied, the i.m. dosage varied between 50 mg/4 hours to 150 mg/2 hours (Table 2.2b), i.v. pethidine bolus doses ranged between 49.5 and 100 mg and i.v. PCA was set at 5–15 mg with a 10-minute lockout (Table 2.2c). Consequently, because of the differences in dosage regimens, the following discussions on maternal and neonatal effects will be based on drug administration route and dosage received.

2.2.1.2 Pain intensity

The lack of consistency among studies also was seen when pain intensity was investigated. Studies measured pain scores at different time intervals, used different tools and reported results differently (Tables 2.2a,b,c). For example, Douma et al. (2010) administered an i.v. fentanyl 50 μg bolus dose before setting the PCA to 20 μg with a 5-minute lockout (no maximum dose specified) and measured pain intensity using the VAS; while Marwah et al. (2012) used an i.v. fentanyl PCA 25–50 μg/3–6-minute lockout (max 1000–1500 μg/4 h) and measured pain levels using the VRS. Therefore, it is not known whether the discrepancies in pain scores (mean 1.4 cm at 1 h and 2.7 at 1 h, retrospectively) were due to differences in drug regimen, mode of measurement and/or some other factor.

Despite these differences, all fentanyl studies that examined pain intensity at 1 hour post-treatment reported clinically significant reductions in pain scores, yet all these studies reported different reductions over different time-points (Table 2.2a). For example, while the study undertaken by Shoorab et al. (2013) used the lowest i.v. fentanyl bolus dose, prescribed in two 25 μg doses with an interval of 1 hour (50 μg

total maximum dose), the study reported the greatest reduction of pain score at 1 hour. In addition, pain scores remained below baseline for 3 hours post-treatment (Table 2.2a). In contrast, a higher bolus dose of i.v. fentanyl (50 µg) and i.v. PCA 20 µg/5-min lockout used in the study by Douma et al. (2010), resulted in a significant reduction in pain score at 1 hour, but pain scores returned to baseline by 3 hours of treatment (Table 2.2a).

The majority of studies that examined the analgesic effect of pethidine also reported significant reductions in pain scores (Tables 2.2b,c). However, findings are difficult to interpret due to the differences in treatment regimens and timing of assessment. For example, when i.m. pethidine was studied using a fixed 100 mg/2 mL dose, a median decrease of 1.1 cm was seen at 30 minutes post-treatment (Tsui et al. 2004). Whereas, the individualised doses of 1mg/kg with 25mg promethazine resulted in a reduction of 2.4cm at 1 hour (Shahriari & Khooshideh 2007).

The one study that examined the effect of i.v. pethidine on labour duration for women experiencing labour dystocia reported the greatest reduction in pain scores (El-Refaie et al. 2012), despite the study using the lowest i.v. pethidine dose (50 mg maximum total dose) (Table 2.2c). In contrast, Blair et al. (2005) reported increased pain scores post-treatment with pethidine (Table 2.3c). This result may be related to adequate analgesia not being achieved prior to the commencement of i.v. PCA as only a small (15 mg) bolus dose was administered (Table 2.2c).

Table 2.2a   Fentanyl dosage administered and analgesic effect

Author/date	Treatment regimen	Total dose	Tool	Pain score change (↓/↑)	Comments
Fleet et al. (2014)	s.c. fentanyl 200µg bolus PRN 50µg/ 15min Max 200µg/h	mean 251µg (±81µg)	NRS	↓1.2cm at 30min	This pilot study used a small convenience sample (n=10) to examine analgesia effect. Treatment duration was not reported. Dosage regimen was based on the current practice of some SA maternity units.
Douma et al. (2010)*	i.v. fentanyl 50µg bolus PCA 20µg/ 5min lockout Max 240µg/h	mean 632µg (±263µg)	VAS	↓1.4cm at 1h ↓0.9cm at 2h ↓0.1cm at 3h	Mean treatment duration 3.3h (SD 1.7h). Pain scores were assessed for 3h post-treatment. Pain scores return to baseline within 3h for all treatment groups.
Halpern et al. (2004)	i.v. fentanyl 100µg over 5min (+50µg/ 5min) PCA 25 - 50µg/ 10min lockout Max n/a	median 940µg IQR (350–1625µg)	VAS	↓1st stage ↓2nd stage	After the 100µg bolus, additional 50µg were repeated every 5min until adequate pain relief was achieved and PCA commenced. PCA dose was increased or decreased at the discretion of the anaesthetist. Treatment duration was not reported. Median pain scores were reported for each time interval (before analgesia, first stage of labour, and second stage of labour).
Marwah et al. (2012)*	i.v. fentanyl PCA 25-50µg/ 3-6min lockout Max 1000-1500µg/ 4h	mean 1,216µg (±1,347µg)	VRS	↓2.7cm at 1h ↓3.5cm at 4h	Mean treatment duration 4.7h (SD 4.7h). Moderate reductions in pain scores were reported throughout the duration of labour. Although pain scores increased with the progress of labour, especially after 5–6 h.
Shoorab et al. (2013)	i.v. fentanyl 25µg/h (0 & 60 min) Max 50µg/h	50µg	VRS	↓5cm at 1h ↓4cm at 2h ↓3cm at 3h	This study examined a fixed dosage regimen of 50µg fentanyl, prescribed in two 25µg doses with an interval of 1h.

* Studies that examined analgesic effect measured by pain scores as the primary outcome, n/a outcome not reported

Table 2.2b   Intramuscular pethidine dosage administered and analgesic effect

Author/date	Treatment regimen	Total dose	Tool	Pain score change (↓/↑)	Comments
Abdollahi et al. (2014)	i.m. pethidine 50 mg Max 50 mg	50mg	VAS	n/a*	A single fixed i.m. dose was administered. All women were also administered promethazine and hyoscine (dose not reported). Pain score was assessed only post-birth. The average labour pain score assessed was 9.6 out of 10.
Khooshideh & Sharhriari (2009)	i.m. pethidine 50 mg Max 50 mg/4 h	50mg	VAS	↓2 cm at 10 min ↓2 cm 1 h	No women received a 2nd dose as treatment was withheld when cervical dilatation was 8 cm.
Sekhavat & Behdad (2009)	i.m. pethidine 50 mg/4 h additional 25 mg after 4 h Max 75 mg/4 h	n/a	n/a	n/a	16% of women received a 2nd dose of pethidine.
Shahriari & Khooshideh (2007)*	i.m. pethidine 1 mg/kg + 25 mg promethazine Max 200 mg	n/a	VAS	↓2.4 cm at 1 h	VAS pain scores were reported to be taken every 15 min until delivery. Data were only reported for the mean VAS score at 60 min.
Tsui et al. (2004)*	i.m. pethidine 100 mg/2 mL Max 100 mg	100mg	VAS	↓1.1 cm at 30 min	A single fixed dose was administered. In the same time period a median increase of 0.4 cm was observed in the placebo group.
Wee et al. (2014)*	i.m. 150 mg/2 h + 10 mg metoclopramide Max 300 mg/2 h	n/a	VAS	↓1.3 cm at 30 min ↓1.3 cm at 1 h ↑ at 3 h	23% of women received a 2nd dose. Dosage regimen reported to be based on the current practice of i.m. pethidine administration in the UK.

* Studies that examined analgesic effect measured by pain scores as the primary outcome, n/a outcome not reported

Table 2.2c   Intravenous pethidine dosage administered and analgesic effect

Author/ date	Treatment regimen	Total dose	Tool	Pain score change (↓/↑)	Comments
Blair et al. (2005)*	i.v. pethidine PCA 15 mg/10-min lockout Max n/a	n/a	VAS	↑ at all-time points	Mean treatment time of 2.4 h (SD 1.2 h). Data for pre- and post-treatment scores were only displayed graphically. Median pain scores shown to increase from baseline at each time-point.
Douma et al. (2010)*	i.v. pethidine 49.5 mg bolus PCA 5 mg/10-min lockout Max 200 mg	mean 133 mg (±50 mg)	VAS	↓0.8 cm at 1 h ↓0.6 cm at 2 h ↓0.2 cm at 3 h	Mean treatment time of 3.1 h (SD 2.0). No participants reached the max dose limit of 200 mg in a 5 h timeframe. Pain scores returned to baseline within 3 h for all treatment groups.
Elbohoty et al. (2012)*	i.v. pethidine 50 mg/10 mL normal saline given over 10 min Max n/a	n/a	VAS	↓1.7 cm at 15 min ↓1.5 cm at 1 h ↓0.8 cm at 2 h ↓0.2 cm at 3 h ↑ 0.4 cm.at 4 h	Further doses could be administered every 4 h until onset of second stage of labour. 20% of women received a 2nd dose. Pain intensity was recorded for the first 4 h of treatment.
El-Refaie et al. (2012)	i.v. pethidine 50 mg/10 mL isotonic saline Max 50 mg	50 mg	VAS	↓0.6 cm at 15 min ↓4.4 cm at 30 min ↓6.2 cm at 1 h ↓5.2 cm in 2nd stage of labour	A single fixed dose was administered. Participants were excluded if they requested pain relief prior to randomisation. Treatment was administered for labour dystocia not for pain relief.
Nelson & Eisenach (2005)*	i.v. pethidine 50 mg bolus Max 50 mg	50mg	VRS	↓2 cm at 15 min	A single fixed dose was administered. Pain score was only recorded at 15 min post-treatment.
Sharma et al. (2004)	i.v. pethidine 50 mg bolus PCA 10–15 mg/10-min lockout or i.v. 50 to 75 mg boluses/2 h Max 400 mg/6 h	n/a	VAS	↓5cm in 1st stage labour	Duration of treatment not reported. Timing of pain scores not stated.
Sosa et al. (2004; 2006)	i.v. pethidine. 100 mg/50 mL saline solution over 15 min Max 100 mg	100mg	VAS	↓at 15 min ↓at 30 min ↓at 1 h ↓in 2nd stage of labour	A single fixed dose was administered. Pain scores were categorised as mild, moderate or severe. Pethidine produced lower severe pain scores at all time-points when compared to placebo.

Author/ date	Treatment regimen	Total dose	Tool	Pain score change (↓/↑)	Comments
Weissman et al. (2009)	i.v. pethidine 50 mg + 25 mg promethazine Max n/a	n/a	NRS	↓2 cm at 30 min	Observations recorded at 30min. Not reported if further doses administered.
Yilmaz et al. (2009)	i.v. pethidine 50mg over 2 min Max 50mg	50mg	n/a	n/a	A single fixed dose was administered. Pain scores were not undertaken.

* Studies that examined analgesic effect measured by pain scores as the primary outcome, n/a outcome not reported

Table 2.3a   Fentanyl sample size requirement base on power analysis

Author/date	Primary outcome	Sample size requirement
Fleet et al. (2014)	n/a	206 parturients to achieve a power of 0.9 with a confidence level of 0.95 and a 0.05 margin of error.
Douma et al. (2010)	To compare the analgesic efficacy of i.v. PCA fentanyl, pethidine, remifentanil, measured by a difference in VAS pain scores	180 parturients (60/group) to detect a difference of 10% (1.0 cm) in VAS pain scores to achieve a power of 0.95 with a 0.05 margin of error.
Halpern et al. (2004)	The incidence of caesarean section in each treatment group.	485 parturients to observe a 5% (absolute) reduction in caesarean section rate to 6%.and achieve a power of 0.8.
Marwah et al. (2012)	To compare the analgesic efficacy of i.v. fentanyl with remifentanil.	102 charts (51 charts/group) to detect a difference of 1.3 cm in verbal pain scores to achieve a power of 0.8 power with a 0.05 margin of error.
Shoorab et al. (2013)	To examine the effect of i.v. fentanyl on the duration of the active phase of labour.	70 parturients based on results from a pilot study of 10 parturients, effect size was obtained at 0.4 hours to achieve a power of 0.80 and confidence level of 0.95.

n/a = not reported

Table 2.3b   Intramuscular pethidine sample size requirement base on power analysis

Author/date	Primary outcome	Sample size requirement
Abdollahi et al. (2014)	n/a	n/a
Khooshideh & Sharhriari (2009)	Duration of labour.	106 parturients (53/group) to detect a 30-min difference in labour duration to achieve a power of 0.80 at a 0.05 significant level.
Sekhavat & Behdad (2009)	n/a	n/a
Shahriari & Khooshideh (2007)	To compare analgesic effect of i.m. pethidine with i.v. remifentanil.	n/a
Tsui et al. (2004)	To detect a difference in VAS pain intensity score after 30 min.	112 parturients (56/group) to detect a 1.3 cm (SD 2.8 cm), between-group difference in VAS pain scores at 30 min, to achieve a power of 0.90 at a 0.05 significant level.
Wee et al. (2014)	Pain relief at 60 min and over 3 h as measured by a change in the VAS pain intensity score.	406 parturients (203/group). Researchers reported this would detect reductions of "around 50%" in Apgar scores at 1 minute and achieve a power of 0.9.

n/a = not reported

Table 2.3c   Intravenous pethidine sample size requirement base on power analysis

Author/date	Primary outcome	Sample size requirement
Blair et al. (2005)	n/a	20 parturients to detect a difference of 2.0 cm (SD 2.1 cm) in VAS for overall pain score and achieve a power of 0.85
Elbohoty et al. (2012)*	To examine the efficacy of the drug to provide analgesia, as measured by a change in the VAS pain intensity score at 15 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after administration.	100 parturients (50/group) to identify a group difference in pain score of 2.1 cm (SD 1.9 cm) and achieve a power of 0.80 and significance level of 0.05, based on the findings of their pilot study.
El-Refaie et al. (2012)	Duration of labour (time from the beginning of the intervention to the time of expulsion of the fetal head) and neonatal acid-base balance in arterial and venous umbilical cord blood samples.	220 parturients to detect a 60 min (SD 158 min) reduction in the length of labour to achieve a power of 0.80, and significance level of 0.05, based on a previous report of the length of labour in a similar population of women.
Nelson & Eisenach (2005)	To detect a 1.4 difference in verbal pain scores	n/a
Sharma et al. (2004)	To evaluate the effects of epidural analgesia during labour on the rate of caesarean section.	2,703 parturients to detect an increase of 3% in the caesarean section rate (from 7% to 10%) to achieve a 0.80 power with less than 0.05 significance.
Sosa et al. (2004; 2006)	The effect pethidine had on labour duration for women diagnosed with labour dystocia.	400 parturients (200/group) to detect a 30 min (SD 110 min) difference in labour duration to achieve a 0.80 power with less than 0.05 significance
Weissman et al. (2009)	To examine the effects of pethidine on maternal heart rate variability.	25 parturients to detect a group difference of 20% in Apgar scores achieved 0.80 power.
Yilmaz et al. (2009)	To examine the duration of first stage labour, second stage labour, and total labour duration from treatment to birth.	39 parturients (13/group) to detect a mean injection-to-delivery interval of 412 vs 194 min, (SD 158 min), power of 0.90 at a 0.05 significant level based on a study by Sharma et al. (2001).

n/a = not reported

2.2.1.3 Satisfaction with treatment

Participant satisfaction with treatment was examined in seven of the 20 studies reviewed (Table 2.4). All studies used different tools and/or times to measure this outcome (Table 2.4). In addition, some studies used the same tool to measure several outcomes. For example, Blair et al., (2005) assessed satisfaction, nausea, anxiety, sedation and pain scores using the VAS (0–10) every 30 minutes during labour and at 2 hours post-birth.

All studies that compared satisfaction levels of the interventions with a placebo reported increased satisfaction with the intervention. Whereas when pethidine was compared to different opioids, satisfaction levels were either lower or equivalent to the comparator (Table 2.4).

Table 2.4 Comparison between groups for satisfaction with treatment

Author/date	Treatment	Tool	Timing of assessment	Satisfaction level	Comments
Blair et al. (2005)	i.v. pethidine	VAS 0–10 (0 represented completely unsatisfied and 10 represented completely satisfied)	Every 30 min during labour and at 2 h post-birth	↓	Satisfaction scores were higher in the remifentanil group at 60 min (median (IQR [range]) 8.0 (7.5–9.0 [4.0–10.0])) than in the pethidine group (6.0 (4.5–7.5 [2.0–10.0]; p=0.029). Overall satisfaction was greater in the remifentanil group (p=0.001).
Halpern et al. (2004)	i.v. fentanyl	VAS 0–10 (0 represented completely unsatisfied and 10 represented completely satisfied)	After birth	↓	Satisfaction scores were lower for women in the fentanyl group (6.8; SD 2.7) compared to women in the epidural group (7.7; SD 2.8) (p=0.02).
Khooshideh & Sharhriari (2009)	i.m. pethidine	5-point descriptive scale (excellent, very good, good, fair or poor)	Within 24 h of birth	=	Approximately 50% of women in the i.m. pethidine group and tramadol groups rated analgesia as good to excellent. Whereas 35% of women in the pethidine group reported dissatisfaction.
Shahriari & Khooshideh (2007)	i.m. pethidine	5-point descriptive scale (excellent, very good, good, fair or poor)	After birth	↓	35% of women rated i.m. pethidine as good to excellent compared to 95% of women in the remifentanil group (p=0.000).
Shoorab et al. (2013)	i.v. fentanyl	n/a	n/a	↑	The majority (68%) of participants administered i.v. fentanyl reported higher levels of satisfaction, 8% reported little satisfaction. However, the assessment tool, timing and placebo group data were not reported.
Tsui et al. (2004)	i.m. pethidine	5-point scale (1=totally dissatisfied and 5=very satisfied)	At 30 min post-treatment	↑	The pethidine group reported greater satisfaction, although the median score was 2 (IQR 2–3) compared to 1 (IQR 1–2) in the placebo group. 8% of women in the pethidine group were totally dissatisfied (score =1), compared with 60% in the control group. No women reported a score of 5.
Wee et al. (2014)	i.m. pethidine	four categories (very dissatisfied or dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied)	n/a	=	34% of women in the i.m. pethidine group were very satisfied compared to 45% of women in the diamorphine group (OR 0.64 (95% CI 0.31 to 1.29).

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a= outcome not reported

2.2.1.4 Rescue analgesia/cross-over to epidural

Cross-over to epidural was reported in five of the 20 studies reviewed (Tables 2.1a,b). No studies under review examined epidural cross-over as a primary outcome and one study excluded participants from analysis if they crossed over to an epidural or requested alternative analgesia (Nelson & Eisenach 2005). Douma et al. (2010) was the only study to directly compare fentanyl with pethidine and reported fewer women in the i.v. PCA fentanyl group, crossed over to epidural compared to women that received i.v. PCA pethidine (Tables 2.5a,c). The majority of studies reported no significant difference between either fentanyl or pethidine and their comparator for cross-over to epidural block (Tables 2.2a,b).

While Tsui et al. (2004) reported similar epidural rates between the i.m. pethidine and placebo groups, it should be noted that women in the placebo group were able to receive rescue analgesia with i.m. pethidine after 30 minutes of treatment. As seen in Table 2.2b Tsui et al. (2004) reported that 48% of women in the placebo group crossed over to receive i.m. pethidine within 75 minutes (95% CI 54 to 95 minutes) of treatment.

2.2.2 Maternal physiological effects

Three sub-themes were identified relating to maternal physiological effects (Tables 2.1a,b). Fifteen of the 20 studies investigated sedation levels, and/or emesis and maternal vital signs (respiration rate, pulse oximetry and blood pressure [MAP]). Few studies examined all vital signs (Tables 2.5a,b,c) and most studies recorded observations at different time-points. Labour duration was investigated in 14 of the 20 studies to determine potential treatment effects on uterine activity, and 13 studies examined mode of birth post-treatment (Tables 2.4a,b,c). Caution needs to be taken when interpreting these results as most studies were not powered for these outcomes (Tables 2.1a,b).

2.2.2.1 Sedation levels, emesis and vital signs

The majority of studies that examined the effects of fentanyl on maternal sedation levels, vomit scores, blood pressure (MAP), pulse, and respiration rate, reported no significant changes or adverse outcomes (Table 2.5a). In particular, fentanyl appeared to result in minimal if any adverse effects when vital signs were compared to women who received a placebo or no pharmacological pain relief (Fleet et al. 2014; Shoorab et al. 2013). In studies that examined i.v. fentanyl compared to i.v. remifentanil, women administered fentanyl experienced less sedation (Marwah et al. 2012) and fewer episodes of oxygen desaturations (Douma et al. 2010; Marwah et al. 2012). No significant differences were noted between groups for nausea, vomiting, hypotension or bradycardia (Table 2.5a).

When pethidine was compared to placebo significantly higher rates of nausea (El-Refaie et al. 2012), drowsiness (El-Refaie et al. 2012; Tsui et al. 2004; Yilmaz et al. 2009), vomiting and dizziness (Yilmaz et al. 2009) were observed (Tables 2.5b,c). Although when pethidine was compared to other opioids, outcomes were similar (Tables 2.5b,c). While nausea and vomiting are commonly seen with the use of opioids, it is less often reported if symptoms had been treated with an anti-emetic, which may further contribute to adverse effects such as sedation. Four studies reported pethidine was administered with a prophylactic anti-emetic, either metoclopramide or promethazine (Abdollahi et al. 2014; Shahriari & Khooshideh 2007; Wee et al. 2014; Weissman et al. 2009). Both metoclopramide and promethazine are known to produce adverse effects, such as sedation and dizziness (Tan et al. 2010), yet only two studies reported outcomes for vomiting and sedation (Shahriari & Khooshideh 2007; Wee et al. 2014).

2.2.2.2 Labour duration

While four studies investigated the effects of fentanyl on labour duration, no comparisons could be made among the studies as each used a different research protocol (Table 2.5a). Inconsistent results were observed in studies that looked at the effects of pethidine on labour duration, although the majority of studies reported no statistical differences among groups (Abdollahi et al. 2014; Blair et al. 2005; El-Refaie et al. 2012; Sekhavat & Behdad 2009; Shahriari & Khooshideh 2007; Sosa et al. 2004).

2.2.2.3 Mode of birth

Of the 20 studies reviewed, only two studies noted differences in mode of birth between treatment groups. Douma et al. (2010) found that statistically more women administered i.v. PCA fentanyl (85%) achieved a spontaneous vaginal birth compared to women administered i.v. PCA pethidine (69%), although no significant differences were found in instrumental and LSCS rates. In contrast, Fleet et al. (2014) reported women who received no pharmacological pain relief were more likely to achieve a spontaneous vaginal birth (94.9%), compared to women who received s.c. fentanyl only (82.7%) or s.c. fentanyl and nitrous oxide and oxygen (87.2%) $p < 0.004$.

Table 2.5a   Subcutaneous and intravenous fentanyl effects on maternal epidural use, emesis, sedation level, vital signs and labour duration

Author/ date	Treatment	EDB	Emesis	Sedation level	Vital signs			Oxygen therapy	Labour duration	Birth mode	Comments
					BP	HR	RR				
Fleet et al. (2014)	s.c. fentanyl	n/a	=	=	=	=	=	n/a	↑2h	= SVB ↑ Assisted = LSCS	No women required an anti-emetic and no sedation was observed. Labour duration was longer in the s.c. fentanyl groups compared to women who used no pharmacological pain relief (p<0.001).
Douma et al. (2010)	i.v. PCA fentanyl	↓	=	=	=	=	=	=	=	↑ SVB = Assisted = LSCS	Epidural use was less for women in the fentanyl group compared to the pethidine group (15% vs 34%; p<0.05). One woman in the fentanyl group required oxygen supplementation. More women in the fentanyl group achieved a SVB (85% vs 69%; p<0.05).
Halpern et al. (2004)	i.v. PCA fentanyl	n/a*	↑	↑	n/a	n/a	=	n/a	↓ 23min	= SVB = Assisted = LSCS	43% of women in the fentanyl group crossed over to epidural. Fentanyl compared to epidural resulted in increased anti-emetic use (17% vs 6.4%; p=0.01) and increased sedation (39% vs 5%; p=0.001). One woman in the fentanyl group experienced respiratory depression, it was not reported if treatment was required. Labour duration was shorter in the fentanyl group (p=0.02).
Marwah et al. (2012)	i.v. PCA fentanyl	=	=	↓	=	=	↓	↓	n/a	n/a	No significant difference was seen between the fentanyl and remifentanil groups for cross-over to epidural (13.7% vs 6.4%; p=0.32). Less sedation (12.5% vs 44.2%; p=0.001), less incidents of oxygen desaturations (<90%) (2% vs 13%; OR 7.32; 95% CI, 0.85 to 63.3) and less oxygen supplementation (17.6% vs 31%) was observed in the fentanyl group.
Shoorab et al. (2013)	i.v. fentanyl	n/a	=	n/a	=	↓	=	n/a	↓2h	n/a	A reduced HR at 30 min post-treatment (88 bpm SD14) was observed in the fentanyl group compared to 100 bpm (SD13) in the placebo group (p=0.001). Fentanyl resulted in a reduction in mean labour duration (p=0.001).

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, n/a* not applicable, SVB spontaneous vaginal birth, Assisted (ventouse or forceps), LSCS lower segment caesarean section

Table 2.5b　　　**Intramuscular pethidine effects on maternal epidural use, emesis, sedation level, vital signs and labour duration**

Author/ date	Treatment	EDB	Emesis	Sedation level	Vital signs			Oxygen therapy	Labour duration	Birth mode	Comments
					BP	HR	RR				
Khooshideh & Sharhriari (2009)	i.m. pethidine	n/a	↑	↑	=	=	=	=	↑0.8h	= SVB = Assisted = LSCS	Pethidine compared to tramadol resulted in higher incidence of nausea and vomiting (35% vs 15%, p= 0.003), drowsiness (80% vs 29%; p< 0.0001) and labour duration (p< 0.0001).
Shahriari & Khooshideh (2007)	i.m. pethidine	n/a	=	=	=	=	=	n/a	=	= SVB = Assisted = LSCS	A prophylactic anti-emetic was administered to all women.
Sekhavat & Behdad (2009)	i.m. pethidine	n/a	n/a	n/a	n/a	n/a	n/a	n/a	=	= SVB = Assisted = LSCS	There was no significant different between the pethidine and placebo groups for length of labour.
Tsui et al. (2004)	i.m. pethidine	=	n/a	↑	n/a	n/a	n/a	=	n/a	= SVB = Assisted = LSCS	12% of women in the pethidine group crossed over to . 48% of women in the placebo group required rescue analgesia with pethidine. Sedation was higher in the pethidine group (64% vs 12%; RR 5.33 (1.77 to 16.05)).
Wee et al. (2014)	i.m. pethidine	=	↑	=	n/a	n/a	n/a	=	↓1.4h	= SVB = Assisted = LSCS	18% of women in the pethidine group crossed over to EDB compared to 24% in the diamorphine group (p=0.07). A prophylactic anti-emetic was administered to all women. Pethidine resulted in increased vomiting at 30min (1% vs 5%; p=0.01) and reduced labour duration (p=0.001).

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, SVB spontaneous vaginal birth, Assisted (ventouse or forceps), LSCS lower segment caesarean section

Table 2.5c   Intravenous pethidine effects on maternal epidural use, emesis, sedation level, vital signs and labour duration

Author/ date	Treatment	EDB	Emesis	Sedation level	Vital signs			Oxygen therapy	Labour duration	Birth mode	Comments
					BP	HR	RR				
Douma et al. (2010)	i.v. PCA pethidine	↑	=	=	=	=	=	=	=	↓ SVB = Assisted = LSCS	34% of women in the pethidine group cross-over to EDB compared to 15% in the fentanyl group (p<0.05). Four women required oxygen. Fewer women in the pethidine group achieved a SVB 69% vs 85%; p<0.05).
Blair et al. (2005)	i.v. PCA pethidine	n/a	n/a	=	=	=	=	=	=	n/a	No significant differences were seen between the pethidine and remifentanil groups.
Sharma et al. (2004)	i.v. PCA & i.v. pethidine	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↓0.6 h in 1st stage ↓13min in 2nd stage	= SVB = Assisted = LSCS	Pethidine resulted in shorter labour compared to the epidural group (p<0.001).
Elbohoty et al. (2012)	i.v. pethidine	n/a	↑	n/a	↑	↑	n/a	n/a	↑3.9h	= SVB = Assisted = LSCS	64% of women experienced one or more incidents of dizziness, blurred vision, vomiting, dyspnea, tachycardia, change in BP compared to no women in the paracetamol group. The pethidine group experienced significantly longer labour (p=0.01).
El-Refaie et al. (2012)	i.v. pethidine	n/a	↑	↑	n/a	n/a	n/a	n/a	=	= SVB = Assisted = LSCS	Pethidine compared to placebo, resulted in higher levels of nausea (25.8% vs 14.2%; p=0.04), vomiting (14.2% vs 5.8% p=0.05) and drowsiness (39.2% vs 4.2% p<0.001).
Nelson & Eisenach (2005)	i.v. pethidine	n/a	n/a	=	n/a	n/a	n/a	n/a	n/a	n/a	Both pethidine and butorphanol groups were observed to experience increased sedation levels compared to pre-treatment levels (p<0.05).

Author/ date	Treatment	EDB	Emesis	Sedation level	Vital signs			Oxygen therapy	Labour duration	Birth mode	Comments
					BP	HR	RR				
Sosa et al. (2004)	i.v. pethidine	n/a	↑	n/a	n/a	n/a	n/a	n/a	n/a	= SVB = Assisted = LSCS	Pethidine resulted in higher levels of vomiting (14.6% vs 7.4% RR1.97 [1.09–3.55]) and dizziness (27.8% vs 5.9% (RR 4.68 [2.59–8.46]) when compared to placebo.
Weissman et al. (2009)	i.v. pethidine	n/a	n/a	n/a	=	↑	=	=	n/a	n/a	Maternal heart rate increased in women who received pethidine (83.9 ± 13 beats/min before analgesia vs 88.4 ± 13.7 after, p< 0.01). No episodes of low oxygen saturation were observed.
Yilmaz et al. (2009)	i.v. pethidine	n/a	↑	n/a	n/a	↓	n/a	n/a	↓1.2 h	= SVB = Assisted = LSCS	Pethidine compared to placebo resulted in more vomiting and dizziness (22.9% vs 4.1%; p<0.05 and 31.3% vs 6.1%; p<0.001). Labour duration was shorter in the pethidine group (p<0.001).

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= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, SVB spontaneous vaginal birth, Assisted (ventouse or forceps), LSCS lower segment caesarean section

2.2.3 Neonatal effects

When neonatal effects were investigated, seven sub-themes were identified (fetal heart rate [FHR], Apgar scores, arterial cord pH, naloxone use, nursery admission, neurologic and adaptive capacity scores and breastfeeding behaviour). No studies looked at all outcomes (Tables 2.6a,b,c). The majority of studies examined neonatal effects as a secondary outcome (Tables 2.1a,b), and therefore may not have been adequately powered to detect a significant difference between groups.

2.2.3.1 Fetal heart rate

In total, nine studies examined FHR to assess potential treatment effects (Tables 2.1a,b). The majority of studies reported no statistically significant differences between groups when FHR was observed (Douma et al. 2010; Elbohoty et al. 2012; Halpern et al. 2004; Khooshideh & Sharhriari 2009; Nelson & Eisenach 2005; Tsui et al. 2004; Wee et al. 2014). Sekhavat and Behdad (2009) was the only study to examine FHR as a primary outcome and observed less beat to beat variability (absent or less than 5 beats per minute) (28% vs 5%, $p<0.05$) and fewer accelerations (37.3% vs 17.3% $p<0.05$) when compared to placebo. Despite this finding there were no reported differences in adverse effects for the neonates (Table 2.6b).

2.2.3.2 Arterial cord blood pH

Another measure of fetal wellbeing is the assessment of arterial cord pH as low arterial cord blood pH is associated with poor neonatal outcomes. Seven of the 20 studies examined this variable (Tables 2.1a,b). For the majority of studies, arterial cord blood pH was reported to be similar between groups (Tables 2.6a,b,c). However, Sosa et al. (2006) undertook a secondary data analysis of this outcome from a previous RCT (Sosa et al. 2004) and found a higher incidence of acidosis in the pethidine group (pH < 7.12; OR 8.59 [3.29, 22.46]) compared to the placebo group (Table 2.6c). Although the

observed number of events were relatively low (14.6%), the investigators reported that the highest frequency of acidosis was encountered when the pethidine-delivery interval was 5 hours (Sosa et al. 2006). It was noted that Sosa et al. (2004; 2006) did not report maternal oxygen saturation or FHR to further explore the possible association between pethidine and neonatal acidosis.

2.2.3.3 Apgar scores at 1 and 5 minutes

Apgar scores taken at 1 and 5 minutes are the most common measures to assess neonatal vital signs and were reported in 18 of the 20 studies to explore treatment effects on neonatal outcomes (Tables 2.6a,b,c). Only two studies (Wee et al. 2014; Weissman et al. 2009), examined Apgar scores as a primary outcome.

The majority of studies reported Apgar scores were comparable between groups (Tables 2.6a,b,c). Although, both i.v. fentanyl and i.v. pethidine were reported to result in more Apgar scores <7 at 1 minute compared to the comparator, no significant differences were seen at 5 minutes (Elbohoty et al. 2012; Marwah et al. 2012). Whereas, Sosa et al. (2004) reported that Apgar scores for term neonates in the pethidine group were lower at 1 and 5 minutes post-birth when compared to placebo (Table 2.6c).

2.2.3.4 Nursery admission

Nursery admission was discussed in six studies that investigated neonatal wellbeing as a secondary outcome (Tables 2.1a,b). No statistical differences were reported between groups for nursery admissions for the majority of studies (Tables 2.6a,b,c). Sosa et al. (2004) was the only study to report a significant difference in nursery admissions for the i.v. pethidine group compared to placebo (9% vs 2% respectively; RR 4.68 [1.62–13.52]), although the total number of admissions were low in both groups.

2.2.3.5 Neurologic and adaptive capacity scores

Neurologic and adaptive capacity scores (NACS) were assessed as a secondary outcome in three studies (Tables 2.1a and 2.1b). Timing of the NACS differed between groups. For example, Blair et al. (2005) observed the NACS at 30 minutes and 2 hours post-birth, Douma et al. (2010) assessed NACS at 15 minutes and 2 hours after birth, and Sosa et al. (2004) undertook the assessment at approximately 20 hours post-birth. All NACS were comparable by the end of the observation period (Tables 2.6a,b,c), including the study by Blair et al. (2005), which found significantly lower NACS for the pethidine group compared to the placebo group at 30 minutes post-birth (Table 2.6c). No explanation was provided for this observation (Blair et al. 2005).

Table 2.6a   Intrapartum administration of fentanyl - neonatal birth outcomes

Author/ date	Treatment	FHR	Apgar scores <7		Arterial cord pH	Naloxone	Nursery	NACS	Comments
			1 min	5 min					
Fleet et al. (2014)	s.c. fentanyl	n/a	=	=	n/a	↑	No admissions	n/a	8.1% of neonates were administered naloxone. No neonate experienced respiratory depression ≥5 min.
Douma et al. (2010)	i.v. PCA fentanyl	=	=	=	=	=	n/a	=	Neonatal outcome were similar to pethidine at 15 min & 2 h.
Halpern et al. (2004)	i.v. PCA fentanyl	=	↓	=	=	↑	n/a	n/a	Significantly more neonates in the fentanyl group had 1 min Apgar <7 (33 of 118 vs 21 of 121; p=0.04), but by 5 min there were very few infants with low scores in either group (5 of 118 vs 4 of 123; p=0.68). 17% of neonates in the fentanyl group were administered naloxone (p<0.001).
Marwah et al. (2012)	i.v. PCA fentanyl	n/a	↓	=	=	=	n/a	n/a	39% of neonates had an Apgar scores <7 at 1 min. No naloxone was administered & umbilical arterial cord pH was within normal range for all neonates.
Shoorab et al. (2013)	i.v. fentanyl	n/a	=	=	n/a	n/a	n/a	n/a	No differences were seen between groups for neonatal outcomes.

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, FHR fetal heart rate, NACS=Neurologic and adaptive capacity scores

Table 2.6b   **Intrapartum administration of intramuscular pethidine—neonatal birth outcomes**

Author/ date	Treatment	FHR	Apgar scores <7		Arterial cord pH	Naloxone	Nursery	NACS	Comments
			1min	5min					
Abdollahi et al. (2014)	i.m. pethidine	n/a	=	=	n/a	n/a	n/a	n/a	Apgar scores for all neonates were >8.
Khooshideh & Sharhriari (2009)	i.m. pethidine	=	=	=	n/a	n/a	n/a	n/a	Apgar scores at 1 and 5 min for all neonates were >7 at 1 and 5 mins.
Sekhavat & Behdad (2009)	i.m. pethidine	↓	=	=	n/a	=	n/a	n/a	Apgar scores were comparable between groups.
Tsui et al. (2004)	i.m. pethidine	=	=	=	=	n/a	=	n/a	No differences were observed between neonatal outcomes. One neonate from each group (pethidine and placebo) was admitted to NICU.
Wee et al. (2014)	i.m. pethidine	=	=	=	=	=	n/a	n/a	Neonates from the pethidine group were assessed as experiencing moderate or severe sedation at 2 h after birth.

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, FHR fetal heart rate, NACS=Neurologic and adaptive capacity scores

Table 2.6c   Intrapartum administration of intravenous pethidine—neonatal birth outcomes

Author/ date	Treatment	FHR	Apgar scores <7		Arterial cord pH	Naloxone	Nursery	NACS	Comments
			1 min	5 min					
Blair et al. (2005)	i.v. PCA pethidine	=	=	=	=	=	n/a	↓ 30min = at 2h	No naloxone was administered to any neonates.
Elbohoty et al. (2012)	i.v. pethidine	=	↓	=	n/a	=	=	n/a	The medium 1 min Apgar score was significantly lower in the pethidine group (6 [range 6–7] vs 7 [range 6–7]); p<0.004. No other adverse neonatal effects were observed. No neonates were admitted to nursery.
El-Refaie et al. (2012)	i.v. pethidine	n/a	=	=	=	=	=	n/a	No naloxone was administered. Two neonates in the pethidine group required admission to NICU compared to three in the placebo group.
Nelson & Eisenach (2005)	i.v. pethidine	=	=	=	n/a	n/a	n/a	n/a	No neonates in the pethidine group received an Apgar score <7 (one neonate in the butorphanol group received a score of 6 at 1 min). All neonates had Apgar scores >7 at 5 min.
Sosa et al. (2004; 2006)	i.v. pethidine	n/a	↓	↓	↓	=	↑	=	Apgar scores at 1 min (12.2% vs 3.0%; RR 4.11 [1.72–9.80]) and 5 min (2.9% vs 0.0%; RR 11.82 [0.66–210.25]) were lower in the pethidine group compared to placebo. More neonates had arterial cord pH <7.1 (14.8% vs 3.6%; RR 3.94 (1.76–8.82). and nursery admissions (9.3% vs 2.0%; RR 4.68 [1.62–13.52]) in the pethidine group. No naloxone was administered to any neonates. NACS were comparable when measured at 20 h post-birth.
Weissman et al. (2009)	i.v. pethidine	n/a	=	=	n/a	n/a	n/a	n/a	Neonatal outcomes were comparable between groups.
Yilmaz et al. (2009)	i.v. pethidine	n/a	=	=	n/a	n/a	=	n/a	No differences were observed between the pethidine and placebo groups. One neonate from the pethidine group required admission to NICU and none from the placebo.

= equivalent to comparator, ↓ decreased compared to comparator, ↑increased compared to comparator, n/a outcome not reported, FHR fetal heart rate, NACS=Neurologic and adaptive capacity scores

2.2.3.6 Breastfeeding behaviour

Only two studies under review examined possible treatment effects on neonatal breastfeeding (Fleet et al. 2014; Wee et al. 2014). Fleet et al. (2014) investigated post-hospital discharge breastfeeding rates for women who had intended to exclusively breastfeed and had either received s.c. fentanyl or no pharmacological pain relief during labour. In the study by Wee et al. (2014) a midwife assessed neonatal breastfeeding behaviour within the first 2 hours post-birth for infants whose mothers had been administered intrapartum i.m. pethidine Fleet et al. (2014) observed breastfeeding rates were similar between groups, with the majority of women (≥96%) breastfeeding their neonates at discharge. Whereas Wee et al. (2014) observed more neonates in the pethidine group experienced moderate or severe sedation at 2 hours post-birth (p=0.04). However, no statistical difference between groups was observed for time from birth to first breastfeed (1.0 h [SD1.0] pethidine group vs 1.2 h [SD1.2] diamorphine group). No other follow up data was provided for either study.

2.3 Chapter summary

Although previous systematic reviews have made recommendations to report research outcome measures consistently (Jones et al. 2012; Ullman et al. 2010), all dosage regimens and/or treatment protocols differed in the studies reviewed here. Even when examining results from studies with similar data collection tools, such as VAS pain scores, all studies reported outcome measures differently and at various time-points. It therefore is unknown if the differences in findings resulted from the various dosage regimens, populations and/or methods used. In addition, the discrepancies in study designs and small sample sizes for some outcome measures, prevented comparisons of those results among studies.

When the analgesic effect of fentanyl administered during childbirth was reviewed, all articles reported clinically important reductions of pain scores and reduced cross-over to epidural, with

few, if any, adverse effects observed for maternal physiological outcomes (Tables 2.2a and 2.5a). Findings differed when the use of pethidine was examined, dependant on the comparator. For example, the three studies that compared pethidine with placebo (El-Refaie et al. 2012; Sosa et al. 2004; Tsui et al. 2004) reported significantly greater reductions of pain scores in the pethidine groups, although the extent of the pain reductions differed (Tables 2.2b,c). It is unclear if dosage regimens and/or variations in timing of assessment contributed to these differences.

In contrast, when pethidine was compared to other opioids only one study demonstrated that pethidine produced greater reductions in pain scores (Khooshideh & Sharhriari 2009). The majority of studies reported pethidine provided less analgesic effect (Abdollahi et al. 2014; Douma et al. 2010; Shahriari & Khooshideh 2007; Wee et al. 2014) or equivalent pain reductions (Blair et al. 2005; Elbohoty et al. 2012; Nelson & Eisenach 2005). In addition, pethidine was associated with increased adverse effects (Tables 2.5a,b,c). Unlike fentanyl, there were higher rates of nausea and vomiting, drowsiness and dizziness in the pethidine groups than in the placebo groups (Tables 2.5a,b,c).

Neonatal adverse effects following the intrapartum use of either fentanyl or pethidine were rare (Table 2.6a,b,c). Few studies examined neonatal effects as a primary outcome, therefore, samples sizes may not have had the statistical power to detect differences. Sosa et al. (2004; 2006) were the only studies to report that pethidine significantly affected the majority of neonatal outcomes measured when compared to the placebo group (Table 2.6c). Nevertheless, the overall number of incidents were relatively low. In contrast, when i.v. PCA fentanyl was compared to i.v. PCA pethidine, neonatal outcomes were comparable between groups (Douma et al. 2010). No studies examined longer term effects on breastfeeding outcomes (post discharge from hospital).

Despite differences in research design, the majority of studies reported that fentanyl and pethidine produced an analgesic effect, although fentanyl appeared to result in fewer maternal and neonatal adverse outcomes. No randomised controlled trials were found that examined the use of s.c. or i.n. fentanyl in childbirth. As these modes of administration have been shown to be effective in non-obstetric populations, further research is needed to examine the potential application of these less-invasive techniques for women in labour. In particular, it is important to investigate whether the mode of administration alters analgesic effect. Therefore, this study investigated the analgesic effects of i.n. fentanyl, s.c. fentanyl and i.m. pethidine when administered during childbirth. The following chapter provides details on the research design and methods used for this Trial to address this aim.

Chapter 3   Research design and methods

In this chapter the experimental design and interventions used to investigate and compare the analgesic effect of i.n. fentanyl, s.c. fentanyl and i.m. pethidine administered during childbirth are described. Information is provided on the setting, recruitment of participants, study protocols, randomisation, allocation concealment, and ethical considerations. Furthermore, the assessment tools, data collection and management are detailed, along with the justification of the sample size and methods of data analysis.

3.1 Trial design

This multi-centred, unblinded randomised controlled trial used a 3-arm parallel group design and was undertaken in two maternity settings. Study participants were recruited between January 2011 and April 2013 until the appropriate sample size was achieved. Parturients were randomised to receive i.n. fentanyl, s.c. fentanyl, or i.m. pethidine. The outcomes were analysed by intention-to-treat.

3.2 The setting

The study was conducted at two venues: the Women's & Children's Hospital, the largest tertiary referral centre for maternal care in Adelaide, and SA and Gawler Health Services, a regional hospital in the outer northern suburbs of Adelaide, SA. The Women's & Children's Hospital birthed a total of 5,013 women in 2011 (Scheil et al. 2013). The delivery suite consisted of a 16-bed combined labour ward and high dependency unit. The Labour and Delivery Suite supported women to birth naturally, assisted, or by operative delivery, depending upon the health requirements of mother and baby. This hospital had theatres and intensive care facilities for both mother and neonate.

During the study period Gawler Health Services provided maternity services to women deemed low to moderate risk. In 2012, a total of 520 women birthed within the regional hospital (S

Angus 2013, pers. comm., 29 April). This hospital was within a rural region close to a metropolitan boundary. It received referrals from three smaller maternity units within the SA Country Health cluster. The maternity unit was staffed by two full-time obstetrics and gynaecology specialists (O&G), a senior obstetrician, midwives, and anaesthetic and paediatric staff. The staff were available on call as required to provide a 24-hour service. In addition, a community midwifery service provided assistance to women when they returned home for the postnatal period.

3.3 Recruitment

Prospective participants were identified through the antenatal clinics at the two venues, the antenatal classes, or one-to-one midwifery group practice. Posters that advertised the Trial and contact details were displayed within the hospitals (Appendix 2). All interested women were provided with an Obstetric Analgesia Information Pack that included a participant information sheet and a consent form (Appendices 3 & 4). Women were provided with details on how to obtain further information regarding the Trial, if required, prior to providing written consent to participate. Potential participants were informed that should they request to use an opioid for analgesia during labour, they had a 66% chance of being allocated to one of the fentanyl interventions, and a 33% chance of receiving pethidine as per the standard treatment of each institution.

While information was provided at the antenatal clinics, written consent was not obtained until a subsequent appointment. This allowed the women time to consider their involvement and provide consent or to obtain additional information prior to the onset of labour. Consent was obtained by the investigating researcher, which provided approval to access and record data from the women's medical records, as well as the women's participation in two follow-up questionnaires—one at 48 hours post-birth and another at 6 weeks after birth.

Written consent was sought before the women went into labour, but the participants were not randomised into the Trial until a request for an opioid was made during labour. This avoided participants being inappropriately randomised into the Trial where pain relief was not required, the woman declined inclusion, or became ineligible for the Trial.

When the woman presented in labour, the attending midwife completed a detailed history and undertook an assessment to determine the woman's suitability for opioid analgesia using the Trial's Criteria checklist (Appendix 5) and reconfirmed consent prior to participation. This assessment confirmed their eligibility to be randomised into the Trial. A final confirmation was made by the attending medical practitioner who subsequently prescribed the order following randomisation. Once the woman was randomised, her details were recorded on the Obstetric Analgesia Trial register (Appendix 6).

3.3.1 Participants - inclusion/ exclusion criteria

The sample for this study included all women who had provided written informed consent prior to the establishment of labour, and met the inclusion/exclusion criteria (Table 3.1).

Table 3.1   Inclusion/Exclusion criteria used in selecting participants

Inclusion criteria	Exclusion criteria
Birthing at term (37 to 42 weeks gestation)	Preterm labour (<37 weeks gestation)
Planned vaginal birth	Pethidine or fentanyl administered within 24 hours of active labour (regular contractions and cervical dilatation of at least 3cm)
Viable single fetus	Antenatal conditions such as, pre-eclampsia, severe bronchial asthma, a history of fits or head injuries, glaucoma, heart or liver problems, diabetes requiring medication, phaeochromocytoma
Vertex presentation	Known allergy or hypersensitivity to fentanyl or pethidine
No known medical conditions	Reliance on opioid substances
Uncomplicated pregnancy	Antidepressant use within the previous 14 days
Aged 18 years and older	Women requiring an interpreter or diagnosed with an intellectual disability
Preference not to use an epidural	

3.4 Interventions

Eligible women were randomised into one of three treatment groups:

Group 1 - Intranasal fentanyl: Participants self-administered a 54 microgram fentanyl dose, sprayed into the nose using a patient-controlled intra-nasal analgesia (PCINA) device (Go Medical Industries, Perth, Western Australia). This device had a 4-minute refill time that acted as a lockout between doses (O'Neil et al. 1997). The maximum hourly dose was 600 micrograms with a maximum total dose set at 1200 micrograms.

Group 2 - Subcutaneous fentanyl: Participants received a 200 microgram bolus dose of s.c. fentanyl. After one hour, additional 50 microgram doses could be administered every 15 minutes, as requested, up to a maximum of 650 micrograms.

Group 3 - Intramuscular pethidine: Participants received a 100 milligrams/2 mL dose of i.m. pethidine. This dose could be repeated once if requested after 3 to 4 hours, with a maximum total dose of 200 milligrams.

3.4.1 Study drug protocols

Study drug protocols were developed to ensure consistency in treatment regimens and staff were provided with training prior to commencement of the study (see Appendices 7, 8 & 9 for the complete drug protocols). Repeat in-service training sessions were held for staff working in the units during the Trial period. Members of the anaesthetic department were available at all times for consultation to support attending staff throughout the study period.

The dosage regimens used for i.m. pethidine and s.c. fentanyl were those currently used in South Australian maternity hospitals. As no protocol existed for the use of i.n. fentanyl for labour analgesia, a regimen was adapted from the i.v. fentanyl protocol used for labouring women at the Women's & Children's Hospital. This was undertaken through consultation with

the Head of the Women's Anaesthesia Department and Director of Pharmacy based on current fentanyl dosage regimens and included consideration of the bioavailability of i.n. fentanyl that has been shown to range between 55% and 89% (Christrup et al. 2008; Lim et al. 2003; Striebel et al. 1993) The treatment protocols, therefore, were considered clinically relevant to provide good external validity for this study. As such, this study compared the effectiveness of current clinical practices rather than the equipotency of each drug.

3.4.1.1 Intranasal fentanyl

The midwife drew up 600 micrograms/2 mL of intranasal fentanyl solution (Orion Laboratories Pty Ltd, Balcatta, Western Australia) and placed into the PCINA device. Tamper-proof tape (Tamper Evident Pty Ltd Cheltenham, Victoria) was fixed to the actuator and bottle of the device to both discourage and enable the detection of any tampering of the applicator once given to the woman for use. The instructions included that the atomiser was to be kept upright for the chamber to refill in a 4-minute timeframe. The midwife instructed the woman on the use of the intranasal applicator and had her verbalise her understanding prior to the first dose being administered. The woman was informed that the midwife was to be in attendance when each dose was administered. The woman was then able to self-administer doses as necessary up to a maximum 1200 micrograms with a maximum hourly dose of 600 micrograms.

3.4.1.2 Subcutaneous fentanyl

An aseptic technique was used by the midwife to insert a size 24 gauge Jelco cannula into the woman's subcutaneous tissue in the area of the subclavicular or upper pectoral region. The cannula was then secured with Opsite and an interlink bung attached. Local anaesthetic (1 mL of 1% plain lignocaine) was administered slowly, prior to giving the first dose of fentanyl. Subsequent doses of fentanyl were smaller and therefore did not require local anaesthetic. An initial dose of 200 micrograms/4 mL fentanyl was administered. After 1 hour, smaller 50 microgram doses could be administered as frequently as every 15 minutes, if requested, up to

a maximum of 650 micrograms. The protocol stated that fentanyl should be administered slowly, over 1 to 2 minutes, undiluted.

3.4.1.3 Intramuscular pethidine

Using a 2–3mL syringe, the midwife drew up pethidine hydrochloride 100 mg/2 mL and administered it as a deep intramuscular injection into the ventrogluteal muscle. A repeat dose could be given in 3 to 4 hours (once only) with a maximum total dose of 200 milligrams.

3.4.2 Tools and survey instruments

Four tools were used for data collection: two of the tools, the Audit tool (Appendix 10) and the Trial Observation Chart (Appendix 11), had been previously developed for a pilot study that examined the physiological effects of s.c. fentanyl on women during and post-birth (Fleet et al. 2014). An additional tool, the Telephone Questionnaire, was developed for this study in order to examine women's experience with breastfeeding and satisfaction with the Trial drug (Appendix 12). The validated LAS questionnaire (Appendix 13) was used to assess feelings of coping and control during childbirth (Hodnett & Simmons-Tropea 1987). These tools are discussed in detail below.

3.4.2.1 Intrapartum data collection

Both facilities provided one-to-one midwifery care during labour following the clinical procedures outlined by the South Australian Perinatal Practice Guidelines. The attending midwife used the Obstetric Analgesia Trial Observation Chart (Appendix 11) to record the time of study drug administration as well as the woman's self-assessed maternal pain scores, and physiological effects (sedation levels, vomit score, blood pressure, temperature, respiration rate and pulse oximetry).

Pain scores were determined using the VAS (Ludington & Dexter 1998). Benefits of the VAS included ease of use, reproducibility of results and applicability to a variety of clinical settings

(Kelly 1998). Furthermore, the VAS is commonly used to measure labour pain (Ludington & Dexter 1998) and has been used across a number of settings to examine the clinical significance of reported pain changes (Gallagher et al. 2001; Kelly 1998; Powell et al. 2001; Todd et al. 1996). Although studies have suggested the NRS and VAS correlate well and are equally efficient for assessment of pain (Jensen Hjermstad 2011), the VAS has been reported as the 'gold standard' for use in research, as well as in clinical practice (Bergh et al. 2012).

Timing of assessment was noted immediately prior to administration of the study drug and again at 30 minutes post-treatment. Pain scores were taken between contractions with the pain score representing pain experienced at the peak of the contraction. Vital signs also were undertaken in conjunction with the measurement of pain scores and recorded on the Obstetric Analgesia Trial Observation Chart within these same timeframes. Continuous pulse oximetry was in place for the first 30 minutes post-treatment. The oxygen saturation probe was placed on the finger prior to administration of the study drug and the lowest level over the 30-minute period recorded. As decreased oxygen saturations were a potential issue of concern, it was desirable to assess the lowest level.

Apart from oxygen saturation levels, all other observations were recorded immediately prior to the first treatment and 30 minutes post-treatment. If the woman received only one treatment then two full sets of observations were documented on the Obstetric Analgesia Trial Observation chart (one pre-treatment and the second 30 minutes post-treatment). For the fentanyl groups, where multiple doses may be administered during a one-hour period, observations were taken pre-treatment and then every 30 minutes while the treatment was in use.

The woman's position also was recorded pre- and post-treatment to confirm whether the participant was in an upright or recumbent position. Other forms of analgesia used were

recorded in conjunction with the treatment, such as nitrous oxide and oxygen. Subsequent analgesia administered also was recorded, such as cross-over to epidural that may have occurred due to unrelieved pain or persistent or problematic symptoms.

Following the birth, the investigating researcher used the audit tool to record data from the participants' medical records including demographic characteristics (age, BMI, gestation, parity, onset of labour (induction of labour or spontaneous onset), birth outcome (mode of birth, blood loss, postnatal stay), and neonatal outcome measures (Apgar scores, time to establish respiration, skin-to-skin within the first hour of birth, breastfeeding within the first hour of birth, birth weight, nursery admission, naloxone administration and arterial cord blood pH).

3.4.2.2 Follow up within 48 hours

The Labour Agentry Scale (LAS) (Appendix 13) was used to assess feelings of coping and personal control during the birth and administered to the women within 48 hours post-birth by the investigating researcher. The LAS is a 10-item scale with underlying factors relating to mastery and sense of control. The scale has a high internal reliability (Cronbach's alpha >0.85) (Hodnett 2003). The 10-item inventory included six positive and four negative descriptors of the perceived degree of control experienced during childbirth. Women ranked the items on a 7-point scale from (1) 'almost all of the time' to (7) 'never, or almost never'. A high score indicated high control (Hodnett & Simmons-Tropea 1987). Appendix 13 provides instructions to score the LAS.

3.4.2.3 Follow up at 6 weeks postpartum

A postnatal data collection tool (Appendix 12, The Telephone Questionnaire) was developed as no existing tools were identified from the literature that examined neonatal breastfeeding behaviour, problems encountered with breastfeeding and sources of support used. As such, the investigating researcher designed a series of closed-ended questions to elicit factual data. The

last question, however, was an open-ended question that explored the participant's level of satisfaction with the treatment.

The investigating researcher contacted the participant by telephone at 6-weeks postpartum to complete this final questionnaire. As both hospitals under study were accredited to provide baby-friendly health initiatives, breastfeeding outcomes were reviewed at this time-point. The Telephone Questionnaire involved asking questions about breastfeeding and known factors that are recognised to impact breastfeeding outcomes such as, intention to breastfeed, level of education, intention to return to work, problems encountered and sources of support (Tawia 2012). In addition, the woman was asked whether she would use the study drug again in a subsequent labour. This question was posed as a dichotomous (yes/no) response, followed by an invitations to provide additional comments relating to her experience and intention to use the treatment again in labour.

3.5 Primary outcome measures

In the past decade, a number of systematic reviews have examined parenteral administration of opioids for labour analgesia and made recommendations for future research to investigate the effectiveness of pethidine in comparison to other opioids (Bricker & Lavender 2002; Jones et al. 2012; Ullman et al. 2010). Currently, it is still unclear which opioid and mode of administration is most effective (Ullman et al. 2010).

Therefore, the primary outcome of this RCT was the comparison of the analgesic effect of i.m. pethidine, i.n. fentanyl, and s.c. fentanyl. Analgesic effect was measured by examining the change in maternal rating of perceived pain intensity using the VAS immediately prior to analgesia and at 30 minutes post-treatment.

3.5.1 Secondary outcome measures

In addition to pain intensity, other variables identified by the Cochrane Collaborative in 2010 that measure analgesic effect were examined that included: satisfaction with pain relief and sense of control in labour (Jones et al. 2012). This is supported by research that identified feelings of control during labour are one of the important factors that contribute to maternal childbirth satisfaction (Gibbins & Thomson 2001). In this study, feeling of personal control during labour were measured on the LAS questionnaire (Appendix 13), and satisfaction with treatment was further explored through the Telephone Questionnaire (Appendix 12) when participants were asked to report their preference to use the treatment again in future labours.

Other secondary outcomes examined included variables associated with the potential for opioids and other methods of pharmacological pain relief to produce adverse maternal and neonatal effects (see Cochrane Review, Jones et al. 2012). These included: levels of sedation (awake or sedated), need for antiemetic administration, cross-over to epidural analgesia, changes to vital signs (blood pressure measured as mean arterial pressure (MAP), respiration and pulse rate (per minute) and oxygen saturation (%), body temperature measured in degrees Celsius (°C), ability to mobilise—defined as upright positions (including ambulating, sitting, standing, all fours and kneeling) or recumbent positions (supine, semi-recumbent and lateral), duration of labour, mode of birth (spontaneous, assisted, or caesarean birth), estimated blood loss, ability to have baby skin-to-skin for the first hour post-birth, intention to breastfeed, breastfeeding in the first hour post-birth and number of days spent in hospital post-birth. Infant feeding also was explored at 6 weeks postpartum to determine method of feeding. Babies were reported to have been exclusively breastfed (BF)—received breast milk directly from the nipple, artificially fed (AF)—an alternative to breast milk, or combine fed (BF and AF).

Neonatal variables examined included the time of birth, time of last dose of study drug administered prior to birth, one and five minute Apgar scores, naloxone administration, arterial cord blood pH and the time taken for the baby to establish breathing. In addition, admission to neonatal intensive care unit (NICU), or special care baby unit (SCBU) was examined.

3.5 Sample size/power calculation

The sample size calculation was undertaken to address the primary outcome to detect a change in pain score. The 30-minute timeframe was based on an expected treatment effect of the different opioids and routes of administration, as previously observed in obstetric populations. Wong et al. (2003) demonstrated a clinically significant reduction in VAS pain scores when i.n. fentanyl was self-administered post LSCS in this timeframe (Wong et al. 2003). The s.c. fentanyl dosage regimen was based on the same protocol used by Fleet et al. (2014), where they observed a clinically important reduction of pain score at 30 minutes. Tsui et al. (2004) used the same 100 mg i.m. pethidine dose as this study, and reported a clinically significant reduction of pain score at 30 minutes.

Although the VAS is frequently used to assess labour pain, studies demonstrate wide variations in interpretation and perception of pain scores (Carvalho et al. 2013). For example, previous studies have identified clinically significant score changes in pain intensity between 0.9 cm and 1.3 cm (Gallagher et al. 2001; Kelly 1998; Powell et al. 2001; Todd et al. 1996). Several power calculations were undertaken using these different scores changes (0.9 cm and 1.3 cm). The smallest change in VAS score (0.9 cm) was chosen to reduce the potential for type II error, as it resulted in the largest sample size to enable the detection of even small changes in pain scores. Kelly et al. (1998) conducted a prospective descriptive study of 152 adults presenting to the accident department experiencing acute pain and reported the minimum clinically significant difference in VAS pain score was 0.9 cm. This study reported good validity and

addressed several weaknesses identified in previous studies, such as those seen when Todd et al. (1996) conducted repeated measures on a much smaller sample size of 48 patients. To reduce the potential for type I error the significance level of the test was targeted at 0.05. The standard deviation of 1.0 cm was used as this is common for labour pain measurements (Ludington et al. 1998) and power was set to 0.85.

A sample size of 23 in each group achieved at least 80% power to detect a 0.9 cm change in VAS score difference with 1.00 cm standard deviation. A paired sample t-test was conducted, with a p value of <0.05 considered significant to determine the mean difference between pain scores at baseline and 30 minutes post-treatment. Recruitment of participants continued until the intended sample size was achieved for women receiving the allocated treatments.

3.6 Data analyses

Data were analysed in the groups to which the women were randomised, regardless of any change to treatment that may have occurred post-randomisation (intention-to-treat principle based on the participant's assignment). Normality of the data were examined using a frequency histogram and Bartlett's test for equal variances. For normally distributed data an ANOVA was performed to measure the baseline characteristics between the three groups. A Kruskal-Wallis test was used to compare the medians of the three groups when data were skewed. A chi-square test also was used to determine significant baseline differences between s.c. fentanyl, i.n. fentanyl and i.m. pethidine groups for categorical variables.

Means and standard deviation were calculated for normally distributed continuous data and median and interquartile range (IQR) was calculated for skewed data. Proportions were presented as percentages of the respective denominator. Missing data were mostly negligible, with the exception of the observations taken at 30-minute intervals after administration of the study drug. Data were missing predominately due to imminent birth, or if the woman declined

treatment. These data were found to be missing completely at random (MCAR) and analysed by Complete-Case (CC) analysis to avoid biasing results (Pigott 2001).

Observations that were taken pre-treatment and again at 30 minutes were analysed using a maximum likelihood based multi-level mixed effect linear regression model applied in STATA (version 13.0) (StataCorp. 2013). This model permits analysis of the treatment effects (adjusted mean change of three groups at each time-point) and interaction effects (overall effects on the three groups at post 30 minutes endpoint). This is a preferred method of parameter estimation and inference in statistics (Myung 2003). For this study, the multivariate analysis was adjusted for age, body mass index, parity, gestation and induction of labour. All analyses were performed with two-sided hypotheses and the level of significance was set at $p<0.05$. Where appropriate, 95% CIs were reported along with p values. Results are described using CONSORT guidelines.

Responses to the open-ended question of the Telephone Questionnaire administered at 6 weeks were grouped into categories, a process called categorisation (Schneider et al. 2013). Comments made by the participants were transcribed verbatim and then formatted and coded in a table to identify categories. Data were then organised by colour code into sub-categories and the frequency of distribution reported. To enhance integrity, categories and sub-categories were confirmed by an independent reviewer.

3.7 Randomisation

A computer-generated number sequence was produced to create study arms of approximately equal sizes using a blocked randomisation sequence of six. Each centre was randomised separately. Although prior consent was obtained, participants were not randomised into the Trial until a request for analgesia was made during labour. This guaranteed that if the woman

did not request the use of an opioid, or was deemed ineligible, she was not entered into the Trial.

3.7.1 Allocation concealment

To ensure allocation concealment, each centre received study protocols that had been placed into sequentially numbered opaque envelopes and sealed with tamper-proof tape. Once a request for analgesia had been made, and if the woman had been assessed as eligible, the midwife would randomise her by selecting the next envelope that identified the treatment to be administered.

3.7.2 Blinding

The study was not blinded due to the different routes of administration and the shorter half-life of fentanyl, which needed to be administered more frequently than pethidine. Therefore, the midwife recording the labour data was aware of treatment allocation, as was the investigating researcher who was responsible for data collection, management and analysis.

3.8 Trial registration

This Trial was registered with the Australian New Zealand Clinical Trials registry [ACTRN12609001027202] on 22 November 2009.

3.9 Ethics approval

Ethics approval was granted by the Children's Youth Women's Health Service Human Research Committee on 27 October 2010 and the Southern Adelaide Clinical Human Research Ethics Committee on 14 December 2010 (ethics application number 380.09 and approval number REC2284/9/13) (Appendix 14). Recruitment commenced in January 2011.

3.9.1 Data management

The investigating researcher was responsible for all data management that included collection of consents, photocopying observation charts (the original remained in the woman's medical record) and recording demographic data from the woman's medical record onto the audit tool (Appendix 10). Data that related to neonatal outcomes also were collected from the medical records on this same tool. The LAS questionnaire (Appendix 13) was administered and collected within 48 hours post-birth. Furthermore, the Telephone Questionnaire also was undertaken by the lead investigator and recorded on the corresponding form (Appendix 12) within the 6-week timeframe. The consort flowchart was used to record the flow of participants through each stage of the Trial (Figure 3.1).

```
┌─────────────────────────────────────────┐
│   Approached for participation (n=)       │
│      Consents obtained (n=)               │
│    • Tertiary hospital (n=)               │
│    • Regional hospital (n=)               │
└─────────────────────────────────────────┘
                    │
                    │          ┌──────────────────────────────────────────┐
                    │          │ Excluded (n=)                            │
                    ├─────────▶│  • Not meeting inclusion criteria (n=)   │
                    │          │  • Declined to participate (n=)          │
                    │          │  • Other reasons (n=)                    │
                    ▼          └──────────────────────────────────────────┘
            ┌───────────────────┐
            │  Randomised (n=)  │
            └───────────────────┘
```

Allocated to i.n. fentanyl intervention (n=)	Allocated to s.c. fentanyl intervention (n=)	Allocated to i.m. pethidine intervention (n=)
• Received allocated intervention (n=) • Did not receive allocated intervention (with reasons) (n=)	• Received allocated intervention (n=) • Did not receive allocated intervention (with reasons) (n=)	• Received allocated intervention (n=) • Did not receive allocated intervention (with reasons) (n=)
Lost to follow-up (with reasons) (n=)	Lost to follow-up (with reasons) (n=)	Lost to follow-up (with reasons) (n=)
Analysed (n=) • Excluded from analysis (with reasons)	Analysed (n=) • Excluded from analysis (with reasons) (n=)	Analysed (n=) • Excluded from analysis (with reasons) (n=)

Figure 3.1   **The CONSORT flowchart** (adapted from Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials).

3.9.2 Safety concerns-Study drug product licensing and marketing in Australia

This Trial examined the use of two formulations of fentanyl that were administered outside current product licensing, namely via the i.n. and s.c. routes. Pethidine hydrochloride was administered within product licensing. A Clinical Trial Notification (CTN) was made to the Australian Therapeutic Goods Administration to advise the supply of unapproved therapeutic goods under the CTN Scheme (Appendix 15).

The formulation of fentanyl used for s.c. administration was fentanyl citrate 100 mcg/2 mL, which is the standard formulation available through the pharmacy department in both hospitals under study. This formulation of fentanyl is an approved and marketed form of opioid analgesic (Category C) for use in pregnancy and labour. While s.c. administration of fentanyl is outside current product licencing, this method of administration has become common practice in various settings that include paediatrics, acute care and palliative care settings. In addition, several South Australian country hospitals have been administering s.c. fentanyl to women in labour over the past 15 years.

Fentanyl used for i.n. administration was purchased through Orion Laboratories, Western Australia: the product name is intranasal fentanyl solution 600 mcg/2 mL. This formulation of fentanyl was purchased by the hospital pharmacy under Section 18 of the *Therapeutic Goods Act*, which defines that exemptions can exist under Schedule 5A – under the circumstances in which "a person" (Orion) can manufacture otherwise unregistered goods. Such goods can only be manufactured for/sold to public hospitals, private hospitals or public institutions under "contract" between the parties. The "person" manufacturing (Orion) must be a manufacturer within Australia and be Therapeutic Goods Administration (TGA) registered. Additionally, the manufacturer must maintain the contract and report the sales to the relevant authority quarterly (via the Drug Evaluation Branch). Prior to purchase of the intranasal fentanyl solution, the Director of Pharmacy needed to agree to enter a contract with the manufacturer. While this formulation has not been used in obstetric areas, it has been used in a number of other settings including other tertiary hospital burn units and the ambulance services throughout Australia.

Pethidine hydrochloride 100 mg in 2 mL injection is an approved and marketed form of opioid analgesic (Category C) for use in pregnancy and labour. It is the current standard practice for

both hospitals under study to offer this opioid as first-line management when parenteral pain relief is requested during labour.

3.9.2.1 Notification of adverse events

Pre-existing clinical standards undertaken by both hospitals for active labour and normal vaginal birth included documenting observations to identify obstetric triggers that would detect potential adverse events. Triggers related to any observations that were outside normal limits included: abnormal maternal temperature ≤ 34.9 or ≥ 38.5 Celsius (°C), pulse ≤ 40 or ≥ 115 bpm, systolic blood pressure ≤ 90 or ≥ 160 mmHg, diastolic blood pressure ≤ 45 or ≥ 90 mmHg, respiratory rate ≤ 10 or ≥ 25 breaths/min and sedation score ≥ 2 as well as FHR abnormalities ≤ 100 or ≥ 160 bpm, or postpartum haemorrhage >500 mL. If any of the obstetric triggers were observed, a medical referral procedure was to be undertaken. These clinical standards enabled the detection of potential risk or complication in which the medical officer would be advised immediately and appropriate management undertaken as required. Any adverse outcomes were to be recorded on the Obstetric Analgesia Trial Register (Appendix 7) for follow-up by the Data and Safety Committee who monitored serious adverse events to ensure suitability for the continuation of the Trial. This committee comprised staff from the obstetric team, Women's Anaesthesia Department and the Neonatal Unit, as delegated by each head of department.

In addition, in the event of a serious adverse event, notification was to be reported to the Research Ethics Committee, and directly to the Therapeutic Goods Administration and Drug Therapeutic Committee. Non-serious adverse events and serious adverse events clearly related to the underlying childbirth process also were to be reported in a collated form in the Annual Report of the Study.

3.10 Summary

The methods that were used to design and conduct this RCT have been described in this chapter. The study protocol was approved by the ethics committees of both participating hospitals and the university, and implemented according to the CONSORT guidelines. The sample size calculation was undertaken to address the primary outcome for this study, which was reduction of pain score as measured using the VAS tool at 30 minutes. The minimum change (0.9 cm) was determined as clinically significant from a prospective descriptive study of acute pain management (Kelly et al. 1998). Data collection instruments were reviewed and statistical analyses described using the intention-to-treat principle based on participant assignment. The following chapters (4 & 5) discuss the results of the study.

Chapter 4   Intrapartum findings

The pain associated with the intrapartum stage of pregnancy can be intense, with the strength of contractions increasing as labour proceeds until the birth of the fetus. Many women request analgesia to help them through this period. At the maternity units under study, i.m. pethidine was the standard practice for providing parenteral pain relief for women in labour. Data collected from this RCT between January 2011 and April 2013 have been analysed to compare the analgesic effect of i.n. fentanyl, s.c. fentanyl and i.m. pethidine when administered for pain relief during childbirth. The findings relating to the primary and secondary maternal outcomes associated with the intrapartum period are presented in this chapter. Neonatal outcomes and data relating to the Telephone Questionnaire administered at 6 weeks postpartum, which explored the woman's breastfeeding experience and satisfaction to use the treatment again in a subsequent labour, are reported in Chapter 5.

4.1 Participant recruitment and progress through the phases of the Trial

In total, 883 women were approached for participation in this Trial, of which 396 (44.8%) women provided consent. Of the 487 women who declined to participate, 136 (27.9%) did not provide a reason. A further 119 (24.4%) women were not eligible due to medical reasons or known allergy, while 82 (16.8%) chose not to use any pharmacological form of pain relief. Twenty-seven (5.5%) women reported a preference not to use any opioid due to concerns about adverse effects. Another 75 (15.6%) women stated a strong preference to use an epidural early in labour; some women 26 (5.3%) requested to use pethidine, while 18 (3.7%) women specified they would not enter the Trial as they would not want to be administered pethidine. Finally, four (0.8%) women advised that they would not participate in the study as they did not want to be in a drug trial.

Of the 396 eligible women who provided prior consent to participate, 240 (60.6%) women were not randomised into the trial, as detailed in the Trial flow chart (Figure 4.1). In total 156 (39.4%) women who requested opioid analgesia in labour were subsequently randomised to either receive i.n. fentanyl (n=52), s.c. fentanyl (n=53), or i.m. pethidine (n=51), (Figure 4.1). After randomisation 48 women (30.8%) did not receive the allocated intervention, but data were included as for intention-to-treat. Figure 4.1 indicates the reasons for deviation from the allocated interventions and reports loss to follow-up at 48 hours and 6 weeks. Recruitment was ceased only once the sample size was reached for women receiving the intervention to ensure adequate power for the primary outcome. As such, primary outcome data relating to pain scores and secondary outcomes for maternal vital signs post-treatment were recorded for 94 women (87.0%) who received the intervention (i.n. fentanyl n=37; s.c. fentanyl n=33; i.m. pethidine n=24). Data were not available for 14 women as they either birthed within 30 minutes of receiving the intervention, or data were not recorded (Figure 4.1). As a large proportion of women did not receive the allocated intervention, a secondary analysis was performed on treated women. Results for all outcomes were comparable with those seen for intention-to-treat (Appendix 16; Table S1).

Approached for participation (n=883)
- Tertiary hospital (n=680)
- Regional hospital (n=203)

Consents obtained (n=396)

Declined to participate (n= 487)
- Not stated (n=136)
- Not eligible (n=119)
- Preference to use no analgesia (n= 82)
- Preference to use an EDB (n= 75)
- Preference not to use an opioid (n=27)
- Preference to use pethidine (n= 26)
- Preference not to use pethidine (n= 18)
- Advised not willing to be in a drug trial (n= 4)

Consented then excluded prior to randomisation (n=240)
- Analgesia not required (n=91)
- Requested EDB (n=82)
- Administered pethidine within 24h (n=28)
- No labour (failed IOL or El LSCS) (n=26)
- Medical condition (n=11)
- Birthed at alt facility (n=1)
- Not recorded (n=1)

Randomised (n=156)

Allocated to i.n. fentanyl (n=52)
Received allocated intervention (n=41)
- Birthed within 30 min (n=1)
- Pre or post pain score not taken (n=3)

Did not receive allocated intervention (n=11)
- Birthed before dose given (n=2)
- EDB- dose withheld (n=6)
- Breach of protocol given pethidine (n=2)
- Withdrew requested pethidine (n=1)

Allocated to s.c. fentanyl (n=53)
Received allocated intervention (n=37)
- Birthed within 30 min (n=3)
- Pre or post pain score not taken (n=1)

Did not receive allocated intervention (n=16)
- Birthed before dose given (n=7)
- dose withheld given EDB- (n=4)
- Excluded due to medical condition (n=3)
- Given pethidine as anaesthetist unavailable (n=2)

Allocated to i.m. pethidine (n=51)
- Received allocated intervention (n=30)
- Birthed within 30 min (n=1)
- Pre or post pain score not taken (n=6)

Did not receive allocated intervention (n=21)
- Birthed before dose given (n=3)
- Declined & requested no analgesia or N2O2 (n=7)
- Declined & requested EDB (n=9)
- Declined & requested i.v. fentanyl (n=2)

Analysed at birth (n=52)
Excluded from analysis (n=0)

Analysed at birth (n=53)
Excluded from analysis (n=0)

Analysed at birth (n=51)
Excluded from analysis (n=0)

Analysed at 48h (n=49)
LAS not returned (n=3)

Analysed at 6 week (n=50)
Participant uncontactable (n=2)

Analysed at 48h (n=51)
ITT withdrew from follow up (n=2)

Analysed at 6 week (n=51)
ITT withdrew from follow up (n=2)

Analysed at 48h (n=44)
ITT withdrew from follow up (n=5)
LAS not returned (n=2)

Analysed at 6 week (n=45)
ITT withdrew from follow up (n=5)

Figure 4.1   Trial flow chart

4.1.1 Characteristics of participants

All women studied were assessed as low risk and birthed at term. The demographic characteristics of participants (age, BMI, gestation, parity, onset of labour) were comparable between groups (Table 4.1). Of the women studied the majority were primagravida, with a BMI in the overweight range, who had obtained a similar level of education and employment (Table 4.1).

Table 4.1   Maternal baseline characteristics for randomised participants

Characteristics	i.n. fentanyl n=52	s.c. fentanyl n=53	i.m. pethidine n=51	p
Maternal				
Age [Mean(SD)]	29.0 (6.3)	29.9 (5.5)	28.6 (4.7)	0.48
BMI [Mean(SD)]	26.9 (5.2)	26.4 (4.3)	26.7 (6.1)	0.89
Gestation (wk) [Mean(SD)]	39.8 (1.2)	39.9 (1.0)	40.0 (1.2)	0.66
Primiparity (%)	40/52 (76.9)	39/53 (73.6)	39/51 (76.5)	0.91
Induction of labour (%)	30/51 (58.8)	23/53 (43.4)	25/51 (49.0)	0.28
Level of education				
High school (%)	13/43 (30.2)	6/46 (13.3)	8/40 (20.0)	0.15
Trade/Certificate/Diploma (%)	16/43 (37.2)	21/46 (46.7)	16/40 (40.0)	0.65
Degree (%)	14/43 (32.6)	18/45 (40.0)	16/40 (40.0)	0.71
Employment				
Employed (%)	37/49 (75.5)	40/52 (76.9)	33/45 (73.9)	0.92

Note. p values are based on one-way ANOVA for continuous measures and chi-square test for categorical measures.

4.2 Study drug dose administered

Dosage was examined between the three study groups (Table 4.2) to identify median (IQR) total dose, number of doses administered and the mean duration of use. Data were then examined to review implications for treatment effects. Although protocols enabled all treatment groups to receive repeat doses of the study drug, proportionately more women in the fentanyl groups requested further treatment compared to women in the i.m. pethidine group (37/41 (90.2%) i.n. fentanyl, 23/37 (62.2%) s.c. fentanyl compared to 3/30 (10.0%) i.m.

pethidine). The majority of women administered pethidine received 100 milligrams. The median total dose of fentanyl administered to women differed depending on the route of administration (Table 4.2). In the i.n. fentanyl group, the total dose ranged from 54 to 1200 micrograms, whereas the s.c. fentanyl group ranged between 200 and 650 micrograms.

Examination of the total drug dose received by the participants showed that the maximum i.n. fentanyl dose (1200 micrograms), which was equivalent to 22 doses (54 micrograms/dose), was self-administered by 5/41 (12.2%) women. The proportion of women that required the applicator to be refilled due to receiving >600 micrograms of intranasal fentanyl was 14/41 (34%). In the s.c. fentanyl group, 2/37 (5.4%) women were administered the maximum 650 microgram dose (10 doses). Only 3/30 (10.0%) women received a second dose of i.m. pethidine to reach the maximum dose of 200 milligrams. Time of first and last dose administered is shown in Table 4.2.

Table 4.2   **Study drug administration comparison between groups**

	i.n. fentanyl n=41	s.c. fentanyl n=37	i.m. pethidine n=30
Number of doses	8.0 (4.0–16.0)	3.0 (1.0–4.0)	1.0 (1.0–1.0)
Total dose (μg/mg)	486.0 (216.0–864.0 μg)	300 (200–350 μg)	100 (100–100 mg)
Duration of treatment (h)	1.9 (1.2–3.9)	1.7 (0.0–3.2)	0.0 (0.0–0.0)
First dose to birth (h)	5.0 (2.2–8.6)	5.2 (2.6–9.5)	6.6 (3.3–10.2)
Last dose to birth (h)	2.0 (0.7–5.1)	2.7 (1.3–7.5)	5.4 (3.0–9.6)

Note. Data were recorded as median (IQR)

4.3 Primary outcome: measurement of pain intensity

A comparison of pain intensity measured using the VAS showed that pain scores for all three treatment groups were similar at baseline and at 30 minutes post-treatment (Table 4.3). In addition, all three groups demonstrated clinically significant reductions in pain scores at 30 minutes (mean range: 1.2–1.6; $p < 0.001$) (Table 4.3). Subsequent pain scores resulted in high numbers of missing data due to differences in treatment protocols. For example, the majority of women in the pethidine group received only one dose (Table 4.2). The number of women in both fentanyl groups also differed (Figure 4.2) between time-points as women birthed or ceased using the treatment over this period of time. The median duration of treatment for the fentanyl groups was <2 hours (Table 4.2). However, some women in the fentanyl groups continued to use the treatment over 7 hours (Figure 4.2). These data indicated that women in the i.n. fentanyl group continued to sustain a significant reduction in pain score (6.9, SD 1.5) at 3 hours, unlike women in the s.c. fentanyl group (8.9, SD 0.8). (Figure 4.2). Of the three women that continued to use i.n. fentanyl at 7 hours, pain scores remained below baseline (Figure 4.2).

Figure 4.2   **VAS pain scores during 7 h of treatment**

Values are mean (SD). Since some women did not request analgesia or had birthed at subsequent time-points the sample size differed from cell to cell. Numbers above columns represent the actual number of participants.

4.4 Key secondary outcomes: Assessment of control during childbirth and satisfaction with treatment

Experiences of personal control during labour and childbirth were measured using the LAS questionnaire, which was completed by the women during their postnatal stay and returned within 48 hours of birth. The questionnaire was completed by 144 women (92.3%). All groups achieved a mean score >50, indicating moderate levels of personal control (Table 4.4). The scale demonstrated high internal reliability (Cronbach's alpha 0.80).

4.5 Maternal physiological effects

In addition to exploring pain scores and experiences of personal control, other physical indicators were recorded to examine pre- and post-treatment effects on vital signs (Table 4.3), antiemetic use, sedation and ability to ambulate during labour (Table 4.5). Effect on labour duration, cross-over to epidural, mode of birth and blood loss also were examined (Table 4.4).

4.5.1 Maternal vital signs, emesis and sedation

Secondary outcomes examined to explore treatment effects on maternal vital signs (respiration rate, body temperature, pulse rate, blood pressure [MAP], and oxygen saturation) identified no significant change within each group (Table 4.3). Even when the maximum dose of either drug was administered, no parturients experienced desaturations from baseline or experienced any period of oxygen saturation <95%. Statistical analysis using a multilevel mixed effect model also demonstrated there were no significant differences observed when baseline and post-treatment measurements were compared between groups (Table 4.3). Results indicated that neither opioid nor route of administration had an effect on the woman's vital signs or oxygen saturation.

Clinically significant differences, however, were observed between the fentanyl and pethidine groups when sedation was analysed pre- and 30 minutes post-treatment (Table 4.5). Both fentanyl groups were observed to have significantly less sedation than the i.m. pethidine group (Table 4.5). Data for antiemetic use, however, could not be analysed due to a breach in the study protocol for women in the i.m. pethidine group, where a high proportion of women 9/24 (33.3%) were administered a prophylactic antiemetic. Despite this breach in protocol, a further 7/24 (25.9%) women still required an antiemetic within 30 minutes of treatment compared to 1/37 (2.4%) woman in the i.n. fentanyl group and no women in the s.c. fentanyl group (Table 4.5). No women in the fentanyl groups were administered a prophylactic antiemetic.

When considering maternal factors, such as ability to mobilise and adopt upright positions during labour, there were no differences within each group when pre- and post-treatment were examined (Table 4.5). The majority of women in the i.n. fentanyl group were in an upright position both pre- and post-treatment, while the majority of women receiving either s.c. fentanyl or i.m. pethidine tended to remain in the semi-reclined position adopted when receiving the treatment (Table 4.5).

Table 4.3 **VAS pain scores and maternal vital signs (pre and 30 minutes post-treatment)**

Efficacy measures	Time	Treatment group [Mean (SD)]			Treatment effect (marginal mean difference/relative risk) (95% CI & p values)[§]	
		i.n. fentanyl n=37	s.c. fentanyl n=33	i.m. pethidine n=24	i.m. pethidine vs i.n. fentanyl	i.m. pethidine vs s.c. fentanyl
VAS score	Baseline	8.0 (1.6)	7.8 (1.4)	8.0 (1.3)	-	-
	Post 30 minutes	6.9 (2.0)	6.7 (1.6)	6.4 (2.2)	0.37 (-0.44–1.19) (p=0.37)	0.48 (-0.38–1.34) (p=0.27)
Temperature (^{0}C)	Baseline	36.4 (0.5)	36.5 (0.6)	36.4 (0.3)		
	Post 30 minutes	36.4 (0.5)	36.6 (0.5)	36.3 (0.4)	0.07 (-0.12–0.26) (p=0.48)	0.12 (-0.07–0.32) (p=0.22)
Pulse (bpm)	Baseline	82.8 (9.1)	83.2 (11.8)	82.3 (9.5)	-	-
	Post 30 minutes	84.0 (9.8)	81.8 (10.9)	80.5 (8.2)	3.08 (-1.07–7.22) (p=0.15)	0.81 (-3.46–5.08) (p=0.71)
Respiratory rate (min)	Baseline	20.1 (2.9)	19.4 (3.8)	18.3 (2.1)	-	-
	Post 30 minutes	19.3 (2.8)	17.9 (2.1)	18.1 (1.9)	-0.44 (-1.89–1.00) (p=0.55)	-1.36 (-2.82–0.11) (p=0.07)
MAP	Baseline	89.4 (9.4)	88.9 (9.1)	92.9 (12.0)	-	-
	Post 30 minutes	89.1 (9.6)	88.8 (10.7)	90.5 (12.2)	1.45 (-1.89–4.78) (p=0.40)	2.96 (-0.49–6.42) (p=0.09)
Oxygen saturation	Baseline	98.4 (1.6)	98.3 (1.6)	98.6 (1.2)	-	-
	Post 30 minutes	98.4 (1.4)	98.1(1.4)	98.3(1.4)	0.31 (-0.36–0.98) (p=0.37)	0.22 (-0.46–0.90) (p=0.53)

A multilevel mixed effect model, (linear regression for continuous measures). §Models were adjusted by age, BMI, parity, gestation and induction of labour. Models were also adjusted by baseline measurements of outcome variables

4.5.2 Cross-over to epidural analgesia

The need for additional analgesia, such as cross-over to epidural, was examined between groups. Although no statistical difference for epidural use was found between groups post-treatment (Table 4.4), 9.7% fewer women in s.c. fentanyl group and 18.4% fewer women in the i.n. fentanyl group crossed over to epidural when compared to i.m. pethidine (Table 4.4). The greatest difference was seen between the i.n. fentanyl and i.m. pethidine group.

4.5.3 Duration of labour

Labour duration was examined to determine whether the opioid or mode of administration had an influence on labour length. It was interesting to note that the duration of labour differed significantly between groups, with both fentanyl groups experiencing a shorter duration of labour than the i.m. pethidine group (Table 4.4). Labour duration was, on average, 2 hours shorter for women receiving fentanyl than those receiving pethidine (Table 4.4). When parity was examined a similar trend was observed (primigravid women i.n. fentanyl 10.1h (4.6), s.c. fentanyl 10.0h (4.7), i.m. pethidine 12.1h (5.6); multigravid women i.n. fentanyl 5.5h (3.1), s.c. fentanyl 5.2h (2.1), i.m. pethidine 7.5h (6.0). No significant differences in length of labour, however, were found between the fentanyl groups (ANOVA).

4.5.4 Birth outcomes

When mode of birth was examined no significant difference between groups was observed (Table 4.4). Vaginal birth represented 75.6% (118/156) of births for all women under study. Maternal blood loss post-birth also was comparable between groups (Table 4.4).

Table 4.4 **Birth details, LAS score and satisfaction to use the treatment again for randomised participants**

	i.n. fentanyl n=52	s.c. fentanyl n=53	i.m. pethidine n=51	p
Intention-to-treat (%)	11/52 (21.2)	16/53 (30.2)	21/51 (41.2)	0.09
Labour duration (h) (Mean(SD))	9.0 (4.7)	8.7 (4.6)	11.0 (6.0)	0.048
Cross-over to epidural (%)	20/52 (38.5)	25/53 (47.2)	29/51 (56.9)	0.17
Spontaneous birth (%)	30/52 (57.7)	29/53 (54.7)	28/51 (54.9)	0.94
Assisted birth (%)	10/52 (19.2)	11/ 53 (20.8)	10/51 (19.6)	0.98
Caesarean birth (%)	12/52 (23.1)	13/53 (24.5)	13/51 (25.5)	0.96
Blood loss (mL) (Mean(SD))	451.0 (355.3)	399.1 (234)	459.8 (310.5)	0.54
LAS score (Mean (SD))	51.2 (9.0)	50.6 (9.3)	50.8 (8.6)	0.94

Note. p values are based on one-way ANOVA for continuous measures and chi-square test for categorical measures.

Table 4.5   **Sedation, antiemetic use and position (pre and 30 minutes post-treatment)**

Effect measures	Time	Treatment group (Mean (SD))			Treatment effect (marginal mean difference/relative risk) (95% CI & P values)§	
		i.n. fentanyl n=37	s.c. fentanyl n=33	i.m. pethidine n=24	i.m. pethidine vs i.n. fentanyl	i.m. pethidine vs s.c. fentanyl
Sedation* observed (%)	Baseline	1 (2.4%)	0 (0.0%)	0 (0.0%)		
	Post 30 minutes	3 (7.3%)	1 (2.9%)	11 (44.0%)	0.18 (0.04–0.89) (p=0.03)	0.06 (0.01–0.54) (p=0.01)
Anti-emetic used (%)	Baseline	1 (2.4%)	3 (8.3%)	9 (33.3%)		
	Post 30 minutes	1 (2.4%)	0 (0.0%)	7 (25.9%)	n/a	n/a
Upright position (%)	Baseline	23 (63.9%)	12 (34.3%)	10 (41.7%)		
	Post 30 minutes	24 (66.7%)	13 (37.1%)	8 (33.3%)	2.21 (0.18–26.40) (p=0.53)	2.30 (0.18–29.59) (p=0.52)

Note. A multilevel mixed effect model (logistic regression for categorical measures). §Models were adjusted by age, BMI, parity, gestation and induction of labour. Models were also adjusted by baseline measurements of outcome variables.

*Relative risk is based on post 30 minutes as there was no sedation observed at baseline in both the s.c. fentanyl and i.m. pethidine groups. Anti-emetic treatment effect could not be analysed using this model due to small numbers in groups, therefore the result has been recorded as not applicable (n/a).

4.6 Summary

Data relating to the primary outcome showed that i.n. and s.c. fentanyl use is as efficacious in relieving labour pain as i.m. pethidine. Other significant intrapartum findings included that women who received i.n. and s.c. fentanyl experienced less sedation, less anti-emetic use, and shorter labour, than women administered i.m. pethidine. However, no differences were seen between groups for physiological effects relating to vital signs, mode of birth and blood loss.

The next chapter reports on secondary postpartum outcomes and data from the Telephone Questionnaire that reviewed breastfeeding intention, any problems encountered with breastfeeding and sources of support. In addition, this questionnaire provided the women an opportunity to indicate satisfaction with treatment and comment on their experience of using the study drug. Data relating to the open-ended question are reported and include a selection of extracts to provide further depth and understanding of the woman's experience.

Chapter 5 Postpartum findings

The transfer of the drug across the placenta to the neonate is an unintended effect of intrapartum opioid analgesia (Anderson 2011). In particular, intrapartum administration of opioids has been associated with adverse neonatal effects such as respiratory depression and low Apgar scores (<7) (Jones et al. 2012). It also has been reported that intrapartum opioid administration may have an effect on the establishment of breastfeeding (Ransjo-Arvidson et al. 2001; Nissen et al. 1997). This chapter examines neonatal outcomes after intrapartum administration of i.n. fentanyl, s.c. fentanyl and i.m. pethidine. In addition, data collected at 6 weeks that related to breastfeeding experience, intention to use the study drug again in a future labour and women's statements about perceived treatment effects are presented.

5.1 Neonatal outcomes

To establish if intrapartum opioid administration was associated with effects on the fetal to neonatal transition, neonates under study were observed for the first hour after birth and data were recorded for time to establish spontaneous breathing, naloxone administration, arterial cord blood pH nursery admission, Apgar scores, birth weight and days in hospital (Table 5.1).

When time to establish spontaneous breathing was examined, no significant differences were observed among groups (median for all groups was 1.0 minute [IQR 1.0–1.0]; p<0.44). It was noted that four neonates exhibited depressed respiration >2 minutes (two in the i.n. fentanyl group and two in the i.m. pethidine group), although all neonates established spontaneous breathing within 5 minutes. No neonate under study received naloxone.

Arterial cord blood pH is a measurement of fetal respiratory condition at birth. An arterial cord pH<7.2 indicates respiratory acidosis due to an inability to clear CO_2 at the placenta (Blackburn 2013). In this study, arterial cord blood was collected and analysed within 30 minutes of birth for 53.2% of neonates. This comprised 29/52 (55.8%) neonates in the i.n. fentanyl group, 31/53

(58.5%) neonates in the s.c. fentanyl group and 23/51 (45.1%) neonates in the i.m. pethidine group. The median arterial cord blood pH was comparable for all three groups (i.n. fentanyl pH 7.3 [IQR 7.3–7.3] and both s.c. fentanyl and i.m. pethidine arterial cord blood pH 7.3 [IQR 7.2–7.3] p<0.72). Of clinical interest, 2/29 (6.9%) neonates in the i.n. fentanyl group and 2/31 (6.5%) in the s.c. fentanyl group were recorded as having arterial cord blood pH<7.2, compared to 4/23 (17.4%) neonates in the i.m. pethidine group.

In relation to neonatal outcomes, the only significant effect observed was nursery admissions, which were significantly higher for neonates in the i.m. pethidine group compared to either fentanyl group (p<0.02) (Table 5.1). Whereas Apgar scores at 1 minute and 5 minutes were similar between groups (Table 5.1), three neonates (5.9%) in the i.m. pethidine group experienced an Apgar <7 at 5 minutes compared to none in the fentanyl groups. No significant differences were found among groups for birth weight or duration of postnatal stay.

Table 5.1   **Neonatal birth outcomes**

Neonatal outcome	i.n. fentanyl n=52	s.c. fentanyl n=53	i.m. pethidine n=51	p
Nursery admission (%)	8/52 (15.4)	5/53 (9.4)	15/51 (29.4)	0.02
Apgar score at 1 min. Median (IQR)	9.0 (8.0–9.0)	9.0 (8.0–9.0)	9.0 (7.0–9.0)	0.45
Apgar score at 5 min. Median (IQR)	9.0 (9.0–9.0)	9.0 (9.0–9.0)	9.0 (9.0–9.0)	0.46
Birth weight (grams) Mean (SD)	3573.1 (476.9)	3603.6 (357.1)	3509.6 (470.5)	0.54
Days in hospital post-birth Mean (SD)	3.3 (1.2)	3.2 (1.5)	3.4 (1.3)	0.88

Note. p values are based on one-way ANOVA for continuous measures and chi-square test for categorical measures.

5.2 Breastfeeding experience: birth to 6-weeks postpartum

Both hospitals in this study were Baby Friendly Health Initiative (BFHI) accredited, requiring breastfeeding intention to be noted in the woman's medical record during the antenatal period. Most women (134/156, 85.9%) expressed an intention to exclusively breastfeed. Within the first hour of birth, all women were encouraged to have skin-to-skin contact with their neonate,

as well as breastfeed. There was a statistically significant difference among groups for the intention to exclusively breastfeed. While no differences were seen between women in the fentanyl groups for preference to exclusively breastfeed; women in the i.n. fentanyl group were significantly less likely to identify an intention to exclusively breastfeed when compared to the i.m. pethidine group (78.4% i.n. fentanyl, 88.7% s.c. fentanyl, 97.9% i.m. pethidine [$p<0.01$]) (Table 5.2). For women who intended to breastfeed, differences were seen in the number of babies receiving skin-to-skin contact within the first hour of birth, but not in the number of neonates that breastfed within the first hour of birth (Table 5.2). No correlation was identified between babies that were admitted to nursery and breastfed at 6 weeks.

At 6-weeks postpartum the Telephone Questionnaire was administered to explore the woman's experience in initiating and maintaining breastfeeding (Table 5.2). It was possible to contact only 146/156 (93.6%) women (Figure 4.1), of who 128 (82.1%) had indicated an intention to breastfeed. The following data were collected from women who intended to breastfeed. While no statistical difference was observed among groups for women who maintained breastfeeding at 6-weeks postpartum, women who received i.m. pethidine reported greater difficulties in establishing breastfeeding (Table 5.2). Women identified the main difficulties experienced in the establishment of breastfeeding included the baby being too sleepy, and difficulties with attachment that resulted in cracked nipples (Table 5.2). The majority of women in both fentanyl groups reported no issues with establishing breastfeeding (60.6% i.n. fentanyl, 55.0% s.c. fentanyl), compared to significantly fewer women (21.2%) in the i.m. pethidine group ($p<0.01$) (Table 5.2).

Table 5.2   **Participant's experience of initiating and maintaining breastfeeding at 6-weeks postpartum**

Initiating breastfeeding	i.n. fentanyl	s.c. fentanyl	i.m. pethidine	p
Intent to exclusively breastfeed (%)	40/51a (78.4)	47/53a,b (88.7)	47/48b (97.9)	0.01
Received skin-to-skin in 1 hour (%)	37/44a,b (84.1)	48/50b (96.0)	36/46a (78.3)	0.04
Breastfed within 1 hour of birth (%)	31/39 (79.5)	38/47 (80.9)	27/44 (61.4)	0.07
Exclusively breastfeeding on discharge (%)	43/52 (82.7)	46/53 (86.8)	46/50 (92.0)	0.37
Maintaining breastfeeding				
Breastfeeding at 6 weeks (%)	31/ 39 (79.5)	39/46 (84.8)	29/43 (67.4)	0.12
No issues establishing breastfeeding (%)	20/33a (60.6)	22/40a (55.0)	7/33b (21.2)	<0.01
Issues with baby being sleepy (%)	1/33 (3.0)	3/40 (7.5)	8/33 (24.2)	n/a
Issues with baby unsettled (%)	0/33 (0.0)	3/40 (7.5)	1/33 (3.0)	n/a
Difficulties with attachment/cracked nipples (%)	9/33 (27.3)	11/40 (27.5)	17/33 (51.5)	0.06
Other issues with breastfeeding (%)	3/33 (9.1)	1/40 (2.5)	0/33 (0.0)	n/a

Note, p values are based on Chi-square test. Post-hoc tests for pairwise comparison with Bonferroni adjustment. Same subscript letters do not show significant difference and different subscript letters show significant difference between pair of groups at the .05 level, n/a indicates sample size was too small to analyse.

5.3 Women's experience of treatment effects

In addition to examining breastfeeding experiences at 6-weeks post-birth, question 10 of the Telephone Questionnaire (Appendix 13) enabled women who received treatment, regardless of allocation, to comment on their experience and intention to use the study drug again in a future labour. In total, 113/156 (72.4%) women received treatment, 41 women received i.n. fentanyl, 37 women received s.c. fentanyl, and 39 women received i.m. pethidine. Of the latter 39 women, 30 were randomised to i.m. pethidine, four women were randomised to i.n. fentanyl but also received i.m. pethidine over the course of their labour due to either a breach in protocol or as rescue analgesia post-treatment; a further five women received i.m. pethidine instead of their allocated treatment (only four of these five participants were contactable at the 6-week follow-up). Figure 4.1, provides details of why these five women received i.m. pethidine instead of their allocated treatment.

Parturients in the s.c. and i.n. fentanyl groups reported significantly higher satisfaction towards using the treatment again than women receiving pethidine i.n. fentanyl 34/41 (82.9%), s.c. fentanyl 29/36 (82.9%), i.m. pethidine 13/29 (44.8%); p<0.01. To provide further meaning comments made by the 112/113 (99.1%) participants were analysed and recurrent words and concepts grouped (Schneider 2013); three categories emerged—the physical, cognitive and emotional effects experienced by the women. These three categories were then classified into sub-categories relating to positive and negative experiences. Finally, the occurrence (frequency) of each sub-category was recorded for each group and a chi-square post-hoc analysis undertaken to examine differences among groups (Table 5.3). Extracts are included to demonstrate the variations in statements. Key words are underlined to provide examples on how the sub-categories were identified. In addition, examples also are provided for statements from women who received both i.n. fentanyl and i.m. pethidine. As seen in Table 5.3, more women from the fentanyl groups reported positive experiences from using the treatment. Even when positive and negative sub-categories were identified, the description of effects differed depending on which treatment was administered.

Table 5.3   Participant's experiences of treatment

Categories	Sub-categories	Frequency of distribution (%)			p
		i.n. fentanyl (n=41)	s.c. fentanyl (n=37)	i.m. pethidine (n=38)	
Physical experience	**Positive:** Excellent pain relief/relieved pain/more pain relief than nitrous oxide and oxygen /enabled relaxation/better break/able to be mobile	29.6	40.0	16.3	0.001
	Negative: Gave no relief/wore off too quickly/slowed everything down/not strong enough/felt sedated/sick	8.2	12.3	47.1	
Cognitive experience	**Positive:** Felt alert/better focused/felt really connected/gave a sense of calm/better able to cope/communicate/felt more in control	14.8	13.1	1.0	n/a
	Negative: felt out of it/didn't have a good experience/not remembering/distant/ disassociated	0	0	10.6	
Emotional experience	**Positive:** loved it/perfect/promoted it/amazing/great/easy to use/wonderful/really impressed/enabled me/didn't need EDB/better than epidural block	45.2	30.8	11.5	0.001
	Negative: lost confidence/left feeling fearful/anxious/disappointed/didn't help/didn't like it/preferred nitrous oxide and oxygen or epidural block	2.2	3.8	13.5	

Note. n/a = sample size was too small to enable a chi-square analysis

5.3.1 Positive physical, cognitive and emotional effects experienced

While the majority of statements made by women in the fentanyl groups identified at least one of the positive sub-categories for physical, cognitive and emotional effects (Table 5.3), statements made by 7/41 (17.1%) women from the i.n. fentanyl group, and 7/37 (18.8%) women from the s.c. fentanyl group included all three positive sub-categories. In contrast, only 1/38 (2.6%) woman administered i.m. pethidine was identified to report all three positive sub-categories. The following statements provide examples to demonstrate the variation in description of treatment effects, despite the identification of the same three positive sub-categories.

Participant 69 received i.n. fentanyl and her statement included the three positive sub-categories:

> *I was really <u>happy</u> with the intranasal fentanyl, it definitely <u>reduced the severity of the pain</u> – <u>numbed the pain</u>. <u>Beneficial</u> in allowing me to <u>cope</u> with the labour. It was <u>great I could self-administer</u>, very <u>happy</u> with the*

effect. Able to time doses well to give maximum benefit. I noticed the difference when I tried not to use it.

Participant 74 also used the i.n. fentanyl and reflected the same three positive sub-categories:

Intranasal fentanyl – <u>loved it</u>. I was really <u>happy</u> with it, would <u>recommend it</u> to everyone. I will want to use again and would chose a hospital based on its availability. I found it really <u>helped reduce the pain</u>, felt in <u>control</u>, think it's <u>brilliant</u>. Didn't need to use anything else.

Participant 33 provides an example of the three positive sub-categories identified when she received s.c. fentanyl:

The subcutaneous fentanyl was <u>really good</u>, definitely helped <u>take the edge off</u> the pain, allowed me to <u>cope</u> with the contractions. The gas (nitrous oxide and oxygen) also helped but by being a distraction rather than help with the pain or removing it. The gas made me feel funny but the fentanyl didn't have that effect. It (fentanyl) <u>was really good</u>.

Participant 138 also was administered s.c. fentanyl and her statement included all three positive sub-categories identified:

I really felt the subcutaneous fentanyl <u>helped</u> give me a sense of <u>calm</u> and <u>relaxation</u> between contractions even very close to birthing. Allowed me to <u>focus better</u> and it (s.c. fentanyl) <u>helped reduce the intensity</u> of the contraction <u>better than the gas</u> (nitrous oxide and oxygen).

Participant 63 was the only woman administered i.m. pethidine to express all three positive sub-categories, though she also experienced a negative physical effect:

With pethidine I was <u>more relaxed</u> between contractions, though it (pethidine) was <u>not very effective for pain</u>. I would consider using pethidine again in the same circumstances. <u>Happy with outcome overall</u>, feel it was a <u>good experience</u>.

When the frequency of identified positive sub-categories was examined, women in the i.n. fentanyl group were more likely to report positive emotional effects ($p<0.001$ chi-square post-hoc test) (Table 5.3), an example is provided by **Participant 64**:

Intranasal fentanyl <u>really helped</u> I <u>didn't need the gas</u> (nitrous oxide and oxygen) once I started using it. It was <u>amazing, I highly recommend it</u>. Definitely hope it becomes more available to women.

In contrast, women in the s.c. fentanyl group most frequently reported positive physical effects ($p<0.01$ chi-square post-hoc test) (Table 5.3). An example of a positive physical and emotional effect is provided by **Participant 88**:

Subcut(aneous) fentanyl definitely <u>took away the pain a lot more than the gas</u> (nitrous oxide and oxygen) did, so found it <u>really helpful</u>. <u>Didn't get any side effects</u>. Found it <u>really helped</u> get me through the labour I liked the gas at the start but it wasn't strong enough. The subcut(aneous) fentanyl <u>reduced the intensity</u> of the contractions.

Only 4/39 (10.3%) women administered i.m. pethidine reported a positive experience without also expressing a negative effect. Unlike the positive effects described by women in the fentanyl groups, the positive sub-categories frequently related to the avoidance of an adverse effect. An example is shown in the comment made by **Participant 123** who experienced both a positive physical and emotional effect:

<u>I'm happy</u> with the effect from pethidine as I don't <u>feel it (pethidine) had any side effects</u>. Seemed to give <u>a little help</u>.

5.3.2 Negative physical, cognitive and emotional effects experienced

Few comments from women in the fentanyl groups included all three negative sub-categories; 5/41 (12.2%) women in the i.n. fentanyl group, 3/37 (8.1%) women in the s.c. fentanyl group, compared to 19/39 (48.7%) women that received i.m. pethidine. Negative sub-categories were most frequently identified in statements made by women who received i.m. pethidine (Table 5.3).

The negative sub-category identified most frequently for all groups was negative physical effects (Table 5.3). Comments made by women that related to negative physical effects often included statements that the treatment did not meet their expectation for pain relief. Examples are provided as follows:

Participant 28 provided an example of a negative physical effect experienced from using i.n. fentanyl:

It <u>didn't feel like the intranasal helped (the pain)</u>, was experiencing a very painful labour, strong contractions. Happy to have the epidural to take all the pain away.

Participant 154 statement is an example of a negative physical effect experienced when s.c. fentanyl was used:

> *I wasn't happy with my birth experience. I wanted to move and vocalise but by being induced I was very restricted. I <u>didn't find benefit</u> from the (s.c.) fentanyl. Felt <u>needed strong relief</u> so accepted advice to use an epidural, the epidural gave complete relief.*

In contrast, women administered i.m. pethidine were more likely to comment on negative physical effects that related to both the absence of pain relief and/or adverse effects experienced ($p<0.001$ chi-square post-hoc test) as seen in the statement by **Participant 41**:

> *It (pethidine) <u>didn't work</u>. I really <u>didn't like</u> the pethidine <u>it didn't help</u> at all with the pain, it just <u>made me feel really drowsy</u>.*

When frequency of sub-categories was analysed, it was noted that while women in the fentanyl groups reported negative effects, their comments frequently also included positive sub-categories. **Participant 61** provided an example of both a negative and positive physical, and positive cognitive sub-categories:

> *I <u>couldn't feel a change</u> in the intensity of the pain but did feel I was able to <u>focus better</u> and <u>cope</u> with the contractions. Was much <u>more relaxed</u> when using the intranasal fentanyl despite still experiencing <u>strong pain</u>. I had hoped not to get the intranasal fentanyl as I thought I would prefer a drug with a longer action so didn't need to use so frequently. I had hoped to get the subcutaneous fentanyl or the pethidine.*

Participant 54 provided an example of a negative physical and a positive cognitive and emotional sub-category when s.c. fentanyl was used:

> *I was more <u>calm</u> with the (s.c.) fentanyl. <u>Liked</u> that I could have it (fentanyl) more frequently when needed. <u>Didn't notice a real difference in pain</u> but did <u>cope better</u> with it (pain).*

In the i.m. pethidine group the majority of statements only focused on the negative effects of the treatment. The comment made by **Participant 8** is an example of a statement that included a description of both negative physical and cognitive effects experienced:

> *The pethidine <u>knocked me out</u>. It (pethidine) <u>didn't help with the pain</u>. Made me sleep between contractions but <u>wasn't a good experience</u>.*

5.3.3 Intramuscular pethidine compared to intranasal fentanyl

As previously identified, four of the women contacted received both i.n. fentanyl and i.m. pethidine. All four women commented that i.n. fentanyl provided more pain relief than i.m.

pethidine. For example, **Participant 7** requested alternative analgesia after 2 hours of i.n. fentanyl use and was administered i.m. pethidine.

The comment made by **Participant 7** included both negative physical and cognitive sub-categories with the use of i.m. pethidine, whereas positive physical and emotional sub-categories were identified from the description of her use of i.n. fentanyl.

> *Pethidine <u>slowed everything down</u>, I really <u>didn't like the experience</u> – I felt <u>really out of it</u>. At the time I wasn't sure if the intranasal fentanyl was helping but after using the pethidine I was more <u>aware that it had been</u>, <u>without causing the high or sedation</u>.*

Participant 44 had been administered pethidine overnight when labour had established and, due to a breach in protocol, was randomised 7.4 hours later to receive i.n. fentanyl an hour before she gave birth. As shown below, the comment by **Participant 44** included both positive emotional and cognitive sub-categories for the description of the use of i.n. fentanyl. This contrasts to the negative cognitive and physical sub-categories identified from her statement about the use of i.m. pethidine.

> *I <u>really liked</u> the intranasal (fentanyl) spray I felt able to <u>cope and focus</u>, it <u>allowed me to push</u> as I had been overwhelmed with the whole induction and frequency of contractions and couldn't do anything due to constant pain, there was no break between contractions. Pethidine though made me <u>feel out of it</u> I <u>kept falling asleep</u> and <u>not remembering</u> what I was doing. The gas was also horrible it made me feel out of control. <u>I couldn't have done it without the intranasal fentanyl</u>.*

5.4 Summary

In this chapter the postpartum findings, including neonatal outcomes, breastfeeding experiences and perceived treatment effects have been reported. Data for neonatal outcomes suggest treatment did not adversely affect Apgar scores or the establishment of breathing. However, the intrapartum administration of i.n. fentanyl and s.c. fentanyl resulted in fewer nursery admissions when compared to i.m. pethidine. Furthermore, women who received either i.n. fentanyl or s.c. fentanyl experienced fewer difficulties in establishing breastfeeding by 6 weeks postpartum.

Examples of comments made by the participants were included to illustrate the depth and diversity of the treatment effects experienced. When the comments were grouped into categories and sub-categories the positive sub-categories were seen most often in women from the fentanyl groups. The positive emotional sub-category was identified with greater frequency among women in the i.n. fentanyl group, compared to women in either the s.c. fentanyl or i.m. pethidine groups. Both fentanyl groups had only low frequencies of negative sub-categories. In contrast, women in the i.m. pethidine group had greater frequency of all three negative sub-categories, with negative physical effects being identified most often. This chapter completes the presentation of the results of the Trial. Chapter 6 discusses the findings and considers the strengths and weaknesses of this Trial together with suggestions for future research.

Chapter 6 Discussion and conclusion

Pethidine administered intramuscularly is the most commonly used opioid for women in labour who are either unwilling or unable to use an epidural, but wish to use an opioid for pain relief. However, pethidine is reported to produce numerous adverse effects. It, therefore, is important that a variety of effective pain relief options be available to enable women more choice to individualise their care.

The present study examined whether fentanyl administered via the i.n. or s.c. routes was at least as efficacious as the standard practice of administering i.m. pethidine. While all treatment groups in this Trial received clinically important reductions in pain scores at 30 minutes (Table 4.3, p. 78), significant differences were observed when examining secondary outcomes. More than 80% of women in the fentanyl groups reported their preference to use the treatment again, compared to only 44.8% of women in the i.m. pethidine group (Table 4.4, p. 80). Women in the fentanyl groups also experienced less sedation and shorter labour durations than those in the pethidine groups (Tables 4.5, p. 81 & 4.4, p. 80 respectively)

Babies born to mothers in the fentanyl groups had significantly fewer neonatal nursery admissions and experienced less difficulty in establishing breastfeeding, than those born to mothers in the pethidine group (Tables 5.1, p. 84 & 5.2, p. 86 respectively). Overall, the findings of this Trial provide evidence that suggest fentanyl administered by either the i.n. or s.c. route during labour produced fewer adverse effects for both mother and neonate, than those who received i.m. pethidine.

6.1 Analgesic effect and satisfaction with treatment drug

The primary outcome of the study was to compare the efficacy of fentanyl administered via the i.n. or s.c. route, with i.m. pethidine for labour analgesia measured using the VAS at 30 minutes post-treatment. Although no studies have been undertaken to validate a clinically important

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change in pain intensity for labouring women (Carvalho & Cohen 2013), studies undertaken in acute care settings have reported a change in VAS pain intensity of 0.9cm–1.3cm to be clinically important (Gallagher et al. 2001; Kelly 1998; Powell et al. 2001;Todd et al. 1996). Thus, the findings from this study support the notion that all treatment groups received a clinically significant reduction in pain scores (mean reduction: 1.2 i.n fentanyl, 1.1 s.c. fentanyl, 1.6 i.m. pethidine1; p<0.001). This result is consistent with two previous studies (Douma et al. 2010; Rayburn et al. 1998) that demonstrated that i.v. fentanyl resulted in equivalent pain relief to i.m. pethidine for women in labour.

When reviewing analgesic effect it should be acknowledged that not all women want to be pain free. Instead, as one review identified, women want to be able to cope with the pain of labour (Ross 1998), and even severe pain is not always reported as having negative effects (Rowland & Permezel 1998). Personal control during childbirth has been identified as an important factor related to women's satisfaction with the childbirth experience (Goodman et al. 2004; Ross 1998). Therefore, it also was considered important to determine the women's overall experience of personal control during childbirth, measured on the LAS, as well as to determine the participants' preference to use the treatment again. In a recent study undertaken by Schwenkglenks and colleagues (2014), patient involvement in decision-making and maintenance of control were considered the main contributing factors when determining satisfaction of pain relief. In addition, Schwenkglenks et al. (2014) identified a positive correlation between satisfaction with treatment for pain management and more pain relief received.

In the current study, no significant difference was detected among groups when examining feelings of personal control during labour (Table 4.4 p. 80). However, the majority of women in the fentanyl groups reported a preference to use the treatment again in a subsequent labour

compared to those in the i.m. pethidine group (Table 4.4 p. 80). It is not known whether satisfaction with the drug was influenced by the differences in treatment regimens, such as having the ability to self-administer the treatment every few minutes (i.n. fentanyl), or the ability to request repeat doses at 15-minute intervals (s.c. fentanyl), in contrast to a repeat dose after 3 hours (i.m. pethidine). Self-determination of the frequency of dosing may have increased the participant's ability for decision-making in pain treatment. Ross (1998) reported involvement in choice of technique, timing and availability of analgesia was critical to satisfaction. It should be noted that high levels of satisfaction with treatment were expressed by women in the fentanyl groups, even though this Trial did not enable the participant to choose which drug or technique was administered.

Satisfaction with the drug, and hence intention to use the treatment again, may also have been influenced by the reduced prevalence of adverse effects and the ability to mobilise (Ross 1998). In this Trial, participants in the fentanyl groups experienced fewer adverse effects than those in the pethidine group. In addition, women in the fentanyl groups were more likely to mobilise, possibly due to less sedation. This mobility may have allowed them to adopt a variety of positions to help ease painful contractions. Statements made by participants when followed up at 6-weeks postpartum supported this notion.

Intention to use the treatment again in a subsequent labour was explored further through a content analysis of statements made by participants to describe the effects of treatment (Table 5.3 p. 88). Results of the analyses demonstrated a greater frequency of positive physical, emotional and cognitive effects for women in the fentanyl groups, than for those in the i.m. pethidine group (Table 5.3 p. 88). Women in the i.m. pethidine group most often reported negative physical effects from treatment and equivocal positive and negative emotional sub-themes. Only one other study was identified that specifically explored women's experiences of

opioid analgesia use during labour (Jantjes et al. 2007), and identified findings similar to this Trial. Jantjes et al. (2007) examined the emotional experiences of primipara women who used pethidine combined with an antihistamine, hydroxyzine, during labour and discussed their experiences, which varied between expressions of joy and happiness to anxiety, anger and despondence (Jantjes et al. 2007), further highlighting the potential for pethidine use to elicit such contrasting emotional responses.

6.2 Maternal physiological effects post-treatment

Labour duration was examined to explore whether the treatment had an effect on the length of labour. In this study, women from both fentanyl groups demonstrated significantly shorter labours by at least 2 hours, when compared to the i.m. pethidine group (Table 4.4 p. 80). When Douma et al. (2010) compared the analgesic effect of pethidine and fentanyl administered via i.v. PCA to women in labour, they did not identify any significant differences in labour length between groups. It is unknown why their findings were different and may relate to differences in research design. Shoorab et al. (2013) also examined i.v. fentanyl and observed a reduction in the active phase of labour by approximately 2 hours. While these results are similar to those seen in this Trial, they are difficult to interpret as the comparator group used a placebo. Findings from previous studies that have examined the effects of pethidine on labour duration also are conflicting (Khooshideh & Shahriari 2009; Sosa et al. 2004; Tamer et al. 2012).

Labour duration is affected by uterine contractibility, nausea, sedation, mobility (Lawrence et al. 2013; Lowe 2002), and epidural use (Anim-Somuah et al. 2005). Although this Trial did not observe frequency or duration of uterine contractions during labour, previous studies have examined the uterine effects of i.v. fentanyl and reported no significant changes to uterine blood flow or tone (Atkinson et al. 1994; Craft et al. 1983), which indicated fentanyl use did not impede uterine activity. As pethidine has been shown to cause muscle relaxation (Jordan

2010), it is plausible to consider that pethidine may decrease uterine activity and thereby increase labour duration.

In this Trial, proportionately more women in the i.m. pethidine group received an anti-emetic and were observed to be sedated during labour (Table 4.5 p. 81). This finding may be explained when the different mechanisms of action of pethidine and fentanyl are considered. Both drugs bind to mu and kappa receptors, which promote sedation. Yet unlike fentanyl, pethidine has a strong affinity to the kappa receptor, which induces both sedation and dysphoria, potentially heightening the experience of these adverse effects (refer to Chapter 1.3.2). Previous studies have demonstrated that pethidine is associated with increased sedation, as well as nausea and vomiting, when compared to other opioids (refer to Cochrane review by Ullman et al. 2010).

Anti-emetics used to treat nausea and vomiting, commonly promethazine or metoclopramide, also have been shown to contribute to adverse effects, such as sedation and dizziness (Tan et al. 2010). In South Australia, prophylactic administration of an anti-emetic has become routine practice with the use of pethidine, even though this practice is discouraged by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, as no benefit has been identified when compared with selective administration (Macintyre et al. 2010). In this Trial approximately one-third of women from the i.m. pethidine group were administered metoclopramide prophylactically, breaching protocol. The common practice of combining these drugs was believed to be the reason for this breach. Despite this breach, an additional 25.9% of women required an anti-emetic within 30 minutes of receiving i.m. pethidine. It therefore is unknown if the women treated prophylactically would have experienced nausea and/or vomiting had they not been treated, or whether the treatment contributed to other adverse effects, such as sedation.

In this Trial, no women in the fentanyl groups were administered a prophylactic anti-emetic and few women required an anti-emetic post-treatment, incidences of sedation also were low (Table 4.5 p. 81). These findings are consistent with those reported by Grape et al. (2010) where the use of fentanyl administered by alternative routes has been shown to be well tolerated (Grape et al. 2010). Similarly, Rayburn et al. (1989) observed reduced sedation and anti-emetic use with the use of i.v. fentanyl, compared to i.v. pethidine.

Mobilisation and adopting upright positions in the first stage of labour have been shown to reduce duration of labour, epidural use, and the risk of caesarean section, without requiring further intervention or resulting in adverse effects on mother or neonate (Lawrence et al. 2013). The position of the parturient in labour also has been identified to significantly affect pain perception, with upright positions observed to reduce pain intensity (Lowe 2002). This may, in part, explain the results from this Trial where more women in the i.n. fentanyl group remained upright throughout labour, both pre and 30 minutes post-treatment, and fewer women crossed-over to epidural analgesia, when compared to both the s.c. fentanyl and i.m. pethidine groups (Table 4.4, p. 80).

Ease of administration of the PCINA device also was postulated to contribute to the participant's ability to remain upright, both immediately prior to and 30 minutes post self-administration of i.n. fentanyl. Whereas, in the s.c. fentanyl and i.m. pethidine groups the need for the midwife to administer an injectable drug may have resulted in the women being asked to adopt a semi-reclined position for administration. Lawrence et al. (2013) suggested recumbent positions are often promoted by care providers because they provide convenient access to the mother.

While mobility was not examined in the study by Douma et al. (2010), significantly more women (34%) in the pethidine group crossed-over to epidural analgesia compared to women

(15%) in the fentanyl group (p<0.05). Douma et al. (2010) also reported significantly more women who utilised i.v. PCA fentanyl achieved a spontaneous vaginal birth (85%), compared to 69% in the i.v. PCA pethidine group (p<0.05). In this Trial no statistical difference was observed for mode of birth. It is unclear if the different route of administration may have contributed to this finding or other differences in research design. However, the most recent South Australian Pregnancy Outcome data reported in 2011 that 55% of women birthing in South Australia had normal spontaneous vaginal births, 6% had an assisted birth and 33% had a caesarean section (Scheil et al. 2013). While the proportion of women who had spontaneous vaginal birth was comparable, the rate of caesarean section was lower in our study (Table 4.4 p. 80). Further research with an appropriate power is warranted to explore this outcome, as increased operative delivery has significant implications for both maternal and neonatal wellbeing.

6.3 Neonatal outcomes post-treatment

The most alarming effect of an opioid reported in the popular press that influences maternal decisions for analgesia in labour, relates to the possibility of respiratory depression in the newborn. There is no conclusive evidence, however, to support this premise. It should be noted that few studies have examined neonatal effects of intrapartum opioid use as a primary outcome. Respiratory depression in the newborn is determined by time to establish breathing, Apgar scores and cord pH. In this study, no statistically significant differences were seen in these parameters. This finding is consistent with the majority of studies undertaken in the past 10 years that have examined the parenteral use of pethidine and fentanyl for labour analgesia (Tables 2.6a,b,c, pp. 44, 45, 46). Similarly, the Cochrane review undertaken by Ullman et al. (2010), which included over 7000 women, concluded that there was no clear evidence of adverse neonatal effects with the use of opioid analgesia during labour. Some studies not included in Ullman et al.'s (2010) review found that pethidine was associated with reduced

arterial cord blood (Mansoori& Cheater 2000; Sosa et al. 2004; Yudkin et al. 1987). This has significant implications, as low arterial cord blood pH at birth has been associated with neonatal mortality and morbidity, including cerebral palsy (Malin et al. 2010).

The most concerning perinatal outcome observed in the current study was the difference in nursery admissions, with significantly more neonates from the i.m. pethidine group compared to neonates in the fentanyl groups being admitted to SCBU (Table 5.1 p. 84). While few recent studies have examined nursery admission (Table 2.1a,b, p. 21, 22), Sosa et al. (2004) reported a significant increase in neonatal care unit admissions for neonates whose mothers had been administered 100mg i.v. pethidine, compared to placebo. In addition, previous research has shown early separation due to nursery admission impacts on mother–infant bonding (Kearvell & Grant 2010). Few studies that examined the effect of intrapartum opioid analgesia in newborns have looked at longer term effects past the neonatal period (Jones et al. 2012).

6.4 Treatment effects on breastfeeding

Early separation of infant and mother due to nursery admission has been related to difficulties in the initiation of breastfeeding (Rajan 1994). This finding may explain the increased difficulties in establishing breastfeeding experienced by women in the i.m. pethidine group in this Trial (Table 5.2 p. 86). Previous studies have suggested pethidine adversely affects establishment of breastfeeding (Nissen et al. 1997; Rajan 1994) as it is associated with neonatal drowsiness and irritability, which may impact on the commencement of breastfeeding at birth (Belsey et al. 1986; Ransjo-Arvidson et al. 2001; Wee et al. 2014). Few studies, however, have explored the effects of perinatal opioid administration on behaviour and breastfeeding past the newborn period. The paucity of studies has been highlighted in the review by Jones et al. (2012), which found that only two out of 57 trials examined the effects of intrapartum pethidine use and none examined the use of fentanyl on breastfeeding as an outcome. In this Trial,

neonatal breastfeeding behaviour was not assessed by an independent practitioner at birth, but at 6 weeks few women recalled issues with their baby being sleepy or unsettled (Table 5.2 p. 86).

Several variables have been attributed to a woman's ability to successfully breastfeed including age, education, return to work and intention to breastfeed (Tawia 2012). In this Trial, when these variables were compared among groups, the only significant difference observed was intention to breastfeed (Table 5.2 p. 86). Despite significantly more women in the i.m. pethidine group reporting their intention to breastfeed, no significant differences were observed at 6 weeks for neonates maintaining breastfeeding. In fact, significantly more women in the i.m. pethidine group reported difficulties establishing breastfeeding, compared to women in either fentanyl group (Table 5.2 p. 86). These results are consistent with two studies that reported a negative association between intrapartum opioid use and the initiation of breastfeeding, but not overall duration of breastfeeding (Crowell et al. 1994; Riordan et al. 2000).

When considering the potential for opioid transfer in breast milk, the Australian and New Zealand College of Anaesthetists reported that fentanyl is safe in the lactating mother and preferred over pethidine (Macintyre et al. 2010). A previous study has shown that fentanyl has low oral bioavailability (33%) and only small amounts of colostrum are consumed in the first few days post-birth, indicating fentanyl was safe for use in breastfeeding women (Steer et al 1992). In contrast, the oral bioavailability of pethidine is 50–60% (Vallejo et al. 2011), this, in addition to the presence of the active metabolite, norpethidine, has been shown to result in considerable levels in breast milk (Quinn et al.1986). Belsey et al. (1981) identified that increased pethidine exposure may significantly impact on the neonate's behaviour for the first few weeks of life; therefore, fentanyl should be recommended to women intending to breastfeed.

6.5 Treatment dosage regimens

This study is the first to provide data relating to fentanyl dosage when administered via the i.n. route to women during labour, and the second to examine the use of s.c. fentanyl for pain relief during childbirth. Larger doses of fentanyl were administered via the i.n. route compared to the s.c. route (Table 4.2 p. 73). This may be explained by the slower absorption and time to peak concentration in the blood of s.c. fentanyl (Capper et al. 2010), as opposed to i.n. fentanyl (Lim et al. 2003).The median total dose of300 micrograms in the s.c. fentanyl group was less than dosages previously reported for i.v. PCA fentanyl in childbirth (mean total dose ranged between 400 and 1025 micrograms; Fleet et al. 2011, 2014; Ullman et al. 2010).While there are limited data available relating to the pharmacokinetics of s.c. fentanyl, Capper et al. (2010) studied a single 200 microgram bolus dose of s.c. fentanyl in healthy male volunteers. Their results identified that the median maximum concentration of fentanyl was reached at 15 minutes and the mean terminal half-life was 10 hours. These results suggest a slower absorption and time to peak concentration in the blood when fentanyl was administered via the s.c. route and may explain the reduced cumulative dose seen in this Trial.

While opioid administration by i.v. PCA has been shown to lead to higher opioid consumption compared to intermittent parenteral administration, i.n. fentanyl administration also requires higher doses (Macintyre et al. 2010) due to the bioavailability of the i.n. route (55–89%) (Christrup et al. 2008; Lim et al. 2003; Striebel et al. 1993). However, the total cumulative dosage used by the i.n. fentanyl group in this Trial also was less than the majority of previous studies that examined i.v. PCA fentanyl (Douma et al. 2010; Fleet et al. 2011), a surprising result. Christrup et al. (2008) reported the i.n. route takes 12.8 minutes to reach maximum concentration in the blood, compared to 6.0 minutes via the i.v. route, although duration of effect does not significantly differ (56 and 59 minutes respectively) between the two routes. It, therefore, is unclear as to why the i.n. fentanyl route in this study resulted in reduced total dose.

Whether physiological changes in pregnancy may have influenced these results is unknown, as there are no published studies on the pharmacokinetics of i.n. or s.c. fentanyl in pregnant women. This finding warrants further investigation as dose reduction is one strategy that can be implemented to minimise the adverse effects of opioids (Swegle & Logemann2006).

Studies that have examined i.m. administration of pethidine have reported various dosage regimens, ranging from fixed 50 to 150 milligram doses (Table 2.2b p. 27) and individualised doses of 1 milligram/kg combined with 25 milligram promethazine (Shahriari & Khooshideh 2007). The highest maximum total dose was set at 300 milligrams/2 hours (Wee et al. 2014), although no studies reviewed reported cumulative doses greater than 150 milligrams (Table 2.2b p. 27). In the current study, only three women requested a further dose following the initial 100 milligram bolus, despite all women having the ability to request an additional dose within 3 to 4 hours. While it might be argued that the differences in treatment regimens for this study may have impacted women's ability to initiate further treatment, Douma et al. (2010) found that even when i.v. PCA pethidine was available at 10-minute intervals, no women exceeded 200 milligrams in a 5-hour period.

This Trial set the maximum dose at 200 milligrams, as previous research has demonstrated higher incidents of adverse neonatal outcomes following multiple doses of pethidine due to the longer time taken for clearance of the drug and the accumulation of the active metabolite norpethidine (Kuhnert et al. 1985). In addition, blood levels of pethidine in the fetus have been reported as comparable to those seen in the mother but are sustained longer, and have been shown to significantly depress neonatal behaviour for the first few weeks of life (Belsey et al. 1981).

6.6 Strengths and weaknesses of the study

This RCT is the first to explore the less-invasive methods of administering i.n. and s.c. fentanyl for women during childbirth. In particular, this study provides useful data relating to dosage and effects of treatment. Due to different techniques for administration of the treatment and drug action times it was not considered feasible to blind this study. Nevertheless, the lack of blinding could contribute to participant or practitioner bias. All women in this study were provided with continuous 1:1 support in active labour, however, differences in technique of administration and practitioners' involvement in care may have influenced expectations, which were not examined in this study.

Dosage regimens were established based on those currently used in practice rather than the equipotency of each drug. While previous studies have examined analgesic effects of different dosage regimens of pethidine and report similar findings to this study, future research is warranted to determine optimal dosage for the use of i.n. and s.c. fentanyl in labour.

The sample size was powered for the primary outcome to determine the analgesic efficacy of the treatment at 30 minutes. Results relating to pain scores measured at subsequent time-points and secondary outcomes need to be interpreted with caution due to small sample sizes. These include, for example, breach of protocol for anti-emetic use where a large proportion of the i.m. pethidine group received a prophylactic anti-emetic, missing data for arterial cord blood pH and pain scores undertaken after the 30-minute time-point. In addition, women enrolled in the study had a preference to avoid an epidural, were predominately primigravida, and the majority underwent inductions of labour. Although this population of women are more likely to require additional analgesia (Kelly et al. 2009), it is acknowledged that this limits the generalisability of these findings to other populations.

Intention-to-treat analysis was undertaken for the majority of data, including baseline characteristics, birth and neonatal outcomes, however, data relating to analgesic effects over time were missing for untreated women, as the study protocol required VAS and vital signs to be recorded immediately prior to administration and 30 minutes post-administration. Therefore, if the participant did not receive the treatment, their data were not recorded for these time periods and could not be included in the analysis. In addition, the majority of women in the i.m. pethidine group only received one treatment so comparisons among groups could not be made for subsequent time-points.

6.7 Recommendations for future research

Factors that require further exploration include; satisfaction with treatment methods, influence of participants' expectations of treatment, practitioner involvement, optimal dosage regimens, analgesic effects for the duration of labour, neonatal outcomes, and economic implications. While reductions in pain scores were similar among groups, significantly more women in the fentanyl groups reported an intention to use the treatment again ($p < 0.01$). This suggests greater satisfaction with fentanyl than pethidine, possibly due to the participants experiencing fewer adverse effects and/or preferring the mode of administration of the treatment. In acute care settings, patient preference for the s.c. route has been established when compared to the i.m. route (Capper et al. 2010) and i.n. fentanyl administration has been shown to have a similar safety profile for children and adults in both the pre-hospital and hospital settings (Panagiotoul & Mystakidou 2010). Although the i.m. route is still used in acute settings, it is no longer the preferred option for opioid administration (Taylor et al. 2007) as it is considered painful and provides no pharmacological benefit (Portenoy 2011). Therefore, there is a strong argument to further explore i.n. and s.c. administration of opioids in childbirth.

One aspect relating to mode of administration that requires further investigation is participants' experience in the technique of administration. Although this current study considered participant satisfaction to use the treatment again, it did not consider this issue. Preference for route of administration may be affected by the perception of autonomy (Hudcova et al. 2006), and may explain the overall generally positive comments made by women in relation to i.n. fentanyl, which was administered using the PCINA device. Yet, preference for route of administration also may be affected by a placebo effect (Hui et al. 2014). This could be influenced by the participants' expectations that a treatment would provide benefit and/or by the practitioners' expressed attitudes towards the treatment provided (Porto 2011). Further research should consider participants' expectations prior to treatment, as well as how practitioners' involvement in care may influence these expectations.

Another area that requires further research is the dosage regimen that would be optimal for the different routes of fentanyl administration. In the current study, when considering differences between the two fentanyl groups, it was noted that larger doses of fentanyl were administered via the i.n. route compared to the s.c. route (Table 4.2 p. 73). This may be explained by the slower absorption and time to peak concentration in the blood (Capper et al. 2010) as opposed to i.n. fentanyl (Grape et al. 2010). However, no studies were found that examined the pharmacokinetics of either i.n. fentanyl or s.c. fentanyl in the obstetric population. Furthermore, a clinically important finding of this study that requires further investigation was the data relating to cumulative dosage. As previously discussed, the median total dose of 300 micrograms in the s.c. fentanyl group and 486 micrograms in the i.n. fentanyl group were less than the total dosage previously reported in the majority of studies that investigated i.v. PCA fentanyl in childbirth (400–1025 micrograms). The identification of suitable techniques that enable the reduction of total opioid consumption, thereby reducing the potential for drug

accumulation while still producing adequate pain relief, have potential benefits for both mother and neonate.

Few studies, including this one, were sufficiently powered to adequately examine a number of clinically important issues including, differences in pain scores between treatment groups over time, epidural rates, length of labour, nursery admissions, effects on the initiation of breastfeeding, and mother–infant bonding. Much larger studies are warranted to determine the effects of opioid treatment on these matters.

If alternative routes of fentanyl administration can be shown to produce fewer adverse effects, not only does this benefit the mother and neonate, it also has economic implications. Both the i.n. and s.c. mode of administration do not rely on availability of anaesthetic staff, or equipment that has the potential for program error. In addition, use is not restricted to controlled settings, thereby enabling its use in all maternity units, including those in rural and remote areas. Additionally, future research is required to examine economic costs that consider use of resources and services; these include potential reduction in anaesthetic costs, nursery admissions, domiciliary services, and medical reviews or referral to lactation consultants. In summary, future research is required to explore patient preference for mode of administration, optimal dosage, maternal and neonatal effects and potential cost implications.

6.8 Implications for clinical practice

This study addressed the need to identify alternative pharmacological forms of pain relief that offer women additional choices to individualise their labour care. Findings of this RCT demonstrated that i.n. and s.c. fentanyl is as effective at relieving labour pain as i.m. pethidine, yet produces fewer adverse effects. This has significant implications for clinical practice that include identification of an alternative opioid and routes of administration to increase options for labour care. The less-invasive i.n. and s.c. routes require few resources, which should

increase access and availability to all maternity settings; in addition, the treatment protocols provide clear guidelines for use, as outlined in more detail below.

6.8.1 Additional choice for parenteral analgesia during childbirth

The i.n. and s.c. routes offer women additional choices for administration of analgesia during childbirth. Benefits include greater flexibility for settings that may have limited resources, as well as reduced labour length by at least 2 hours, potentially decreasing labour ward stay. In addition, fentanyl is recommended as safe for lactating women and is preferred over pethidine. Advantages of the i.n. route include self-administration through the use of a PCINA; the disposable device provides a controlled dose and increases autonomy, without restricting mobility. The ability to mobilise in labour is associated with reduced pain intensity, shorter labours and the potential to reduce epidural use. This is significant for women who may prefer to avoid an epidural or when epidural analgesia is ineffective or unavailable. Furthermore, the i.n. route is non-invasive and offers women with a needle phobia an option to receive parenteral opioid administration in labour.

6.8.2 Availability and access

Both i.n. and s.c. fentanyl require few resources and use is not restricted to controlled settings. These routes of administration do not require specialised anaesthetic staff, enabling use in all maternity settings, including those in rural and remote areas. Fewer adverse effects have significant implications to reduce the need for resource use, such as anaesthetic services, transfer to neonatal nursery, domiciliary services, and/or lactation consultants. These services have both economic and social costs to mother, neonate and community.

6.8.3 Treatment protocols

The treatment protocols developed for this study provide a baseline for future clinical practice and research in obstetric populations. These treatment regimens demonstrated reduced total cumulative dosage when compared to i.v. PCA, which has safety and cost implications.

6.9 Conclusion

In summary, while both fentanyl and pethidine were shown to produce effective pain relief in labour, the Trial findings are consistent with other studies that demonstrated pethidine negatively affected maternal outcomes, including increased nausea and vomiting, sedation, prolonged labour and also influenced the woman's ability to adopt upright positions. This current study also supports findings that have been shown in other non-obstetric settings, that fentanyl administered via alternative routes was well tolerated, efficacious and produced few adverse effects. In the neonate, pethidine was associated with increased admission to neonatal nursery and difficulties with initiation of breastfeeding.

Pain relief choices for women in labour are often limited to what is available at the different hospitals. While pethidine continues to be reported as the most commonly administered opioid in obstetrics, it is no longer the preferred option for most acute care settings. This study provides an important contribution for pain relief options in labour that are less invasive and previously unreported in the obstetric setting. These alternative modes of fentanyl administration offer women additional choices for labour care and reduced potential for adverse effects. Furthermore, facilities with limited resources and/ or in rural and remote areas may benefit with the potential to use fewer specialist services and reduced neonatal transfer.

Appendix 1a: Fentanyl studies reviewed (n=5)

Author/ country	Title/Study type/ NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Douma et al. (2010)* The Netherlands	***Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour.*** Level II Double-blinded RCT Aim: To compare the analgesic efficacy of i.v. PCA remifentanil, i.v. PCA fentanyl and i.v. PCA pethidine for pain relief in labour. Findings: PCA remifentanil provided better analgesia than fentanyl and pethidine for the first hour of treatment; remifentanil [-3.2 (SD 2.9) cm], fentanyl [-1.4 (2.4) cm], pethidine [-0.8 (2.2) cm]. In all groups, pain scores returned to pre-treatment values within 3h after the initiation of treatment. Significantly less women in the fentanyl group crossed over to epidural analgesia compared to pethidine group (15% vs 34%). 85% of women in the fentanyl group achieved a spontaneous vaginal birth compared to 69% in the pethidine group.	**159 parturients** healthy term pregnancies. **Group 1**: i.v. PCA remifentanil 40µg loading dose and 40µg per bolus with a lockout of 2min and a max limit of 1200µg/ h (n=52). **Group 2**: i.v. PCA pethidine 49.5mg loading dose and 5 mg boluses with a lockout of 10min and a maximum overall dose limit of 200mg (n=53). **Group 3**: i.v. PCA fentanyl 50µg loading dose and boluses of 20µg with a lockout of 5min and a max limit of 240µg/h (n=54). **Primary outcome** was to compare the analgesic efficacy of remifentanil with pethidine and fentanyl as measured by a difference in VAS pain scores.	Sample size not achieved. Sample size calculation required 60/group to achieve power
Fleet et al. (2014) South Australia	***Subcutaneous administration of fentanyl in childbirth: An observational study on the clinical effectiveness of fentanyl for mother and neonate.*** Level III-3 Retrospective audit and small prospective pilot study convenience sampling Audit Aim: To investigate maternal and neonatal effects when s.c. fentanyl was administered during labour Pilot Study aim: To examine analgesic effect of s.c. fentanyl for pain relief during childbirth. Audit findings: Fentanyl was associated with a longer duration of labour than women who did not receive pharmacological pain relief. Length of hospital stay, breastfeeding rates and neonatal outcomes were comparable between groups. Pilot findings: Fentanyl was efficacious in providing pain relief.	Audit: **467 parturients** with uncomplicated term pregnancies. **Group 1:** s.c. fentanyl 200µg bolus dose. After 1h, additional 50µg doses every 15min prn (n=75). **Group 2:** nitrous oxide and oxygen prior to s.c. fentanyl 200µg bolus dose. After 1h, 50µg doses could be administered every 15min prn (n=196). **Group 3:** no pharmacological pain relief (n=196). Pilot: **10 parturients** with uncomplicated term pregnancies. **Primary outcome** not stated. Objective to explore the maternal and neonatal effects of s.c. fentanyl administration	Not randomised. Retrospective audit. Baseline characteristics differed; more women in the fentanyl group had an induction of labour. Small sample size of 10 for the pilot study.

*Only study under review to directly compare i.v. PCA fentanyl with i.v. PCA pethidine

Author/ country	Title/ Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/ primary outcome	Limitations
Halpern et al. (2004) Canada	***A Multicentre Randomized Controlled Trial Comparing Patient-Controlled Epidural with Intravenous Analgesia for Pain Relief in Labor*** Level II Multicentre RCT Aim: To determine whether epidural analgesia increases the incidence of caesarean delivery when compared to i.v. fentanyl. Findings: No difference between groups for caesarean or instrumental birth. Shorter duration of second stage of labour in fentanyl group by a median of 23min. However, 43% of the fentanyl group crossed over to epidural analgesia	**242 parturients** healthy, term nulliparous singleton pregnancy in vertex presentation **Group 1**: i.v. fentanyl 100μg over 1–5min, an additional 50μg was given and repeated every 5min until adequate pain relief achieved. PCA bolus set at 25-50μg of fentanyl with a 10min lockout. Dosage increased or decreased at discretion of the anaesthesiologist (n=118). **Group 2**: PCEA with 0.08% bupivacaine and fentanyl 1.6μg/mL (n=124). **Primary Outcome** Reduction in caesarean delivery rate.	Non-blinded study Approximately 485 patients per group were needed. Study underpowered
Marwah et al. (2012) Canada	***Remifentanil versus fentanyl for intravenous patient-controlled labour analgesia: an observational study.*** Level III-3 Retrospective cohort study Aim: To compare i.v. PCA remifentanil with fentanyl for analgesic efficacy and adverse maternal/neonatal effects in labour. Findings: Both remifentanil and fentanyl provided moderate pain relief, maternal oxygen desaturation was more common with remifentanil. Fentanyl was associated with increased neonatal resuscitation.	**98 parturients** >24 weeks of gestation at Mount Sinai Hospital. **Group 1**: i.v. PCA remifentanil bolus 0.25μg/kg with a lockout interval of two minutes, a 4h limit of 3mg, and a background infusion of 0.025–0.05μg/kg/min (n=47). **Group2**: i.v. PCA fentanyl bolus 25–50μg with a lockout interval of 3–6 minutes and a 4h limit of 1–1.5mg (n=51). **Primary outcome** To compare the analgesic efficacy of remifentanil with fentanyl.	Not randomised. Retrospective study. Missing data. Higher mean gestational age for remifentanil group 38.5wks compared to 36.5wks gestation for fentanyl group. Neonatal weight significantly different.

Author/ country	Title/ Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/ primary outcome	Limitations
Shoorab et al. (2013) Iran	***The Effect of IV Fentanyl on Pain and Duration of the Active Phase of First Stage Labor.*** Level II Single centre RCT Aim: to examine the analgesic efficacy of fentanyl and effect on the duration of the active phase of labour. Findings: Fentanyl provided good analgesic effect for pain management during labour and demonstrated a reduced duration of the active phase of labour by 2h.	**70 Parturients** healthy term multiparous **Group 1:** i.v. fentanyl 50µg in two doses with an interval of 1h (diluted in 4 cc normal saline (total volume 5 cc - 25 µg /5 ml during 10min infusion) and repeated 1h later 25 µg /5 ml) (n=35). **Group 2:** no treatment (n=35). **Primary outcome** to examine the effect of fentanyl on the duration of the active phase of labour.	Non-blinded convenience sampling. Randomisation undertaken from a coin toss. Ethics approval not reported. Power analysis unclear based on findings of a pilot study effect size obtained at 0.4h

Appendix 1b: Pethidine studies reviewed (n=15)

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/ primary outcome	Limitations
Abdollahi et al (2014) Iran	*Intravenous paracetamol versus intramuscular pethidine in relief of labour pain in primigravid women* Level II RCT placebo study Aim: To compare efficacy and safety of single dose i.v. paracetamol with i.m. pethidine for labour pain. Finding: Paracetamol compared to pethidine resulted in significantly lower VAS pain scores (average labour pain 8.366 out of 10, 9.612 out of 10, respectively, P < 0.001).	**80 parturients** uncomplicated singleton term pregnancies **Group 1:** i.m. pethidine 50mg (n=31). **Group 2:** i.v. paracetamol 1000mg and 300cc of normal saline (n=30). **i.**v. promethazine and hyoscine were administered to each patient at the first stage of delivery. **Primary outcome** Not reported.	Not analysed by ITT. 19 women excluded from analysis. Sample size calculation not provided. Patients were reported to have been blinded but treatment regimens differed. Extra analgesia reported but not what was given. VAS taken at end of delivery but exact timing not stated. Researchers acknowledged no pre or post-treatment pain scores undertaken
Blair et al. (2005) UK	*Patient controlled analgesia for labour: a comparison of remifentanil with pethidine* Level II Double-blinded RCT Aim: To compared the analgesic efficacy and safety of PCA remifentanil and pethidine for women in established labour. Findings: No differences between groups were seen for VAS pain scores, maternal arterial oxygen saturation, nausea, anxiety and sedation. Satisfaction with analgesia was higher for remifentanil than for pethidine. Neurologic & adaptive capacity scores at 30 min were higher for remifentanil than for pethidine but not at any other time-point.	**39 parturients** uncomplicated singleton pregnancies **Group 1:** i.v. PCA remifentanil 40μg with a 2min lockout (n=20). **Group 2:** i.v. PCA pethidine 15mg with a 10min lockout (n=19). **Primary outcome** not reported. The study was powered to detect a difference of 2cm on the VAS for overall pain.	Not analysed by ITT. Study required a sample size of 20/group to achieve power. Small sample sizes underpowered to determine safety of interventions. Researchers did not report any limitations of their study

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Elbohoty et al (2012) Egypt	***Intravenous infusion of paracetamol versus intravenous pethidine as an intrapartum analgesic in the first stage of labor*** Level II Single centred, RCT Aim: To examine the analgesic efficacy and adverse effects of an i.v. infusion of 1000mg of paracetamol with 50 mg i.v. pethidine during active labour. Findings: Both paracetamol and pethidine resulted in significant reductions in pain at 15 minutes, 1h and 2h (P<0.001). Pethidine resulted in a significantly greater reduction of VAS pain score at 15 minutes (P=0.004). None of the women in the paracetamol group had adverse effects, as compared with 64% of the women receiving pethidine.	**102 parturients** with uncomplicated singleton, term pregnancies **Group 1**: i.v. paracetamol 1000mg/100mL infusion over 15min (n=52). **Group 2**: i.v. pethidine hydrochloride 50mg with 10mL of normal saline, over 10 min (n=50). **The primary outcome** was the analgesic efficacy as measured by a change in the VAS pain intensity score.	Although pain scores were reported to have been taken by a person blinded to the drug administration, participant and clinicians were not blinded to treatment. The researchers did not report any limitations to their study.
El-Refaie et al. (2012) Egypt,	***Meperidine for uterine dystocia and its effect on duration of labor and neonatal acid-base status: A randomized clinical trial*** Level II Double-blinded RCT, placebo study Aim: To evaluate if 50mg i.v. pethidine effected the duration of labour and neonatal acid-base status at birth, when administered to women with uterine dystocia. Findings: Pethidine compared to placebo resulted in no statistically significant difference between length of labour or umbilical cord arterial pH.	**240 parturient** healthy, uncomplicated singleton term pregnancies with a vertex presentation, and diagnosed with prolonged labour due to uterine dystocia during the first stage of labour. **Group 1**: i.v. pethidine 50mg in 10mL of isotonic saline administered over 2min. (n=120). **Group 2**: i.v. isotonic saline 10mL (n=120). Oxytocin was started at a dose of 4mU/min, and increased by 4mU/min every 30 min to a maximum of 32mU/min. **Primary outcome** measure was duration of labour.	Women were excluded from the trial if they made a request for pain relief prior to randomisation. Therefore, while significant reductions in VAS score were observed this may not be representative of the general population. The researchers reported the low dose of i.v. pethidine may not have been sufficient to demonstrate an effect on uterine dystocia.

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/ primary outcome	Limitations
Khooshideh & Sharhriari (2009) Iran	*A comparison of tramadol and pethidine analgesia on the duration of labour* Level II Blinded RCT Aim: To compare the outcome of i.m. pethidine and i.m. tramadol for labour analgesia. Findings: Tramadol and pethidine provided moderate analgesia in first stage of labour. Tramadol produced shorter duration of labour and lower incidence of maternal adverse effects. However, pethidine provided greater analgesia especially in the second stage of labour.	**160 parturients** with uncomplicated singleton, term pregnancies. **Group 1:** i.m. pethidine 50mg (n=80). **Group 2:** i.m tramadol 100mg (n=80). **Primary outcome** was the duration of labour. Investigators reported a reduction of 30 minutes was clinically significant.	Researchers acknowledged 50mg i.m. pethidine to be a low dose despite demonstrating analgesic efficacy.
Nelson & Eisenach (2005) North Carolina USA	*Intravenous Butorphanol, Meperidine, and Their Combination Relieve Pain and Distress in Women in Labor.* Level II Double-blind RCT Aim: to examine the analgesic efficacy of butorphanol, pethidine and their combination to reduce pain intensity. Findings: Both pethidine and butorphanol reduced pain intensity 15 minutes after administration though the combination of these drugs did not improve their therapeutic benefit. All groups experienced significant increases in sedation post-treatment.	**30 parturients** healthy term pregnancies. **Group 1**: i.v. butorphanol 1mg (n=15). **Group 2**: i.v. pethidine 50mg (n=15) **Group 3**: i.v. pethidine 25mg plus 0.5mg butorphanol (n=15). **Primary outcome** to examine pain scores. Study powered to observe a 30% reduction in pain intensity.	Not analysed by ITT. Additional opioid analgesia could be administered after 30min but total dose received not reported. Sample size calculation not provided although investigators report the study was powered to detect a difference among treatment groups of 1.4 on the VRS.

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/ intervention/ primary outcome	Limitations
Sekhavat & Behdad (2009) Iran	***The Effects of Meperidine Analgesia during Labor on Fetal Heart Rate*** Level II RCT. (The examiner that reviewed the FHR tracing was blinded to treatment). Aim: To examine the effect of pethidine on FHR recordings within 40min of treatment compared to placebo Findings: Pethidine compared with placebo, resulted in statistically significantly less beat to beat variability and lower proportion of accelerations. FHR deceleration were significantly less in the placebo group.	**150 parturients** healthy with singleton term pregnancies requesting analgesia during active labour. **Group 1:** i.m. pethidine 50mg (n=75) additional 25mg could be administered after 4h. **Group 2:** normal saline (n=75). **Primary outcome** not reported.	Power analysis not reported to justify sample size. No limitations reported by the authors.
Shahriari & Khooshideh (2007) Iran	***A Randomized Controlled Trial of Intravenous Remifentanil Compared with Intramuscular Meperidine for Pain Relief in Labor*** Level II Non-blinded RCT Aim: To compare the analgesic effect and safety of i.v. remifentanil and i.m. pethidine during uncomplicated labour. Findings: Remifentanil resulted in lower VAS pain scores at 1h and during the first stage of labour when compared to pethidine. 95% of women rated analgesia as good to excellent in remifentanil group as compared with 35% of women in the pethidine group.	**40 parturients** term singleton pregnancies and cephalic presentation. **Group 1:** i.v. remifentanil infusion (25–50μg every 4min) i.m. 25mg promethazine (n=20). **Group 2:** i.m. pethidine (1mg/kg) i.m. 25mg promethazine. After 4h the same dose could be repeated or half of the initial dose if requested within 4h. (n=20). **Primary outcome** to compare analgesic effect of i.v. remifentanil with i.m. pethidine.	Non-blinded RCT. Power analysis not reported to justify sample size. Small sample size when examining secondary outcomes for adverse maternal and fetal effects

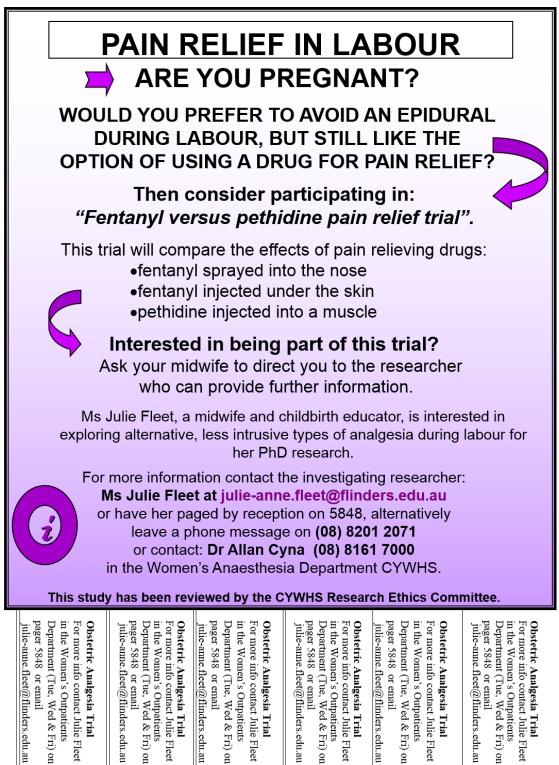| Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Sharma et al. (2004) Texas USA	***An individual patient meta-analysis of 2,703 nulliparous women randomised to receive either epidural analgesia or IV opioids for pain relief during labour.*** Level I All studies were RCT Aim: To examine if epidural analgesia increased the rate of caesareans compared to pethidine. Findings: No differences between groups for rates of caesareans. Epidural resulted in significantly longer first and second stages of labour and more forceps deliveries compared to the pethidine group. Women in the epidural group reported lower pain scores during labour and delivery compared to the pethidine group.	**2,703 parturients** nulliparous (2,188 healthy and 515 with pregnancy-induced hypertension). **Study 1:** Bolus 0.25% bupivacaine, continuous 0.125% bupivacaine with 2μg/mL fentanyl (n=338) i.v. 50 to 75mg pethidine, 2h prn (n=355) **Study 2:** Combined spinal/epidural with 10μg intrathecal sufentanil continuous 0.125% bupivacaine with 2μg/mL fentanyl (n=336) i.v. 50 to 75mg pethidine boluses 2h prn (n=314) **Study 3:** Initial bolus 0.25% bupivacaine, continuous0.125% bupivacaine with 2μg/mL fentanyl (n=197) Bolus i.v. pethidine 50mg bolus, PCA; 10–15 mg every 10min prn, maximum 400mg in 6h (n=189) **Study 4**: Initial bolus 0.25% bupivacaine, continuous 0.125% bupivacaine with 2μg/mL fentanyl (n=242) Bolus i.v. pethidine 50mg bolus, PCA 10–15 mg every 10min prn, maximum 400mg in 6h (n=273) **Study 5**: Bolus 0.25% bupivacaine, PCA 0.0625% bupivacaine with 2μg/mL fentanyl; 5mL every 15min prn (n=226) Initial bolus i.v. 50 mg pethidine, PCA; 10–15mg every 10min prn, maximum 400mg in 6h (n=233) **Primary outcome** to evaluate the effects of epidural analgesia during labour on the rate of caesarean delivery.	Non-blinded studies. Analysed by ITT but high cross-over rate from pethidine to epidural in first 2 trials (PCA available in subsequent studies) Difference in dosage for first 2 trials may not have provided adequate analgesia and may have influenced results. Timing of assessment of pain scores not stated.

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Sosa et al. (2004) Uruguay South America	***An evaluation to determine whether meperidine decreases the length of labour in patients diagnosed with dystocia in the first stage of labour.*** Level II Double-blinded RCT Aim: To examine whether the i.v. pethidine decreases the length of labour in women with dystocia during the first stage of labour. Findings: Pethidine compared with placebo, resulted in no statistical differences for length of labour, forceps or LSCS by intention-to-treat analysis. However, pethidine resulted in lower Apgar scores, umbilical artery acidosis, and increased admission to neonatal care units when compared to placebo.	**407 parturients** term singleton pregnancies who received a diagnosis of dystocia and required an active management of labour. **Group 1:** i.v. pethidine 100mg in 50 mL saline solution over 15min (n=205). **Group 2:** placebo (isotonic sodium chloride solution) (n=202). **Primary outcome** to evaluate whether the administration of pethidine decreases the length of labour in patients diagnosed with dystocia during the first stage of labour.	23% missing data for VAS post-birth. Differences in time-point for neurologic & adaptive capacity scores assessment.
Sosa et al. (2006) Uruguay South America	***To examine the effects of pethidine during the first stage of labour on the acid-base status at birth*** Level II Double-blinded RCT Aim: To examine the effect of pethidine administered in the first stage of labour on the presence, type and timing of neonatal acidosis at birth. Findings: Pethidine resulted in higher incidences of acidosis when compared to placebo. The highest frequency of acidosis occurred when pethidine-delivery interval was 5h.	**383 parturients** term singleton pregnancies with dystocia and required active management of labour. **Group 1:** i.v. pethidine 100mg in 50mL saline solution over 15min (n= 194). **Group 2:** i.v. isotonic sodium chloride solution (placebo) (n=189). **Primary outcome** to evaluate if pethidine was associated with increased risk of newborn acidosis, compared to placebo.	Researchers reported post-randomisation factors varied including (augmentation and oxytocin). Low observed number of events for reported statistical significance.

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Tsui et al. (2004) Hong Kong	***A placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour*** Level II Double-blinded RCT Aim: To examine the analgesic efficacy of pethidine in labour. Findings: Pethidine resulted in significantly reduced VAS pain score and greater satisfaction when compared to placebo. However, pethidine also resulted in more sedation. Neonatal outcomes were similar between groups.	**50 parturients** uncomplicated singleton term pregnancies and cephalic presentations. **Group 1:** i.m. pethidine 100mg/2mL (n=25). **Group 2:** i.m. saline 2mL (n=25) **Primary outcome** VAS pain score after 30min	The study was terminated after recruitment of the first 50 parturients. Underpowered as the sample size calculation required 56/group
Wee et al. (2014) UK	***A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a two-centre randomised blinded controlled trial*** Level II Double-blinded RCT Aim: To examine the analgesic efficacy and adverse effects of diamorphine and pethidine when administered for labour pain. Findings: Pethidine was not as effective in providing pain relief at 60min, compared to diamorphine, mean difference 1cm, over the 3h. Pethidine resulted in shorter labour by 82min, reducing the experience of pain over time. There were no statistically significant differences in neonatal outcomes.	**484 parturients** term singleton pregnancies **Group 1**: i.m. pethidine 150mg (n=240) **Group 2**: i.m. diamorphine 7.5mg (n=244) Maximum of two doses of opioid were given with a minimum interval of 2h if additional analgesia required. Metoclopramide 10mg was given to each participant with the first dose. **The primary maternal outcome** reduction in pain intensity from baseline (VAS) at 60min and over the 3h period after drug administration. **The primary neonatal outcomes** were need for neonatal resuscitation and Apgar score <7 at 1min.	The researchers reported only observed short-term neonatal outcomes. Neonatal sedation was only followed up until 2h post-birth. Potential longer term effects on feeding behaviour may not have been observed.

Author/ Country	Title/Study type/NHMRC level of evidence/aim/key finding	Sample/intervention/primary outcome	Limitations
Weissman et al. (2009) Israel	***The effects of meperidine and epidural analgesia in labour on maternal heart rate variability*** Level III-2 Prospective observational study (Analysed by investigator blinded to the method of analgesia and outcome of labour). Aim: To compare the effects of epidural and i.v. pethidine on the autonomic nervous system modulation of maternal heart rate variability in labouring women. Findings: Pethidine significantly increased maternal heart rate compared to those who had epidural analgesia.	**64 parturients** healthy pregnancies. **Group 1:** epidural infusion of 0.125% bupivacaine with fentanyl 2 µg/mL at 8–12 mL/min. A 3–5mL bolus dose was added 5min until a T10 sensory block was obtained. Max 3 boluses were given. (n=33). **Group 2:** i.v. pethidine 50mg with promethazine 25mg (n=31). **Primary outcome** to compare effects of epidural to i.v. pethidine on the autonomic nervous system modulation of labouring women's heart rate variability.	Non-randomised trial. The researchers reported breathing patterns and depth were not recorded.
Yilmaz et al. (2009) Turkey	***Meperidine versus valethamate bromide in shortening the duration of active labor*** Level II Double-blind, RCT placebo study Aim: To compare pethidine to valethamate bromide and placebo when administered to shorten the duration of active labour and examine the efficacy, safety, and adverse effects. Findings: Pethidine but not valethamate bromide, significantly shortened the duration of active labour in nulliparous women with a singleton pregnancy at term.	**160 parturients** nulliparous, singleton, vertex presentation, term or postdates who needed induction of labour for oligohydramnios, ruptured membrane or post-term **Group 1**: i.v. pethidine 50mg over 2min (n=53) **Group 2**: i.v. valethamate bromide 16mg over 2min (n=53) **Group 3**: 10mL normal saline solution over 2min (n=54) All women received oxytocin 6mU/min, increased by 6mU/min every 20min to a max 42mU/min. **Primary outcome** To examine the duration of first stage labour; second stage labour; and total labour duration from treatment to birth.	Power calculation not clearly explained. Small sample size to assess safety. Although not primary outcomes researcher acknowledged they did not assess pain scores or cord pH.

PAIN RELIEF IN LABOUR

ARE YOU PREGNANT?

WOULD YOU PREFER TO AVOID AN EPIDURAL DURING LABOUR, BUT STILL LIKE THE OPTION OF USING A DRUG FOR PAIN RELIEF?

Then consider participating in:
"Fentanyl versus pethidine pain relief trial".

This trial will compare the effects of pain relieving drugs:
- fentanyl sprayed into the nose
- fentanyl injected under the skin
- pethidine injected into a muscle

Interested in being part of this trial?
Ask your midwife to direct you to the researcher
who can provide further information.

Ms Julie Fleet, a midwife and childbirth educator, is interested in exploring alternative, less intrusive types of analgesia during labour for her PhD research.

For more information contact the investigating researcher:
Ms Julie Fleet at julie-anne.fleet@flinders.edu.au
or have her paged by reception on 5848, alternatively
leave a phone message on **(08) 8201 2071**
or contact: **Dr Allan Cyna (08) 8161 7000**
in the Women's Anaesthesia Department CYWHS.

This study has been reviewed by the CYWHS Research Ethics Committee.

Obstetric Analgesia Trial
For more info contact Julie Fleet in the Women's Outpatients Department (Tue, Wed & Fri) on pager 5848 or email julie-anne.fleet@flinders.edu.au

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CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS) HUMAN RESEARCH ETHICS COMMITTEE (HREC) PATIENT INFORMATION SHEET

Lay title

"A comparison of fentanyl with pethidine for pain relief during childbirth."

Scientific title

"Obstetric analgesia: A comparison of intranasal or subcutaneous fentanyl with intramuscular pethidine during childbirth".

Julie Fleet is a PhD candidate undertaking research comparing the effects of fentanyl administered either into the nose or skin, with that of pethidine injected into a muscle on both mother and baby when given during childbirth.

Purpose of the study

You are invited to participate in a study to explore the effectiveness of fentanyl given for pain relief during childbirth.

Traditionally, pethidine has been the drug most often offered to women for pain relief during childbirth and is currently the standard treatment for women requesting a drug for pain relief at the Children, Youth & Women's Health Service. Pethidine is cost effective and after being ordered by a doctor, can be given by a midwife. Pethidine, however, may produce some unwanted side effects, such as nausea (feeling sick) and sleepiness.

Fentanyl is an alternative drug that may be offered for pain relief, but was originally developed to be injected into a vein. This requires a small tube (cannula) to be placed into the woman's vein, and an anaesthetist to give the drug. Research is now focusing on the use of fentanyl when given by different, less intrusive routes, such as when sprayed into the nose (intranasal) or injected into the skin (subcutaneous) by a nurse or midwife. Previous studies exploring the use of these alternative routes of administering fentanyl have been conducted on babies, children and adults requiring emergency treatment and post-operative care. These studies showed that fentanyl administered via these routes are effective, resulting in fewer side effects than other drugs. However, the effects of fentanyl given via these routes have not been studied in women during labour.

Therefore, this study aims to explore the effectiveness of fentanyl when administered intranasally or subcutaneously during childbirth. These effects will then be compared with labouring women who have been given pethidine injected into the muscle.

Selection

To participate in this study you will need to meet the following criteria:

Have a preference not to use an epidural

Be in good health with an uncomplicated pregnancy, birthing at 37-42 weeks pregnancy

Have no known allergies to opioid drugs or be on any pre-existing medications that would interact with the study drugs

Should you meet the criteria and then request a pain relieving drug during labour you will be randomly placed into any one of the following three groups.

Group 1. fentanyl to be sprayed into the nose or

Group 2. fentanyl to be injected into the skin or

Group 3. pethidine injected into a muscle

Participation in this study will not restrict you from choosing other forms of pain relief, such as nitrous oxide and oxygen (gas) or an epidural, if you are not satisfied with the pain relief provided by the drug in the study.

What will happen in this study

Before birth: You will have been given information about pain relief options for labour during your antenatal care. If you choose to participate in this study your consent should be given before you are in labour. Providing early consent does not mean that you will have to use a drug in labour. It simply allows you more time to discuss your options. Should you then choose to use a drug in labour, the midwife providing your care will reconfirm your consent to participate in this trial at that time.

In addition, your consent will enable the researcher to access information from your medical record relating to your labour and birth. This information will include the mode of birth you experienced, the length of your labour, if you needed to use any other medication to help with the labour pain and the standard observations recorded for your baby at the time of birth. No other involvement is required at this stage.

During labour: If you request a drug for pain relief, you will be randomised to receive only one of the three pain relief options listed in the groups above. If, however, you are not satisfied with the pain relief provided by the drug in the study you may request another pain relief option, such as gas or an epidural.

Before you are given the pain relief you will be asked a question relating to your pain level. This question will be repeated 30 minutes after you have been given the drug. In addition, your blood pressure, pulse and temperature will be taken and recorded. This is standard treatment when given a drug during labour. The midwife also will monitor you to see if you have any other effects such as nausea or sleepiness.

To help the midwife monitor the effect of the drug a sleeve will be placed gently on the end of your finger which monitors your oxygen levels for the first 30 minutes after you have been given the drug. There will be no additional observations required other than the normal care your midwife will provide to monitor you and your baby throughout your labour.

After birth: Within 48 hours you will be contacted by a member of the research team to complete a brief questionnaire. The questionnaire will take approximately 15 minutes to complete and asks questions relating to how you felt that you coped during labour.

At six weeks after giving birth, the researcher will telephone you to enquire about your baby's behaviour, in particular, your baby's feeding patterns along with any sources of support that you have used. This information is being collected as little research has explored the effects of drugs given during labour on babies' behaviour after birth. Previous studies suggest that if babies become sleepy following birth due to the effects of the drugs, they may be less likely to breastfeed successfully. However, there are many factors that can influence a mother's decision to breastfeed including the

woman's original intention to breastfeed and the support that she has been given throughout this period. The short telephone interview will enable us to review your experience and should take approximately 20 minutes to answer. This will complete your involvement in the study.

The possible benefits from the study

The purpose of this study is to determine whether fentanyl provides as much pain relief as pethidine but with fewer side effects, such as nausea and sleepiness, for both mother and baby.

In addition, results of this study may benefit women in rural and remote areas who are often disadvantaged due to the limited medical services available to them, such as, a lack of staff trained in inserting cannulas into a vein and/or an anaesthetist to administer the drug. These communities would benefit from identifying an alternative safe and effective form of pain relief that does not require these specialised services.

Possible risks

Drugs, such as fentanyl and pethidine, provide pain relief for most people suffering severe pain. However, like all drugs, they may have unwanted side-effects in a few people. Some of the more common side effects are as follows: nausea, vomiting and feeling sleepy. Sometimes these drugs can cause muscle twitching, increased heart rate, slowing down of breathing, an itchy rash or mood changes, such as an exaggerated sense of well-being. Both pethidine and fentanyl can transfer to the baby, so there is a chance that your baby may experience some of these effects. Some people may get other side effects after being given these drugs. In cases of overdose the first sign is usually a marked slowing of your breathing. There is another drug, called naloxone, which can be used to reverse these effects, if it is required. You will be constantly observed to determine whether you or your baby experiences any of these unwanted effects.

Confidentiality

All records containing personal information will remain confidential and no information which could lead to your identification will be released, except as required by law. This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however, we have an obligation to inform you of this possibility.

Publication

The project outcomes will be published in conference papers, journals and/or other venues as appropriate. In no case will any information that identifies you be included.

Withdrawal

You are entirely free to withdraw from the trial at any time or decline to have this information used in any publication. Withdrawal from the study will not affect your's or your baby's care in any way.

Reimbursement for participation

Your participation in this study is on a voluntary basis and, therefore, there will be no payment made. Please be assured, that your participation will not incur any additional costs.

Outcomes

All participants, including those who withdraw from the study, may ask the researcher for details of their personal data and a summary of the results.

Contact

Should you require further details about this project, either before, or after the study, you may contact the investigating researcher, Ms Julie Fleet at julie-anne.fleet@flinders.edu.au or a phone message left on ph (08) 8201 2071. Alternatively, you can contact the researcher's supervisors Dr Ingrid Belan, Flinders University ph (08) 8201 5136 or Dr Meril Jones, Flinders University ph (08) 8201 3391 or Dr Allan Cyna, Senior Consultant Anaesthetist Children, Youth & Women's Health Service, Women's Anaesthesia ph (08) 8161 7000.

Ethics approval

This study has been given approval by the Children, Youth & Women's Health Service Research Ethics Committee. If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Secretary of the Committee (Ms Brenda Penny, Research Secretariat, ph 8161 6521).

CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS)
HUMAN RESEARCH ETHICS COMMITTEE (HREC)
PATIENT INFORMATION SHEET

CONSENT FORM

LAY TITLE

"A comparison of fentanyl with pethidine for pain relief during childbirth."

SCIENTIFIC TITLE

"Obstetric analgesia: A comparison of intranasal or subcutaneous administered fentanyl with intramuscular administered pethidine during childbirth".

I _____

hereby consent to my involvement in the research project entitled:

Obstetric analgesia: A comparison of intranasal or subcutaneous administered fentanyl with intramuscular administered pethidine in childbirth

1.   The nature and purpose of the research project described on the attached Information Sheet has been explained to me. I understand it and agree to taking part.

2.   I understand that I may not directly benefit by taking part in this study.

3.   I acknowledge that the possible risks and/or side effects, discomforts and inconveniences, as outlined in the Information Sheet, have been explained to me.

4.   I understand that I can withdraw from the study at any stage and that this will not affect medical care or any other aspects of my relationship with this healthcare service.

5.   I understand that there will be no payment to me for taking part in this study.

6.   I have had the opportunity to discuss taking part in this research project with a family member or friend, and/or have had the opportunity to have a family member or friend present whilst the research project was being explained by the researcher.

7.   I agree to the accessing of my medical records for the purposes of the study.

8.   I understand that my information will be kept confidential as explained in the information sheet except where there is a requirement by law for it to be divulged.

Signed: ....

Full name of patient: ....
Dated:............................
I certify that I have explained the study to the patient and consider that she understands what is involved.
Signed: .... Title: ....
Dated: ....

Appendix 5: Criteria checklist

Obstetric Analgesia Trial Inclusion/ exclusion criteria checklist	Affix patient identification label in this box UR No: Surname:\..................... Given Names: .... DOB: ...../...../.......... Sex: ....

Complete this form prior to randomising the woman into the trial

Inclusion criteria	Yes	No
The woman has requested obstetric analgesia but prefers not to use an epidural	☐	☐
No known medical conditions and an uncomplicated pregnancy	☐	☐
Singleton, viable fetus, vertex presentation and planning a vaginal birth	☐	☐
At least 18 years of age	☐	☐
Birthing at term (between 37 to 42 weeks gestation)	☐	☐

If any inclusion questions have been answered NO, the woman is NOT eligible to enter the trial.

Exclusion criteria	Yes	No
Woman has received pethidine or fentanyl within 24 hours prior to the establishment of active labour (regular contractions and a cervical dilatation of at least 3cm)	☐	☐
Woman has an antenatal condition requiring ongoing medical management such as, pre-eclampsia, premature labour, severe bronchial asthma, a history of fits or head injuries, glaucoma, heart or liver problems, diabetes, phaeochromocytoma	☐	☐
History of allergy to any opioid	☐	☐
History of hypersensitivity to opioid substances	☐	☐
Reliance on opioid substances such as oxycodone, OxyContin, methadone, buprenorphine, naltrexone	☐	☐
Woman with depression taking or have taken medications, such as monoamine oxidase inhibitors (MAOI) including phenelzine (Nardil®), selegiline (Eldepryl®) tranylcypromine (Parnate®) and moclobemide (Aurorix®), selective serotonin reuptake inhibitors or tricyclic antidepressants within the previous fourteen days	☐	☐
Woman unable to provide a verbal response to the visual analogue scale due to non-English speaking, requiring interpreter or intellectual disability	☐	☐

If any exclusion questions have been answered YES, the woman is NOT eligible to enter the trial.
If not eligible please speak to the MO for alternative pain relief options

To participate in this trial all inclusion criteria and no exclusion criteria must be met.

If eligible the woman may now be randomised into the trial. Please select the next consecutively numbered envelope to confirm which study drug is to be used and notify the attending anaesthetic staff member who will confirm eligibility and prescribe the study drug. Please also place an identification label on the Obstetric Analgesia Trial Register.

Checklist completed by:

Name: **Designation:**   **Date:**

Signature:

Appendix 6: Obstetric analgesia trial register

Envelope No.	Date	Affix patient identification label in this box	Adverse event Yes/No	Signature/ Designation
1				
2				
3				
4				

Appendix 7: Intranasal fentanyl protocol

Intranasal fentanyl in labour

Drug Name (Generic):

Intranasal fentanyl solution 600mcg/2mL

Description:

Opioid analgesia

Indication for use:

Analgesia to mother in established labour

Adverse Effects:

Maternal: respiratory depression, nausea and vomiting, drowsiness.
Neonate: respiratory depression and drowsiness

Inclusion criteria:

- Women who request obstetric analgesia but who express a preference not to use an epidural
- No known medical conditions with uncomplicated pregnancy
- Singleton, viable fetus, vertex presentation and planning a vaginal birth
- At least 18 years of age
- Birthing at term (between 37 to 42 weeks gestation)

Exclusion criteria:

- Women who have received a narcotic within 24 hours prior to the establishment of active labour (regular contractions and a cervical dilatation of at least 3cm)
- Women with an antenatal condition requiring ongoing medical management such as, pre-eclampsia, premature labour, severe bronchial asthma, a history of fits or head injuries, glaucoma, heart or liver problems, diabetes requiring medication, phaeochromocytoma
- History of allergy to any opioid
- History of hypersensitivity to opioid substances
- Reliance on opioid substances
- Women with depression requiring, taking or have taken medications, such as monoamine oxidase inhibitors (MAOI) including phenelzine (Nardil®), selegiline (Eldepryl®) tranylcypromine (Parnate®) and moclobemide (Aurorix®), selective serotonin reuptake inhibitors or tricyclic antidepressants within the previous fourteen days
- Women unable to provide a verbal response to the visual analogue scale due to non-English speaking, requiring interpreter or intellectual disability

Dose:

- Doctor to confirm participant's eligibility and prescribe study drug as per medication order attached.
- Using a 2-3 mL syringe midwife to draw up 600mcg/2mL of intranasal fentanyl solution into the Go-Medical intranasal device. Device to be primed as per instruction card. Tamper proof tape will then be fixed to the actuator and

bottle of the device to discourage and enable the detection of any tampering of applicator once given to the woman for use (refer to Figure 1).

- Each spray administers 0.18mL (54 µg intranasal fentanyl) and has a lockout of 4 minutes (A maximum hourly dose of 600µg has been set. Atomizer may be refilled with a further 600mcg/2mL if needed). The atomiser is to be kept upright for the chamber to refill in a four minute timeframe.
- Midwife to instruct the woman on the use of the intranasal applicator and have her verbalise her understanding prior to first dose being administered. Midwife to inform woman she is to be in attendance when each dose is administered
- Woman to self-administer doses as necessary up to a maximum 1200mcg. If further pain relief is required, discuss alternative options with the attending medical officer
- Nitrous oxide and oxygen may be used in conjunction with intranasal fentanyl solution
- The protocol for discarding a Schedule 8 drug will then be followed with two midwifes and the discarded volume recorded. The midwife will remove the tamper proof tape and using a 1 mL syringe will measure the remaining volume, so the total dose administered can be accurately calculated and recorded on the observation chart and DDA register
- As per protocol the total dose administered should then be recorded in the DDA register and patients charts

Route of Administration:

- Woman to self-administer fentanyl via the intranasal route, the applicator is gently placed into a nostril and when depressed delivers a spray in small droplet form.

Initiator Eligibility:

Registered midwife appropriately trained in the intranasal application- Labour & Delivery Suite and the Midwifery Group Practice

Initiator Expectation:

The onset of action is within 10 minutes with 30-60mins duration of action.

Observations:

- Utilise the attached observation chart to document time of administration and observations required. All observations need to be recorded immediately prior to the first administration and 30 minutes post administration of each dose.
- If the woman only administers one dose then two full sets of observations are required to be documented on this form (one pre study drug administration and the second 30 minutes post administration). Where multiple doses are self-administered, observations should be taken pre administration and then every 30 minutes while the intranasal spray is in use.
- Record pain scores on the enclosed Visual Analogue Scale (VAS) timing of assessment should be between contractions with the score representing pain experienced at the peak of the contraction.
- Vital signs are to be recorded on the form within these same timeframes and can be undertaken in conjunction with measurement of pain scores.
- Continuous pulse oximetry is only required for the first 30minutes post administration of the first dose with the oxygen saturation probe to be placed

on the finger prior to administration of the study drug. Record the saturation level between contractions at 30minutes post administration.

- Record the woman's position (pre and post administration) i.e., ambulating forward leaning, sitting, on all fours, left lateral etc.
- Record any other forms of analgesia used in conjunction with fentanyl, such as nitrous oxide and oxygen
- Record any subsequent analgesia utilised, such as epidural, should the study drug have been ceased due to unrelieved pain or persistent or problematic symptoms.
- Post-birth record time of birth, Apgar score at 1 and 5 minutes and time to establish breathing
- Where possible, cord blood pH should be collected for all neonates and arterial result recorded on the observation chart

If any of the following observations are observed cease administering the narcotic and report to the team leader:

- respiration rate <8/minute and shallow
- unrelieved pain and or/dissatisfaction with pain management
- persistent or problematic additional symptoms e.g. nausea, restlessness etc. prophylactic anti-emetics are not to be used however if symptoms are noted they may be ordered as appropriate
- Any evidence of tampering with the intranasal device should also be reported to the attending anaesthetist.

If respiratory depression (respiration rate <8/minute) occurs the team leader will initiate a code blue obstetric Medical Emergency Team response. A paediatrician will also be called to attend if fentanyl is administered within 15 minute prior to birth. Any adverse outcomes or evidence of tampering are to be recorded on the study drug register for followed up by the data monitoring and safety committee.

Documentation

Study drug register, national medication chart, patient notes, drugs of dependency administration (DDA) register (checked by two midwives) and attached observation form.

Figure 1.

Appendix 8: Subcutaneous fentanyl protocol

Subcutaneous fentanyl in labour

Drug Name (Generic):

Fentanyl citrate (100mcg/2mL)

Description:

Opioid analgesia

Indication for use:

Analgesia to mother in established labour

Adverse Effects:

Maternal: respiratory depression, nausea and vomiting, drowsiness.
Neonate: respiratory depression and drowsiness

Inclusion criteria:

- Women who request obstetric analgesia but who express a preference not to use an epidural
- No known medical conditions with uncomplicated pregnancy
- Singleton, viable fetus, vertex presentation and planning a vaginal birth
- At least 18 years of age
- Birthing at term (between 37 to 42 weeks gestation)

Exclusion criteria:

- Women who have received a narcotic within 24 hours prior to the establishment of active labour (regular contractions and a cervical dilatation of at least 3cm)
- Women with an antenatal condition requiring ongoing medical management such as, pre-eclampsia, premature labour, severe bronchial asthma, a history of fits or head injuries, glaucoma, heart or liver problems, diabetes requiring medication, phaeochromocytoma
- History of allergy to any opioid
- History of hypersensitivity to opioid substances
- Reliance on opioid substances
- Women with depression requiring, taking or have taken medications, such as monoamine oxidase inhibitors (MAOI) including phenelzine (Nardil®), selegiline (Eldepryl®) tranylcypromine (Parnate®) and moclobemide (Aurorix®), selective serotonin reuptake inhibitors or tricyclic antidepressants within the previous fourteen days
- Women unable to provide a verbal response to the visual analogue scale due to non-English speaking, requiring interpreter or intellectual disability

Dose:

- Doctor to confirm participant's eligibility and prescribe study drug as per medication order attached.
- 200 µg stat dose, wait one hour and then 50 µg every 15 minutes, as required up to a maximum of 650 µg
- If further pain relief is required, discuss alternative options with the attending medical officer

Route of Administration:

- Using aseptic techniques insert a Jelco cannula size 24G into the subcutaneous tissue in the area of the subclavicular or upper pectoral region and secure with Opsite, and interlink bung attached
- Inject 1ml of local anaesthetic (1% plain lignocaine) slowly prior to first dose and wait one minute before injecting the fentanyl
- Give fentanyl slowly, over 1 to 2 minutes, undiluted

Initiator Eligibility:

Registered midwife appropriately trained to insert a subcutaneous cannula - Labour & Delivery Suite and Midwifery Group Practice.

Initiator Expectation:

Analgesia within 15 minutes of administration. Lasting up to 2 hours.

Observations:

- Utilise the attached observation chart to document time of administration and observations required
- If the woman has been administered only one dose then two full sets of observations are required to be documented on this form (one pre administration and the second 30 minutes post administration). If a second or subsequent doses are given then these observations are to be taken again pre administration and 30 minutes post administration of the study drug.
- Record pain scores on the enclosed Visual Analogue Scale (VAS) timing of assessment should be between contractions with the score representing pain experienced at the peak of the contraction.
- Vital signs are to be recorded on the form within these same timeframes and can be undertaken in conjunction with measurement of pain scores.
- Continuous pulse oximetry is only required for the first 30minutes post administration of the first dose with the oxygen saturation probe to be placed on the finger prior to administration of the study drug. Record the saturation level between contractions at 30minutes post administration.
- Record the woman's position (pre and post administration) i.e., standing/ forward leaning, sitting, on all fours, left lateral etc.
- Record any other forms of analgesia used in conjunction with fentanyl, such as nitrous oxide and oxygen
- Record any subsequent analgesia utilised, such as epidural, should the study drug have been ceased due to unrelieved pain or persistent or problematic symptoms.
- Post-birth record time of birth, Apgar score at 1 and 5 minutes and time to establish breathing
- Cord blood pH needs to be collected for all neonates and result recorded on the observation chart

If any of the following observations are observed cease administering the narcotic and report to the team leader:

- respiration rate <8/minute and shallow
- persistent drowsiness
- unrelieved pain and or/dissatisfaction with pain management
- persistent or problematic additional symptoms e.g. nausea, restlessness etc.

If respiratory depression (respiration rate <8/minute) occurs the team leader will initiate a code blue Obstetric Medical Emergency Team response. A paediatrician will also be called to attend if fentanyl is administered within 15 minute prior to birth. Any adverse outcomes are to be recorded and followed up for data monitoring and safety.

Documentation

Study drug register, national medication chart, patient notes, drugs of dependency administration (DDA) register (checked by two midwives) and attached observation form.

Appendix 9: Intramuscular pethidine protocol

Intramuscular pethidine in labour

Drug Name (Generic):

Pethidine hydrochloride 100mg in 2mL injection

Description:

Opioid analgesia

Indication for use:

Analgesia to mother in established labour

Adverse Effects:

Maternal: respiratory depression, nausea and vomiting, drowsiness
Neonate: respiratory depression and drowsiness

Inclusion criteria:

- Women who request obstetric analgesia but who express a preference not to use an epidural
- No known medical conditions with uncomplicated pregnancy
- Singleton, viable fetus, vertex presentation and planning a vaginal birth
- At least 18 years of age
- Birthing at term (between 37 to 42 weeks gestation)

Exclusion criteria:

- Women who have received a narcotic within 24 hours prior to the establishment of active labour (regular contractions and a cervical dilatation of at least 3cm)
- Women with an antenatal condition requiring ongoing medical management such as, pre-eclampsia, premature labour, severe bronchial asthma, a history of fits or head injuries, glaucoma, heart or liver problems, diabetes requiring medication, phaeochromocytoma
- History of allergy to any opioid
- History of hypersensitivity to opioid substances
- Reliance on opioid substances
- Women with depression requiring, taking or have taken medications, such as monoamine oxidase inhibitors (MAOI) including phenelzine (Nardil®), selegiline (Eldepryl®) tranylcypromine (Parnate®) and moclobemide (Aurorix®), selective serotonin reuptake inhibitors or tricyclic antidepressants within the previous fourteen days
- Women unable to provide a verbal response to the visual analogue scale due to non-English speaking, requiring interpreter or intellectual disability

Dose:

- Doctor to confirm participant's eligibility and prescribe study drug as per medication order attached.
- Pethidine hydrochloride 100mg in 2mL injection
- A repeat dose maybe given in 3 to 4 hours (once only) with a maximum total dose of 200mg

- If further pain relief is required, discuss alternative options with the attending medical officer

Route of Administration:

Deep intramuscular injection

Initiator Eligibility:

Registered midwife- Labour & Delivery Suite and the Midwifery Group Practice.

Initiator Expectation:

Analgesia within 30 minutes of administration. Lasting up to 3 to 4 hours.

Observations:

- Utilise the attached observation chart to document time of administration and observations required.
- If the woman has been administered only one dose then two full sets of observations are required to be documented on this form (one pre administration and the second 30 minutes post administration). If a second dose is given then these observations will be taken again pre administration and 30 minutes post administration
- Record pain scores on the enclosed Visual Analogue Scale (VAS) timing of assessment should be between contractions with the score representing pain experienced at the peak of the contraction.
- Vital signs are to be recorded on the form within these same timeframes and can be undertaken in conjunction with measurement of pain scores.
- Continuous pulse oximetry is only required for the first 30minutes post administration of the first dose with the oxygen saturation probe to be placed on the finger prior to administration of the study drug. Record the saturation level between contractions at 30 minutes post administration.
- Record the woman's position (pre and post administration) i.e., standing/ forward leaning, sitting, on all fours, left lateral etc.
- Record any other forms of analgesia used in conjunction with pethidine, such as nitrous oxide and oxygen
- Record any subsequent analgesia utilised, such as epidural, should the study drug have been ceased due to unrelieved pain or persistent or problematic symptoms.
- Post-birth record time of birth, Apgar score at 1 and 5 minutes and time to establish breathing
- Cord blood pH needs to be collected for all neonates and result recorded on the observation chart

If any of the following observations are observed cease administering the narcotic and report to the team leader:

- respiration rate <8/minute and shallow
- persistent drowsiness
- unrelieved pain and or/dissatisfaction with pain management
- persistent or problematic additional symptoms e.g. nausea, restlessness etc.

If respiratory depression (respiration rate <8/minute) occurs the team leader will initiate a code blue Obstetric Medical Emergency Team response. A paediatrician will also be called to attend if fentanyl is administered within 15 minute prior to birth. Any adverse outcomes are to be recorded and followed up for data monitoring and safety.

Documentation

Study drug register, national medication chart, patient notes, drugs of dependency administration (DDA) register (checked by two midwives) and attached observation form.

Appendix 10: Audit tool

	Age	Gest	G:P	BMI	Onset of labour IOL/ Spont.	Method of delivery SVB/ Assisted/ CS	IF CS Why? FTP/ CPD/ FD/ other	Blood loss mL	Duration of labour	Drugs administered Peth/i.n. fent/ s.c. fent /N₂O₂/EDB		Apgar		DOB & Time	Narcan use Yes/No	Time to est. breath-ing	Skin to skin contact 1st hr	Admitted to NICU Yes/No	Cord blood gases	Date of D/C
										Total Dose	Time of last dose	1min	5min							
															Sex & weight	Time of 1st BF				

UR: unit record, Gest: gestation, G:P: Gravity and parity, IOL: induction of labour, Spont: spontaneous, SVB: spontaneous vaginal birth, CS: caesarean section, FTP: failure to progress, CPD: cephalopelvic disproportion, FD: fetal distress, N₂O₂: nitrous oxide and oxygen, EDB: epidural block, DOB: date of birth, D/C: discharge, BF: breastfed

Appendix 11: The observation chart

Obstetric Analgesia Trial **OBSERVATION CHART**	**Affix patient identification label in this box** UR No: Surname: .... Given Names: .... DOB: ..../......./..........Sex: ....

Date: **Please circle the drug and route used** **Study drug: Fentanyl Pethidine** **Route: i.n. s.c. i.m.**	**Other analgesia used:** **N_2O+O_2 EDB**

TIME	DOSE	OBSERVATIONS T P R BP			SaO_2	PAIN SCORE	SEDATION SCORE	VOMIT SCORE	ANTI EMETIC	MATERNAL POSITION

Total dose administered_____ Time of last dose administered prior to birth_____

Time of birth_____   **Apgar 1min _____**   **Apgar 5 min_____**

Time to est. breathing _____   **Cord pH_____**

Observations:
1) Prior to administration of narcotic **and**
2) 30 minutes after **each dose** of s.c. or i.m. **or**
3) Prior to first administration of i.n. fentanyl then **every** 30 minutes whilst using i.n. spray

PAIN SCORE (VAS)	SEDATION SCORE	VOMIT SCORE
0 = No pain to 10 = Worst pain imaginable	0 = Awake 1 = Sedated/Asleep easy to rouse 2 = Sedated/Asleep hard to rouse Or new agitation/confusion 3 = Unrousable	0 = Nil 1 = Nausea no treatment 2 = Nausea only -treatment 3 = Vomiting -treatment 4 =Vomiting not responding to treatment
MATERNAL POSITION 1 = Ambulating 2 = Sitting 3 = Kneeing/ on all fours 4 = Forward leaning 5 = Semi recumbent Or other please specify	*NB. Continuous pulse oximetry is required for the first 30 minutes and can then be discontinued if Sa0₂ remain within normal limits*	*NB. Prophylactic anti-emetics are not to be given*

Appendix 12: Telephone Questionnaire

Telephone Questionnaire at 6 week postpartum

This questionnaire should take approximately 20 minutes to complete and involves asking a few questions about breastfeeding intentions, problems encountered and sources of support.

Section one. This data will be collected from the medical records

Baby's date of birth: _____

Baby received skin to skin contact for first hour post-birth Yes □   No □

Analgesia utilised

Nitrous & O$_2$ □   i.m. pethidine □   i.n. fentanyl □   s.c. fentanyl □

Epidural □   Spinal □

Mode of birth: Vaginal □   Assisted □   CS □

Section two.

1. Level of education:

High school □   Trade/certificate/diploma □   Degree □

2. Employment status

Unemployed □   Employed □

2a.If employed when do you expect to return to work? (To the nearest month)

1 month □   2 months □   3 months □   4 months □

5 months □   6+ months □

3. Intention to feed prior to birth

Breastfeed □   Bottle feed □   undecided □

4. If you had planned to breastfeed how long did you intend to breastfeed (to the nearest month)

1 month □   2 months □   3 months □   4 months □

5 months □   6+ months □   undecided □

5. How were you feeding your baby in hospital?

Breastfeed □   Bottle feed □   combined □

6. How are you currently feeding your baby?

Breastfeed ☐ Bottle feed ☐ combined ☐

7a. If the intention was to breastfeed but currently bottle feeding, why did you decide to bottle feed? e.g.

Baby being too sleepy ☐ Baby being unsettled ☐ nursery admission ☐

Difficulties with attachment ☐ Cracked nipples ☐

Other ☐
specify_____

7b. If breastfeeding how has your experience been so far? e.g.

Baby being too sleepy ☐ Baby being unsettled ☐

Difficulties with attachment ☐ Cracked nipples ☐

No issues ☐

Other ☐ please
specify_____

8. Do you feel you received adequate support with your choice of feeding?

Midwife Yes ☐ No ☐

Partner Yes ☐ No ☐

Other Yes ☐ No ☐
specify_____

9. Have you used any of the following supports?

Community midwife ☐

Lactation Consultant ☐

Mother's group ☐

Breastfeeding Association ☐

Other ☐ please specify

_____

Section 3

Would you use this form of pain relief in labour again?

Nitrous & O_2	Yes	☐	No	☐	N/A	☐
i.m. Pethidine	Yes	☐	No	☐	N/A	☐
i.n. fentanyl	Yes	☐	No	☐	N/A	☐
s.c. fentanyl	Yes	☐	No	☐	N/A	☐
Epidural	Yes	☐	No	☐	N/A	☐

Please Comment_____

_____
Thankyou for your participation

Appendix 13: Labour Agentry Scale (LAS) questionnaire

Your Feelings About Your Childbirth Experience

Just as no two women are exactly alike, no two women have exactly the same experiences during childbirth. Please try to recall your labour and your baby's birth as vividly as you can. Think about your feelings during labour and birth. Of course, you probably had many different feelings, but try to remember what it was generally like for you during this time.
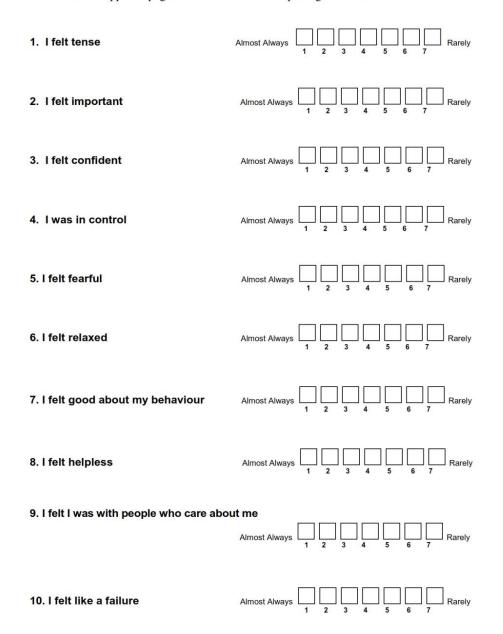
HOW TO USE THE SCALE:

This question is used as an example.

I felt confident   Almost Always ☐☐☐☐☐☐☐ Rarely
1 2 3 4 5 6 7

If you felt confident **almost all of the time**   tick the box in this position:
Almost Always [√]☐☐☐☐☐☐ Rarely
1 2 3 4 5 6 7

If you felt confident **a lot but not always**   tick the box in this position:
Almost Always ☐☐☐☐☐☐☐ Rarely
1 2 3 4 5 6 7

If you felt confident **a little more than half the time**   tick the box in this position:
Almost Always ☐☐[√]☐☐☐☐ Rarely
1 2 3 4 5 6 7

If you felt confident **about half the time**   tick the box in this position:
Almost Always ☐☐☐☐☐☐☐ Rarely
1 2 3 4 5 6 7

If you felt confident **slightly less than half the time**   tick the box in this position:
Almost Always ☐☐☐[√]☐☐☐ Rarely
1 2 3 4 5 6 7

If you **sometimes** felt confident   tick the box in this position:
Almost Always ☐☐☐☐☐[√]☐ Rarely
1 2 3 4 5 6 7

If you **never or almost never** felt confident   tick the box in this position:
Almost Always ☐☐☐☐☐☐☐ Rarely
1 2 3 4 5 6 7

Please try to rate each statement on its own. Do not consider the other statements.
The position of the boxes in relation to 'almost always' and 'rarely' is what is important, not the numbers under the boxes.

Your Feelings About Your Childbirth Experience

Please see the opposite page for instructions on completing this scale.

1. **I felt tense**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

2. **I felt important**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

3. **I felt confident**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

4. **I was in control**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

5. **I felt fearful**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

6. **I felt relaxed**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

7. **I felt good about my behaviour**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

8. **I felt helpless**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

9. **I felt I was with people who care about me**

   Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

10. **I felt like a failure**

    Almost Always | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Rarely

Scoring the Labour Agentry Scale (LAS)

A high score denotes a high level of personal control, and a low score denotes a low level.

The anchors for each item are "Almost Always" (beside the line above "1") and "Rarely" (beside the line above "7").

The LAS consists of both positively-worded and negatively-worded statements.

For negatively-worded statements, such as "I felt powerless" and "I felt tense," do not alter the item score. Thus, a respondent who marked "1" or "2" felt powerless (or tense) almost always, while a respondent who marked "6" or "7" she rarely felt that way.

Reverse the scoring on positively-worded statements, such as "I felt in control" and "I felt relaxed." Thus a "1" (denoting the extreme of "almost always") becomes a "7", while a "7" (denoting the extreme of "rarely") becomes a "1.

To do this on computer, programming is simple: for every positively-worded item, insert a command to multiply the item score by (-1) and add 8.

After you have converted the item scores, sum them.
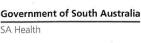
Appendix 14: Ethics approval

10th November 2010

Government of South Australia

SA Health

Women's & Children's Hospital

Ms J Fleet
PhD candidate, School of Nursing & Midwifery
Flinders University
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ADELAIDE SA 5001

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Dear Ms Fleet

**Re: Obstetric analgesia: A Comparison of intranasal or subcutaneous administered
         fentanyl with intramuscular administered pethidine during childbirth.
         REC2284/9/13**

I refer to your letter dated 3rd November 2010 in response to matters raised by the CYWHS Human Research Ethics Committee (meeting 22nd September 2010). I am pleased to advise that your protocol has been granted full ethical approval and that it meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

I enclose herewith the CTN form duly signed. Although TGA advises that the study may proceed once the attached CTN form (and payment) has been forwarded, it also advises that if TGA has a problem with the CTN form, e.g. incomplete information, then the CTN form may be invalidated. Therefore, you should not proceed until you receive a letter from TGA acknowledging that it has received the CTN and have also forwarded a copy of the letter to the Ethics Committee.

I note you have provided your National Police Check and signed Confidentiality Agreement. If in the future, the study involves other non-CYWHS staff, you are reminded of the institutional requirements for a National Police Check and the signing of a Confidentiality Agreement. The study may proceed on this proviso.

I remind you approval is given subject to:
• immediate notification of any serious or unexpected adverse events to subjects;
• immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
• submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
• immediate advice, giving reasons, if the protocol is discontinued before its completion;
• submission of an annual report on the progress of the study, and a final report when it is completed. Please note it is your responsibility to provide these reports – without reminder from the Ethics Committee.

Approval is given for three years only, and if the study is more prolonged than this, a new submission will be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval notification form online at http://www.adelaide.edu.au/ethics/human/guidelines/ within 14 days of receiving this ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerely

TAMARA ZUTLEVICS (DR)
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix 15: Clinical trial notification

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

File Number: 2012/005178

Julie Fleet
Principal Investigator
School of Nursing & Midwifery
GPO Box 2100
Flinders University, ADELAIDE SA 5001

CTN Scheme (Drugs): Acknowledgement of Additional Trial Sites

Your notification to conduct a clinical trial under the Clinical Trial Notification (CTN) Scheme, pursuant to Schedule 5A of Regulation 12 of the Therapeutics Goods Regulations, has been received by the Office of Scientific Evaluation (OSE).

Trial Number: 2010/0636
Protocol Number: 2284/9/13
Drug Name(s):

Drug Active Name	Trade Name	Code Name	Strength
fentanyl	Fentanyl Intranasal Spray solution	N/A	600mcg/2mL
fentanyl citrate	DBL Fentayl injection	N/A	100mcg/2mL

It is noted that:

i. the approval of the goods for this trial was given in accordance with Item 3 of Schedule 5A of the Therapeutic Goods Regulations by the body or organisation conducting the trial at each additional site.

ii. the representative of the Ethics Committee for each additional site has certified that the Committee is constituted and operates in accordance with the NHMRC "National Statement on Ethical Conduct in Human Research" has considered this clinical trial, and has provided advice to the body or organisation conducting the trial.

The Therapeutic Goods Administration has not carried out an assessment of the quality, safety or efficacy of any drug product in relation to this notification.

Please note that, in the event that the Secretary of the Commonwealth Department of Health and Ageing becomes aware that to undertake or continue the clinical trial would be contrary to the public interest, the Secretary has the authority to direct that use of the drug product(s) for this clinical trial must cease.

Vanessa Van Der Zwart
Experimental Products Section
Office of Scientific Evaluation
01 February 2012

Experimental Products Section, TGA, PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 02 6232 8101   Fax: 02 6232 8112   Email: edp@tga.gov.au   www.tga.gov.au

TGA Health Safety Regulation

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

CTN Scheme (Drugs): Clinical Trial Site List

This document lists all sites acknowledged to date for the following clinical trial:

Sponsor: 14550 - Flinders University of SA

Protocol Number: 2284/9/13

Trial Number: 2010/0636

Date Acknowledged	Site Name	State
21 December 2010	Women and Children's Hospital	SA
01 February 2012	Gawler Health Service	SA

Experimental Products Section, TGA, PO Box 100   Woden ACT 2606   ABN 40 939 406 804
Phone: 02 6232 8101   Fax: 02 6232 8112   Email: eds@tga.gov.au   www.tga.gov.au

TGA Health Safety Regulation

Appendix 16: Birth details, LAS scores and satisfaction to use the treatment again for participants treated as per protocol.

Table S1. Birth details, LAS score and satisfaction for participants treated as per protocol

	i.n. fentanyl n=41	s.c. fentanyl n=37	i.m. pethidine n=30	p
Labour duration (h) (Mean(SD))	8.9 (4.4)	9.4 (5.1)	11.2 (5.7)	0.15
Crossover to epidural (%)	15/41 (36.6)	16/37 (43.2)	17/30 (56.7)	0.24
Spontaneous birth (%)	24/41 (58.5)	19/37 (51.4)	16/30 (53.3)	0.81
Assisted birth (%)	8/41 (19.5)	6/37 (16.2)	7/30 (23.3)	0.76
Caesarean birth (%)	9/41 (22.0)	12/37 (32.4)	7/30 (23.3)	0.53
Blood loss (mL) (Mean(SD))	413.4 (310.4)	425.7 (240.5)	453.3 (324.0)	0.85
Apgar score at 1 min (Median(IQR))	9.0 (8.0-9.0)	9.0 (8.0-9.0)	9.0 (7.0-9.0)	0.75
Apgar score at 5 min (Median(IQR))	9.0 (9.0-9.0)	9.0 (9.0-9.0)	9.0 (9.0-9.0)	0.38
Nursery admission (%)	6/41 (14.6)	2/37 (5.4)	10/30 (33.3)	<0.01
Birth weight (grams) (Mean(SD))	3550 (478.0)	3599.5 (370.4)	3578.3 (466.9)	0.88
LAS score (Mean (SD))	51.8 (8.7)	50.1 (9.8)	49.8 (9.1)	0.59
Days in hospital post-birth (Mean (SD))	3.4 (1.2)	3.3 (1.6)	3.4 (1.4)	0.93
Exclusively breastfeeding on discharge (%)	24/30 (80.0)	28/33 (84.9)	14/24 (58.3)	0.06
Breastfeeding at 6 weeks (%)	25/31 (80.7)	28/33 (84.9)	17/28 (60.7)	0.07
No issues establishing breastfeeding (%)	16/27 (59.3)	16/29 (55.2)	3/20 (15.0)	<0.01
Satisfaction – would use treatment again (%)	34/41 (82.9)	29/36 (80.6)	13/29 (44.8)	<0.01

p values are based on one way ANOVA for continuous measures and Chi-square test for categorical measures.

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