Prophylactic ondansetron does not prevent shivering or decrease shivering severity during caesarean delivery under combined spinal epidural anaesthesia: a randomized trial

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Abstract

Background and Objectives

Caesarean delivery is commonly performed under regional anaesthesia, which is often associated with maternal shivering. This can cause maternal distress and interfere with monitoring. The study objective was to evaluate the anti-shivering efficacy of ondansetron, which reduces the incidence and severity of shivering in non-obstetric patients. We hypothesized that there would be a significant decrease in the incidence and/or severity of shivering, from the time of initiating anaesthesia until leaving the post anaesthesia care unit, in women given intravenous ondansetron 8 mg prior to combined spinal epidural anaesthesia, when compared to placebo.

Methods

A randomized, double-blinded, parallel-group, placebo-controlled trial of 118 women scheduled for elective caesarean delivery. Women received either intravenous ondansetron 8 mg (n=58) or an equivalent volume of normal saline (n=60) prior to combined spinal epidural anaesthesia (intrathecal hyperbaric bupivacaine 0.5% 2.2-2.5 ml plus fentanyl 15 mcg). The incidence and severity of shivering, the latter measured on a validated 5 point scale, and
other outcomes such as nausea, itch, headache or satisfaction, were assessed at three time points during the surgery and postoperative period.

**Results**

The incidence of shivering did not significantly differ between groups at any time: overall ondansetron 41% vs. placebo 47% (p=0.54). The incidence of severe shivering was not significantly different: ondansetron 32% vs. placebo 33% (p=0.79). There were no significant differences between the groups for the secondary outcomes.

**Conclusions**

Intravenous ondansetron 8 mg prior to performing combined spinal epidural anaesthesia in women undergoing elective caesarean delivery does not decrease the incidence or severity of shivering.

Australian New Zealand Clinical Trials Registry: ACTRN12609000445279
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Publications, abstracts and presentations arising from this research

Browning RM, Fellingham WH, O'Loughlin EJ, Brown NA, Paech MJ.

Abbreviations

ASA = American Society of Anesthesiologists
CSE = combined spinal epidural
e.g. = for example
et al = and others
Feb = February
FHMRF = Fremantle Hospital Medical Research Foundation
fig = figure
G = gauge
GA = general anaesthesia
HAD score = Hospital Anxiety and Depression score
h = hour
Hz = hertz
IBM = International Business Machines
i.e. = id est / “in other words”
i.m. = intramuscular
i.v. = intravenous
Jan = January
kg = kilogram
mcg = microgram
mg = milligram
min = minutes
ml = millilitre
n = number
NMDA = N-methyl-D-aspartate
NHMRC = National Health and Medical Research Council
NNT = number needed to treat
P = p-value
PACU = post anaesthesia care unit
r² = co-efficient of determination
SAS = statistical analysis system
SD = standard deviation
SPSS = statistical product and service solutions
TRP = transient receptor potential
USA = United States of America
y = years
5HT-3 = 5-hydroxytryptamine 3
°C = degrees Celsius
Δ = change
**Statement of Candidate Contribution**

This thesis was written solely by myself, with source documents and references acknowledged and clearly identified in the thesis.

Chapter two is an expanded version of the article published in Regional Anesthesia and Pain Medicine in Jan 2013 (see page 9). The majority of this article was authored by me. Dr Ed O’Loughlin contributed to the study design, statistical analysis and manuscript review. Prof Michael Paech provided early advice on study design and assisted with the manuscript review. Dr Will Fellingham co-ordinated study conduct at Rockingham hospital and assisted in writing the methodology. Dr Nick Brown assisted in the ethics approval process, design of patient information and data collection forms and co-ordination of study conduct at Kaleeya Hospital.
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Chapter two of this thesis contains material from a published paper which was co-authored. The author of this thesis was the first author on this published paper. A detailed description of the contribution by the various authors of this paper has been provided separately (page 13 of the thesis). A copy of this paper is included as appendix 6.

Student Signature

Coordinating Supervisor Signature
Chapter One: Literature Review

1.1 Introduction

Shivering is defined as an involuntary repetitive activity occurring in skeletal muscles, which is usually initiated as a defensive response to maintain core temperature during hypothermia. It occurs commonly in patients undergoing neuraxial anaesthesia, with a pilot audit at King Edward Memorial Hospital demonstrating an incidence of 37% in women undergoing elective caesarean delivery. Shivering can be distressing and problematic for both the mother and the anaesthetist. Severe shivering interferes with monitoring of blood pressure, electrocardiogram and pulse oximetry. This chapter will review the current theories regarding thermoregulation in humans. It will also discuss the various mechanisms thought to contribute to shivering in the setting of neuraxial anaesthesia and post-general anaesthesia. The evidence for both pharmacological and non-pharmacological methods to manage shivering will be presented and some summary recommendations made, based on this evidence.

1.2 Thermoregulation

1.2.1 Basic overview and evolution

Shivering is but one component of the complex thermoregulatory system which tightly controls core body temperature in humans. This section attempts to present a basic overview of the current theories used to describe
and explain the human thermoregulatory system. This basic knowledge is required in order to provide us with a conceptual framework which will allow us to understand the differing causes of anaesthesia-related shivering and the rationale behind the investigation of potential therapeutic strategies, such as administration of 5HT3 (serotonin) antagonists like ondansetron. A highly detailed review of thermoregulation is outside the scope of this thesis but for those who are interested, this is well covered in a recent article (Nakamura 2012).

Current theories now propose that there is no single thermoregulatory integrator and that responses, such as shivering, can be triggered throughout various levels of the nervous system, with facilitation or inhibition of these responses at levels above and below. It has also been postulated that the thermoregulatory reflexes evolved out of biological systems that were originally used for other purposes (Satinoff 1978) in a process known as co-adaptation. This may explain why the thermoregulatory system appears to be closely linked to other homeostatic systems, such as the system regulating pain - they could have evolved together. Supportive evidence for this concept is provided by the observation that pain and temperature information is transmitted along similar neural systems into the dorsal horn of the spinal cord; and that many anti-shivering drugs also possess analgesic properties (e.g. pethidine (meperidine), clonidine, tramadol). This extraordinary complexity helps explain why there does not appear to be one single pathway
mediating thermoregulatory shivering and why drugs or strategies to treat shivering may have unintended or unwanted effects in other domains.

### 1.2.2 Sensors / Afferent input

At the most basic level thermal information is sensed by transient receptor potential (TRP) ion channels in sensory neurons, with subtypes activated by warm or cold stimuli respectively (Nakamura 2012). These neurons are found throughout the body on the skin surface, in peripheral tissues, core organs, and in the neuraxis. Cutaneous thermal information is transmitted to the spinal and trigeminal dorsal horns, from where it is relayed to higher centres in the central nervous system. The spinal cord has multiple thermoregulatory functions. It is involved in temperature sensation and modulation and transmission of information to higher centres (Guieu, Hardy et al. 1970). Core body temperature is also sensed within the brain itself, including the preoptic area of the hypothalamus and the nucleus raphe magnus (De Witte, Sessler et al. 2002).

### 1.2.3 Control and Integration

Thermoregulatory information is modified and integrated at a number of sites and levels in the nervous system, with the preoptic region of the anterior hypothalamus thought to be the dominant region in mammals. These regions also receive many non-thermal inputs, involving emotional stimuli, blood
pressure, arousal state, glucose concentration, reproductive hormones and noxious stimuli. This helps explain the observation whereby conditions, for example anxiety or pain, are observed to induce or alter thermoregulatory responses such as shivering or vasoconstriction.

A very large number of molecules and receptors have been implicated in the neurotransmission and modulation of thermoregulatory information (Nakamura 2012). Many of these receptors are potential targets for pharmacological intervention in the modification of shivering and this is discussed in more detail in section 1.4.

1.2.4 Effector mechanisms

Humans are homoeothermic, meaning that they actively maintain their core temperature within a narrow range (36.5 to 37.3 °C) which is thought to be optimal for cellular and metabolic function. When core temperature moves outside this “interthreshold range”, effector mechanisms are activated in an orderly fashion to bring the temperature back to normal in the most efficient manner possible. The temperature at which a response is triggered is termed the “threshold temperature”. The threshold temperature for vasoconstriction is 36.5°C and is 36.0°C for shivering. The major effectors or mechanisms used to control core temperature can be divided into behavioural and autonomic or involuntary responses.
Behavioural responses:

These usually predominate over autonomic responses and are usually more efficient and effective. Examples of behavioural responses include putting on clothing, seeking shelter or turning on a heater. These behavioural responses are usually unavailable to an individual under general anaesthesia. Behavioural responses are possible in an awake patient under neuraxial anaesthesia, however due to the patient’s immobility they are severely limited but remain possible, for example asking for an extra blanket.

Autonomic responses:

ii) Hot defences:

Cutaneous vasodilatation allows redistribution of heat from the core to the periphery and thus increased heat loss from the skin surface, via mainly radiation and convection. Sweating also occurs, with significant dissipation of heat in the form of the latent heat of vaporisation occurring via evaporation. This is very effective but comes at an increased cost to the organism, with water and electrolyte losses and a potential for dehydration.

i) Cold defences:

The first response triggered, vasoconstriction, is the most efficient. It decreases heat transfer from the core to the periphery and then loss from the periphery to the environment. Non-shivering thermogenesis is the production
of heat from cellular metabolic activity not involved in mechanical work, such as occurs in brown fat. It is important in neonates but occurs to a much lesser extent in adults. Shivering is the final response to occur, usually when the behavioural and vasoconstriction responses have been inadequate. It can briefly increase metabolic rate by a factor of four or more but is metabolically inefficient and has a number of potential disadvantages. Shivering will discussed in greater depth in section 1.3

1.2.5 Effects of anaesthesia on thermoregulation

1.2.5.1 General Anaesthesia

Anaesthetised patients are unable to use behavioural responses to regulate their temperature. Therefore they must rely upon their autonomic responses and the actions of the individuals looking after them. Almost all commonly used general anaesthetic drugs are known to significantly impair normal autonomic thermoregulatory responses. The response to increased temperature (warm response) is only slightly altered, with the sweating response relatively well preserved. In contrast the cold response is markedly impaired, with the thresholds to trigger vasoconstriction and shivering lowered by 2-4°C (Sessler 2008).
Figure 1: Under general anaesthesia the interthreshold range is significantly widened, due primarily to a 2-4°C decrease in the threshold temperature for vasoconstriction and shivering (Doherty, Buggy 2006).

General anaesthesia usually leads to core hypothermia in three recognised phases. During the first phase there is a rapid decrease in core temperature during the first hour of anaesthesia, when anaesthesia-induced vasodilatation leads to redistribution of heat from the core to peripheral tissues. Following this initial phase further gradual heat loss due to peripheral vasodilatation can occur and core temperature continues to slowly fall. Eventually the new lower threshold for vasoconstriction is triggered and in most circumstances this
prevents any further drop in temperature. A plateau is reached during which core temperature is low but remains steady.

### 1.2.5.2 Neuraxial Anaesthesia

Neuraxial anaesthesia also has a number of effects on thermoregulation. Epidural (Ozaki, Kurz et al. 1994) and spinal (Kurz, Sessler et al. 1993) anaesthesia, like general anaesthesia, decrease the vasoconstriction and shivering thresholds in the body areas above the block. The decrease is not as great as with general anaesthesia and is approximately 0.6°C (see fig 2). The mechanism by which this decrease occurs is unknown, but it is proportional to the number of spinal segments blocked (Leslie, Sessler 1996) (see fig 3). It is unlikely to be due to the action of systemic absorption of local anaesthetic medication (Ozaki, Kurz et al. 1994). This is supported by the observation that despite widely differing doses of local anaesthetic, epidural and spinal anaesthesia have very similar effects and intravenously administered lignocaine has no effect on central thermoregulation (Glosten, Sessler et al. 1991).
**Figure 2:** Spinal anaesthesia increased the sweating threshold but reduced the thresholds for vasoconstriction and shivering. (Sessler 2008)

![Graph showing the effect of dermatomes blocked on shivering threshold](image)

**Figure 3:** The shivering threshold was reduced more by extensive spinal blocks than by less extensive ones ($\Delta$ threshold = 0.74 – 0.06 (dermatomes blocked); $r^2 = 0.58$, $P < 0.006$). The curved lines indicate the 95% confidence intervals for the slope. (Leslie, Sessler 1996)

The vasoconstriction and shivering responses are less effective because they can only occur above the block and are decreased in maximum intensity and gain. All of these factors predispose to the development of hypothermia during neuraxial anaesthesia. Shivering often occurs during neuraxial anaesthesia and is discussed in detail in section 1.3.5
Patients are less likely to realise they are hypothermic because thermal perception is determined more by skin temperature, which may often actually increase (Glosten, Sessler et al. 1992).

In contrast to general anaesthesia, behavioural thermoregulatory responses are also impaired, but not completely removed. If patients do feel cold they are unlikely to be able to personally do much about it, but they may be able to alter their environment by requesting an intervention, for example by asking for a warm blanket.

In summary, during neuraxial anaesthesia the cold defence responses are triggered at a lower temperature; they are less effective; and patients have less ability to sense hypothermia or initiate behavioural responses.
1.3 Shivering

1.3.1 Physiology

Shivering is defined as an involuntary repetitive activity occurring in skeletal muscles, and is usually initiated as a defensive response to maintain core temperature during hypothermia, although there are non-thermoregulatory causes as well. The muscular activity which occurs is uncoordinated and characterised by rapid electromyographic activity (250 Hz), with an overall 4-8 cycle/min pattern of waxing and waning (Israel, Pozos 1989). The efferent pathway for shivering is thought to initiate from the preoptic region of the hypothalamus and is mediated by a postulated central descending shivering pathway. Spinal alpha motor neurons and their axons provide the final common path for both shivering and voluntary movement. Shivering has been described by some authors as a “last resort” response to hypothermia and this makes sense, as shivering is metabolically less efficient than vasoconstriction (Sessler 2009). Shivering is usually triggered about one degree lower than the vasoconstriction response, if this has proven inadequate in preventing a continued fall in body temperature. Shivering can temporarily increase metabolic heat production by up to a factor of four or more, but over longer time periods and in the elderly, the increase is significantly less. The heat produced by shivering is produced mainly in large muscles in the body periphery and much of this heat may then be dissipated into the environment rather than retained in the core where it is needed.
1.3.2 Measurement of shivering

A standardised approach to the definition and method used to grade the severity of shivering is important because it allows comparison of research performed by different groups. We used the following scale as it has been the most widely used in previous shivering research: (Wrench, Cavill et al. 1997).

0 = no shivering
1 = piloerection or peripheral vasoconstriction but no shivering
2 = muscular activity in only one group
3 = muscular activity in more than one muscle group but not generalized shivering
4 = shivering involving the entire body

This instrument has been criticised for not being particularly user friendly or easy to interpret (Crowley, Buggy 2008). During neuraxial anaesthesia usually only the unblocked regions of the upper body are able to shiver and in clinical practice it is hard for most observers to differentiate between the grades. An alternative and simplified but more practical 3 point scale has been proposed (Crowley, Buggy 2008) for use in patients under neuraxial anaesthesia:

0 = no shivering
1 = shivering not interfering with monitoring or causing patient distress
2 = shivering interfering with monitoring or causing patient distress
1.3.3 Adverse consequences of shivering

Shivering per se, when activated as a normal thermoregulatory response, has the beneficial effect of correcting hypothermia. This benefit however comes at the expense of a number of potentially undesirable or deleterious effects. Shivering may double oxygen consumption, carbon dioxide production, increase plasma catecholamines and increase cardiac output (Ciofolo, Clergue et al. 1989), (Frank, Higgins et al. 1995). These effects may be undesirable, particularly in the elderly or patients with cardiovascular or respiratory disease. The rhythmic movement of shivering may interfere with monitoring of electrocardiography, pulse oximetry and blood pressure. (De Courcy 1989)

Shivering is perceived by many patients as unpleasant. The unwanted movement can aggravate postoperative pain, and in parturients it can interfere with maternal bonding, by discouraging the mother from holding her newborn child.

Shivering is particularly undesirable in patients with myotonic dystrophy (Harris 1984), where it can lead to myotonic contractures.
1.3.4 Post-general anaesthesia

Shivering occurs commonly during recovery from general anaesthesia. The majority of shivering observed in the post anaesthesia care unit is due to the return of the normal thermoregulatory response to hypothermia. The commonly held explanation is that as general anaesthesia dissipates, the threshold temperature for shivering normalises and any hypothermia present triggers a shivering response. Post-anaesthesia shivering is often undesirable, for many of the reasons mentioned in the previous section (1.3.3), and a number of prophylactic or therapeutic measures are commonly employed to manage it (Kranke, Eberhart et al. 2004).

Shivering can also be seen in normothermic patients and is thought to be due an increase in the thermoregulatory set point (e.g. fever), with common explanations including pyrogens released from injured tissue, true infection, and atelectasis.

Some other types of muscular activity, such as tonic stiffening, can occur during recovery from isoflurane anaesthesia (Sessler, Rubinstein et al. 1991) and this activity is thought to be unrelated to shivering or thermoregulation.
1.3.5 Shivering during neuraxial anaesthesia

1.3.5.1 Causes

Shivering during neuraxial anaesthesia is very common. In a review of shivering during neuraxial anaesthesia, Crowley et al found the median incidence of shivering, in the control arm from a sample of 21 studies, to be 55%. This is very similar to the incidence of 47% found in our study.

Sessler, in his review of perioperative thermoregulation, (Sessler 2008) states that shivering during neuraxial anaesthesia has four potential explanations:

1. Normal shivering occurring in response to hypothermia which develops as heat redistributes from the core to the periphery. This is probably the most common causative mechanism.

2. Direct stimulation of cold receptors in the neuraxis by the injected local anaesthetic solutions, which are usually at room temperature and thus “cold” relative to core body temperature. This theory is plausible as the spinal cord is known to have thermoreceptors (Cabanac 1975) and some studies in pregnant women found that those receiving colder epidural injectates shivered more (Shehabi, Gatt et al. 1990), (Ponte, Collett et al.1986). However further studies in volunteers failed to confirm these findings (Ponte, Sessler 1990).

3. Normal shivering in normothermic patients who are developing a fever. This cause probably accounts for only a small proportion of patients who shiver during neuraxial anaesthesia. Hyperthermia, in association with labour and epidural analgesia, is discussed in detail in section 1.3.6.
4. Non-thermoregulatory muscular activity. Other types of muscular activity that resemble shivering can occur and have been observed in women during labour (Panzer, Ghazanfari et al. 1999) or in patients following surgery. The activity is associated with pain and thought to be mediated by sympathetic nervous system activity (Horn, Schroeder et al. 1999).

Moderate to severe shivering during neuraxial anaesthesia usually causes either distress or interference with monitoring and often results in some form of treatment. Pharmacological therapies are discussed in detail in section 1.4.
1.3.5.2 Non-Pharmacological Therapies

Non-pharmacological strategies are attractive because they avoid many of the obvious disadvantages inherent to pharmacological treatments – for example unwanted side effects in the mother or fetus. A number of non-pharmacological strategies have been studied:

Beneficial Strategies:

1. Preoperative forced air warming: By actively warming a patient this reduces the temperature gradient between the core and periphery. When heat redistributes following initiation of the block there is a reduction in the subsequent core temperature drop. Horn et al pre-warmed women having an elective caesarean under epidural anaesthesia for 15 minutes using a forced air warmer set at 43°C (Horn, Schroeder et al. 2002). They found less shivering and higher maternal core temperatures. They also demonstrated significantly higher rectal temperatures and umbilical vein pH in the neonate. Chung et al investigated the use of pre-warming with a forced air warming device prior to caesarean delivery under spinal anaesthesia and also found less maternal shivering and higher maternal core temperatures (Chung, Lee et al. 2012), but no improvement in neonatal parameters.

2. Perioperative warming of intravenous fluids: The warming of intravenous fluids administered before and during surgery seems logical and four studies in women undergoing caesarean delivery have investigated this strategy (Workhoven 1986, Chung, Lee et al. 2012). All studies demonstrated
beneficial effects on maternal core temperature but one (Woolnough, Allam et al. 2009) did not observe a decrease in shivering and another, surprisingly, did not assess shivering at all (Yokoyama, Suzuki et al. 2009). These results suggest that warming of intravenous fluids during caesarean delivery should probably be performed routinely.

3. Warming of epidural injectate solutions: There is some evidence that this technique decreases the incidence of shivering. See the discussion in section 1.3.5.1

No Benefit:

4. Intraoperative forced air warming: A study investigating the application of intraoperative forced air warming to the lower limbs of women having caesarean delivery under spinal anaesthesia found no reduction in shivering or improvement in maternal core temperature (Butwick, Lipman et al. 2007).

5. Aluminium space blanket use: One study investigating the use of an aluminium space blanket in women using epidural labour analgesia found a reduced severity but not incidence of shivering (Buggy, Gardiner 1995).

6. Wrapping of lower limbs in elastic bandages: One study found this helped prevent hypotension but had no benefit on maternal hypothermia or shivering (Sun, Ling et al 2004).
1.3.6 Peripartum shivering

There is a well-recognised association between epidural analgesia in labour and hyperthermia (Fusi, Steer et al. 1989, Camann, Hortvet et al. 1991). There are many theories as to the possible causes (Mercier, Benhamou et al. 1997), including the labour itself, possible pregnancy-related hormonal effects, placental inflammation (Reilly, Oppenheimer 2005) and even feto-maternal transfusion (Goodlin, O’Connell et al. 1976). The majority of cases of shivering in pregnant women during neuraxial analgesia or anaesthesia are probably a result of normal thermoregulatory shivering in response to hypothermia. It should be borne in mind however that in certain situations some maternal shivering may occur due to pregnancy-specific factors that are still relatively poorly understood.
1.4 Pharmacologic modification of shivering

1.4.1 Introduction

In clinical practice the most commonly used intervention to treat or prevent shivering is the administration of a pharmacological agent. In this section all the known anti-shivering drugs are discussed, as are the mechanisms thought to explain their anti-shivering properties, their efficacy, adverse effects and the literature supporting their use. Some drugs have been studied in the setting of general or neuraxial anaesthesia but not necessarily both. Another subtle but important point is whether a drug is used for the treatment or prophylaxis of shivering. When a drug is used for prophylaxis against shivering, as was the case in our study, it is important to note that a significant number of patients who were never going to shiver anyway receive the drug. Therefore any study investigating prophylaxis has to prove not just that it is efficacious, but also that the incidence and severity of adverse effects does not outweigh any benefit. At the end of this section I will summarise the current evidence base and provide some basic recommendations for the population in our study: women having caesarean delivery under neuraxial anaesthesia. For drugs with demonstrated efficacy the final decision to use that drug should also include some assessment of the relative financial costs of the different agents.
1.4.2 Endogenous Substances

A large number of endogenous substances in the human nervous system are known to modulate thermoregulation and shivering. These include biogenic monoamines (e.g. serotonin, noradrenaline and dopamine), acetylcholine, cations, endogenous peptides, N-methyl-D-aspartate (NMDA) receptors and potentially others not yet described (De Witte, Sessler 2002). A detailed understanding of these endogenous substances should help identify suitable pharmacological agents. Drugs which interact with these endogenous substances and their receptors will have the potential to modulate shivering. However the actions and interactions of many of these substances are complex, vary between species and can have different or opposing actions in different parts of the nervous system. Many drugs have actions on multiple receptors and simple explanations for the anti-shivering effects of many remain elusive.

1.4.3 Anti-Shivering Drugs

A large number of drugs with widely varying pharmacologic actions have been studied in relation to their effects on shivering. A meta-analysis of 61 randomized controlled trials, published in 2012, identified clonidine, pethidine, tramadol, nefopam and ketamine as the five most frequently studied and efficacious medications (Park, Mangat et al. 2012). In the following section I will focus discussion on, and summarise the evidence for,
those drugs of the most relevance to our study population, i.e. the treatment or prophylaxis of shivering in women undergoing caesarean delivery under neuraxial anaesthesia.

1.4.3.1 Opioids

The endogenously occurring opioid peptides (endorphins, enkephalins, endomorphin) are known to be involved in thermoregulation (Clark, Lipton 1985). Consistent with this, a range of opioid drugs are known to show anti-shivering efficacy. Many of these opioids are already used in anaesthesia, often for their analgesic actions, making them particularly suitable agents to consider for the management of shivering in the setting of this study. Some of these drugs can also be administered via a number of routes, including via the neuraxis. Their efficacy and adverse effect profile can differ depending upon the route of administration, so this has been considered when discussing these particular opioids. The mechanism of the anti-shivering action of opioids has not been fully elucidated but potential explanations have been proposed and are discussed in detail (De Witte, Sessler 2002).
1.4.3.1.1 Pethidine

Pethidine is unique in that it is known to be a significantly more effective anti-shivering drug than other opioids. It is an old drug and one of the most widely studied and used anti-shivering agents.

Pethidine differs from other opioids in that it disproportionately reduces the shivering threshold in comparison to its effect on the vasocostriction threshold. Proposed explanations for its unique anti-shivering properties include kappa agonism, serotonin / noradrenaline reuptake inhibition, NMDA receptor antagonism, stimulation of alpha-2 adrenoceptors or a unique combination of more than one of these actions (De Witte, Sessler 2002).

Pethidine is one of the most widely applied anti-shivering drugs and its efficacy has been summarised in a recent meta-analysis (Park, Mangat et al. 2012). The pooled results from 16 randomised controlled trials demonstrate a relative benefit of 2.23 (i.e. patients receiving pethidine are 2.23 times less likely to shiver compared to placebo) and a number needed to treat (NNT) of 2.0 (i.e. one of every two patients treated will benefit compared to placebo). The effective intravenous dose in these studies was 20-50 mg.

Epidural pethidine: Three small studies have investigated the efficacy of epidural pethidine. The first study (Brownridge 1986) administered either
epidural pethidine 25 mg or placebo in a blinded fashion to 22 women who
were shivering during labour. All women receiving pethidine ceased to shiver,
compared to only 3 of 11 in the placebo arm. In a later study (Brownridge,
Plummer et al. 1992) the same group investigated five different combinations
of epidural solutions for labour analgesia, two of which contained pethidine.
They noted that shivering was significantly less common in those who
received epidural pethidine. Another study (Sutherland, Seaton et al. 1991)
investigated 94 women undergoing elective caesarean section under epidural
anaesthesia with bupivacaine 0.5%, with the addition of either epidural
pethidine 25 mg or placebo. Only 11% of those receiving epidural pethidine
shivered, versus 36% in the placebo arm. Importantly in this study, which
administered the drug prophylactically, there was no increase in adverse effects
such as maternal nausea, vomiting, drowsiness, itch or lower neonatal Apgar
scores. This is in contrast to most of the studies of intrathecal pethidine, as
discussed below.

Spinal (intrathecal) pethidine studies have investigated the properties of
intrathecal pethidine since the 1980s (Naguib, Famewo et al. 1986). However
the focus of most of these earlier studies was the efficacy of spinal anaesthesia
when pethidine was used as the sole drug; or its ability to provide more
prolonged postoperative analgesia when it was used as an adjunct to a local
anaesthetic. Six studies have specifically investigated intrathecal pethidine, in
doses ranging from 10-25 mg, to prevent shivering during spinal anaesthesia and four studies were in obstetric patients (Anaraki, Mirzaei 2012), (Khan, Zanjani et al. 2011), (Hong, Le 2005), (Roy, Girard et al. 2004) and two in urological patients (Chun, Kil et al. 2010), (Davudi, Mousavi-Bahar et al. 2007). All studies demonstrated that intrathecal pethidine was very effective in preventing shivering. Another two studies, where shivering was not the primary outcome of interest, have been performed in obstetric patients and adverse events were discussed (Yu, Ngan Kee et al. 2002), (Booth, Lindsay et al. 2000). Among the six studies conducted on obstetric patients undergoing caesarean delivery, 4 of 6 of the investigator groups recommended against the use of intrathecal pethidine in the obstetric setting, because they considered that the incidence of nausea and vomiting was increased to such a degree that this problem outweighed the demonstrated benefit (decreased shivering or longer analgesia). Another study investigated the anti-emetic efficacy of a dose of i.v. dexamethasone prior to spinal anaesthesia with bupivacaine and intrathecal pethidine, for patients undergoing hernia surgery. The drug enhanced postoperative analgesia and decreased postoperative nausea and vomiting (Movafegh, Soroush et al. 2007). No studies combining anti-emetics and intrathecal pethidine have been performed in obstetric patients but this strategy appears worthy of future investigation.
Relevance to patients undergoing caesarean delivery under neuraxial blockade:

Intravenous pethidine - is effective and a dose of 20-50 mg should be considered for treatment of established moderate to severe shivering. Caution should be used before administering intravenous pethidine prior to delivery (especially in the higher dose range) due to trans-placental transfer of drug to the fetus and the potential for neonatal respiratory depression.

Epidural pethidine – 25 mg is effective for both prophylaxis and treatment of shivering. The incidence of adverse effects does not appear to be increased, although these conclusions are based on a very limited amount of data from only three studies, two of which were very small. Further studies to better assess the optimal dose and confirm the absence of any increase in adverse effects (in particular nausea) are warranted, because this finding is in contradiction to the results of intrathecal pethidine studies (see below).

Intrathecal pethidine – is effective at decreasing shivering but is not currently recommended for routine use due to the clinically relevant increased incidence of nausea and vomiting consistently reported.
1.4.3.1.2 Fentanyl

Intravenous fentanyl: One study in 100 patients with established shivering compared intravenous fentanyl, pethidine, morphine and placebo (Pauca, Savage et al. 1984). Pethidine was effective but fentanyl and morphine were no more effective than placebo. Another study (Dabir, Jahandideh et al. 2011) again compared these three opioids in patients with shivering post general anaesthesia (GA) and found no difference between them after 30 minutes. However this study failed to include a placebo arm and post-GA shivering is known to abate spontaneously over time, making it difficult to form conclusions.

Epidural fentanyl: Five studies have assessed the efficacy of epidural fentanyl to prevent or treat shivering in obstetric patients, in doses ranging from 25-100 mcg – all studies demonstrated a positive effect (Abreu, Vieira et al. 2004) (Wheelahan, Leslie et al. 1998) (Liu, Luxton 1991) (Sinatra, Goldstein et al. 1991). A landmark study published in the BMJ (Murphy, Henderson et al. 1991) demonstrated that the combination of bupivacaine and fentanyl was superior to bupivacaine alone for labour analgesia, providing better analgesia and possibly more normal deliveries, less motor block and less shivering. A study (Fan, Ji et al. 2011) that compared epidural tramadol or fentanyl as adjuncts to bupivacaine for labour analgesia found no significant difference in the incidence of shivering.
Intrathecal fentanyl: Seven studies have assessed the effect of intrathecal fentanyl on shivering (Techanivate, Rodanant et al. 2005) (Bogra, Arora et al. 2005) (Techanivate, Urusopone et al. 2004) (Kang, Tsai et al. 1998) (Palmer, Voulgaropoulos et al. 1995) (Chu, Shu et al. 1995) (Chow, Cho 1994) and six found a significant decrease in incidence or severity. Importantly, the majority of studies also found that there was a significant decrease in nausea and vomiting, which contrasts with the effect of intrathecal pethidine. Other beneficial effects noted in some studies were better initial postoperative analgesia and longer duration of block. The only unwanted effect, an increase in pruritus, was commented on in three studies.

Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous fentanyl: This is not recommended as other i.v. treatments appear more effective.

Epidural fentanyl: Effective for either prophylaxis or treatment of shivering in a dose of 50-75 mcg.

Intrathecal fentanyl: Effective for prophylaxis of shivering in a dose of 10-25 mcg.
1.4.3.1.3 Sufentanil

Intravenous sufentanil: One study in patients under GA compared intraoperative infusion of pethidine or sufentanil with respect to the incidence of postoperative shivering (Alfonsi, Sessler et al. 1998). Similar to most other pure mu-opioid receptor agonists, at equipotent analgesic doses sufentanil was not as effective as pethidine, suggesting that more effective intravenous drugs should be used in preference.

Epidural sufentanil: In contrast to intrathecal sufentanil (see below) there is no convincing evidence of an anti-shivering efficacy from standard analgesic doses of epidural sufentanil (10-30 mcg) in the obstetric setting (Bachmann-Mennenga, Veit et al. 2005), (Bachmann-Mennenga, Veit et al. 2005 – another trial, see bibliography), (Vertommen, Vandermeulen et al. 1991). This is despite a case report that reported a marked anti-shivering effect after a single larger dose of epidural sufentanil of 100 mcg (Johnson, Sevarino et al. 1989).

Intrathecal sufentanil: Three studies have investigated the use of intrathecal sufentanil in patients undergoing caesarean delivery (de Figueiredo Locks 2012), (Chen, Qian et al. 2010), (Qian, Chen et al. 2008) and one studied patients undergoing lower limb surgery (Kumar, Bajwa 2011). All four studies demonstrated decreased rates of shivering from a dose range 2.5 – 5 mcg. None of the studies noted an increase in the incidence of adverse effects and
one study (Qian, Chen et al. 2008) noted a beneficial decrease in vomiting in
the sufentanil arm.

Relevance for patients undergoing caesarean delivery under neuraxial
blockade:
Intravenous sufentanil: Not recommended as other i.v. treatments appear
more effective.

Epidural sufentanil: Not recommended for either prophylaxis or treatment of
shivering (in standard doses of 10-30 mcg).

Intrathecal sufentanil: Effective prophylaxis against shivering in a dose of 2.5-
5 mcg.
1.4.3.1.4 Morphine

Intrathecal morphine: Only one study (Hong, Lee 2005) has directly assessed the anti-shivering efficacy of intrathecal morphine (comparators were spinal bupivacaine only or intrathecal pethidine). This study found only a very modest and probably clinically unimportant benefit when compared to bupivacaine alone. A number of other studies (de Figueiredo Locks 2012, Techanivate, Rodanant et al. 2005, Roy, Girard et al. 2004) included intrathecal morphine in their control arm but still noted shivering rates of 50-85%, suggesting that although commonly used for its excellent postoperative analgesia, if the primary aim is a clinically significant decrease in shivering, morphine is relatively ineffective.

1.4.3.1.5 Tramadol

Tramadol is a well documented anti-shivering agent. It is an opioid agonist which also has actions on central mono-aminergic pathways via its inhibition of the neuronal reuptake of serotonin and noradrenaline. It is postulated that its anti-shivering efficacy results from these central inhibitory actions.

Intravenous tramadol: The efficacy of intravenous tramadol was summarised in a recent meta-analysis (Park, Mangat et al. 2012). The pooled results from nine randomised controlled trials demonstrate a relative benefit of 2.16 (i.e. patients receiving tramadol are 2.16 times less likely to shiver compared to
placebo) and a NNT of 2.0 (i.e. one of every two patients treated will benefit compared to placebo). The effective intravenous dose in these studies was 0.5-3 mg/kg. One study (Chan, Ng et al. 1999) specifically investigated the use of low dose intravenous tramadol to treat established shivering during caesarean delivery under regional anaesthesia. They demonstrated that a dose of 0.25 mg/kg was effective and well tolerated, with no increase in adverse effects. One small study (Tsai, Chu 2001) compared the treatment of established shivering during caesarean delivery using tramadol 0.5 mg/kg, pethidine 0.5 mg/kg or amitriptyline 15/20 mg. They demonstrated similar efficacy with tramadol or pethidine but significantly less somnolence in the tramadol arm. Another study in non-obstetric surgery under spinal anaesthesia compared clonidine 0.5 mg/kg with tramadol 0.5 mg/kg for the treatment of shivering (Shukla, Malhotra et al. 2011). This study demonstrated similar treatment efficacy but in the tramadol arm the response was slower and there was significantly more nausea, vomiting and dizziness.

Epidural tramadol: One study has investigated epidural tramadol in the obstetric population (Fan, Ji et al. 2011). The investigators compared labour analgesia with bupivacaine 0.125% and fentanyl 3 mcg/ml to bupivacaine 0.125% and tramadol 5 mg/ml and noted a non-significant decrease in the incidence of shivering in the tramadol arm.
Intrathecal tramadol: There is only one study investigating the use intrathecal tramadol in obstetric patients (Frikha, Ellachtar et al. 2007). This study compared bupivacaine and sufentanil to bupivacaine and tramadol in a combined spinal epidural (CSE) technique for labour analgesia. They presented no data on the incidence of shivering but there was a significant increase in vomiting in those receiving intrathecal tramadol.

Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous tramadol: Effective but low doses of 0.25 - 0.5 mg/kg should be used as higher doses are associated with increased nausea and vomiting.

Epidural tramadol: Not recommended at present due to paucity of supportive evidence (only one study in labour analgesia).

Intrathecal tramadol: Not recommended due to increased incidence of vomiting.
1.4.3.1.6 Other opioids

Diamorphine and buprenorphine have been studied and are used as opioid adjuncts in neuraxial anaesthesia for caesarean delivery but there are no data in the literature about their effect on shivering. Intravenous alfentanil has been shown to have a very temporary anti-shivering effect in one study (Lyons, Carroll et al. 1995) and no effect in another (Wrench, Cavill et al. 1997). High dose intraoperative remifentanil during GA has been associated with increased postoperative shivering (Nakasuji, Nakamura et al. 2010).
1.4.3.2 Alpha-2 adrenergic agonists

1.4.3.2.1 Clonidine

Clonidine, an alpha-2 agonist, is one of the best studied anti shivering drugs, with 25 randomized double-blind studies identified in a recent meta-analysis (Park, Mangat et al. 2012).

Intravenous clonidine: The intravenous route was the most studied and across a broad range of doses (1-5 mcg/kg or 30 -150 mcg). Pooled analysis of 15 studies demonstrate a risk reduction of 1.58 (i.e. patients receiving clonidine are 1.58 times less likely to shiver compared to placebo) and a NNT of 3.9 (i.e. one of every four patients treated will benefit compared to placebo). This suggests that i.v. clonidine has benefit but that it is probably less effective than either pethidine or tramadol.

Epidural clonidine: The evidence for epidural clonidine is conflicting. One study investigating the addition of clonidine 4.5 mcg/ml to bupivacaine and fentanyl for labour analgesia demonstrated a lower incidence of shivering in the clonidine arm (Paech, Pavy et al. 2000). In contrast a study investigating the addition of clonidine 150 mcg to bupivacaine for surgery under epidural anaesthesia (Ghatak, Chandra et al. 2010) found the incidence of shivering was significantly increased compared with either epidural placebo or magnesium.
Intrathecal clonidine: One study in orthopaedic patients under spinal anaesthesia, (Jeon, Jeon et al. 2005) found that intrathecal clonidine in a dose of 150 mcg did not decrease shivering (but also confirmed that intravenous clonidine was effective).

Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous clonidine: Effective and could be considered for treatment in a dose of 30 – 150 mcg. Higher doses are likely to cause significant sedation and possibly hypotension or bradycardia. Intravenous pethidine or tramadol are probably more effective.

Epidural clonidine: Not recommended for either prophylaxis or treatment of shivering as evidence supporting effectiveness is conflicting.

Intrathecal clonidine: Not recommended for either prophylaxis or treatment of shivering.
**1.4.3.2.2 Dexmedetomidine**

Dexmedetomidine is another alpha-2 agonist that shows anti shivering efficacy when given intravenously (Park, Mangat et al. 2012). Only one study has investigated patients receiving neuraxial anaesthesia. Patients having minor surgery under spinal anaesthesia received prophylactic intravenous dexmedetomidine or placebo and the active arm demonstrated a reduction in the incidence of shivering from 57% to 10%. (Usta, Gozdemir et al. 2011)

**Relevance for patients undergoing caesarean delivery under neuraxial blockade:**

Intravenous dexmedetomidine: Effective and could be considered for treatment of shivering in a dose of 1 mcg/kg. Routine prophylactic use is probably not justifiable due to the high incidence of undesirable effects, such as sedation, dry mouth and bradycardia.

Neuraxial dexmedetomidine: Not recommended due to a lack of data. Studies of epidural dexmedetomidine have shown benefit in areas such as analgesia, block onset and duration but unfortunately these studies did not investigate shivering.
1.4.3.3 5HT-3 Antagonists

5HT-3 antagonists are anti-emetics used frequently by anaesthetists to treat or prevent perioperative nausea and vomiting. Thirteen studies have investigated the use of different 5HT-3 antagonists (ondansetron, granisetron, dolasetron and ramosetron) for prophylaxis of shivering but none have investigated their efficacy for the treatment of established shivering. 5-HT3 antagonists are non-sedating and largely devoid of cardiovascular or respiratory effects. These features make them a particularly attractive option for the study population of pregnant women having caesarean delivery under neuraxial anaesthesia.

Unlike other types of surgery under neuraxial anaesthesia (e.g. orthopaedic surgery), women are usually keen to avoid sedation because it interferes with memory formation of an important life event or makes interaction with the newborn child more difficult. One study has demonstrated that ondansetron inhibited shivering following GA and that this was independent of the intraoperative core temperature. This suggests central inhibition of the shivering response. (Powell, Buggy 2000) It has been proposed that inhibition of serotonin reuptake in the preoptic anterior hypothalamic region may be involved. (Kelsaka E 2006)
1.4.3.3.1 Ondansetron

Ondansetron is the 5HT-3 antagonist most extensively studied in the setting of shivering prophylaxis.

Post general anaesthesia: Three studies (Abdollahi, Forouzannia et al. 2012, Asl, Isazadefar et al. 2011, Powell, Buggy 2000), investigated ondansetron for prophylaxis of post-GA shivering and all showed a positive result. The first study performed, by Powell and Buggy, found a dose of 8 mg superior to a more traditional 4 mg anti-emetic dose. All subsequent studies have used the larger 8 mg dose and for this reason we also chose 8 mg for our study.

During neuraxial anaesthesia: Two studies (Shakya, Chaturvedi et al. 2010), (Kelsaka, Baris et al. 2006) have investigated the use of prophylactic ondansetron in patients undergoing spinal anaesthesia. Both demonstrated that ondansetron decreased the incidence of shivering. It is important to note that in both of these studies, the spinal anaesthesia consisted of intrathecal bupivacaine 12.5 – 15 mg only, whereas in our study intrathecal fentanyl was also included and this is an effective anti shivering drug (see 1.4.3.1.2 earlier).
1.4.3.3.2 Granisetron

Four studies have examined the efficacy of granisetron for the prevention of shivering, two in patients post-GA (Iqbal, Ahmed et al. 2009, Sajedi, Yaraghi et al. 2008) and two in patients undergoing spinal anaesthesia (Eldaba, Amr 2012, Sagir, Gulhas et al. 2007). All four of these studies reported a positive benefit compared to placebo, although one noted that intravenous ketamine 0.5 mg/kg was superior. Again of note, the two studies evaluating patients under spinal anaesthesia involved hyperbaric bupivacaine only, with no intrathecal fentanyl (or sufentanil).

1.4.3.3.3 Dolasetron and Ramosetron

Post general anaesthesia: In the prevention of post-GA shivering, two studies, of which one used dolasetron (Bock, Bauer et al. 2007) and the other ramosetron, (Song, Lee 2013) demonstrated the efficacy of these drugs in decreasing the incidence of shivering.

During neuraxial anaesthesia: One study of patients under spinal anaesthesia (using hyperbaric bupivacaine only) for orthopaedic surgery found that ramosetron decreased shivering. (Kim, Kim et al. 2010)
Summary for 5HT-3 Antagonists

Relevance for patients undergoing caesarean delivery under neuraxial blockade:

All 12 studies show a positive result, although there are two important points to note:

1 – None of these studies specifically investigated women undergoing caesarean delivery.

2 – In the five studies with patients under spinal anaesthesia they all received bupivacaine alone and no adjuvant fentanyl or sufentanil, both of which have previously been demonstrated to decrease shivering.

Prophylaxis: Based on this evidence (excluding the results of our study, which are discussed in section 2), it would be reasonable to recommend prophylactic ondansetron 8 mg, ramosetron 0.3 mg or granisetron 1.5-3 mg prior to spinal anaesthesia conducted using bupivacaine alone, without fentanyl or sufentanil.

Treatment: There is no evidence to recommend the use of any 5HT-3 antagonist to treat established shivering.
1.4.3.4 Ketamine

Ketamine is a racemic centrally acting NMDA receptor antagonist used primarily as an analgesic or anaesthetic agent and also one of the four most extensively studied anti-shivering drugs. Ketamine is thought to exhibit anti-shivering effects via the NMDA receptor (which is involved in thermoregulation at a number of sites within the nervous system) and as a direct central nervous system sympathomimetic drug, via inhibition of postganglionic noradrenaline reuptake. Ketamine appears less suitable in our subjects because it causes sedation and can induce hallucinations or other unpleasant psychological effects. These are reported to be reduced with the use of S(+) ketamine, a preparation unavailable in Australia but one that has been confirmed to retain anti shivering efficacy in a single study (Piper, Beschmann et al. 2008).

There have been 11 studies assessing the anti-shivering activity of ketamine and all demonstrated significant anti shivering effects. Seven studies were included in the pooled meta-analysis (Park, Mangat et al. 2012) and showed a risk reduction of 1.84 (i.e. patients receiving ketamine are 1.84 times less likely to shiver compared to placebo), with a NNT of 2.8 (i.e. one of every three patients treated will benefit compared to placebo). The doses used in these positive studies were 0.25 – 0.75 mg/kg i.v. or 1 mg/kg i.m. (intramuscular). Three studies specifically investigated the efficacy of i.v. ketamine to prevent shivering in patients under a neuraxial block (Honarmand, Safavi 2008),
(Shakya, Chaturvedi et al. 2010), (Wason, Jain et al. 2012) and all found good anti-shivering efficacy. However all three studies noted a significantly higher incidence of sedation compared to the comparator groups (placebo, clonidine, tramadol, ondansetron). In many patient groups under neuraxial anaesthesia sedation is desirable but this is often not the case for women undergoing caesarean delivery. These patients prefer to be alert so that they can remember and actively participate in the birth of their child.

One study demonstrated a positive anti-shivering effect from epidural ketamine (doses of 0.2 mg/kg and 0.4 mg/kg) in men undergoing transurethral prostate surgery under epidural anaesthesia with ropivacaine 0.75% (Han, Jeong et al. 2010). Despite administration via the epidural route, increased sedation occurred in both ketamine groups.

Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous ketamine: Effective and could be considered but due to sedation and its potential for adverse psychological effects it appears less suitable than other effective intravenous agents, such as pethidine or tramadol. The usual dose is 0.25 – 0.75 mg/kg.

Neuraxial ketamine: Effective in a dose of 0.2 – 0.4 mg/kg but likely to cause sedation, so routine prophylactic use is probably not justified.
1.4.3.5 Nefopam

Nefopam is a centrally acting non-opioid analgesic drug structurally related to orphenadrine and diphenhydramine. It is available in some countries but not in Australia or the USA. In the meta-analysis (Park, Mangat et al. 2012) there were 8 studies identified, all of which confirmed it is an effective anti-shivering drug. The pooled analysis showed a risk reduction of 2.12 (i.e. patients receiving nefopam are 2.12 times less likely to shiver compared to placebo) and a NNT of 1.9 (i.e. one of every two patients treated will benefit compared to placebo). This places nefopam (along with tramadol and pethidine) in the three most effective anti-shivering drugs. The usual dose used was 0.15 mg/kg or 10-20 mg.

Only 2 studies have specifically investigated the efficacy of nefopam to prevent shivering in patients under neuraxial block, both in patients undergoing orthopaedic surgery. One study demonstrated that nefopam was better than tramadol or placebo in the prevention of shivering. (Bilotta, Pietropaoli et al. 2002) The other study noted that nefopam was as effective as pethidine at preventing shivering but that 16% of patients experienced injection pain from i.v. nefopam. (Kim, Kweon et al. 2013)
Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous nefopam: Effective and if available can be considered for treatment of shivering in a dose of 0.15 mg/kg.

Neuraxial nefopam: Cannot be recommended as there have been no studies of neuraxial administration.

1.4.3.6 Magnesium

Intravenous magnesium has been demonstrated to be an effective anti-shivering drug in four studies. (Miyakawa, Matsumoto et al. 1991)(Gozdemir, Usta et al. 2010),(Yousef, Amr 2010),(Ryu, Kang et al. 2008). Three of these studies were included in the meta-analysis (Park, Mangat et al. 2012), with the pooled analysis showing a risk reduction of 1.39 (i.e. patients receiving magnesium are 1.39 times less likely to shiver compared to placebo) and a NNT of 3.8 (i.e. one of every four patients treated will benefit compared to placebo). To put this into context, these data indicate that intravenous magnesium is effective but less so than many other better studied agents (e.g. pethidine, tramadol and nefopam). One study (Miyakawa, Matsumoto et al. 1991), demonstrated that pethidine was significantly more effective than magnesium for post anaesthesia shivering.
Another study investigated the use of i.v. magnesium (80 mg/kg bolus plus an infusion at 2 g/h) versus placebo in patients under spinal anaesthesia for prostate surgery and demonstrated a shivering incidence of only 6.7% in the magnesium arm versus 66.7% in the placebo arm. (Gozdemir, Usta et al. 2010) Two studies have investigated epidural magnesium. One reported that it reduced the incidence of shivering, as well as increasing the time to onset of postoperative pain. (Yousef, Amr 2010) The other study, using epidural bupivacaine for surgery, compared magnesium to saline or clonidine, and found a higher incidence of shivering after epidural clonidine (Ghatak, Chandra et al. 2010).

There have been a number of studies of intrathecal magnesium as a component of spinal anaesthesia, primarily investigating its effect on block duration and analgesia. (Pascual-Ramirez, Gil-Trujillo et al. 2013) Only one study (Faiz, Rahimzadeh et al. 2013) specifically investigated the effect on shivering and demonstrated that, when added to bupivacaine only spinal anaesthesia, intrathecal magnesium sulphate decreased the incidence of shivering in women undergoing caesarean delivery. Data from clinical use in relation to the potential for neurotoxicity appears reassuring but further toxicological study is warranted before routine clinical use can be recommended.
Relevance for patients undergoing caesarean delivery under neuraxial blockade:

Intravenous magnesium: Effective but not as good as other agents so not currently recommended for either prophylaxis or as first-line treatment. It may be indicated for other reasons (e.g. severe pre-eclampsia, hypertension or tocolysis), in which case it should be continued perioperatively.

Epidural magnesium: Not recommended as only limited data from two studies, only one of which demonstrated a positive effect.

Intrathecal magnesium: One study has demonstrated decreased shivering, but further research to confirm safety is required before it can be recommended.
1.5 Summary and recommendations

When making recommendations specifically relevant to women undergoing caesarean delivery under CSE anaesthesia it should be acknowledged that these recommendations are in large part based on evidence extrapolated from studies in other patient groups or those with post-GA shivering. The following recommendations are a reasonable summary of current evidence.

Prophylaxis:

Pharmacological agents with reasonable evidence for efficacy and acceptable adverse effect profiles include:

1) Intrathecal fentanyl 10-25 mcg
2) Intrathecal sufentanil 2.5-5 mcg
3) Epidural pethidine 25 mg
4) Intravenous granisetron 1.5-3 mg or ramosetron 0.3 mg or ondansetron 8 mg (but not if one the above neuraxial opioids has already been included, based on the results of our study- see section 2)
Treatment:

The following drugs have sufficient evidence to recommend their use as treatments for established shivering. All have possible unwanted adverse effects, such as nausea or sedation, so the decision to use them is probably only justified if the shivering is causing distress or problems with monitoring and the benefits are likely to outweigh their adverse effects.

1) Pethidine i.v. 20-50 mg or epidural 25 mg
2) Tramadol i.v. 0.25-0.5 mg/kg
3) Clonidine i.v. 30-150 mcg
4) Dexmedetomidine i.v. 1 mcg/kg
5) Nefopam i.v. 0.15 mg/kg
6) Ketamine i.v. 0.25-0.75 mg/kg
Chapter Two: Prophylactic Ondansetron To Prevent Shivering During Caesarean Delivery Under Combined Spinal Epidural Anaesthesia

2.1. Introduction

In Australia, elective caesarean delivery is most commonly conducted under neuraxial anaesthesia. Neuraxial techniques are associated with a significant incidence of shivering, both intraoperatively and postoperatively (Brownridge 1986). An audit done prior to our study demonstrated an incidence of 37% in women undergoing elective caesarean delivery. The cause of this shivering is incompletely understood but probably involves a number of mechanisms; including changes in body heat distribution, changes in thermoregulatory thresholds, reductions in body core temperature and the effect of the temperature of fluids injected into the neuraxis. (Crowley, Buggy 2008)

Shivering can be distressing and problematic for both the mother and the anaesthetist. Severe shivering interferes with monitoring of blood pressure, electrocardiogram and pulse oximetry. It often occurs during the period when a sympathetic block combined with aortocaval compression can make hypotension or arrhythmias more likely. Shivering may cause maternal discomfort and interfere with her ability to hold and interact with her baby. (Ostheimer, Datha 1981)
A number of drugs are known to be effective for preventing or treating neuraxial anaesthesia-related shivering, with those most commonly used in Australia being pethidine (meperidine), clonidine and tramadol. These drugs have analgesic or sedative properties and unfortunately adverse effects such as nausea, bradycardia, and hypotension occur. Anaesthetists may be reluctant to administer such drugs prior to delivery because of concerns about unwanted effects on the mother and the fetus (Mattingly, D’Alessio et al. 2003).

5-HT₃ antagonists such as ondansetron are widely used as anti-emetics during both pregnancy and surgery. A number of studies have demonstrated their anti-shivering properties, both following general anaesthesia and during neuraxial anaesthesia (Kelsaka, Baris et al. 2006). If effective, they offer potential advantages in the obstetric population because of their very low incidence of sedation, adverse cardiovascular effects or risk to the neonate. They may also provide beneficial anti-emetic and anti-pruritic activity. (Yeh, Chen et al. 2000)

The administration of prophylactic intravenous ondansetron to prevent shivering had not been studied previously in an obstetric population.

We decided to conduct the following study: “A randomised controlled trial of Ondansetron to prevent Shivering during Cæsarean section (The OSCAR trial)”
2.2 Hypothesis

2.2.1 Null Hypothesis:

That there is no difference in the incidence or severity of perioperative shivering in women given intravenous ondansetron 8 mg, compared with placebo, prior to performing combined spinal epidural anaesthesia for elective caesarean delivery.

2.2.2 Alternative Hypothesis

The alternative hypothesis is that intravenous ondansetron 8 mg given to women prior to performing combined spinal epidural anaesthesia for elective caesarean delivery is superior to placebo, producing a significant decrease in the incidence or severity of perioperative shivering.
2.2.3 Aims

1. To demonstrate that, by administering intravenous ondansetron 8 mg prior to performing combined spinal epidural anaesthesia for women undergoing caesarean delivery, both a statistically and clinically significant decrease in the incidence and severity of shivering would result.

2. To demonstrate that this method did not result in an increase in adverse effects for either the woman or her newborn.

3. To assess whether this method had any other desirable outcomes, such as a decrease in the incidence of nausea or pruritus.

2.3 Methods

2.3.1 Study Design

This study was a randomized, double-blinded, parallel-group, placebo-controlled clinical trial involving 118 American Society of Anesthesiologists (ASA) class 1 or 2 women over the age of 18 years and scheduled for elective caesarean delivery. These women had elected for combined spinal epidural (CSE) anaesthesia, were recruited from Kaleeya and Rockingham General Hospitals, Western Australia.
2.3.2 Study Endpoints

2.3.2.1 Primary Endpoints

- The overall incidence of shivering, defined as shivering occurring at any time point after anaesthesia until discharge from the PACU.
- The incidence of severe shivering, defined as a shivering score of 2 or greater occurring at any time point after anaesthesia until discharge from the PACU.

2.3.2.2 Secondary Endpoints

- Nausea
- Vomiting
- Itch
- Headache
- Neonatal Apgar scores
- Change in body temperature
- Maternal satisfaction scores
2.3.3 Participants

Eligible women booked for elective caesarean delivery at either Kaleeeya or Rockingham General hospitals were approached at either the pre-admission clinic or on the ward prior to surgery by a member of the Department of Anaesthesia. If the patient agreed to participate, written informed consent was obtained and they were asked to complete a preoperative questionnaire.

2.3.3.1 Inclusion Criteria:

1. American Society of Anesthesiologists (ASA) class 1 or 2
2. Age 18 years or greater
3. Scheduled for elective caesarean delivery
4. Scheduled for combined spinal epidural (CSE) anaesthesia

2.3.3.2 Exclusion Criteria:

1. Preoperative use of ondansetron, tramadol, pethidine or clonidine
2. Contraindication to CSE technique
3. Intolerance or allergy to ondansetron
4. Shivering present prior to study drug administration
5. Failure to identify the subarachnoid space
6. Conversion to general anaesthesia
7. Administration of intrathecal or epidural morphine
2.3.4 Blinding & Group Assignment

An anaesthetist not involved in obstetrics that day and following a well-defined process was asked to open the randomization envelope in a private office suite. Randomization was in a 1:1 ratio, using a computer generated random number sequence and group allocation preoperatively was by sealed opaque envelope. The study drug was then prepared in a standard 5 ml syringe, labeled only with the patients name and study number, containing either:

1. intravenous ondansetron 8 mg in 4 ml saline (group O) or

2. saline placebo 4 ml (group C)

The randomization envelope was destroyed and the study drug was delivered to the anaesthetist in the obstetric theatre prior to the commencement of anaesthesia.

The patient and all those responsible for data collection (the treating doctors, post anaesthesia care unit (PACU) nurses and the research team members) were blinded to the group allocation.
2.3.5 Study Drug Administration & Conduct of Anaesthesia

After arrival in the operating theatre the staff conducted the anaesthesia according to the following protocol:

1. Insertion of 16 gauge (G) intravenous cannula
2. Administration of study drug
3. Combined spinal epidural anaesthesia (performed with a 16 G Tuohy epidural needle using loss of resistance to saline and a 27 G Whitacre spinal needle).
4. Hyperbaric bupivacaine 0.5% 2.2 – 2.5 ml plus fentanyl 15 mcg
5. 1000 – 1500 ml unwarmed Hartmann’s iv crystalloid fluids
6. Exposed skin covered
7. Postoperative analgesia provided by Go-Medical* patient controlled epidural analgesia device delivering a pethidine 20 mg bolus with 15 min lockout. This was not allowed to be used until the patient had arrived in PACU.

Explanatory note: there is some evidence in the literature that the volume and temperature of fluids injected into the neuraxis influence the incidence of shivering. (Shehabi, Gatt et al. 1990), (Ponte, Collett et al. 1986) Combined spinal epidural anaesthesia using loss of resistance to saline is the most commonly used anaesthetic technique for this surgery in our hospitals. We considered that it was possible spinal anaesthesia alone or a loss of resistance
to air technique may have altered the incidence of shivering, so in order to avoid random and uneven allocation of these techniques based on operator preference, we specified that they should not be used.

Management of intraoperative pain or shivering

- Shivering: If considered by either the patient or the anaesthetist to be significant enough to require treatment, the anaesthetist could administer 30 mcg of intravenous clonidine.
- Intra-operative pain: If required the treating anaesthetist was instructed to give epidural local anaesthetic; nitrous oxide, intraperitoneal or wound local anaesthetic infiltration; or small doses of intravenous fentanyl or ketamine** as appropriate. Anaesthetists were instructed not to administer IV or epidural pethidine intraoperatively because it was known to prevent shivering.

* Go-Medical = Go Medical Industries Pty Ltd, 200 Churchill Ave, Subiaco WA 6008, Australia

** Ketamine is also known to prevent shivering and in retrospect this should not have been specified as an option on the instruction sheet. However during the study no participants actually received ketamine, so this did not effect the findings.

2.3.6 Assessment and Data Collection
Preoperative:

Prior to surgery the following baseline demographic data were collected:

- age
- ASA grade
- parity
- weight
- previous caesarean delivery
- history of previous shivering during this surgery
- participants were also asked to complete the validated 14 question Hospital Anxiety and Depression score (HAD score), to investigate whether preoperative anxiety might influence shivering incidence and intensity.

Intraoperative:

The following intraoperative data was collected:

- body temperature on arrival in theatre (tympanic)
- times of arrival in theatre, administration of spinal drugs, and completion of surgery
- spinal medications administered
- loss of resistance technique
- analgesic adjuvants if used; drug and dose
- nausea (visual analog scale 0 -10)
- headache (visual analog scale 0 -10)
- itch (visual analog scale 0-10)

Shivering: a comprehensive assessment of shivering was performed at three time points:

1. before insertion of CSE
2. after the CSE but before surgery
3. during surgery

- Was shivering present? yes / no
- If present the severity was assessed using the following validated scale (Wrench, Cavill et al. 1997):

  0 = no shivering
  1 = piloerection or peripheral vasoconstriction but no shivering
  2 = muscular activity in only one group
  3 = muscular activity in more than one muscle group but not generalized shivering
  4 = shivering involving the entire body

- They were also asked to assess whether the shivering caused:
- discomfort or distress
- interfered with monitoring
- prevented interaction with the neonate
- required pharmacologic treatment

Postoperative:

In the PACU further data collected included:

- a full re-assessment of shivering, itch, nausea, and headache as described above
- body temperature on arrival in theatre (tympanic)
- neonatal Apgar scores*
- maternal satisfaction score (visual analog scale 1-10)

On the ward midwives were asked to assess adequacy of breastfeeding.

* Apgar score = a scoring system used to assess the health of a newborn immediately after birth, composed of 5 criteria: Appearance, Pulse, Grimace, Activity and Respiratory effort.

2.3.7 Sample size calculation
In a pilot audit of 54 women having elective caesarean section under CSE anaesthesia we found an incidence of shivering of 37%. We considered a reduction in incidence from 37% to 15% in the intervention group would be clinically significant enough to lead to a change in anaesthesia practice. We chose an alpha of 0.05, beta of 0.8 and calculated 58 patients would be required in each study arm. Allowing for withdrawals, we aimed to recruit 120 women.

2.3.8 Statistical Methods

Standard descriptive statistics (frequencies and percentages for categorical variables, and means and standard deviations for variables measured on a continuous scale) were used to summarize the profile of the subjects recruited to each treatment group. Comparisons between groups at baseline were carried out using either the Chi-square test, Fisher’s exact test (categorical variables), or t-tests (continuous variables). The non-parametric Wilcoxon 2-sample test was used when the data were skewed. The primary and secondary endpoints were compared between groups in a similar manner. For all comparisons, a p-value < 0.05 was considered significant. The data were analyzed using SAS version 9 statistical software package (SAS Institute, Cary, NC, USA, 2008). The 95% confidence intervals for the difference in means between groups for the primary endpoints were calculated using SPSS version 20 statistical software package (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).
2.3.9 Ethical Issues

The Human Research Ethics Committee of the South Metropolitan Area Health Service of Western Australia approved the study protocol. This trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12609000445279).

All patients received written information sheets and completed written informed consent prior to enrolment in the study.

This study was conducted according to ethical principles outlined by the NHMRC (National Health and Medical Research Council) as discussed below:

2.3.9.1 Research Merit and Integrity

Justification for any study is an important ethical principle. Shivering is common in this group of patients and is an ongoing important clinical problem which justifies further study. The use of ondansetron to prevent shivering in this group of patients had not been studied before. Caesarean delivery is one of the most common operations in the world and the results of this study had the potential to benefit the very large number of patients who undergo this operation every year. Ondansetron is a relatively cheap medication that is widely available in both developed and lower resource countries. The study design was appropriate, such that it was likely to be able
to detect a clinically relevant benefit (and it was adequately powered for the study population).

2.3.9.2 Justice

We believe that the inclusion / exclusion criteria for this study were fair, not overly exclusive and that the majority of women presenting for elective caesarean delivery at these centres were eligible to participate. This enhanced the external validity and wider applicability of the results. At the time this research was conducted there were no other clinical trials being performed on this group of patients and there was no unfair burden of participation being placed on them. The results of this study have now been published in the international literature, which has given fair access to the results of this research within the wider community.

2.3.9.3 Beneficence

Beneficence implies that the research proposed has taken into account and balanced the possible risk of harm against the potential for benefit. We felt that the potential for harm was extremely low, in that ondansetron had been used widely in pregnancy for many years and was known to have very few adverse effects. However steps were taken in study design to ensure that any potential harm or adverse effects could be detected and measured. This included the recording of data for known potential adverse effects, for
example headache, and an assessment of the neonate for harm by means of recording Apgar scores and breastfeeding success on the ward.

The study protocol recognized that some women in the study were likely to experience significant or distressing shivering or intraoperative pain, so specific measures that could be used to treat and alleviate these symptoms, should they occur, were designated.

2.3.9.4 Respect

Respect is another important ethical value espoused in the NHMRC guidelines. It includes abiding by the previously mentioned values but also having due regard for the participants own beliefs, values, and cultural sensitivities.

In practical terms in relation to this study, respect implies the maintenance of privacy and confidentiality for participants and provision of sufficient information to allow women approached to participate to make an autonomous decision whether or not to do so.

Participants were provided with detailed written information and an opportunity to ask questions either on the ward or in the pre-admission clinic prior to study participation. It was made clear to women that participation was voluntary and that should they decline to participate, this would in no way affect their subsequent care.
All patient information was kept in a locked, secure environment within the participating hospitals and over the long term in a locked cabinet in the research office at Fremantle Hospital. Data were de-identified before being entered into an electronic database prior to analysis.

2.3.9.5 Research Governance

This study was conducted in accordance with the NHMRC Guidelines on Human Research and the Australian Code for the Responsible Conduct of Research. The researchers were required to send regular updates to the local ethics committee. The research staff had no conflicts of interest in this research. A documented complaints procedure was in place and specified on the written patient information sheet.
2.3.10 Funding sources and budget

An initial budget was proposed in accordance with guidance received during coursework for the Masters of Clinical research:

**Table 1:** Initial budget

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron: (8mg = $2.80, 70 patients x $2.80 = 200)</td>
<td>$200</td>
</tr>
<tr>
<td>Disposables / equipment: (syringes/saline/thermometer)</td>
<td>$430</td>
</tr>
<tr>
<td>Labour – research nurse (8 h/week – 12 month annual salary @ $68000)</td>
<td>$13600</td>
</tr>
<tr>
<td>Office stationery</td>
<td>$50</td>
</tr>
<tr>
<td>Biostatistician (4 hours x $125)</td>
<td>$500</td>
</tr>
<tr>
<td>Travel costs – conference to present results</td>
<td>$2000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$16780</strong></td>
</tr>
</tbody>
</table>

We identified early on that the Fremantle Hospital Medical Research Foundation (FHMRF) had research grants available for novice investigators, but unfortunately these were limited to a maximum of $10000. We managed to identify some strategies to decrease the amount of funds we would require, so that the trial could be conducted successfully within the limits of the amount available from a FHMRF grant:
Ondansetron and Pharmacy Costs

We approached the pharmacy department and explained that many (if not the majority) of women were already being given anti-emetics during their caesarean delivery. In view of this and using the argument that ondansetron 8 mg (at $2.80 acquisition cost) was required for only half the women in the study was likely to be cost neutral, the pharmacy agreed to supply the ondansetron from within the general hospital budget.

We considered the option of asking the pharmacy to prepare blinded syringes of study drug as a “gold standard” method of assuring blinding of group allocation. With the limited funding that we had available we realized however that this was not an affordable option. After careful consideration we decided instead to use an anaesthetist working in another theatre, and not involved in obstetric patient care that day, to perform this task on the day.

Labour

The major cost of a study of this sort is to pay for the labour and time of the staff involved, especially those recruiting participants and collecting data. A large proportion of this work was provided (without specific funding) by anesthesiology staff working in obstetric health care at both Kaleeya and Rockingham Hospitals. These staff members, with permission from their respective heads of department, generously agreed to perform these extra tasks whilst performing their usual clinical duties. Direct funding for the salary
of our research nurse was sought to cover the time required for patient recruitment, data collection, computer entry and tabulation of data.

**Biostatistician**

Funding for the professional services of a qualified biostatistician was required.

**Stationery and Disposables**

The Heads of Anaesthesia at both Kaleeya and Rockingham hospitals agreed to cover the small costs represented by the syringes, needles and stationery used in the conduct of the study.

**Travel Costs**

Funding for this was not requested, due to the limited overall funds available. Dissemination of the results of any research is important but unfortunately this aspect of the budget was felt to be less critical than funding required for other tasks.

The following revised budget was submitted to FHMRF and the submission was successful in receiving the full $10000 requested. For the research unit in which this study was conducted, these funds were placed into a general pool, along with funds from other sources, to support payment of staff involved specifically in research activities.
Table 2: Revised budget

<table>
<thead>
<tr>
<th>Revised Budget – Fremantle Medical Research Foundation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour – research nurse (5.5hrs/wk) 12 month annual salary @ $68000</td>
</tr>
<tr>
<td>Biostatistician (4 hours x $125)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
2.4 Results

2.4.1 Study population

Between September 2009 and March 2011, 118 women were recruited from both Kaleeya and Rockingham Hospitals, with patient flow through the study summarized in the CONSORT 2010 Diagram.
Figure 4  CONSORT 2010 Flow Diagram

**Enrollment**
Assessed for eligibility (n = not recorded)

Randomized (n = 118)

**Allocation**

Allocated to placebo (n = 60)
- Received allocated

Allocated to ondansetron (n = 58)
- Received allocated intervention (n = 57)
- Did not receive allocated intervention (envelope lost prior to theatre) (n = 1)

**Follow-Up**

Lost to follow-up (n = 0)
Discontinued intervention (n = 0)

Discontinued intervention (failed spinal, no data collected) (n = 1)

**Analysis**

Analysed (n = 60)
- Excluded from analysis (n = 0)

Analysed (n = 56)
- Excluded from analysis (previous 2 cases - no data recorded) (n = 2)
### 2.4.2 Demographics

#### TABLE 3. Baseline demographics

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Placebo</th>
<th>Ondansetron</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>60</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>30.6 (6.3)</td>
<td>31.8 (5.1)</td>
<td>0.25*</td>
</tr>
<tr>
<td>ASA score (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>67</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td>1.7 (1.1)</td>
<td>2.1 (1.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Parity</td>
<td>0.3 (0.7)</td>
<td>0.8 (1.3)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.4 (13.4)</td>
<td>84.8 (18.7)</td>
<td>0.86*</td>
</tr>
<tr>
<td>Previous caesarean delivery (%)</td>
<td>71</td>
<td>77</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous shivering during caesarean delivery (%)</td>
<td>57</td>
<td>74</td>
<td>0.12</td>
</tr>
<tr>
<td>HAD scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.0 (3.7)</td>
<td>5.7 (3.3)</td>
<td>0.29*</td>
</tr>
<tr>
<td>Depression</td>
<td>1.9 (2.5)</td>
<td>2.2 (2.3)</td>
<td>0.57*</td>
</tr>
<tr>
<td>Mean dose bupivacaine – ml (SD)</td>
<td>2.31(0.16)</td>
<td>2.32(0.17)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean temperature on arrival in theatre (SD)</td>
<td>36.8 (0.5)</td>
<td>36.6 (0.6)</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Values are mean (SD). SD = standard deviation. HAD = Hospital Anxiety and Depression. ASA = American Society Anesthesiologists. P-values are calculated using the Chi-Square test or t-test (*) as appropriate.

2.4.3 Primary Endpoints

<table>
<thead>
<tr>
<th>TABLE 4: Shivering: incidence and severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Any shivering (%)</td>
</tr>
<tr>
<td>Severe shivering score at any time (%)</td>
</tr>
</tbody>
</table>

Severe shivering was defined as a score in the range 2-4.

The incidence of shivering at any time point (our primary outcome) did not significantly differ between groups: ondansetron 41% vs. placebo 47% (P = 0.54). The incidence of severe shivering (defined as a score 2-4) at any time was also not significantly different: ondansetron 32% vs. placebo 33% (P = 0.79).

Based on these results the null hypothesis is rejected.
### Secondary Endpoints

**TABLE 5: Incidence of severe shivering (score 2-4) at different time points**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Ondansetron</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Before CSE</td>
<td>4</td>
<td>7</td>
<td>0.28</td>
</tr>
<tr>
<td>After CSE, before surgery</td>
<td>9</td>
<td>8</td>
<td>0.91</td>
</tr>
<tr>
<td>During surgery</td>
<td>13</td>
<td>11</td>
<td>0.79</td>
</tr>
<tr>
<td>In the PACU</td>
<td>10</td>
<td>9</td>
<td>0.90</td>
</tr>
</tbody>
</table>

CSE = combined spinal epidural. PACU = post-anaesthesia care unit.
**TABLE 6: Clinical consequences of shivering (at any time point)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Ondansetron</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Interference with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>6</td>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td>Holding the baby</td>
<td>4</td>
<td>0</td>
<td>0.11†</td>
</tr>
<tr>
<td>Reported as distressing by mother</td>
<td>8</td>
<td>7</td>
<td>0.97</td>
</tr>
<tr>
<td>Drugs given to treat shivering</td>
<td>3</td>
<td>0</td>
<td>0.24†</td>
</tr>
<tr>
<td>Any clinical consequence</td>
<td>11</td>
<td>9</td>
<td>0.90</td>
</tr>
</tbody>
</table>

† Fisher’s Exact test rather than Chi-square test

There was no statistically significant difference in the clinical consequences of shivering between groups at any time. Of note three patients in the placebo arm were treated with clonidine versus none in the ondansetron arm, however this difference was not statistically significant.
**TABLE 7: Non-shivering secondary endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ondansetron</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (0-10)</td>
<td>Mean</td>
<td>Mean</td>
<td>0.52</td>
</tr>
<tr>
<td>Headache (0-10)</td>
<td>2.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Itch (0-10)</td>
<td>0.32</td>
<td>0.71</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>1.0</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Post-operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (0-10)</td>
<td>0.3</td>
<td>0.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Headache (0-10)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Itch (0-10)</td>
<td>1.3</td>
<td>0.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Satisfaction score (0-10)</td>
<td>8.4</td>
<td>8.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Apgar score (1 min)</td>
<td>8.4</td>
<td>8.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Apgar score (5 min)</td>
<td>9.1</td>
<td>9.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Temperature change (° C)*</td>
<td>-0.6</td>
<td>-0.6</td>
<td>0.17‡</td>
</tr>
</tbody>
</table>

P-values are calculated from the Wilcoxon 2-sample test (non-parametric) because of skewness in these scores. ‡ P-value calculated from a t-test.

* Temperature prior to surgery – temperature in PACU.

There was no significant difference in the incidence or severity of any of the non shivering secondary endpoints.

The data for breastfeeding outcomes were poorly recorded and therefore not reported.
TABLE 8: Predictors of intraoperative shivering

<table>
<thead>
<tr>
<th>Shivering in current study</th>
<th>Recall of previous shivering</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>28</td>
</tr>
</tbody>
</table>

P 0.027

This table is based on the participants who had had a previous caesarean section.

We analyzed all the baseline demographic data to see if there were any variables which would be useful in predicting which patients were likely to experience shivering. Patients who recalled shivering during a previous caesarean delivery were significantly more likely to experience shivering again compared with those who didn’t. None of the other variables, including preoperative anxiety status (as assessed by the HAD scores) were predictive of shivering.
2.5 Discussion

2.5.1 Summary

The most important finding of our study was that we did not demonstrate any significant reduction in the incidence or severity of shivering when intravenous ondansetron 8 mg was given prior to combined spinal epidural anaesthesia. These results were based on repeated perioperative assessments and two rating methods (one functional) of shivering severity. Women in the placebo arm received more pharmacological rescue for shivering than those in the ondansetron group (3 versus 0), but this was not statistically significant (table 6).

We confirmed that in this population, women having caesarean delivery under combined spinal epidural anaesthesia, shivering was common. Shivering occurred at some stage in 44% of all study participants (table 4). The majority of these women (42%) were also described as experiencing a clinical consequence of this shivering - for example maternal distress, interference with monitoring or difficulty holding their baby (table 6).

We found no difference in the incidence of any of the other measured secondary outcomes. This included the symptoms nausea and itch, both of which ondansetron has been shown to reduce in other settings. (George RB, Allen TK et al. 2009)
The only preoperative variable we identified as a useful predictor for which women were more likely to shiver was patient recollection of shivering during previous caesarean delivery.

### 2.5.2 Prophylactic ondansetron to prevent shivering during caesarean surgery

This study is significant because it is the first to find no benefit from the prophylactic administration of a 5-HT$_3$ antagonist. Five previous studies have investigated 5-HT$_3$ antagonists to prevent shivering during neuraxial anaesthesia in non-obstetric patients and all found benefit. (Eldaba, Amr 2012), (Shakya, Chaturvedi et al. 2010), (Kim, Kim et al. 2010), (Sagir, Gulhas et al. 2007), (Kelsaka, Baris et al. 2006).

Seven studies investigating the use of 5-HT$_3$ antagonists to prevent shivering after general anaesthesia also found a prophylactic effect. (Iqbal, Ahmed et al. 2009), (Sajedi, Yaraghi et al. 2008), (Powell, Buggy 2000), (Asl, Isazadefor et al. 2011), (Abdollahi, Forouzannia et al. 2012), (Bock, Bauer et al. 2007), (Song, Lee 2013)

There are several other possible explanations as to why this study found no effect from ondansetron.
The first possibility is that despite the previous positive studies, ondansetron (or 5-HT\textsubscript{3} antagonists in general) do not in fact actually possess anti-shivering properties. This is unlikely to be the case as 12 other studies demonstrating a benefit is a reasonable body of evidence. Negative studies are however less likely to be published than positive studies (Dickersin, Chan et al. 1987). It is possible that other studies finding no benefit for 5-HT\textsubscript{3} antagonists to prevent shivering may exist but have not been published leading to a publication bias.

One factor that may have contributed to the negative outcome in our study was our use of intrathecal fentanyl 15 mcg in addition to hyperbaric bupivacaine. This has been the standard practice in our and many other institutions for many years, due to the fact it prolongs the block, enhances immediate postoperative analgesia and decreases nausea and vomiting (see section 1.4.3.1.2). In all five previous studies of patients under spinal anaesthesia in which prophylactic 5-HT\textsubscript{3} antagonists did decrease shivering, hyperbaric bupivacaine alone was administered. Intrathecal fentanyl has been shown in previous studies to decrease shivering (see section 1.4.3.1.2). It is possible that in the presence of the intrathecal fentanyl, which was probably already providing an anti-shivering effect, intravenous ondansetron was not sufficiently effective to produce additional benefit.

Our study subjects differed in a number of ways from those in the other studies. They were all female, pregnant and relatively young. It may be that
one or more of these patient factors modified the anti-shivering effect of ondansetron.

There is evidence that shivering in pregnancy and the peripartum period differs in a number of ways to that of thermoregulatory shivering seen in the non-pregnant population. For example shivering is common in laboring women using epidural analgesia, despite the fact they often have an increased temperature (Fusi, Steer et al. 1989). Some investigators postulate that peripartum shivering is partly an immunological response to feto-maternal transfusion (Ravid, Gidoni et al. 2001).

It is possible that ondansetron does have an anti-shivering effect in this clinical setting, but it is much smaller than what we considered to be clinically significant, and that our study had insufficient power to detect it. Using an example to explain this: it is possible a much larger (and considerably more expensive) study involving thousands of women may have been able to demonstrate a decrease in shivering from 40% to 35%. However we felt that most anaesthetists would consider this result not clinically important and would not change their practice or use prophylactic ondansetron for such a minor improvement in shivering.

Finally, the 8 mg dose of ondansetron used may have been less effective in our cohort of patients, due to maternal physiological changes such as the increased blood volume and cardiac output that are present in late pregnancy.
2.5.3 Limitations

The women in this study were all undergoing elective surgery. Our results may not be applicable to women undergoing non-elective surgery.

It is possible and even likely that there is a difference in the baseline incidence of shivering dependent upon the neuraxial technique that is used. Our results may not be applicable to women undergoing different neuraxial techniques, such as spinal or epidural anaesthesia. We decided to specify that women receive a combined spinal epidural anaesthetic technique (CSE) because this was the most commonly used technique in our hospitals at that time. In retrospect we probably should have considered allowing any neuraxial technique. By means of stratification of randomization the different techniques could have been distributed evenly and this would have increased the generalisability of our results so that they were of greater interest to anaesthetists who don’t routinely use the CSE technique.

If we had the opportunity to repeat this study or to conduct a similar study in the future, we would definitely use a different method to assess the severity of shivering. When designing our study we decided to use a previously published scale (Wrench, Cavill et al. 1997) as below:

0 = no shivering

1 = piloerection or peripheral vasoconstriction but no shivering

2 = muscular activity in only one group
3 = muscular activity in more than one muscle group but not generalized shivering

4 = shivering involving the entire body

This was chosen because it was the most commonly used measurement tool in the relevant literature. However it was designed for use to assess shivering post general anaesthesia and there are number of reasons why it may not be optimal for assessing shivering occurring in association with neuraxial anaesthesia. Vasoconstriction or piloerection in the upper body can be a normal compensatory response to the lower body sympathetic block that occurs during neuraxial anaesthesia, and may be unrelated to shivering. In practice most personnel involved in the study found it difficult to actually interpret these definitions (for example the number of muscle groups involved in the shivering). Whilst anaesthetized by a neuraxial block, the lower body is unable to move and so our participants, no matter what the severity of shivering, could not be rated as experiencing scale 4 shivering intensity (entire body shivering). Since the design of our study, other authors (Crowley, Buggy 2008) have proposed that studies assessing shivering under neuraxial block use the following simplified assessment scale and we agree with this recommendation for future studies:

0 = no shivering

1 = shivering not interfering with monitoring or causing patient distress

2 = shivering interfering with monitoring or causing patient distress
We were only able to fully describe the participant flow through the study after recruitment, in accordance with the CONSORT statement on reporting of randomized trials. (Schulz, Altman et al. 2010) A valid criticism of the conduct of our study was that we did not keep accurate records of all the patients screened for inclusion in the study and thus were unable to report the number of women who were approached, excluded, or declined to participate. The investigators failed to specify collection of these data during the initial study design, but would now recommend collecting these data in any future trials.

In this study we used an anaesthetist working in an unrelated theatre to prepare the study syringes in a blinded manner. We are unaware of any problems or possibly protocol violations using this method, but ideally if funding had allowed, the risk of failure of blinding and the introduction of bias might have been most robustly minimized had this been done by pharmacy, using coded syringes.

**2.5.4 Future studies**

Our study demonstrates that even in patients who receive intrathecal fentanyl, perioperative shivering is a persistent problem. The optimal management to prevent and treat shivering during caesarean delivery under neuraxial blockade continues to elude us. Unfortunately the results of this study do not support
the use of prophylactic intravenous ondansetron as an effective strategy to reduce this problem.

Most of the proven pharmacological options for prophylaxis or treatment of shivering during neuraxial anaesthesia also have the potential for unwanted adverse effects. In effect the anaesthetist must “trade off” relieving or preventing shivering against the potential for more side effects, for example nausea (e.g. from intrathecal pethidine) or sedation (e.g. from intravenous ketamine). This issue of patient preferences in relation to various adverse symptoms during caesarean delivery has been investigated previously. (Carvalho, Cohen et al. 2005) The authors asked 100 women booked for neuraxial anaesthesia for caesarean delivery to rank in importance specific intraoperative and postoperative adverse effects. In this study, of 10 possible adverse effects, women ranked shivering as the sixth most important to avoid, coming in behind pain, nausea, vomiting and itching but slightly above somnolence or anxiety. Future studies which investigate the efficacy of any drug, either for prevention or treatment of shivering in this group of patients, also needs to be carefully performed to ensure the incidence of all potential adverse effects is recorded and patient satisfaction with therapy assessed, since many symptoms are considered by patients to be less desirable than shivering itself.

Keeping in mind the above caveats, there are some possible strategies that are worthy of further investigation:
One interesting area of investigation would be the combination of intrathecal pethidine and antiemetic drugs, including a 5HT-3 antagonist like ondansetron. Intrathecal pethidine has been demonstrated to be quite effective at preventing shivering yet most investigators have recommended it be avoided due to the unacceptably higher incidence of nausea and vomiting. (Yu, Ngan Kee et al. 2002), (Booth, Lindsay et al. 2000). The co-administration of a 5HT-3 antagonist antiemetic such as ondansetron, with or without other anti-emetic therapies, seems like an attractive solution. It could possibly prevent nausea, while potentially also having anti-shivering activity. A useful study design might be to compare the combination of intrathecal bupivacaine and fentanyl with intrathecal bupivacaine and pethidine plus ondansetron, noting all adverse event rates.

Another productive area for future investigation is to identify more effective methods (e.g. a monitor or risk score based on identifiable risk factors) to better predict which women are likely to experience moderate to severe shivering. We know only 35-55% of women shiver and of these only a fraction warrant an intervention. If we knew reliably beforehand which women were likely to experience severe shivering then this would inform “targeted” administration of effective anti-shivering treatments when benefits appeared likely to outweigh side effects. More importantly this avoids administering anti-shivering drugs (with adverse effects) to women who were never going to shiver in the first place. Our study identified only a single risk
factor predictive of shivering, namely a history of shivering during previous caesarean delivery.

Further investigation of epidural pethidine in patients undergoing caesarean delivery under either epidural or combined spinal epidural anaesthesia is also warranted for a number of reasons. There are only a small number of studies that support its use so more data are required to confirm effectiveness and assess possible side effects such as nausea or vomiting, the limiting problem with intrathecal pethidine.

Both intrathecal and epidural magnesium are also therapies which deserve further investigation. Neuraxial magnesium improves postoperative analgesia, prolongs block duration (Pascual-Ramirez, Gil-Trujillo et al. 2013) and decreases shivering (Faiz, Rahimzadeh et al. 2013), but further studies are needed to confirm these beneficial effects and demonstrate lack of clinically significant neurotoxicity.

It is also possible that other 5-HT₃ antagonists or a higher dose of ondansetron is more efficacious in this setting and future studies to investigate these could be considered. In centres which do not routinely use intrathecal fentanyl or sufentanil in the spinal anaesthetic for caesarean delivery, prophylactic 5-HT₃ antagonists are likely to decrease shivering.

2.5.5 Conclusion
In conclusion, our study found that the prophylactic administration of intravenous ondansetron 8 mg did not prevent shivering or decrease its severity among women undergoing combined spinal epidural anaesthesia with intrathecal bupivacaine and fentanyl for caesarean delivery. Its use for this purpose is not indicated.

Appendix 1 – Copy of Ethics approval
Appendix 2 – Copy of patient information sheet
A randomised controlled trial of Ondansetron to prevent Shivering during Caesarean section (The OSCAR trial)

Principal Investigators: Dr Roger Browning; Professor Michael Paech; Dr Ed O'Loughlin; Dr Nick Brown

We invite you to participate in a clinical research study to find out whether administering a common anti nausea medication to you will prevent or decrease the severity of shivering, which is a common side effect of spinal / epidural anaesthesia.

You may be suitable for the study if you are having an elective Caesarean section under combined spinal / epidural anaesthesia.

**Background**

Caesarean section is one of the most commonly performed operations in Australia. In Australia most women have a spinal or epidural (or combination of these) anaesthetic. These techniques are associated with a significant
incidence of shivering both during and after the operation. Ondansetron is a common anti-nausea drug which has been used in Australia for many years, to prevent or treat nausea and vomiting. Studies in patients having other types of surgery have shown that ondansetron reduces the incidence and severity of shivering associated with both spinal and general anaesthetics.

**Why we are doing this study**

Shivering during a caesarean section can be problematic for a number of reasons. Most women describe it as unpleasant, and if severe it can prevent them from holding their baby after delivery. Shivering can make it difficult for the anaesthetist to monitor your blood pressure, heart rate and oxygen levels because the movement interferes with the devices we use to measure these important variables. The medications which have traditionally been used to treat or prevent shivering (e.g. pethidine) have a number of unwanted side effects such as nausea, sedation and lowered blood pressure. Ondansetron would be a useful drug to use to prevent shivering during Caesarean section because it is very safe and has very side effects compared to these other medications. Ondansetron has also been shown to decrease nausea and itching which are other common side effects of spinal / epidural anaesthesia.

**What does the study involve?**
One hundred and twenty women booked for elective caesarean section under combined spinal / epidural anaesthesia will be recruited.

You will be required to give written informed consent prior to participation in the study. The study has been approved by the South Metropolitan Area Health Service Human Research Ethics Committee.

You will not be suitable for the study if you have a known hypersensitivity to ondansetron, have an anaesthetic technique other than combined spinal / epidural, have received any medications known to affect shivering prior to your surgery, or are planning to have either spinal or epidural morphine for postoperative pain relief.

On the morning of your caesarean, you will be asked to fill in a questionnaire which includes information such as your age, weight, and anxiety levels. When you arrive in theatre the anaesthetist will administer the study drug into your intravenous cannula before placing the spinal / epidural block. You will receive either a dose of the study drug (ondansetron) or placebo (saline solution). Neither you nor the anaesthetist will know what medication you have received.
Throughout your time in theatre in addition to receiving the usual care all women receive, we will also record whether you shiver, its severity and other related information such as your body temperature. We will also record this information whilst you are in recovery for the 2 hours following your caesarean section.

If you do experience shivering, which either yourself or the anaesthetist would like to treat, they will be able to give you a dose of another anti-shivering medication (clonidine).

Benefits and Risks

There are not expected to be any significant risks associated with participation in the study. This study requires only the administration of a single dose of either the study drug (ondansetron) or saline (salt water) and following this the collection of data over a 3 hour period. Ondansetron is an anti-nausea medication which has been available in Australia for many years, with a very low incidence of unwanted side effects. Ondansetron has been administered to many patients including pregnant women and those having caesarean sections without any safety concerns having been identified in the past.

Safety to Baby
It is possible but extremely unlikely that a single dose of ondansetron would cause any adverse effect on your baby.

**Withdrawal from the study**

Your participation in this study is entirely voluntary. You may withdraw from the study at any time without explanation and your future treatment will not be affected.

Further information

The information collected in this study will be kept confidential, and the results of the study may be published, but names will not be used.

If you have any questions about the study, please contact Dr Nick Brown, Dr Ed O’Loughlin or Dr Roger Browning through the switch board at Fremantle Hospital, phone 9431-3333

If you have any complaints about the conduct of the study please contact the Chairman of the South Metropolitan Area Health Service Human Research Ethics Committee on 9431 2929.
Appendix 3 – Participant consent form

CONSENT FORM
A randomised controlled trial of Ondansetron to prevent Shivering during CAesaRean section
(The OSCAR trial)

Patient's Name: ............................................ Date of Birth: ............................................

1. I agree entirely voluntarily to take part in the OSCAR Trial.
   I am over 18 years of age.

2. I have been given a full explanation of the purpose of this study, of the procedures involved
   and of what will be expected of me. The doctor has explained the possible problems that
   might arise as a result of my participation in this study.

3. I agree to inform the supervising doctor of any unexpected or unusual symptoms I may
   experience as soon as possible.

4. I understand that I am entirely free to withdraw from the study at any time and that this
   withdrawal will not in any way affect my future standard or conventional treatment or
   medical management.

5. I understand that the information in my medical records is essential to evaluate the results
   of this study. I agree to the release of this information to the research staff and the clinical
   trial staff on the understanding that it will be treated confidentially.

6. I understand that I will not be referred to by name in any report concerning this study. In
   turn, I cannot restrict in any way the use of the results that arise from this study.

7. I have been given and read a copy of this Consent Form and Information Sheet.

Signature by patient .......................................................... Signature by doctor ..........................................................

Signed: ........................................................................ Signed: ........................................................................

Date: ........................................................................ Date: ........................................................................
Appendix 4 – FHMRF Funding grant

Dr Roger M Browning
Consultant Anaesthetist
Department of Anaesthesia
B6 Fremantle Hospital

Dear Dr Browning

On behalf of the Fremantle Hospital Medical Research Foundation I am delighted to advise that your research project has been successful in attracting a 2010 Research Award.

Your project “A study investigating the medication ondansetron to prevent Shivering during CæsarRean section: The OSCAR trial” has been fully funded in the amount of $10,510.

It is a condition of the grant award that the enclosed “Acceptance of Offer of 2010 Research Award” is signed by you as Chief Investigator. Additionally, you are required to complete and return the Cost Centre Maintenance form that will allow you to access your funds. Once the completed forms are received and you have advised the Foundation that the project has received Ethics Committee approval (if required), which you are responsible for obtaining, the Hospital’s Finance Department will be requested to establish a special purpose account for your project, and you will be notified of further details. The funds will be made available from the beginning of January 2010.

The Awards will be presented at the Foundation’s cocktail function, which will take place at 6.00pm on Tuesday 1 December 2009 in “The Creatures Loft” located at Fishing Boat Harbour (the old Harbourside, now part of Little Creatures). It is always an elegant and enjoyable function, which once again is being sponsored by the M G Kails Group and is therefore complimentary for the successful researchers and their partners. I would therefore be grateful if you could extend this invitation to the other members of your research team.

As you would be aware, research award sponsorships have been taken up by different companies and individuals from between $10,000-$15,000 each year. These sponsorships provide much needed funds for research while allowing the sponsoring organisations and research teams to become acquainted over the period of the project, and hopefully establish lasting relationships. Your team is very fortunate this year to have been awarded the Tony and Elva van Merwyk Research Award. Tony was the previous Chairman of the Foundation’s Scientific Advisory Committee, and he and his wife have personally sponsored this award and they will present your team with its trophy at the awards evening.

Please RSVP by 18 November advising the names of those who will be attending by telephoning Jacky Jarrett on 9431 2133, email jacky.jarrett@health.wa.gov.au.

I wish you every success with this project.

Yours faithfully,

Chairman
Scientific Advisory Committee

22 October 2009    Anna Street, Fremantle, Western Australia
## Appendix 5 - Data collection form

### (The OSCAR trial) - Data collection sheet

**PREOPERATIVE DATA**

**OSCAR TRIAL NUMBER:**

Date:

Age _____ years  ASA: 1 / 2  Parity:  Weight:  Kg

Prev C Section: Y / N  If Y: Did they shiver during Section? Y / N

### HAD Score

"Doctors are aware that emotions play an important part in most illnesses. This questionnaire is designed to help you doctor know how you feel.

Please read each item and colour in the reply which comes closest to how you have been feeling in the last week.

Don't take too long over the answers, your immediate reaction to each item will probably be more accurate than a long thought out response."

<table>
<thead>
<tr>
<th>Item</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel tense or 'wound up'</td>
<td>Most of the time  A lot of the time  Time to time, occasionally  Not at all</td>
</tr>
<tr>
<td>I still enjoy the things I used to enjoy</td>
<td>Definitely as much  Not quite so much  Only a little  Not at all</td>
</tr>
<tr>
<td>I get a sort of frightened feeling like something awful is about to happen</td>
<td>Very definitely and quite badly  Yes, but not too badly  A little, but it does not worry me  Not at all</td>
</tr>
<tr>
<td>I can laugh and see the funny side of things</td>
<td>As much as I always could  Not quite so much now  Definitely not so much now  Not at all</td>
</tr>
<tr>
<td>Worrying thoughts go through my mind</td>
<td>A great deal of the time  A lot of the time  From time to time, but not too often  Only occasionally</td>
</tr>
<tr>
<td>I feel cheerful</td>
<td>Not at all  Not often  Sometimes  Most of the time</td>
</tr>
<tr>
<td>I can sit at ease and feel relaxed</td>
<td>Definitely  Usually  Not often  Not at all</td>
</tr>
</tbody>
</table>

I feel as if I am slowed down

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nearly all of the time  Very often  Sometimes  Not at all</td>
</tr>
</tbody>
</table>

I have lost interest in my appearance

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely  I don't take as much care as I should  I may not take quite as much care  I take just as much care as ever</td>
</tr>
</tbody>
</table>

I get a sort of frightened feeling like 'butterflies in the stomach'

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all  Occasionally  Quite often  Very often</td>
</tr>
</tbody>
</table>

I feel restless as if I have to be on the move

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much indeed  Quite a lot  Not very much  Not at all</td>
</tr>
</tbody>
</table>

I look forward with enjoyment to things

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>As much as I ever did  Rather less than I used to  Definitely less than I used to  Hardly at all</td>
</tr>
</tbody>
</table>

I get sudden feelings of panic

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very often indeed  Quite often  Not very often  Not at all</td>
</tr>
</tbody>
</table>

I can enjoy a good book or radio or TV programme

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often  Sometimes  Not often  Very seldom</td>
</tr>
</tbody>
</table>
INTRAOPERATIVE DATA:

Body Temp on Arrival in theatre:

Arrival Time in Theatre: ____ hrs
Time of Intrathecal injection: ____ hrs
Time of end of surgery: ____ hrs

Spinal drugs given: mls 0.5% Heavy marcain + 15 mcg fentanyl

Analgesic supplementation: Y/N ↔ Yes: Epidural LA - ____ mls____%
N2O Y/N
IV Fentanyl bolus mcgs
IV ketamine bolus mgs
Intraperitoneal LA Y/N
Wound infiltration LA Y/N

SHIVERING

Severity Scoring System
Please use this validated scoring system
0. No Shivering
1. Any one of the following BUT WITHOUT visible muscular activity
   a. Piloerection
   b. Peripheral vasoconstriction
   c. Peripheral cyanosis without other cause
2. Visible muscular activity confined to one muscle group
3. Visible muscular activity in MORE than one muscle group
4. Gross muscular activity involving the ENTIRE upper body

Did the Patient Shiver?

<table>
<thead>
<tr>
<th></th>
<th>Y / N</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before placing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the CSE</td>
<td>Y / N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After placing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the CSE but</td>
<td>Y / N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During surgery</td>
<td>Y / N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity (please circle)
Did the shivering cause any of the following? Please circle

- interfere with monitoring (ECG, SpO2, NIBP) Y / N
- interfere with ability to hold baby Y / N / not applicable
- cause distress / discomfort to the mother Y / N
- was any anti-shivering medication given Y / N
  IF Y What given? _________________
  Efficacious? Y/N

Intra Op Nausea

1 None Mild Moderate Severe 10

Intra Op Headache

1 None Mild Moderate Severe 10

Intra Op Itch

1 None Mild Moderate Severe 10
POST OP DATA - On return to PACU

Temperature on arrival:

SHIVERING

Severity Scoring System
Please use this validated scoring system

0. No Shivering

1. Any one of the following BUT WITHOUT visible muscular activity
   a. Piloerection
   b. Peripheral vasoconstriction
   c. Peripheral cyanosis without other cause

2. Visible muscular activity confined to one muscle group

3. Visible muscular activity in MORE than one muscle group

4. Gross muscular activity involving the ENTIRE upper body

Did the Patient Shiver?  Severity (please circle)

- Whilst in recovery  Y / N  0 1 2 3 4

Did the shivering cause any of the following?

Please circle

- Interfere with monitoring (ECG, SpO2, NIBP)  Y / N

- Interfere with ability to hold baby  Y / N / not applicable

- Cause distress / discomfort to the mother  Y / N

- Was any anti-shivering medication given  Y / N

IF Y What given? __________________

Efficacious? Y/N

Post Op Nausea

1. None  Mild  Moderate  Severe  10
Post Op Headache

1 None Mild Moderate Severe 10

Post Op Itch

1 None Mild Moderate Severe 10

Thanks a million for your assistance. Please return to box in anaesthetic dept.
Appendix 6

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