การศึกษาเปรียบเทียบประสิทธิผลของนาลบูฟีน ทรามาดอล และออนแดนซีตรอน ในการรักษาอาการสั่นภายหลังได้รับมอร์ฟีนเข้าช่องไขสันหลัง ในผู้ป่วยทำการผ่าตัดทำคลอดทางหน้าท้อง

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COMPARISON OF EFFICACY BETWEEN NALBUPHINE, TRAMADOL, AND ONDANSETRON IN TREATMENT OF POSTANESTHETIC SHIVERING AFTER INTRATHECAL MORPHINE FOR CESAREAN DELIVERY

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เดชา ทำดี: การศึกษาเปรียบเทียบประสิทธิผลของนาลบูฟีน ทรามาดอล และออนแดนซีตรอน ในการรักษาอาการสั่นภายหลังได้รับมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้อง(Comparison of Efficacy Between Nalbuphine, Tramadol, and Ondansetron in Treatment of Postanesthetic Shivering After Intrathecal Morphine for Cesarean Delivery) อาจารย์ที่ปรึกษา: รศ. นพ. สมรัตน์ จารุลักษณานันท์, พบ., วว.(วิสัญญีวิทยา), วทม., อาจารย์ที่ปรึกษาร่วม : รศ.ดร.ศิริวรรณ ไกรสุรพงศ์, 74 หน้า. ISBN 974-17-1451-3

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลของการใช้ยานาลบูฟีน 0.05 มิลลิกรัมต่อกิโลกรัม ยาทรามาดอล 0.5 มิลลิกรัมต่อกิโลกรัม และยาออนแดนซีตรอน 0.1 มิลลิกรัมต่อกิโลกรัม ฉีดเข้าทางหลอดเลือดดำในการรักษาอาการสั่นภายหลังได้รับยาชาและมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้อง

รูปแบบการทดลอง: การทดลองทางคลีนิคแบบสุ่มทดลองโดยมีกลุ่มเปรียบเทียบ

สถานที่ทำการวิจัย: โรงพยาบาลจุฬาลงกรณ์ ซึ่งเป็นโรงพยาบาลระดับตติยภูมิ

วิธีการศึกษา: ผู้ป่วยหลังการผ่าตัดคลอดทางหน้าท้องโดยวิธีฉีดยาชาและมอร์ฟีนเข้าช่องไขสันหลัง ที่มีอาการสั่นระดับปานกลางถึงมากจำนวน 225 คน ได้รับการสุ่มแบ่งกลุ่มด้วยการสุ่มแบบธรรมดาเป็น 3 กลุ่ม กลุ่มแรกได้รับยานาลบูฟีน 0.05 มก./กก. กลุ่มที่ 2 ได้รับยาทรามาดอล 0.5 มก./กก กลุ่มที่ 3 ได้รับยาออนแดนซีตรอน 0.1 มก./กก. ฉีดเข้าทางหลอดเลือดดำประเมินอาการสั่นและผลข้างเคียงอื่นๆ ที่ 15 นาทีภายหลังการบริหารยา และประเมินผลความพึงพอใจของผู้ป่วยหลังผ่าตัด 24 ชั่วโมง

ผลการศึกษา: นาลบูฟีน ทรามาดอล และออนแดนซีตรอน ฉีดเข้าทางหลอดเลือดดำมีประสิทธิผลในการรักษาอาการสั่นในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้องโดยวิธีฉีดยาชาและมอร์ฟีนเข้าช่องไขสันหลังเท่ากับ 81.3%, 88.2% และ 62.2% ตามลำดับ (p-value < 0.001) ประสิทธิผลของนาลบูฟีนและออนแดนซีตรอน, ทรามาดอลและออนแดนซีตรอนต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.009 และ p-value < 0.001ตามลำดับ) ประสิทธิผลของนาลบูฟีนและทรามาดอลไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.243) โดยมีอัตราการเกิดการสั่นซ้ำภายใน 4 ชั่วโมงหลังการรักษาครั้งแรกสำเร็จของนาลบูฟีน ทรามาดอลและออนแดนซีตรอน เท่ากับ 14.8%, 13.4% และ 13.0% ตามลำดับ (p-value =0.963) สำหรับอัตราการเกิดอาการข้างเคียงอื่นๆได้แก่ อาการคลื่นไส้หรืออาเจียน อาการง่วงซึม อาการปวด อาการคัน และอาการมึนงง หลังการฉีดยาไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ความพึงพอใจต่อการให้บริการของแผนกวิสัญญีโดยรวมของผู้ป่วยทั้ง 3 กลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.953) แต่ความพึงพอใจต่อการรักษาอาการสั่นของผู้ป่วยที่ได้รับนาลบูฟีนและออนแดนซีตรอน, ทรามาดอลและออนแดนซีตรอนมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.002 และ p-value < 0.001 ตามลำดับ)

สรุป: นาลบูฟีน 0.05 มก./กก. และทรามาดอล 0.5 มก/กก. ฉีดเข้าทางหลอดเลือดดำมีประสิทธิภาพสูงกว่าออนแดนซีตรอน 0.1 มก./กก. ในการรักษาอาการสั่นภายหลังได้รับการฉีดยาชาและมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้องโดยเกิดอาการข้างเคียงในอัตราต่ำและไม่รุนแรงความพึงใจของผู้ป่วยต่อประสิทธิผลของยาในการรักษาอาการสั่นนั้น ผู้ป่วยที่ได้รับนาลบูฟีนและทรามาดอลมีความพึงพอใจสูงกว่าออนแดนซีตรอน

หลักสูตร การพัฒนาสุขภาพ	ลายมือชื่อนิสิต.....
สาขาวิชา การพัฒนาสุขภาพ	ลายมือชื่ออาจารย์ที่ปรึกษา.....
ปีการศึกษา 2545	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

##4475423730: MAJOR HEALTH DEVELOPMENT

KEYWORDS: NALBUPHINE/ TRAMADOL/ ONDANSETRON/ INTRATHECAL MORPHINE/ SHIVERING/ CESAREAN SECTION.

DECHA TAMDEE: COMPARISON OF EFFICACY BETWEEN NALBUPHINE, TRAMADOL, AND ONDANSETRON IN TREATMENT OF POSTANESTHETIC SHIVERING AFTER INTRATHECAL MORPHINE FOR CESAREAN DELIVERY. THESIS ADVISOR: ASSOC.PROF. SOMRAT CHARULUXANANAN, M.D., M.Sc., THESIS CO-ADVISOR: ASSOC.PROF. SIRIWAN GRISURAPONG, Ph.D. 74 pp. ISBN 974-17-1451-3

Objective: To compare the efficacy between 0.05 mg/kg nalbuphine, 0.5 mg/kg tramadol and 0.1 mg/kg ondansetron, in treatment of postanesthetic shivering in cesarean section patients after intrathecal morphine.

Design: Randomized double-blind controlled trial.

Setting: King Chulalongkorn Memorial hospital, which is the tertiary care center.

Method: Two hundred and twenty five parturients who have moderate to severe shivering were randomly allocated into 3 groups by simple randomization. Group 1 received 0.05 mg/kg nalbuphine, group 2 received 0.5 mg/kg tramadol, and group 3 received 0.1 mg/kg ondansetron. The success rate of treatment and other adverse effects were determined at 15 minutes after study drug administration. The patient satisfaction was also evaluated within 24 hours after operation.

Result: The success rate of treatment of shivering in nalbuphine, tramadol, and ondansetron groups were 81.3%, 88.2% and 62.2% respectively (p-value<0.001). The success rate between nalbuphine and ondansetron groups, tramadol and ondansetron groups were statistically significant different (p-value = 0.009 and p-value < 0.001 respectively). The success rate between nalbuphine and tramadol groups was not statistically significant different (p-value = 0.243). The recurrence rate of moderate to severe shivering within 4 hours after first successful treatment in nalbuphine, tramadol, and ondansetron groups were 14.8%, 13.4%, and 13.0% respectively, which were not statistically significant different (p-value = 0.963). Other side effects such as pruritus, sedation, nausea, vomiting, pain, and dizziness were not significantly different. The patient satisfactions with the care provided by the Department of Anesthesiology in general among three groups were not statistically significant different (p-value = 0.953). But the patient satisfactions regarding treatment of shivering in nalbuphine and tramadol groups were statistically significantly greater than in ondansetron group (p-value = 0.002 and p-value < 0.001 respectively).

Conclusion: Nalbuphine 0.05 mg/kg and tramadol 0.5 mg/kg were more efficacious than 0.1 mg/kg ondansetron in treatment of postanesthetic shivering after intrathecal morphine for cesarean section patients with few and minor side effects. The patient satisfaction score concerning treatment of shivering in nalbuphine and tramadol groups were also higher than in ondansetron group.

Department	Health Development	Student's signature……
Field of study	Health Development	Advisor's signature……
Academic year	2002	Co-advisor's signature……..

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CHAPTER 1

INTRODUCTION

Rationale and background

Nowadays, spinal anesthesia is a safe and an increasingly popular technique for elective cesarean section, because of its rapid onset, low dose of local anesthetic used and postoperative analgesia provided by intrathecal morphine. (1,2,3) The addition of morphine to intrathecally injected local anesthetics provides effective, long lasting postoperative analgesia following cesarean section. The patient who has received spinal anesthesia for cesarean delivery should be an excellent candidate for this treatment. As well as providing excellent pain relief, an additional benefit might be an improvement of the maternal ability to care for and interact with her baby. However, a common side effect after intrathecal administration of local anesthesia includes the development of shivering. The incidence of post regional anesthesia shivering is between 33% - 66%. (1,2,4) Shivering in association with regional anesthesia is reported to resemble true thermogenic shivering.(4) It is generally regarded as a nuisance rather than as a factor in morbidity although it has been reported to cause significant distress. (5)

In a survey on 33 clinical problems, anesthesiologists ranked postanesthetic shivering the 8th when its frequency was considered and the 21st when asking about the important of preventing this complication. This suggests that most anesthesiologists do not consider shivering to be a true medical problem. However, there are some consequences of postanesthetic shivering in shivering patients. (6) Theoretically, shivering during epidural anesthesia in labor might increase maternal oxygen demand and have adverse effects upon maternal and fetal biochemistry, but there is no evidence

to suggest that this happens in clinical practice. (7) The etiology of shivering remains unknown, but its effects include increased metabolic rate about 200%, increased plasma catecholamine concentrations, and patients discomfort. Moreover, shivering in response to hypothermia increases tissue oxygen demand by as much as 400% to 500%. This excessive oxygen demand initiates increasing of minute ventilation to facilitate oxygen uptake. Cardiac output must also increase simultaneously to assure delivery of oxygen for maintenance of aerobic metabolism. Unless cardiopulmonary compensation can occur, anaerobic cellular metabolism will ensure with the resultant production of excess lactic acid. Progressive metabolic acidosis may in tern adversely affect cardiopulmonary function. In addition, certain vital organs (heart and brain) may suffer tissue ischemia with subsequent cellular necrosis. Oxygen uptake and delivery must be increased during shivering. Any imbalance between oxygen demand and supply during shivering may be particularly crucial in patients with intrinsic cardiopulmonary disease. Ventilatory embarrassment or fixed, low cardiac output during shivering represents potentially hazardous situations. (8,9,10,11) Also, hypothermia may trigger vasoconstriction and thus increase vascular resistance. Therefore, in a patient with already limited myocardial oxygen supply because of arteriosclerosis, shivering may further compromise myocardial function. Shivering may also increase intraocular and intracranial pressure, and it may contribute to increase wound pain. (12)

Although postanesthetic shivering in obstetric patients is sometime distressing, it is not a cause of morbidity in this group of young patients. However, postanesthetic shivering is one of the most common troublesome side effects in the postanesthetic care unit. Although there is general agreement that it is a thermoregulartory phenomenon, i.e.; a physiological response to anesthesia-induced core hypothermia, there is some evidence that it may also have a non-thermoregulartory component. However, in the postoperative period, muscle activity may be increased even with normothermia suggesting that other mechanism than heat loss and subsequent decrease in core temperature may contribute to the development of shivering. These include uninhibited spinal reflex, postoperative pain, decrease sympathetic activity, pyrogen release, adrenal suppression and respiratory alkalosis. (12) The neurotransmitter pathways conveying signals from central nervous system control centers, such as the

hypothalamus, to skeletal muscle are not clearly understood, but probably involve multiple levels of information integration and numerous neurotransmitters.

Many drugs are used to prevent and treat postanesthetics shivering, including clonidine, nalbuphine, meperidine, tramadol, ketanserin, propofol, nefopam, physostigmine, fentanyl, alfentanyl, sufentail, doxapram, dexamethasone, and metamizol. Meperidine is an effective treatment for shivering than equianalgesic doses of other μ-opioids agonist. This special anti-shivering activity may be based on its κ-receptor activity. (13,14,15,16) However, the effectiveness of opioids in the treatment and prevention of shivering after neuraxial opioids is limited by the risk of respiratory depression, sedation, pruritus and nausea. (17,18) There are side effects of other drugs such as: 1) Clonidine can cause homodynamic effect that may lead to hypotension, bradycardia and sedation, 2) Doxapram may increase heart rate and diastolic arterial pressure, 3) Physostigmine increases heart rate, blood pressure, causes nausea and vomiting, and increase oxygen demand of myocardium, 4) Ketanserin also causes hypotension. (19,20,21) Although, there are many drugs to prevent and treat shivering but the ideal drug has still not been found. In several published studies, shivering was treated successfully by nalbuphine, tramadol and ondansetron. Nalbuphine, a mixed agonist-antagonist opioid, has a high affinity for κ-opioid receptors. Tramadol is a centrally acting analgesic with weak opioid agonist properties, affects on the spinal inhibition of pain, and inhibits the reuptake of serotonin and norepinephrine in the spinal cord. Both nalbuphine and tramadol have no hemodynamic side effect.(16,22) Ondansetron is a specific 5-HT_3 antagonist. It is one of effective drugs to treat postanesthetic shivering which has no innocuous effects on cardiovascular system. (23,24) Therefore nalbuphine, tramadol, and ondansetron should be suitable for treatment of postanesthetic shivering after spinal morphine in cesarean section patients. However, there is no study that compares the efficacy between nalbuphine, tramadol and ondansetron for treating postanesthetic shivering in this group of patients who should not be treated with meperidine.

The incidence of postanesthetic shivering in post cesarean delivery patients at King Chulalongkorn Memorial Hospital is about 60% of which 40%needs treatment. With cesarean section rate about 3,500 cases per year, there would be 1,400 cases of parturient with shivering that need treatment in our institute. Therefore, a randomized, double blind study should be undertaken to find out the suitable agent for treating this group of patients.

CHAPTER 2

REVIEW OF RELATED LITERATURE

2.1 Literature search strategy:

The literature search strategy used to locate the information in this review is the Pub-MED reference database and additionally by going through the reference list of other articles and institutional database. The keywords used were **anesthesia**, **complication**, **intrathecal morphine**, **shivering**, and **cesarean section**. The year covered by the search was from 1986 – 2001.

2.2 Anesthesia for cesarean section:

In obstetric anesthesia, anesthesiologists are responsible in choosing and carrying out an anesthetic technique. The anesthesiologists must have a clear understanding of maternal and fetal physiology. In addition, knowledge of placental drug transfer and drug effects on the neonate are essential. There is considerable evidence to indicate that neither regional nor general anesthesia will cause harm to the fetus if the anesthetics are administered properly. Apgar scores and blood gas value are virtually identical. Neurobehavioral scores, for what they are worth, tend to be better in newborns of patients receiving regional anesthesia. Neurobehavioral scores are scores that attempt to evaluate the cognitive function of the newborn. When first applied, they were meant to improve over Apgar scores and blood gases. Although neurobehavioral changes have been associated with general anesthesia immediately after birth, there is no evidence that these changes last more than a few days or have long lasting effects. (25) For the mother, it is not quite the same. In recent years it has become increasingly

more evident that general anesthesia poses a considerably greater risk to the mother than does regional anesthesia. Maternal mortality in cesarean section is quoted to be about 20 times that for vaginal delivery. Anesthesia is responsible for about ten percent of all maternal deaths. About half of the anesthetic related maternal deaths are caused by aspiration of gastric contents, and the other half by failure to intubate the trachea following induction. Almost all these anesthesia related maternal deaths are associated with the administration of general anesthesia. (26) Therefore, regional anesthesia such as epidural anesthesia and spinal anesthesia is accepted widely among obstetric anesthesiology.

2.3 Spinal anesthesia in obstetrics

The use of spinal anesthesia for surgical procedures dates back to 1885 but it wasn't until the 1940s when Adriani and associates established safe, standardized techniques that this method of analgesia became popular in obstetrics. (27,28) By the mid-1950s, over half a million subarachnoid blocks had been performed in pregnant patients in the United States. (28) The major physiological concerns about this technique center around the hypotension associated with the block and its potential maternal and fetal effects. With increasing understanding of the physiological changes in pregnancy and the technological advances that have occurred, more precise determination of the effects of spinal anesthesia in the parturient have become possible. Prophylactic measures such as prehydration, positioning and vasopressors have all been used to minimize hypotension associated with this technique.

Another bothersome problem with the subarachnoid approach is the high incidence of postdural puncture headache, which is more common in the young, female population. Smaller gauge needles, non-cutting tips and newer bevel designs have now decreased the incidence of postdural headache to an acceptable level. (29)

Advantages of spinal anesthesia include the speed of onset of the drug when given into the subarachnoid space and the generally reliable nature of the block. The presence of cerebrospinal fluid (CSF) as a definitive end point allows for a more certain

outcome than with epidural anesthesia. (29) Therefore, this technique may be used in situations where epidural anesthesia has been attempted and failed or when there is some degree of urgency to administer an anesthesia to facilitate delivery. (29) The extremely small dose of local anesthetic used nearly eliminates the possibility of a systematic toxic reaction and will not cross the placenta to any appreciable degree.

Spinal anesthesia reached its peak in obstetrical anesthesia and analgesia in the 1950s when it was the most frequently used anesthetic technique for vaginal delivery and cesarean section. (30) Its advantages revolved around its simplicity of administration, its reliability of action and its minimal side effects. The danger of aspiration and fetal or neonatal depression associated with general anesthesia were avoided. Improved technical developments in the administration of local anesthesia by the epidural route and the developments of longer acting local anesthesia agents led to a decline in popularity of spinal anesthesia in the latter half of the 1960s. Associated complications, including hypotension and postdural puncture headaches, as well as inability to provide continuous analgesia without a fear of neurological damage paved the way for the rapid advancement of the epidural technique of analgesia. However, spinal anesthesia in obstetrics has some obvious advantage over the epidural route, and with the development of small gauge needles and newer bevel designs, this method has recently enjoyed resurgence in popularity in the obstetrical anesthesia world.

2.3.1 Maternal effects of spinal anesthesia

The most frequent important physiological effect of spinal anesthesia is the hypotension that results from the block. The decrease in arterial pressure is more severe and can occur much more rapidly than in the non-pregnant counterpart. The associated hypotension resulted from a decrease in peripheral resistance and peripheral venous pooling leads to decreased venous return, cardiac output and arterial blood pressure. In the parturient, the gravid uterus plays a critical role in the compression of the inferior vena cava, pelvic veins and the aorta and its branches. (31)

The incidence of hypotension with spinal anesthesia is less in laboring than in non-laboring patients. This may result from the autotransfusion of the vascular system

with approximately 300 ml of blood that occurs with each uterine contraction. Other physiological effects of spinal anesthesia include nausea and vomiting. Although the mechanism is unclear, it may be a secondary effect relating to the maternal hypotension, which in turn causes decreased cerebral blood flow. Correction of the hypotension usually improves these symptoms. As technology has advanced, the ability to determine more accurately both the maternal and fetal effects of spinal anesthesia has become possible. Cardiac output may be calculated from Doppler ultrasound measurement of ascending aortic blood flow velocity combined with cross-sectional echocardiography of the aortic orifice area. (31)

2.3.2 Fetal effects of spinal anesthesia

Spinal anesthesia has no direct fetal effects since the amount of local anesthetic used is too small to reach the fetal circulation. (31) However, a decrease in maternal blood pressure and cardiac output may have deleterious effects. A decrease in uteroplacental blood flow and intervillous perfusion may alter transfer of oxygen, carbon dioxide and nutrients to the fetus. Stenger et al. found that neonates born of mothers who had uncorrected hypotension secondary to spinal anesthesia had an increased oxygen capacity, reduced oxygen content and saturation and an increase in oxygen utilization. (28) The changes in carbon dioxide tension resulted in a lower pH in infants in the uncorrected hypotensive group than in the corrected group. Further studies indicated that persistent maternal hypotension could have effects on the fetal heart rate pattern often manifested by late decelerations. (28,31)

2.3.3 Indication of spinal anesthesia

The advantages of spinal anesthesia are several. The first is that it is easily administered. The appearance of CSF serves as a clear end-point and, therefore, presumably will increase the reliability of the block. (32) The action of the local anesthetics administered into the subarachnoid space is rapid and predictable. (33) A very considerable advantage is that the dose of local anesthetic is extremely small and, therefore, the chance of systemic reaction is almost negligible. Some of the other

advantages of spinal anesthesia, such as the ability of the mother to be awake for the birth of her child and improve bonding, do not differ from those of epidural anesthesia.

Specific indications for spinal anesthesia versus epidural anesthesia have been suggested. In situations where large doses of local anesthetic need to be avoided, spinal anesthesia would be a better alternative. (33) As well, spinal anesthesia may have a role in the patient who requires urgent Cesarean section. Moreover, there are several study conclude that subarachnoid anesthesia was reasonable method of anesthesia for cesarean section for fetal distress in patients who do not have an epidural already in place.

The administration of opioids by the subarachnoid route may have some advantages in the high-risk obstetrical patients in labor. These include patients in whom the cardiovascular and neuromuscular effects of regional anesthesia are undesirable. Patients with cardiac disease such as aortic stenosis, Eisenmenger's syndrome, coarctation of the aorta or pulmonary hypotension can receive analgesia in labor with spinal opioids. Spinal anesthesia may be more easily administered than epidural anesthesia to the morbidly obese parturient. Spinal anesthesia may be used in the patients who suffering from pregnancy-induced hypertension provided that there are no contraindications to spinal anesthesia. (34) In patients with altered vertebral anatomy, epidural anesthesia may be technically difficult to perform and may be associated with a higher degree of complications. Spinal anesthesia may be indicated in these patients, specifically for cesarean section where a general anesthesia might otherwise be given. Spinal anesthesia has been successfully administered to a patient with spina bifida who wished to remain awake for her cesarean section. (35) Many reports on regional anesthesia following spinal surgery have reinforced the fact that regional anesthesia, usually epidural, is safe but not always successful or easily performed. (36,37) The used of spinal anesthesia in these patients may not only be more easily performed but also associated with a more reliable block. (38)

2.4 Postanesthetic shivering

Along with nausea and vomiting, postanesthetic shivering is one of the leading causes of discomfort for patients recovering from general anesthesia. The distinguishing factor during electromyogram recordings between patients with postanesthetic shivering and shivering in fully awake patients is the existence of clonus similar to those recorded in patients with spinal cord transection. Clonus coexists with the classic waxing signals associated with cutaneous vasoconstriction (thermoregulatory shivering). The primary cause of postanesthetic shivering is perioperative hypothermia, which sets in because of anesthetic induced inhibition of thermoregulation. However, shivering associated with cutaneous vasodilatation (non-thermoregulatory shivering) also occurs, one of the originals of which is postoperative pain. Postanesthetic shivering is an involuntary movement that may affect on several muscle groups, and which generally occurs in the early recovery phase after general anesthesia. (39)

2.4.1 Shivering during labor with and with out neuraxial anesthesia

Hormonal factors are likely to influence thermoregulartory responses during labor and delivery. Progesterone release during the normal menstrual cycle is associated with elevated circulating norepinephrine concentrations, which in turn slightly augment core temperature. (40) The production of metabolic heat, which needs to be dissipated to the environment to maintain thermal steady state, is probably augmented further by the work of labor. On the other hand, heat loss may be exaggerated if laboring women are exposes too long to a relatively cool hospital environment. Clinical interventions, such as intravenous infusion of cold fluid, can further exacerbate heat loss. Hyperthermia is a generic term used to indicate an abnormally elevated core body temperature resulting from various causes. A reasonable clinical definition of hyperthermia is a temperature greater than 38 ^{0}c, because core temperature normally never exceeds this value. Fever, in contrast, is a regulated elevation in body temperature. It is likely that labor, and especially delivery, is associated with the release of fetal-placental products that trigger fever. (41) However, the extent to which fever contributes to observed thermoregulatory patterns during and

after delivery remains unknown. Neuraxial anesthesia also complicates the thermoregulatory situation by centrally impairing thermoregulatory control. Specifically, It impairs behavioral regulation and decreases the vasoconstriction and shivering thresholds (triggering core temperature), which increases the sweating-to-vasoconstriction inter threshold range (temperatures that do not trigger thermoregulatory responses). (42)

Shivering has a reported incidence of nearly 20% during labor without neuraxial anesthesia, and it is thought to be even more common with epidural anesthesia and spinal anesthesia. The incidence of post regional anesthesia shivering in the patients undergoing cesarean section is between 33% - 60%. (1,2,4,5,39)

2.4.2 Epidemiology of postanesthetic shivering

According to studies, the incidence of postanesthetic shivering ranges between 6.3% and 66%. (33% - 66% in regional anesthesia) (1,2) Some studies consider male more prone to postanesthetic shivering, whereas others make no distinction between genders. However, being a young adult seems to be a determinant factor. Other risk factors identified are the length of the anesthesia or surgery (the longer the more likely), and if no active perioperative rewarming procedure is used. However, while some authors did not find a relationship between a drop in body temperature and the incidence of postanesthetic shivering, others found the link exists. (39) In fact, mild perioperative hypothermia does not necessarily occur before the appearance of postanesthetic shivering but it encourage it, and the more serious the hypothermia, the higher the probability of postanesthetic shivering. Lastly, the incidence of postanesthetic shivering differs depending on the anesthetic used. The use of a halogenated agent or pentothal, the administration only perioperatively of small quantities of opiates encourage the appearance of shivering. In contrast, the incidence of shivering is less common with the use of propofol. (43,44)

2.4.3 Pathophysiology of postanesthetic shivering

2.4.3.1 Mechanism of postanesthetic shivering

Several hypotheses have been raised to explain the occurrence of postanesthetic shivering. These include perioperative hypothermia, postoperative pain, perioperative heat loss, the direct effect of certain anesthetics, hypercapnia or respiratory alkalosis, the existence of pyrogens, hypoxia, early recovery of spinal reflex activity and sympathetic overactivity. (39)

For slightly more than 10 years, different studies have provided clearer insight into the origins of postanesthetic shivering. First of all, the recording of postanesthetic shivering electromyographic (EMG) patterns enables the identification of three types of EMG signals: tonic EMG activity, spontaneous EMG clonus similar to pathological clonus observed in patients with spinal cord transection, and waxing and waning signals identical to those obtained during cold-induced shivering in non-anesthetized patients. Furthermore, waxing and waning in unstimulated volunteers is always preceded by cutaneous vasoconstriction confirming their central thermoregulatory origin. One hypothesis used to explain the clonic movements is that they correspond to spinal reflex hyperactivity, which results from the inhibition of descending cortical control by residual concentrations of anesthetics. (39) These EMG signals are compatible with the clinical descriptions of abnormal reflexes observed during the early recovery phase.

Recently, Horn et al. (45) observed 120 patients who were divided into two groups according to the intraoperative temperature management. Forty patients became hypothermia while the others (n=80) were actively rewarmed in order to obtain a postoperative core temperature higher than the measured preoperative temperature. The authors noticed that the frequency of shivering was approximately 50% (20 patients) in the control group compared with 22% (20 patients) in the rewarmed group. In the latter group, 55% of patients (11 patients) displayed shivering associated with vasodilatation. This means that 15% of actively rewarmed patients (11 out of 80) present shivering, which does not correspond to a thermoregulatory response.

So we can say that, there are two types of postanesthetic shivering. The first corresponds to thermoregulatory shivering that is associated with cutaneous

vasoconstriction and which is the physiological response to the hypothermia developed during the perioperative period. The second corresponds to shivering associated with cutaneous vasodilatation or non-thermoregulatory shivering. The mechanisms responsible for non-thermoregulatory shivering are not fully unknown. However, the existence of a link between postoperative pain and the incidence of the postanesthetic shivering has been confirmed by a study comparing the frequency of postanesthetic shivering after knee arthroscopy in patient who received and those who did not receive intra-articular lidocaine at the end of the operation. The existence of greater pain in patients who did not receive local anesthesia was accompanied by a higher incidence of postanesthetic shivering. Of all the different hypothesis raised to explain the incidence of post anesthetic shivering, only perioperative hypothermia and pain have been clearly verified. Furthermore, it is indeed a drop in core temperature that facilitates the emergence of shivering and not a reduction in the heat content of the patient. In fact, the initial decrease in central temperature during the inhibition of thermoregulatory by anesthetics is first of all due to an internal redistribution of the heat content, which is carried out with a quasi zero heat balance. (11) As hypothermia and pain are known to initiate sympathetic overactivity, it is difficult to specifically evaluate the influence of sympathetic overactivity on postanesthetic shivering. (45)

On the basic of several factors, we can assume that there is a relationship between a possible early recovery of spinal reflex activity facilitated by the residual effect of anesthetics on the inhibiting control exercised by supraspinal structures and the incidence of postanesthetic shivering. This link provides an explanation for the existence of EMG recorded clonus. Furthermore, there is a lower frequency of postanesthetic shivering with propofol compared to other anesthetics such as pentothal or halogenated agents, (43) which cannot be explained by the differences of effect on thermoregulation. However, it is plausible that the effect of low concentrations of propofol is less significant on certain central structures such as the reticular formation compared to these other drugs, thus enabling a faster recovery of the descending inhibiter control.

Among the other hypotheses raised to define the causes of postanesthetic shivering, some of them such as hypercapnia or hypoxia are unlikely to be involved

since they reduce the thresholds for the appearance of shivering in volunteers. The same applies to respiratory alkalosis since arterial blood samples taken during postanesthetic shivering have a normal or slightly acid pH. Secondary, the residual effects of anesthetic agents that facilitate hypercapnia in patients recovering from anesthesia. (39,42)

2.4.3.2 Consequences of postanesthetic shivering

The first clinical consequence of postanesthetic shivering is discomfort for the patient. Moreover, the patient has a stressful sensation of coldness that is systematically associated with postanesthetic shivering. Most patients mention shivering and the sensation of coldness as priorities when queried about the events that should be avoided after an operation. Another consequence of postanesthetic shivering on the comfort of the patient is the increased pain caused by muscular contractions on the operated site. Lastly, after optholmological surgery, postanesthetic shivering increases intra-ocular pressure that can be pernicious. (39)

The main effect of postanesthetic shivering is increased metabolic rate about 200%, and plasma catecholamine concentrations. Moreover, shivering in response to hypothermia increases tissue oxygen demand by as much as 400% - 500%. By affecting several muscular groups for periods of 45 minutes or more, postanesthetic shivering triggers an increase in metabolic demand, which generally translates into higher oxygen consumption combined with increased minute ventilation. Sometimes, but this is quite rare, metabolic demand can exceed the capacity to deliver oxygen peripherally and result in anaerobic metabolism. However, the impact of the increased oxygen consumption on perioperative cardiac morbidity is difficult to evaluate.

It is important to stress that mild perioperative hypothermia increases postoperative cardiac morbidity. With regard to increased oxygen consumption, the report in the previous studies are very variable, ranging from 7 to 700%. (46,47) The increase of oxygen consumption linked to shivering is proportional to the affected muscular mass.

2.5 Clinical studies:

There are many articles concerning shivering in postanesthetic patients. Most of the studies were comparison of the efficacy of drugs used to treat shivering in postanesthetic patients. Moreover, there are several articles that compare the efficacy between drugs for prevention of shivering. The followings are the articles that related to treatment or prevention of shivering.

A comparison of urapidil, clonidine, meperidine and placebo in preventing postanesthetic shivering. (17)

Piper, et al. performed placebo-controlled trial to evaluate the efficacy of urapidil compared with clonidine and meperidine in preventing postanesthetic shivering. They studied 120 patients undergoing elective abdominal or orthopedic surgery under standardized general anesthesia. After surgery, patients were randomly assigned to one of four groups that were group A. received 0.2 mg/kg urapidil; group B. 3 ug/kg clonidine; group C. 0.4 mg/kg meperidine; and group D. saline 0.9% as placebo. They concluded that both clonidine and meperidine are effective in preventing postanesthetic shivering, whereas urapidil in this setting and dosage was not effective.

A comparison among nalbuphine, meperidine, and placebo for treating postanesthetic shivering. (16)

Wang ,et al designed a prospective, double blind, randomized study to evaluated the value of nalbuphine, compared with meperidine and saline, for treating postanesthetic shivering after general anesthesia. Ninety patients were included in the study. Group 1. received IV nalbuphine 0.08 mg/kg, group 2. received IV meperidine 0.4 mg/kg, and group 3. received IV saline. They conclude that the differences between nalbuphine and meperidine were not significant. Both nalbuphine and meperidine provide a similar rapid and potent anti-shivering effect with high response rates of 80% and 83% compared with those of saline 0%.

Double blind comparison between doxapram and pethidine in the treatment of postanesthetic shivering. (20)

Singh, et al studied in 60 patients who had undergone routine orthopedic or otolaryngological surgery and developed shivering after general anesthesia within 10

min of admission to recovery room. In addition, each patient received an I.V. injection of 1.5 mg/kg doxapram, 0.33 mg/kg of pethidine and saline. They concluded that pethidine had a significantly greater success rate at 3 and 7 min after administration of treatment, with a success rate of 100%, compared with 83% for doxapram.

Tramadol in the treatment of postanesthetic shivering. (13)

Witte ,et al designed a randomized, placebo controlled, double blind study, to assessed the effects of tramadol (0.5 mg/kg, 1 mg/kg, and 2 mg/kg) or normal saline on shivering in post general anesthesia patients. They concluded that tramadol's distinct features in the treatment of shivering reside in its high safety profile and weak sedative properties, particularly in-patients with poor cardiorespiratory reserve, in outpatients and on recurrence of shivering.

Control of shivering under regional anesthesia in obstetric patients with tramadol. (22)

Chan,et al. designed a randomized, double blind study, to evaluate the effectiveness of tramadol (0.5 mg/kg and 0.25 mg/kg) and normal saline, in the treatment of shivering after regional anesthesia. Thirty six parturients who shivered during cesarean section were allocated to one of three groups for I.V. treatment. They concluded that 80% of parturient in 0.5 mg/kg group and 92% in 0.25 mg/kg group were judged by observer to have shivering controlled compare with 27% in normal saline group. There was no increased incidence of side effects in the treatment groups.

Clonidine and ketanserin both are effective treatment for postanesthetic shivering. (48)

Joris, et al designed a randomized, controlled double blind study to investigate the efficacy of clonidine and ketanserin in treating postanesthetic shivering compared with normal saline. They concluded that clonidine 150 ug and ketanserin 10 mg both are effective treatment for postanesthetic shivering.

Tramadol reduces the sweating, vasoconstriction, and shivering thresholds. (49)

DeWitte, et al evaluated the effects of the analgesic tramadol on the three major thermoregulartory responses: sweating, vasoconstriction, and shivering. They concluded that tramadol reduces the sweating, vasoconstriction, and shivering thresholds with only slight thermoregulartory effects. Its use is thus unlikely to provoke hypothermia or to facilitate fever.

A comparison between meperidine, clonidine and urapidil in the treatment of postanesthetic shivering. (18)

Konrad, et al performed a randomized, double-blinded study to compare the effects of meperidine, clonidine and urapidil on postanesthetic shivering. Sixty patients shivering during recovery from general anesthesia were treated with those three drugs. They concluded that clonidine stopped shivering in all 20 patients, meperidine stopped the shivering in 18 of 20 patients, and urapidil was less effective. Clonidine and meperidine were both nearly 100% effective in treating. By comparison, urapidil was only 60% of patients treated.

Dolasetron for preventing postanesthetic shivering. (50)

Piper, et al designed the placebo control trial to assess the efficacy of dolasetron compared with clonidine and placebo in prophylaxis of postanesthetic shivering in 90 patients undergoing elective abdominal or urologic surgery. This concluded that clonidine is effective in preventing shivering when given before surgery, whereas dolasetron, at the dose used, is not effective.

The use of tramadol hydrocholride in the treatment of postanesthetic shivering. (51)

Pausawasdi, et al investigated the efficacy of tramadol (1 mg/kg) for the treatment of postanesthetic shivering in 110 patients. This study shows that tramadol is highly effective for the treatment of postanesthetic shivering. At the dosage of 1 mg/kg body weight it stopped shivering in all patients after a short period of time with very few side effects.

Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. (23)

Powell, et al performed a randomized, placebo controlled double-blinded study to evaluate the effect of ondansetron, given before the induction of anesthesia. They concluded that ondansetron 8 mg intravenous given during the induction of anesthesia prevents postanesthetic shivering without affecting analgesia.

Therefore, 0.05 mg/kg of nalbuphine, (52) 0.5 mg/kg of tramadol, (13,22) and 0.1 mg/kg ondansetron (23,24) were chosen for evaluation in this study.

2.6 Patient satisfaction:

Measurement of patient satisfaction has become increasingly important in health care. It correlates with outcome and can be vital to the economical success of a hospital. (53) Measuring patient satisfaction with anesthesia service has become important too; ensures the quality of anesthesia care, (54) improves and intensifies the anesthesiologist-to-patient relationship, (55) and can also be seen as a marketing tool in term of customer orientation. (56) Measuring patient satisfaction can prove to be difficult task. Patients frequently have problems analyzing and assessing the quality of anesthesia care independently from the overall care during treatment. Furthermore, the asymmetry of the physician-to-patient relationship and the subjective feeling of gratefulness after a successful operation often prevent an objective and valid evaluation by the patient. In addition of this factor, the methods used to measure patient satisfaction involve specific problems. With regard to the questionnaire, the “trend towards the center” is a well-known phenomenon while the interviewer-patient interaction tends to reduce the relevance of the evaluation in the interviewing technique. (57,58)

Postoperative patient satisfaction is often correlated with control of both pain and adverse effects. (59) Maternal satisfaction, however, is a complex psychological response to childbirth. It has been assumed that an ingredient of maternal satisfaction with labor and delivery is effective analgesia during labor.

In this study we also assess the patients satisfaction in term of direct anesthesia service treatment of side effect and overall anesthesia care service satisfaction.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research questions:

3.1.1 Primary research question.

Among 0.05 mg/kg nalbuphine, 0.5 mg/kg tramadol, and 0.1 mg/kg ondansetron, which agent is more efficacious in treating postanesthetic shivering after intrathecal morphine in cesarean section patients?

3.1.2 Secondary research questions.

1. Are there any differences in side effects among three groups? (decrease analgesic effect, nausea, vomiting, pruritus, sedation, respiratory depression and etc.)
2. Are there any differences in patient satisfaction concerning, anesthesia service and treatment of side effects among three groups?

3.2 Objectives:

1. To compare the efficacy between 0.05 mg/kg nalbuphine, 0.5 mg/kg tramadol, and 0.1 mg/kg ondansetron in treating postanesthetic shivering in cesarean section patients after intrathecal morphine.
2. To compare incidence of side effects (decrease analgesic effect, nausea and vomiting, pruritus, sedation, respiratory depression, and etc.) among this three groups of postanesthetic shivering in cesarean section patients after intrathecal morphine.

3. To compare the patient satisfaction concerning for anesthesia service among three groups of postanesthetic shivering in cesarean section patients after intrathecal morphine.

3.3 Hypothesis:

Research hypothesis

Null hypothesis: The efficacy of three treatments is the same proportion

Alternative hypothesis: The efficacy of three treatments is different proportion (at least one pair is not equal)

Statistical hypothesis

Ho: $P1 = P2 = P3$

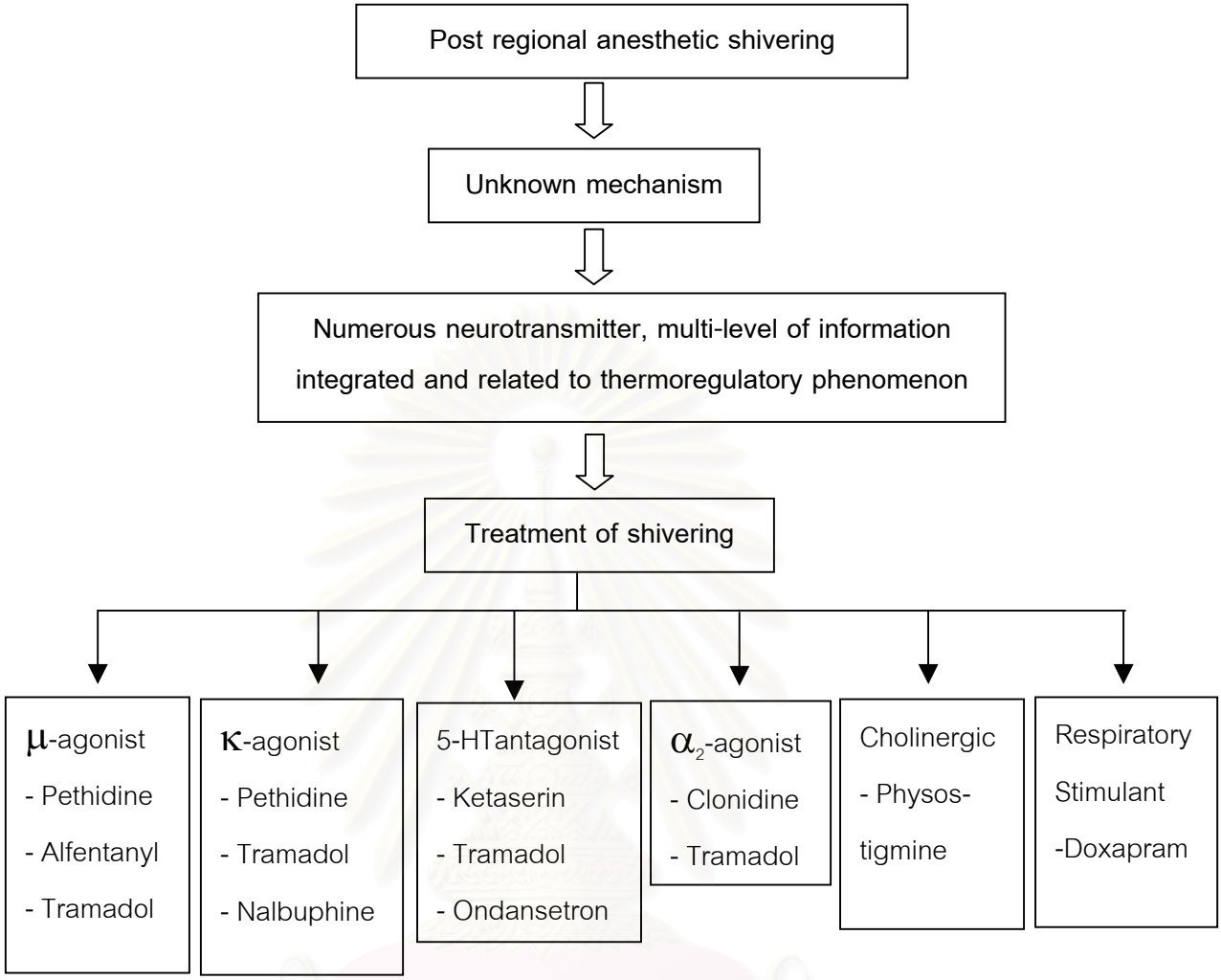
Ha: $P1 \neq P2 \neq P3$ (at least one pair is not equal)

P1 = the efficacy of 0.05 mg/kg nalbuphine in treating of postanesthetic shivering in cesarean section patients after intrathecal morphine.

P2 = the efficacy of 0.5 mg/kg tramadol in treating of postanesthetic shivering in cesarean section patients after intrathecal morphine.

P3 = the efficacy of 0.1 mg/kg ondansetron in treating of postanesthetic shivering in cesarean section patients after intrathecal morphine.

3.4 Conceptual framework:



3.5 Assumption: (none)

3.6 Keywords: Nalbuphine, Tramadol, Ondansetron, Intrathecal morphine, Shivering, and Cesarean section

3.7 Operational definition:

- **Intrathecal morphine**: Intrathecal morphine is administered via spinal needle during subarachnoid block by mixing with local anesthetic before injection. The synonym of intrathecal morphine is spinal morphine.

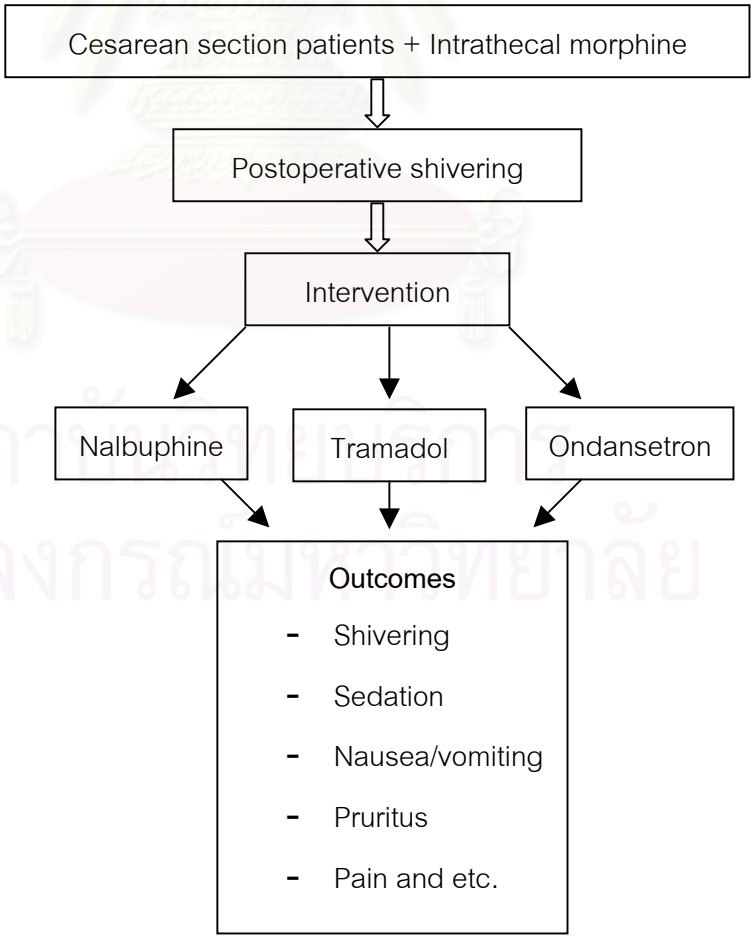
3.8 Research design:

This study had been carried out as a randomized double blind controlled trial. Since shivering, analgesia, nausea, vomiting, pruritus, verbal numeric pain level, and etc are subjective outcomes, they should be evaluated blindly. The eligible patients will be randomly assigned into three treatment groups with nalbuphine (0.05mg/kg) or tramadol (0.5 mg/kg) or ondansetron (0.1 mg/kg) after moderate shivering (grade 3) occurred. The randomization can avoid allocation bias, tends to produce comparable groups and assures the validity of statistical tests of significance.

3.9 Research design model:

Shivering – N – NE – Randomization → Nalbuphine 0.05 mg/kg = 4 cc.
Shivering – N – NE – Randomization → Tramadol 0.5 mg/kg = 4 cc.
Shivering – N – NE – Randomization → Ondansetron 0.1 mg/kg = 4 cc.

Study protocol:



3.10 Research method

3.10.1 Population

Target population

Post cesarean section patients under spinal anesthesia with intrathecal morphine who suffer from shivering.

Sampled population

Post cesarean section patients under spinal anesthesia with intrathecal morphine, at the postanesthetic care unit, King Chulalongkorn Memorial Hospital who meet the following criteria:

A. Inclusion criteria

1. Post cesarean section patients of ASA physical status 1 or 2 (appendix 1)
2. Scheduled to have the cesarean section under spinal anesthesia with intrathecal morphine.

B. Exclusion criteria

1.Contraindication to regional anesthesia.
2. History of allergy to nalbuphine, tramadol, ondansetron or morphine.
3. History of any disease associated with shivering such as Malaria, Thyroid, Epilepsy, etc.
4. History of any disease associated with neurobehavior.
5. Patient who does not agree to participate in the study.
6. Patient who is unable to understand how to rate the measurement scale such as verbal numeric pain scale.

3.11 Sample size:

Since the outcome is proportion of successful treatment of patients in each group, the sample size formula for comparing two proportions of two independent groups was used. (60,61) This formula is derived from equal size group.

$$n/group = \left(\frac{Z_{\alpha/2}\sqrt{2\bar{P}\bar{Q}} + Z_{\beta}\sqrt{P_1Q_1 + P_2Q_2}}{P_1 - P_2} \right)^2$$

where α = 0.05

Z_{α} = 1.96 (two-tailed)

Z_{β} = 1.28 (power = 90%) or Z_{β} = 0.84 (power = 80%)

P_1 = proportion of successful treatment of shivering in Tramadol groups $Q_1 = 1 - P_1$

P_2 = proportion of successful treatment of shivering in Nalbuphine Groups $Q_2 = 1 - P_2$

$\bar{P}$ = (P1 + P2) / 2 and $\bar{Q} = 1 - \bar{P}$

From pilot study of 20 patients in each group, the efficacy of tramadol is 85%, nalbuphine is 60% and ondansetron is 60 %.

Table 1: The sample size estimation for two comparing independent groups.

Proportions of successful treatment of shivering	Power = 80%	Power = 90%
	n/group	n/group
Nalbuphine = 0.60, Tramadol = 0.85	49	68
Nalbuphine = 0.60, Ondansetron = 0.60	0	0
Tramadol = 0.85, Ondansetron = 0.60	49	68

The table demonstrates the sample size calculation using difference proportion of successful treatment of shivering between nalbuphine and tramadol, nalbuphine and ondansetron, and tramadol and ondansetron at different power of 80% and 90%. (Data from pilot study of 20 subjects in each group.)

From pilot study and sample size calculation, the highest number of sample size by comparing the proportions between nalbuphine and tramadol, and tramadol and

ondansetron is chosen with 90% of power. So the total estimated sample size would be 68 patients per group.

10% drop out rate: $N = n / (1 - R)$ $= 68/ (1 – 0.1)$ ≈ 75

To allow for an expected 10% drop out rate, a total 225 patients (75 patients per group) will be randomized.

3.12 Randomization:

Simple randomization was conducted in the study. The patients who met the selection criteria were randomly divided into nalbuphine, tramadol and ondansetron groups according to random number table. The random number was written in a paper and enclosed in a sealed envelope. The intervention agents were prepared by nurse anesthetist not involved in the study. The code was kept in the post anesthetic care unit without broken until the patients were discharged and all data were collected or in case of serious side effects occurred.

3.13 Experimental maneuver

3.13.1 Pre-anesthetic period

The patient who met criteria was admitted for cesarean section. The routine preoperative preparation is done. The patient had been explained about detail of the study and informed consent signed in all cases.

3.13.2 Anesthesia and operative period

After starting intravenous route and foleys catheterization, all patients were placed in left lateral position and received anesthetic consisting of 2.2 ml of hyperbaric bupivacaine or 5% xylocaine 1 – 2 c.c. with 0.2 ml (0.2 mg) of morphine. Intravenous fluid and ephedrine were administered as appropriate to maintain systolic arterial blood pressure to within 30% of its preoperative value or systolic blood pressure > 100 mmHg. After testing for a satisfactory spinal block using loss of pinprick sensation, the cesarean section was performed in the usual way.

3.13.3 Postanesthetic period

After cesarean section, women who were observed of shivering while in the post anesthesia care unit (PACU) (2 hours after completion of the cesarean section) were evaluated by the investigator. The patients whose shivering score > 2 (1 = no shivering, 2 = mild shivering, treatment not necessary, 3 = moderate shivering, treatment necessary, 4 = severe shivering, treatment necessary) (22,49,62,63) as determined by the investigator were assigned to receive either 0.05 mg/kg nalbuphine or 0.5 mg/kg tramadol or 0.1 mg/kg ondansetron according to randomization sequence. After treatment the treatment response was observed by the investigator. Fifteen minutes after treatment, the patients were assessed by the same investigator. In the absence of a positive response (shivering score of 3 or 4) the result was considered failure of treatment and shivering was titrately treated by 20 milligrams propofol intravenous injection. If the treatment was successful, the patients were evaluated every 15 minutes for 2 hours according to postanesthetic care unit protocol and follow up for 4 hours to determine the duration of the anti-shivering response and recurrence of shivering.

At the same time that the patient was evaluated for shivering, the level of sedation was assessed using a 4-point sedation rating scale, the pruritus was assessed by 4-point rating scale, the nausea and vomiting was assessed by 4-point rating scale, and the pain level was assessed by verbal numeric pain scale (0 = no pain, 10 = worst imaginable pain). Ten milligrams of metoclopramide was administered for nausea and vomiting as required. Chlorpheniramine 10 milligram intravenously was prescribed for pruritus as required. After each drug administration, blood pressure, heart rate, body temperature, dizziness, extrapyramidal effect and respiratory depression were recorded.

3.14 Outcomes measurement:

The variables being measured were as followed:

3.14.1 Demographic and baseline variables

- Age (years)
- Body Weight (kilograms)

- Height (centimeters)
- BMI (kg/m^2)
- Body temperature at recovery room (^{0}C)
- Duration of surgery (min)
- Recovery room temperature (^{0}C)
- Total intravenous fluid (ml)

3.14.2 Outcome variables

Shivering (22,49,62,63)

4 – point rating scale for shivering

1 = no shivering

2 = mild shivering, treatment not necessary

3 = moderate shivering, treatment necessary

4 = severe shivering, treatment necessary

The result of treatment of shivering is considered **success** (shivering score 1 or 2), and **failure** (shivering score 3 or 4)

Sedation (49,64)

4 – point sedation scale

1 = patient fully awake

2 = patient somnolent, responds to call

3 = patient somnolent, responds to tactile stimulation

4 = patient asleep, responds to painful stimulation

Pruritus (49,65)

4 – point rating scale for pruritus

1 = no pruritus

2 = minimal pruritus, treatment not necessary

3 = moderate pruritus, treatment necessary

4 = severe pruritus and scratching, treatment necessary

Nausea and vomiting (49,66)

4 – point rating scale

1 = no nausea or vomiting

2 = queasy

3 = severe nausea

4 = vomiting

The level of pain (49,53,67)

Verbal numeric pain scale, with 0 representing no pain and 10 representing the worst imaginable pain.

3.14.3 Patient satisfaction outcomes:

Patient satisfaction was assessed by conducting a structured, questionnaire based interview, 24-48 hours postoperatively. During this interview, patients were asked to rate their satisfaction on a five-point scale (5=very satisfied, 4=somewhat satisfied, 3=neither satisfied nor dissatisfied, 2=somewhat dissatisfied, 1=very dissatisfied) (56) with following questions:

1. How satisfied were you with the spinal anesthetics?
2. How satisfied were you with postoperative analgesia?
3. How satisfied were you with postanesthetic shivering therapy?
4. How satisfied were you with treatment of other postanesthetic side effects?
5. How satisfied were you with the care provided by the department of anesthesiology in general?

This structure questionnaire was tested for reliability and the reliability coefficient is 0.8003. The value was acceptable based on the cut of point of 0.7 set for internal consistency. (68)

3.15 Reliability test of outcome variables

In this study, the postanesthetic shivering score (as the main outcome) was measured using the 4-point rating scale according to previous studies. (22,49,62,63) And the patients satisfaction towards anesthesia service were also measured using a newly constructed questionnaire. The validity of this constructed questionnaire was tested for item correlation by 3 experts. The measurement tool had also been tested for its reliability.

3.15.1 Reliability of postanesthetic shivering rating scale

The reliability of the postanesthetic shivering rating score was estimated by 2 observers (nurses anesthesiologist) who independently applied the same postanesthetic shivering rating score to the same subjects. (inter observer agreement)

Table 2 demonstrates observer A's and B's classifications of postanesthetic shivering score of 20 patients in pilot study, into 4 category ordinal scale. We were interested in all type of postanesthetic shivering score. For this 4-point ordinal scale, there are 4 levels of agreement i.e. perfect agreement (e.g. postanesthetic shivering score 1 VS postanesthetic shivering score 1), 1 scale point disagreement (e.g. Postanesthetic shivering score 1 VS postanesthetic shivering score 2, Postanesthetic shivering score 2 VS postanesthetic shivering score 3), 2 scale point disagreement (e.g. postanesthetic shivering score 1 VS postanesthetic shivering score 3, postanesthetic shivering score 2 VS postanesthetic shivering score 4), and 3 scale point (maximum, perfect) disagreement (e.g. postanesthetic shivering score 1 VS postanesthetic shivering score 4). These 4 different levels of agreement have different importance, that is, 1 scale point disagreement is considered to be less serious than 2 scale point disagreement and 2 scale point disagreement is less serious than 3 scale point disagreement.

Table 2: The frequency of postanesthetic shivering rating scale of 20 patients in pilot study by 2 observers.

Patient number	Shivering score rating by observer A	Shivering score rating by observer B
1	4	4
2	2	2
3	2	2
4	4	4
5	1	2
6	4	4
7	2	2
8	3	3
9	2	2
10	3	3
11	3	3
12	3	3
13	2	2
14	3	3
15	2	2
16	2	2
17	2	2
18	3	3
19	3	3
20	1	1

Table 3: Observed frequency of shivering rating scale rated by 2 observers.

PAS O1	PAS O2				Total
	PAS Score 1	PAS Score 2	PAS Score 3	PAS Score 4	
PAS Score 1	1	1			2
PAS Score 2		8			8
PAS Score 3			7		7
PAS Score 4				3	3
Total	1	9	7	3	20

Table 4: The expected frequency of shivering rating scale rated by 2 observers.

PAS O1	PAS O2				Total
	PAS Score 1	PAS Score 2	PAS Score 3	PAS Score 4	
PAS Score 1	0.1	0.9	0.7	0.3	2.0
PAS Score 2	0.4	3.6	2.8	1.2	8.0
PAS Score 3	0.4	3.2	2.4	1.0	7.0
PAS Score 4	0.2	1.3	1.1	0.5	3.0
Total	1.0	9.0	7.0	3.0	20.0

Table 5: Level of agreement of shivering rating scale rated by 2 observers.

Level of agreement	Weight	Frequencies	
		Observed	Expected
Perfect agreement	1	(1+8+7+3)=19	(0.1+3.6+2.4+0.5)=6.6
1-point disagreement	2/3	1	(0.4+3.2+1.1)+(0.9+2.8+1.0)=9.4
2-point disagreement	1/3	-	(0.4+1.3)+(0.7+1.2)=3.6
Perfect disagreement	0	-	0.2+0.3=0.5

The formula for calculation of reliability for inter observer agreement or weighted kappa is as follow: (69,70)

$$Kw = \frac{Pow - Pew}{1 - Pew}$$

Pow = 1/20 (1(19)+2/3(1))

= (1/20) x 19.67

= 0.9835

Pew = 1/20 (1(6.6)+ 2/3(9.4)+1/3(3.6)+0(0.5))

= 1/20 x 14.068

= 0.7034

$$Kw = \frac{0.9835 - 0.7034}{1 - 0.7034} = \frac{0.2801}{0.2966}$$

= 0.9444

The calculation revealed the inter rater agreement (weighted kappa) of post-anesthetic shivering score of 0.9444. The obtained results indicated that there was a very good agreement between two observers. (71)

3.15.2 Validity and Reliability of patients satisfaction questionnaire

Validity of patients satisfaction questionnaire

Validity concerns the extent to which an instrument measures what it is intended to measure. Content validity refers to the adequacy with which the universe of content is sampled by a test. To verify content validity of the proposed measuring tool, copies of Thai version of the newly developed questionnaire was sent to 3 experts. All experts were asked to evaluate the relevance and the adequacy of this questionnaire to measures patients satisfaction. The scoring system is as followed:

+1 for relatively valid item

0 for not sure

-1 for relatively irrelevant item

The obtained scores from each item were calculated to demonstrate the validity of each item by using the formula below: (72)

$$IC = \frac{\sum R}{N}$$

Where IC = item correlation

R = total score of that item

N = number of experts

The results of this content validity testing are showed in table 6.

Table 6: Results of content validity testing of patient satisfaction questionnaire.

Item number and stem	1	2	3	IC
1. How satisfied were you with the spinal anesthetics?	1	1	1	1
2. How satisfied were you with postoperative analgesia?	1	1	1	1
3. How satisfied were you with postanesthetic shivering therapy?	1	1	1	1
4. How satisfied were you with treatment of other postanesthetic side effects?	1	1	1	1
5. How satisfied were you with the care provided by the department of anesthesiology in general?	1	1	1	1

The result showed in the above table indicated the experts' acceptability of the questionnaire.

Reliability of patient satisfaction questionnaire

The reliability can be defined as an estimate to which a test scores in free from error, that is, to what, extent observed scores vary from true score. As it is not possible to know the true score, the true reliability of a test can never be calculated. Therefore, other parameters are used to define degree of test reliability. Such parameters include variance, reliability coefficient, test-retest reliability, rater reliability, internal consistency and so on. As this will be delivered as self-administered questionnaire, therefore test for rater reliability is not necessary. To scale was tested for its reliability by calculating its internal consistency.

The important kind of reliability testing in this setting is test for internal consistency. In this study, the data collected from pre-test in 30 patients were analyzed and Cronbach's alpha will be computed using computer program SPSS version 10. The formula for calculation of Cronbach's alpha is as followed: (73,74)

$$\text{alpha} = \frac{n}{n-1}\left(\frac{\sum Si^2}{(1 - St^2)}\right)$$

When n = number of items

Si^2 = item variance = $\frac{\sum (X - \bar{X})^2}{n - 1}$

St^2 = total variance = $\frac{n\sum Xt^2 - \sum (Xt)^2}{n\,(n-1)}$

To get this information, the 5-item questionnaire was tested in the 30 patients. The responses from 30 patients were then analyzed for the internal consistency using the computer software SPSS version 10 (for windows). The calculation revealed the Cronbach's coefficient of 0.8003. The obtained results indicated the good reliability (alpha exceeded 0.8) of the scale. The details of the reliability testing using Cronbach's alpha as an indicator are demonstrated in table 7.

Table 7: The item-total statistics of the pretested questionnaire

Item number	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Alpha if item deleted
1. How satisfied were you with the spinal anesthetics?	17.4333	4.5989	0.6045	0.7551
2. How satisfied were you with postoperative analgesia?	17.8000	4.0276	0.6934	0.7245
3. How satisfied were you with postanesthetic shivering therapy?	17.5667	4.2540	0.5975	0.7616
4. How satisfied were you with treatment of other postanesthetic side effects?	17.5667	4.3230	0.8378	0.6856
5. How satisfied were you with the care provided by the department of anesthesia in general?	17.1000	6.3690	0.2128	0.8437

3.16 Data collection

The data was collected in a data collection form. One nurse (the investigator) blinded to intervention agents recorded the shivering rating scale, sedation rating scale, nausea/vomiting rating scale, pruritus rating scale, the pain level and other side effects. Time of occurrence of shivering and time of successful treatment were also recorded.

3.17 Data analysis methods:

3.17.1 Demographic and baseline variables

Demographic and baseline data of patients in all three groups such as: age, weight, height, body mass index, postanesthetic care unit temperature, and etc were quantitative data, range, mean and standard deviation were demonstrated as summarized (Table 8)

Table 8: The demographic and baseline variables.

Variables	Type of variables	Statistics
1. Age (years)	Continuous	Range, mean, S.D.
2. Weight (kg)	Continuous	Range, mean, S.D.
3. Height (cm)	Continuous	Range, mean, S.D.
4. Body temperature (^{0}C)	Continuous	Range, mean, S.D.
5. Body mass index (kg/m^2)	Continuous	Range, mean, S.D.
6. Recovery room temperature (^{0}c)	Continuous	Range, mean, S.D.
7. Duration of surgery (min)	Continuous	Range, mean, S.D.

3.17.2 Outcomes variables

The outcome variables were described and compared between groups using the appropriate inferential statistics (Table 9).

Table 9: The inferential statistics used to compare outcome variables

Variables	Type of data	Statistics
1. Shivering rating scale ⇩ treatment success	Binary	Chi-square* 95% CI of diff. By Z-test
2. Sedation rating scale	Ordinal	Kruskal-Wallis 1-way ANOVA
3. Nausea, vomiting rating scale	Ordinal	Kruskal-Wallis 1-way ANOVA
4. Pruritus rating scale	Ordinal	Kruskal-Wallis 1-way ANOVA
5. Verbal numeric rating scale	Ordinal	Kruskal-Wallis 1-way ANOVA

* Fisher's exact test if necessary

Differences are considered significant at P-value < 0.05

Analysis was performed by using "intention to treat" approach. Proposal violator was included as long as they had measurements both at baseline and on treatment; statistical tests are two-tailed with significant level taken at 0.05. SPSS version 10

program was used for data analysis and STATA program was also used for statistical analysis of difference of successful rates with 95% CI.

3.17.3 Patients satisfaction outcome variables:

The patient satisfaction outcome variables were ordinal scale. Therefore Kruskal-Wallis 1-way ANOVA test for the ordinal scale was used for statistical analysis, p-value< 0.05 is considered to be significant.

3.18 Ethical Consideration:

The study protocol was explained to the patient and informed consent was obtained in all cases.

Intrathecal morphine is currently accepted as satisfactory method for providing long duration of postoperative analgesia. This study had been conducted to treat side effects. In case of failure of treatment, propofol was used as a rescue drug. Other side effect was also treated. If any serious complication occurred the code would be broken to search for actual cause and prompt treatment. Therefore the intervention would provide more benefit than harm.

3.19 Limitation of this study:

This study was confined to the patients in Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital and the period of follow up was short, so there was low possibility of loss to follow up except patients who do not agree to participate there after. All patients had been informed about the protocol and advice thoroughly before giving informed consent.

The generalizability of this study was limited to obstetric patients with post intrathecal morphine shivering. Further study is required to determine the efficacy of drugs in non-obstetric patients.

3.20 Expected benefit and application:

This is the first trial that compared the efficacy of 3 agents (tramadol, nalbuphine and ondansetron) in treatment of neuraxial opioids. If there is agent posses most potent antishivering effect with lowest side effects, or equipotent antishivering effect with lower side effects; it should be recommended.

3.21 Obstacles:

Possible obstacle is the patient who cannot understand how to rate measurement scale such as verbal numeric pain scale, etc. The amount of cesarean section patients might not be enough during the study period. Hence the study can be extended.

CHAPTER 4

RESULTS

4.1 Demographic and baseline data

Seven hundred thirty six parturient undergoing cesarean section under spinal anesthesia with intrathecal morphine at King Chulalongkorn Memorial Hospital during the 8 month-period from April to November 2002 provide the event rate of postanesthetic shivering of 51.09%. Among 376 cases with mild to severe shivering (shivering score 2 – 4), 225 cases (30.57%) with moderate to severe shivering (shivering score $\geq$ 3) were allocated to the Nalbuphine group (n = 75), Tramadol group (n = 76), and Ondansetron group (n = 74). The baseline characteristics of patients in all groups were comparable regarding age, body weight, height, BMI, body temperature, postanesthetic care unit temperature, vital sign, oxygen saturation, amount of intravenous fluid and onset of postanesthetic shivering (table 10). The onset of postanesthetic shivering appeared 20 – 180 minutes after neuraxial administration of morphine.

Table 10: The demographic characteristics, baseline data, and onset of postanesthetic shivering in mean (SD), minimum, maximum, and number (%)

	Nalbuphine group (n=75)	Tramadol group (n=76)	Ondansetron group (n=74)
Age (yrs.)	30.12 (5.36)	30.03 (5.18)	31.00 (5.49)
	[20, 42]	[20, 42]	[20, 43]
Weight (kg)	66.60 (9.35)	68.53 (9.40)	67.40 (9.75)
	[50, 100]	[50, 92]	[48, 99]
Height (cm)	155.81 (5.97)	157.10 (5.22)	155.27 (5.14)
	[140, 170]	[140, 170]	[143, 167]
BMI kg/m^2	27.49 (3.96)	27.82 (3.49)	27.89 (3.86)
	[21.10, 40.18]	[20.39, 35.49]	[19.78, 36.49]
ASA I/ASA II	72 (96%)*	74(97.4%)*	73(98.60%)*
	3 (4%)	2(2.6%)	1(1.40%)
Temperature in PACU (^oC)	23.19 (0.43)	23.29 (0.49)	23.35 (0.50)
	[22.4, 24.9]	[22, 25]	[22.5, 25.0]
Body Temperature(^oC)	36.48 (0.45)	35.37 (0.43)	36.39 (0.38)
	[35.1, 37.6]	[35.5, 37.3]	[35.4, 37.2]
Respiratory Rate (/min)	18.21 (0.70)	18.29 (0.71)	18.37 (0.86)
	[16, 20]	[18, 20]	[18, 22]
HR (/min)	81.55 (13.03)	79.53 (11.59)	81.65 (14.06)
	[59, 124]	[54, 112]	[58, 119]
SBP (mmHg)	114.37 (13.55)	115 (13.36)	111.80 (10.64)
	[91, 162]	[90, 147]	[91, 143]
DBP (mmHg)	67.09 (9.82)	67.92 (8.51)	65.36 (9.22)
	[50, 99]	[48, 90]	[42, 94]
$SatO_2$ (%)	98.43 (1.12)	98.61 (1.26)	98.63 (1.17)
	[95, 100]	[95, 100]	[95, 100]

Table 10: The demographic characteristics, baseline data, and onset of postanesthetic shivering in mean (SD), minimum, maximum, and number (%). (Continued)

	Nalbuphine group (n=75)	Tramadol group (n=76)	Ondansetron group (n=74)
Preoperative fluid (cc)	590 (173) [200, 1000]	635 (194) [200, 1,100]	588 (205) [60, 1000]
Intraoperative fluid (cc)	856 (345) [300, 2,650]	879 (297) [100, 1,800]	864 (262) [400, 1,500]
Postoperative fluid (cc)	141 (355) [0, 3000]	140 (192) [0, 1000]	122 (150) [0, 700]
Duration of Surgery (min)	52.67 (15.43) [35, 105]	52.83 (16.90) [20, 130]	48.38 (13.50) [30, 100]
Onset of postanesthetic shivering (min)	74.95 (34.92) [22, 160]	82.45 (37.80) [30, 180]	74.88 (33.69) [20, 180]

Value are expressed as mean (SD), [min, max], and number (%)

4.2 Primary outcome analysis

4.2.1 Treatment success rate

The treatment success rates for moderate to severe degree of postanesthetic shivering in nalbuphine, tramadol, and ondansetron groups were 81.3% (61 in 75 patients), 88.2% (67 in 76 patients), and 62.2% (46 in 74 patients) respectively. The result was considered statistically significant (p-value < 0.001) by chi-square test. The success rates between nalbuphine group and ondansetron group, tramadol group and ondansetron group in treatment of postanesthetic shivering were statistically significant different (p-value =0.009 and p-value < 0.001) by chi-square test with bonferroni correction for multiple comparison. The success rate between nalbuphine and tramadol was not statistically significant different (p-value = 0.243) as shown in table 11. The

differences of success rate between nalbuphine and ondansetron groups, tramadol and ondansetron groups, and nalbuphine and tramadol groups equaled to 19.1%, 95%CI (4.9,33.2), 26.0%, 95%CI (12.8,39.2), and 6.9%, 95%CI (-4.5,18.3) respectively.

4.2.2 Recurrence rate of moderate to severe shivering within 4 hour after first successful treatment.

The number of patients who need more antishivering agents within 4 hours after first successful treatment by either of intravenous nalbuphine or tramadol or ondansetron were 9/61, 9/67, and 6/46 respectively, as shown in table 12. The result was not statistically significant different (p-value = 0.963). Moreover, within 24 hours there was no further reported of shivering.

4.3 Secondary outcome analysis

4.3.1 Pruritus rating scale

Number of patients who have pruritus score = 2 were 6, 10 and 9 after administration of nalbuphine, tramadol, and ondansetron respectively, pruritus score = 3 were 0, 2 and 2 after administration of nalbuphine, tramadol, and ondansetron respectively, as shown in table 13, which was not statistically significant different (p-value = 0.280).

Most patients with pruritus score $\geq$ 3 were successfully treated by chlorpheniramine 10 mg. Intravenously.

4.3.2 Nausea/vomiting rating scale

Number of patients who have nausea/vomiting score 2 were 3, 3 and 1 after administration of nalbuphine, tramadol, and ondansetron respectively, as shown in table 13, which was considered non statistically significant different (p-value = 0.565).

Two patients in tramadol group with moderate nausea/vomiting (nausea/vomiting score $\geq$ 3) were successfully treated by metoclopramide 10 milligrams intravenously.

4.3.3 Sedation ration scale

There was no patient who has sedation score □ 2 in all groups after administration of nalbuphine, tramadol, and ondansetron.

4.3.4 Verbal numeric pain scale

There were not different among number of patients who have pain score □ 4 after administration of nalbuphine, tramadol, and ondansetron, as shown in table 13, which was not statistically significant different (p-value = 0.789).

4.3.5 Other side effects

Number of patients with dizziness after administration of nalbuphine, tramadol, and ondansetron were 1, 4, and 1 cases respectively, as shown in table 13, which was not statistically significant different (p-value = 0.245).

There was no extrapyramidal effect or respiratory depression observed in all groups of patients.

4.3.6 Apgar score

There was no neonate with Apgar score at 1 and 5 min less than 7 after delivery in all 3 groups.

Table 11: The treatment success rate of study drugs.

	Nalbuphine group	Tramadol group	Ondansetron group	P-value
Success	61 (81.3%)	67 (88.2%)	46 (62.2%)	< 0.001*
Failure	14 (18.7%)	9 (11.8%)	28 (37.8%)	
Total	75 (100%)	76 (100%)	74 (100%)	

Using Chi-square test

Table 12: The recurrence rate of moderate to severe shivering with in 4 hours after first successful treatment.

	Nalbuphine group	Tramadol group	Ondansetron group	P-value
Recurrence	9 (14.8%)	9 (13.4%)	6 (13.0%)	0.963
Non-recurrence	52 (85.2%)	58 (86.6%)	40 (87.0%)	
Total	61	67	46	

Using Chi-square test

Table 13: Frequency and percentage of side effects after treatment of postanesthetic Shivering

Side effects	Nalbuphine group (n=75)	Tramadol group (n=76)	Ondansetron group (n=74)	P-value
Pruritus rating scale				
1	69 (92%)	64 (84.2%)	63 (85.1%)	0.280
2	6 (8%)	10 (13.2%)	9 (12.2%)	
3	0	2 (2.6%)	2 (2.7%)	
4	0	0	0	
Nausea/vomiting rating scale				
1	72 (96%)	73 (96.1%)	73 (98.6%)	0.565
2	3 (4%)	1 (1.3%)	1 (1.4%)	
3	0	2 (2.6%)	0	
4	0	0	0	
Verbal numeric pain scale				
0	67 (89.3%)	67 (88.2%)	66 (89.2%)	0.789
1	3 (4%)	3 (3.9%)	3 (4.1%)	
2	2 (2.7%)	0	1 (1.4%)	
3	3 (4%)	5 (6.6%)	1 (1.4%)	
4	0	0	1 (1.4%)	
5	0	1 (1.3%)	2 (2.8%)	
Dizziness	1 (1.3%)	4 (5.3%)	1 (1.4%)	0.245

Data Express as number (%)

Using Kruskall Wallis test

4.5.3 Patient satisfaction outcome

The questionnaire for measuring patient satisfaction was assessed within 24 hours on the day after operation. The patients who were enrolled in this study were all adult females (age 20 – 43 years). All assessed the satisfaction with willingness to report their opinion. The data of patient satisfaction were shown in table 14.

Table 14: The frequency of the response rate of patient satisfaction score.

Question number	Very dissatisfied (1)	Somewhat dissatisfied (2)	Neither satisfied nor dissatisfied (3)	Somewhat satisfied (4)	Very satisfied (5)	Total
No. 1	-	-	3 (1.3%)	27 (12%)	195(86.7%)	225
No.2	-	4(1.8%)	25 (11.1%)	58 (25.8%)	138 (61.3%)	225
No.3	4 (1.8%)	12 (5.3%)	39 (17.3%)	59 (26.2%)	111 (49.3%)	225
No.4	-	7 (3.1%)	23 (10.2%)	65 (28.9%)	130 (57.8%)	225
No.5	-	-	15 (6.7%)	50 (22.2%)	160 (71.1%)	225

The assessment of patient satisfaction was done in 225 patients (nalbuphine group = 75, tramadol group = 76, and ondansetron group = 74). The majority of patients in all groups reported somewhat satisfied and very satisfied, there were 4 patients who reported very dissatisfied, which were only the satisfactions of analgesia and antishivering treatment questions. The satisfaction level of each item in all patients was shown in table 15. The satisfaction levels of each item in 3 groups have not statistically significant difference in item 1, 4, and 5. Only the 2 item 2 and 3 (analgesic effects and treatment of shivering) were considered statistically significant different (p-value = 0.016 and p-value < 0.001 respectively).

Table 15: The frequency of patient satisfaction with anesthesia care service provider.

Satisfaction question	Nalbuphine group (n=75)					Tramadol group (n=76)					Ondansetron group (n=74)					P-value
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	
Satisfied with spinal anesthetic	0	0	3 (4%)	8 (10.7%)	64 (85.3%)	0	0	0	13 (17.1%)	6 (82.9%)	0	0	0	6 (8.1%)	68 (91.9%)	0.245
Satisfied with postoperative analgesic	0	1 (1.3%)	9 (12%)	18 (24%)	47 (62.7%)	0	0	5 (6.6%)	17 (22.4%)	54 (71.1%)	0	3 (4.1%)	11 (14.9%)	23 (31%)	37 (50%)	0.016*
Satisfied with postanesthetic shivering therapy	0	4 (5.3%)	11 (14.7%)	18 (24%)	42 (56%)	1 (1.3%)	2 (2.6%)	7 (11.8%)	19 (25%)	45 (59.2%)	3 (4.1%)	6 (8.1%)	19 (25.7%)	22 (29.7%)	24 (32.4%)	<0.001*
Satisfied with treatment of postanesthetic side effects	0	3 (4%)	9 (12%)	22 (29.3%)	41 (54.7%)	0	3 (3.9%)	6 (7.9%)	24 (31.6%)	43 (56.6%)	0	1 (1.4%)	8 (10.8%)	19 (25.7%)	46 (62.2%)	0.605
Satisfied with the care provided by the department of anesthesiology in general	0	0	4 (6%)	19 (25%)	52 (69%)	0	0	6 (7.9%)	14 (18.4%)	56 (73.7%)	0	0	5 (6.8%)	17 (23%)	52 (70.2%)	0.890

* Using Kruskall Wallis test (p-value = 0.05)

Note: 1 = very dissatisfied, 2 = somewhat dissatisfied, 3 = neither satisfied nor dissatisfied, 4 = somewhat satisfied, 5 = very satisfied

CHAPTER 5

DISCUSSION, CONCLUSION, AND RECOMMENDATION

5.1 Discussion

Nowadays, spinal anesthesia is a safe and an increasingly popular anesthetic technique for elective cesarean section, because of its rapid onset, using low dose of local anesthetic and postoperative analgesia provided by intrathecal morphine. However, a common side effect after intrathecal administration of local anesthesia has been development of shivering. Shivering, as nausea/vomiting or pruritus never becomes chronic and it is unlikely to kill a patient. However, in postanesthetic shivering patients, left ventricular systolic work index and oxygen consumption index may increase. (75)

This study revealed a 51.09% incidence of postanesthetic shivering with 30.57% of postanesthetic shivering requiring treatment (shivering score □ 3), confirming previous studies. (1,2,4,5,7,15,48) Since postanesthetic shivering usually occurred within a few hours after spinal anesthesia, therefore we observed the patients for 2 hours in the postanesthesia care unit to enroll all patients with postanesthetic shivering. The number of nalbuphine group (n = 75), tramadol group (n = 76), and ondansetron group (n = 74) were not exactly equal because simple randomization could not guarantee the equal number in each group.

The mechanism of shivering under regional anesthesia is not fully understood. Possible contributing factor is a decrease in core temperature. A decrease in core temperature may be due to sympathetic blockade, which results in peripheral vasodilatation, increased cutaneous blood flow, and subsequent increased heat lost via skin. (76) Other reasons may be a cold operating room temperature, (77) or the direct effects of cold anesthetic solutions upon thermosensitive structures within the spinal cord. As well, local anesthetics introduced into the extradural space might modify

environmental thermal cues, with resultant in appropriate thermal response to false information. Treatment modalities have included covering the patient with blankets, application of radiant heat and warm the operating room suite. (78) The use of warm local anesthetic solution or warm intravenous fluid (79) has met with varying degrees of success. Addition of various opioids extradurally also reduced the incidence of shivering. (80) Moreover, several hypotheses have also been raised to explain the occurrence of postanesthetic shivering. These included postoperative pain, perioperative heat lost, the direct effect of certain anesthetics, hypoxia, hypercapnia or respiratory alkalosis, the existence of pyrogens, early recovery of spinal reflex activity and sympathetic overactivity. On the basis of several factors, we can assume that there is a relationship between a possible early recovery of spinal reflex activity facilitated by the residual effect of anesthetics on the inhibiting control exercised by supra spinal structures and the incidence of postanesthetic shivering. (39)

The study was designed to standardize these possible confounding factors while reflecting the usual practice in our institution. Postanesthesia care unit temperature was held about 22-25 ^{o}C, intravenous fluid and drugs were administered at room temperature and a blanket was used for all patients to cover the whole body. Body temperature was also recorded at the beginning of postanesthesia care unit. All patients received intrathecal morphine for postanesthetic analgesia.

Demographic data such as age, weight, height, body mass index, and ASA physical status were similar in all three groups. The postanesthetic care unit temperature and body temperature, vital signs, and oxygen saturation were also not different among three groups. The amount of intravenous fluid, preoperative fluid, intraoperative fluid, postoperative fluid and duration of surgery among three groups were not different which were considered non statistical significant (p-value = 0.239, p-value = 0.889, p-value = 0.881, and p-value = 0.136) respectively.

The measurement tool for postanesthetic shivering,(22,49,62,63) sedation, (49,64) nausea or vomiting, (49,66) pruritus, (49,65) and pain level (49,53,67)was according to previous studies. As shivering is the primary outcome, we also tested for inter-rater agreement (weighted kappa = 0.9444), which was considered as a very good agreement. (71)

In this study, we were able to demonstrate that the success rate of treatment with 0.05 mg/kg nalbuphine, 0.5 mg/kg tramadol, and 0.1 mg/kg ondansetron were statistically significant different (p-value < 0.001). The success rate of treatment with nalbuphine was also significantly greater than ondansetron: 81.3% VS 62.2% (p-value = 0.009), the result was confirmed by difference of success rate equaled to 19.1% with 95% confidence interval of 4.9 to 33.2. The success rate of treatment with tramadol was significantly greater than ondansetron: 88.2% VS 62.2% (p-value < 0.001), the result was confirmed by difference of success rate equaled to 26% with 95% confidence interval of 12.8 to 39.2. However success rate of nalbuphine and tramadol groups was not different which was considered non statistically significant (p-value = 0.243), the result was confirmed by difference of success rate equaled to 6.9% with 95% confidence interval of -4.5 to 18.3.

Therefore, this study indicated that both nalbuphine and tramadol were more effective than ondansetron for treating post spinal anesthetic shivering in the parturient undergoing cesarean section.

The success rate of nalbuphine group and tramadol group was corresponding to previous study. Wang et al. showed that 0.05 mg/kg nalbuphine was effective for treating postanesthetic shivering after general anesthesia with 80% success rate.(16) Chan et al. showed that 80% of parturient who develop shivering after regional anesthesia were successfully treated by 0.5 mg/kg tramadol.(22) Tsai et al. showed that 0.5 mg/kg tramadol was effective for treating postepidural anesthetic shivering in parturients with 87% success rate in 15 min.(81) The success rate for treatment of postanesthetic shivering with ondansetron in this study was 62.2%, which was less effective than nalbuphine and tramadol groups (p-value = 0.009 and p-value < 0.001 respectively). Powell et al. performed a randomized, placebo control double blind study to evaluate the effect of ondansetron given before the induction of anesthesia, the prevention success rate for shivering by 4 mg ondansetron was 67% (23) which was comparable to the success rate of treatment of 62.2% in our study.

Among the successfully treated patients, 9 of 61 (14.8%) in the nalbuphine group, 9 of 67 (13.4%) in tramadol group and 6 of 46 (13%) in the ondansetron group reported recurrence of moderate to severe shivering (shivering score $\geq$3) within 4 hours

after first successful treatment, which were not statistically significant different (p-value = 0.963). From a recent systematic review of pharmacological treatment of postanesthetic shivering, (82) there was a direct relationship between the length of observation period and success rate of treatment of shivering. The relative risk for further shivering compared with placebo decreased overtime, i.e., the antishivering efficacy decreased with increases in length of the observation period. (82) Therefore, this was the first study to observe long-term outcome for 4 hours after treatment. Moreover, there was no further reported of shivering in all three groups within 24 hours.

The pruritus rating score, sedation rating score, nausea/vomiting rating score, and verbal numeric pain score in all three groups were not statistically significant different. No patient in any group developed sedation or desaturation after injection of the study drugs (nalbuphine, tramadol, and ondansetron). Only two patients in tramadol group required metoclopramide as antiemetic after treatment, but the different were also not statistically significant (p-value = 0.560) when compared with other two drugs. No patient in all three groups developed extrapyramidal effect after injection of study drugs. Moreover, some reported side effects associated with ondansetron such as headache, abdominal pain, and cardiac arrhythmias were not observed. There were no reported of respiratory depression and hallucination in our study.

Pharmacologic drugs remain the most popular mode for treatment and prevention of shivering. Pethidine is a commonly used medication for controlling shivering in patients without neuraxial opioids administration. The mechanism of pharmacologic anti-shivering effect has yet to be fully elucidated. Intravenous pethidine controlled shivering better than equianalgesic dose of pure μ-opioid agonist such as fentanyl, alfentanyl, sufentanyl, or morphine. The anti-shivering effects of pethidine were not reversed by small dose naloxone, which blocks most μ-opioid receptors, but they were reversed by large dose of naloxone, (14,83) which block both μ-receptors and κ-receptors. These data suggest that κ-opioid receptor may play a more important role than μ-opioid receptors in the treatment of postanesthetic shivering. Nalbuphine, a semisynthetic opioid related to both naloxone and oxymorphone, has the characteristics of μ-antagonist and κ-agonist activity. It has high affinity to κ-opioid receptors in the central nervous system. (84) Theoretically, nalbuphine may have significant effect on

postanesthetic shivering. In this study, we found that nalbuphine demonstrated a potent antishivering effect on postanesthetic shivering. Tramadol is an analgesic with agonist properties on opioid receptors. Tramadol also activates the monoaminergic receptors of the descending spinal inhibitory pathway of pain. The main opioid effect of tramadol is mediated via μ-receptor with minimal effect at κ-receptor. (85) In similar to pethidine used to treat postanesthetic shivering, tramadol has a potent antishivering effect which its κ-receptors activity. Moreover, tramadol inhibits the neuronal reuptake of norepinephrine and 5-hydroxytryptamine and facilitates 5-hydroxytryptamine releases. Each of these actions is likely to influence a thermoregulatory control. However, tramadol had only slight thermoregulatory effects. Thus, it is unlikely to provoke hypothermia or to facilitate fever. Another potent antinociceptive effect of tramadol is significant decreasing α_2-adrenoceptor antagonists, which is in this respect; tramadol is similar to clonidine, a partial α_2-adrenoceptor agonist that is also useful in the treatment of postanesthetic shivering. (48) Therefore, the interaction of κ-opioid and α2-adrenoceptor mechanism working in a complementary on synergistic manner to produce antishivering effect seems to be a possible explanation. Ondansetron has been shown to produce a dose dependent reduction in shivering by given before induction of general anesthesia. (23) The possible explanation of its action is a specific $5HT_3$ receptor antagonist which giving the variety on neurotransmitter system, known to be also involved in regulating shivering. An inhibitory effect at the $5\text{-}HT_3$ receptors probably results from a generalized thermoregulatory inhibition at the level of hypothalamus, where the bulk of thermoregulatory control occurs. (23)

In contrast to some other drugs used to treat postanesthetic shivering, we found that our study drugs (nalbuphine, tramadol, and ondansetron) have innocuous effect on the cardiovascular system and other systems. While, clonidine may be associated with significant hypotension, bradycardia, and sedation. (48) Doxapram is associated with significant hemodynamic effects. (20) Physostigmine increased heart rate and blood pressure, which may be detrimental to myocardial oxygen demand in some patients with coronary artery insufficiency.(21) Pethidine increases the risk of respiratory depression, nausea/vomiting, and sedation than other opioids at equivalent dosages.

Like other clinically oriented outcomes, patient satisfaction is a valid patient related outcome measurement. With the emphasis on patient centered medical care, patient satisfaction has become an important indicator of quality of medical care. However, there are many questions regarding the methodology of measuring patient satisfaction, reflecting the fact that the concept of patient satisfaction is multidimensional and quite complex. Moreover, the perception of patients, along with quality assurances, is an important component of the evaluation of the quality of service in medical care. Even though perceptions are subjective, this information is important to health care provider. The secondary objective of this project was to determine whether the satisfaction questionnaire could detect difference in maternal satisfaction among three study drugs for treatment of postanesthetic shivering after intrathecal morphine. As patient satisfaction is secondary outcome, we also have constructed new questionnaire for evaluation of outcome of treatment. Our newly constructed questionnaire was tested for content validity by 3 experts, which was acceptable. The reliability of this questionnaire was also tested in pilot study of 30 patients with the reliability coefficient of 0.8003. The value was acceptable based on the cut point of 0.7 set for internal consistency. (68)

Analyses of the data demonstrated high maternal satisfaction in all three groups and in all questions (almost of patients in study group reported satisfaction score $\geq$ 4). There were: 1) For the satisfaction with spinal anesthesia; 96% in nalbuphine group, 100% in tramadol group, and 100% in ondansetron group reported the satisfaction score $\geq$ 4. 2) For the satisfaction with postanesthetic analgesia showed that 86.7% in nalbuphine group, 94.4% in tramadol groups, and 81% in ondansetron group reported the satisfaction score $\geq$ 4. 3) For the satisfaction with postanesthetic shivering therapy; the patient reported high level of satisfaction (satisfaction score $\geq$ 4) in nalbuphine and tramadol groups which was 80% and 84.2% respectively, while only 62.2% in ondansetron group reported satisfaction score $\geq$ 4). For the satisfaction with the treatment of postanesthetic side effect; 84.4% in nalbuphine group, 88.2% in tramadol group, and 87.9% in ondansetron group reported high level of satisfaction (satisfaction score $\geq$ 4). And for the overall satisfaction with the care provided by the Department of

Anesthesiology, 94%, 93.1%, and 93.2% of patients reported satisfaction score $\geq$ 4 in nalbuphine, tramadol, and ondansetron groups respectively. The high level of patient satisfaction score in all three group and in all questions were consistent with previous study. (86, 87, 88, 89) Cherian et al. suggested that the high level of satisfaction in maternal after cesarean section could partly be a result of the euphoria of having a new baby and to the extra attention given by a sympathetic investigator who spent extra time with them. (86) Wu et al concluded that there are several advantages of regional anesthesia, including superior postanesthetic analgesia, which increased in higher level of patient satisfaction. Patient receiving a postoperative regional analgesia technique (epidural analgesia or spinal analgesia) generally had lower VAS pain score and a high level of satisfaction at the same time. (87) Borgeat et al showed that patient who have lower incidence of side effects with regional analgesic technique may also have higher levels of satisfaction. (88) Morgan et al studied in healthy obstetric patient, he conducted that expectations for an excellent experience are high, quality assurance audits of the obstetric experience have frequently included satisfaction parameters, and the response of patients in this group of patients is high level too. (89)

In present study, we compared the patient satisfaction among 3 groups of treatment. We found that there were statistically significant different in question of the satisfaction with postanesthetic analgesia and the satisfaction with postanesthetic shivering therapy, which was considered statistically significant different (p-value = 0.016 and p-value < 0.001 respectively). Then we compare the patient satisfaction between groups by using Mann-Whitney U test. The result showed that: the satisfaction with postanesthetic analgesia in tramadol was significant different greater than in ondansetron group, which was considered statistically significant different (p-value = 0.004). And the satisfaction with postanesthetic shivering therapy in nalbuphine and tramadol groups was both statistically significant greater than in ondansetron group (p-value = 0.002 and p-value < 0.001 respectively). The successful rates of postanesthetic shivering treatment with nalbuphine and tramadol were both greater than in ondansetron group, therefore the patients in nalbuphine and tramadol group reported higher satisfaction score than in ondansetron group. However, it was rather difficult to explain about the satisfaction with postanesthetic analgesia because in our study, no difference

was noted among the numeric pain score among 3 study groups. This may be due to statistical difference without clinical significant difference. Another explanation is satisfaction is complex; one who feels comfort and gets improvement from shivering may also give high satisfaction score with postanesthetic analgesia. On the other hand, whenever they still have moderate to severe shivering, the patient will give low score for the other satisfaction's question too. This result is consistent with previous study by Morgan et al having noted the difference in maternal satisfaction related to the side effects they got, the lower side effect they got, the higher satisfied they are. (89)

5.2 Conclusion

This study showed that 0.05 mg/kg nalbuphine and 0.5 mg/kg tramadol are superior to 0.1 mg/kg ondansetron for treatment of postanesthetic shivering after intrathecal morphine for cesarean section patients. The recurrence rate among three groups were not statistically significant different. The side effects were not significantly different between groups. When focusing on the patient satisfaction about treatment of shivering, this study also showed that the patients in nalbuphine group and tramadol group had higher satisfaction score than in ondansetron group. There were not statistically significant differences in the satisfaction with spinal anesthetic, satisfaction with treatment for other postanesthetic side effects and the satisfaction with the care provided by the department of anesthesia in general. However, the patients in all three groups rated high satisfaction score of care provided by the Department of Anesthesiology.

5.3 Recommendation

The author would recommend that 0.5 mg/kg tramadol and 0.05 mg/kg nalbuphine administered intravenously are suitable for treatment of postanesthetic shivering after intrathecal morphine for cesarean section patients. Further study about economic analysis of the study drugs or factors related to incidence of shivering and efficacy study of the 3 drugs among non-obstetric patients should be considered.

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APPENDICES

APPENDIX 1

ASA PHYSICAL STATUS CLASSIFICATION

ASA 1	A normal healthy patient
ASA 2	A patient with a mild systemic disease (mild diabetes, controlled hypertension, anemia, chronic bronchitis, morbid obesity)
ASA 3	A patient with a severe systemic disease that limits activity (angina, obstructive pulmonary disease, prior myocardial infarction)
ASA 4	A patients with an incapacitating disease that is a constant threat to life (heart failure, renal failure)
ASA 5	A moribund patient not expected to survive 24 hours (ruptured aneurysm, head trauma with increasing intracranial pressure)

For emergency operation, add the letter E before classification

APPENDIX 2

ข้อมูลที่ผู้ป่วยควรทราบ (Patient Information sheet)

ชื่อโครงการ การศึกษาเปรียบเทียบประสิทธิผลของนาลบูฟีน 0.05 มก./กก. ทรามาดอล 0.5 มก./กก. และออนแดนซีตรอน 0.1 มก./กก. ในการรักษาอาการสั่นภายหลังได้รับมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้อง

สถานที่ทำวิจัย โรงพยาบาลจุฬาลงกรณ์

ผู้ทำการวิจัย นายเดชา ทำดี

อาจารย์ที่ปรึกษา รองศาสตราจารย์นายแพทย์สมรัตน์ จารุลักษณานันท์
รองศาสตราจารย์ดอกเตอร์ศิริวรรณ ไกรสุรพงศ์

บทนำ

การผ่าตัดคลอดเด็กทางหน้าท้องในโรงพยาบาลจุฬาลงกรณ์ ส่วนใหญ่กว่าร้อยละ 90 จะได้รับการให้ยาระงับความรู้สึกโดยการฉีดยาชาและมอร์ฟีนเข้าช่องไขสันหลังซึ่งมีผลดีต่อมารดาและทารก ได้แก่การที่มารดาไม่รู้สึกเจ็บปวดเป็นเวลา 24 ถึง 36 ชั่วโมงภายหลังการผ่าตัด และมารดาสามารถเคลื่อนไหวและดูแลทารกได้โดยเร็ว เนื่องจากมีความเจ็บปวดน้อย อย่างไรก็ตามภายหลังการได้รับยาระงับความรู้สึกอาจเกิดอาการสั่น ซึ่งสถิติในโรงพยาบาลจุฬาลงกรณ์พบได้ถึงร้อยละ 60 และโดยร้อยละ 40 สมควรได้รับการรักษา ที่ผ่านมามีการศึกษาวิจัยเกี่ยวกับยาซึ่งใช้รักษาอาการสั่นหลังผ่าตัดเป็นจำนวนมาก แต่การศึกษาเฉพาะในผู้ป่วยที่ได้รับมอร์ฟีนเข้าช่องไขสันหลังสำหรับระงับปวดมีน้อย ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และคณะพยาบาลศาสตร์ มหาวิทยาลัยเชียงใหม่ จึงเห็นสมควรศึกษาเพื่อหายาที่เหมาะสมและปลอดภัยในการรักษาอาการสั่น ซึ่งเป็นอาการที่พบได้บ่อยหลังการผ่าตัดคลอดเด็กทางหน้าท้อง

ยาที่ทำการศึกษาเปรียบเทียบได้แก่ ยานาลบูฟีน และยาทรามาดอล ซึ่งเป็นยาที่ใช้แพร่หลายในประเทศไทยมานานกว่า 10 ปี ซึ่งนอกจากมีฤทธิ์บรรเทาอาการปวด อาการคัน และยังรักษาอาการสั่นได้ด้วย ส่วนยาออนแดนซีตรอนนั้นเป็นยาที่ศึกษาพบว่าสามารถใช้ป้องกันการเกิดอาการสั่นในคนไข้หลังผ่าตัดทำคลอดทางหน้าท้องและสามารถใช้รักษาอาการคลื่นไส้และอาเจียนได้อีกด้วย และในกรณีที่การรักษาไม่ได้ผลจะได้รับยาอื่นได้แก่ยาพรอพโพฟอล และการดูแลจากวิสัญญีแพทย์โดยใกล้ชิด

ท่านได้รับเชิญให้เข้าร่วมในโครงการศึกษาวิจัยนี้ท่านควรอ่านและทำความเข้าใจรายละเอียดก่อนตัดสินใจเข้าร่วมโครงการวิจัย

วัตถุประสงค์

1. เพื่อเปรียบเทียบประสิทธิผลของนาลบูฟีน 0.05 มก./กก. ทรามาดอล 0.5 มก./กก. และออนแดนซีตรอน 0.1 มก./กก. ในการรักษาอาการสั่นภายหลังการได้ยามอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้อง

2. เพื่อศึกษาเปรียบเทียบอาการข้างเคียงที่เกิดขึ้นภายหลังจากการได้รับยาในการรักษาอาการสั่นไปแล้ว เช่น อาการคลื่นไส้อาเจียน อาการคัน ฤทธิ์ในการกดประสาทของยา การกดศูนย์การหายใจ เป็นต้น

3. เพื่อประเมินระดับความพึงพอใจของผู้ป่วยต่อการได้รับยาระงับความรู้สึก การระงับอาการปวด การรักษาอาการสั่น การรักษาอาการคัน การรักษาอาการคลื่นไส้อาเจียน และระดับความพึงพอใจต่อการได้รับบริการโดยรวมของแผนกวิสัญญีวิทยา

วิธีการและระยะเวลา

การศึกษาเพื่อเปรียบเทียบประสิทธิผลของยาในการรักษาอาการสั่นนี้ จะใช้วิธีการฉีดยาเข้าเส้นเลือดดำให้ผู้ป่วยเมื่อเกิดอาการสั่นถึงระดับที่ต้องการการรักษาเท่านั้น (ซึ่งการประเมินอาการสั่นนั้นจะประเมินโดยแพทย์และพยาบาล) และจากนั้นจะมีการติดตามประเมินอาการสั่นอย่างใกล้ชิดทุก 15 นาที เป็นเวลาอย่างน้อย 2 ชั่วโมง และเมื่ออาการสั่นไม่ดีขึ้นจะมีการให้ยาซ้ำเพื่อรักษาอาการสั่นให้ดีขึ้น เมื่อผู้ป่วยหายสั่นและอาการดีขึ้นจะมีการซักประวัติและเก็บรวบรวมข้อมูลเบื้องต้นต่างๆ หลังจากนั้นจะมีการติดตามประเมินผลผู้ป่วยต่ออีกครั้งภายใน 24 ชั่วโมงเพื่อติดตามอาการข้างเคียงต่างๆและเพื่อประเมินระดับความพึงพอใจของผู้ป่วยด้วย

จำนวนผู้เข้าร่วมโครงการ

จะมีผู้ป่วยเข้าร่วมโครงการนี้ทั้งสิ้นประมาณ 225 ราย

คุณสมบัติของผู้เข้าร่วมโครงการ

เป็นผู้ป่วยหลังได้รับยาชาและมอร์ฟีนเข้าช่องไขสันหลัง เพื่อผ่าตัดทำคลอดทางหน้าท้องที่มีอาการสั่นในระดับที่ต้องการการรักษา ซึ่งได้รับการประเมินระดับของอาการสั่นโดยแพทย์และพยาบาลผู้ทำวิจัย โดยผู้ป่วยจะต้องไม่มีประวัติแพ้ยานาลบูฟีน ยาทรามาดอล ยาออนแดนซีตรอน และมอร์ฟีน นอกจากนั้นต้องไม่มีประวัติเคยเจ็บป่วยด้วยโรคที่เกี่ยวกับอาการสั่น เช่น มาลาเรีย คอพอกเป็นพิษ โรคชัก และโรคทางระบบประสาทอื่นๆด้วย

การรักษาความลับ

ข้อมูลทางการแพทย์ของท่านจะถูกเก็บเป็นความลับ โดยแพทย์ผู้ทำการศึกษาและเจ้าหน้าที่โครงการจะไม่นำมาเปิดเผยต่อสาธารณะ ยกเว้นการเปิดเผยนั้นจะเป็นที่ต้องการทางกฎหมาย

ข้อมูลที่ได้รับจากการศึกษาในส่วนที่ไม่ได้ระบุความเป็นตัวของท่าน อาจถูกนำออกเปิดเผยเป็นผลงานวิจัยในประเทศไทยหรือต่างประเทศเพื่อเผยแพร่ความรู้ทางการแพทย์

คณะกรรมการจริยธรรมของการศึกษานี้ และหน่วยงานที่มีหน้าที่รับผิดชอบอาจทบทวนบันทึกข้อมูลทางการแพทย์ของท่านที่เก็บไว้ในโรงพยาบาล โดยมีวัตถุประสงค์เพื่อตรวจดูความถูกต้องของข้อมูลและวิธีการต่างๆของการศึกษาวิจัย และข้อมูลทางการแพทย์ของท่านอาจถูกนำไปจัดเก็บไว้ในคอมพิวเตอร์

จากการที่ท่านลงนามในเอกสารนี้ ท่านอนุญาตให้ดูบันทึก เก็บข้อมูล และโอนย้ายข้อมูลดังกล่าวข้างต้น

การลงนาม

เพื่อเข้าร่วมโครงการศึกษาวิจัย ท่านหรือผู้แทนโดยชอบด้วยกฎหมายต้องลงนามพร้อมวันที่ในกระดาษที่แนบด้วยกันนี้

กรณีที่มีข้อสงสัยท่านสามารถติดต่อ นายเดชา ทำดี ได้ที่หมายเลขโทรศัพท์ 01-3831092 หรือ รองศาสตราจารย์นายแพทย์สมรัตน์ จารุลักษณานันท์ ใบประกอบวิชาชีพเวชกรรมเลขที่ 7-12297 ได้ที่ภาควิชาวิสัญญีวิทยาหมายเลขโทรศัพท์ 02-2564215 และ 02-2544295

APPENDIX 3

CONSENT FORM

ใบยินยอมของผู้เข้าร่วมโครงการวิจัย

การวิจัยนี้เป็นการศึกษาของภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ร่วมกับ คณะพยาบาลศาสตร์ มหาวิทยาลัยเชียงใหม่ โดยการศึกษานี้คณะผู้วิจัยได้ทำการศึกษาเพื่อเปรียบเทียบประสิทธิผลของยานาลบูฟีน ยาทรามาดอล และยาออนแดนซีตรอนในการระงับอาการสั่น ซึ่งเป็นอาการที่พบได้บ่อยมากภายหลังการฉีดยาชาเข้าช่องไขสันหลังสำหรับการผ่าตัดทำคลอดทางหน้าท้อง

ยานาลบูฟีน และยาทรามาดอล เป็นยาที่มีการศึกษาพบว่ามีประสิทธิภาพในการรักษาอาการสั่นในคนไข้หลังผ่าตัดทำคลอด มีอาการข้างเคียงต่อคนไข้น้อยมาก และมีใช้ในประเทศไทยมานานกว่า 10 ปีแล้ว ส่วนยาออนแดนซีตรอนนั้นเป็นยาที่มีการศึกษาพบว่าสามารถใช้ป้องกันการเกิดอาการสั่นในคนไข้หลังผ่าตัดทำคลอดทางหน้าท้อง

ทางผู้วิจัย ขอเชิญท่านเข้าร่วมโครงการวิจัยครั้งนี้ โดยความ **<u>สมัครใจ</u>** ของตัวท่านเอง

ถ้าท่านตกลงเข้าร่วมโครงการ ท่านจะได้รับการดูแลตามปกติที่ได้รับจากโรงพยาบาลจุฬาลงกรณ์ โดยไม่มีค่าใช้จ่ายเพิ่มเติม

ถ้าท่านไม่เข้าร่วมโครงการ ท่านยังคงได้รับการดูแลตามปกติที่ได้รับจากโรงพยาบาลจุฬาลงกรณ์เช่นเดิม

ท่านสามารถตัดสินใจเข้าร่วมโครงการหรือไม่ก็ได้ โดยความสมัครใจโดยจะไม่มีผลกระทบใดๆต่อการดูแลด้านการแพทย์ของโรงพยาบาล

ข้าพเจ้าได้อ่านข้อมูลด้านบนแล้ว และได้รับการอธิบายจากคณะผู้ทำวิจัย และสมัครใจเข้าร่วมโครงการ

.....	.....	.....
(ชื่อผู้ป่วย)	(ลายเซ็นต์)	(วันที่)
.....	.....	.....
(ผู้ทำวิจัย)	(ลายเซ็นต์)	(วันที่)
.....	.....	.....
(ชื่อพยาน)	(ลายเซ็นต์)	(วันที่)

APPENDIX 4

CASE RECORD FORM

Title: Comparison the efficacy between 0.05 mg/kg nalbuphine, 0.5 mg/kg tramadol and 0.1 mg/kg ondansetron in treatment of postanesthetic shivering after intrathecal morphine for cesarean delivery.

Protocol:……..……Code:……..……..……Date: ....../……/……..…

Firstname:……..…Lastname:……..……Age……years.HN:…….

Ward:……Weight…..……..……kg.Height.……cm.BMI …….…… kg/m^2

Duration of surgery ……min. Pre-operative fluid ……ml. Intraoperative fluid ……ml.

Postoperative fluid (postop. Until shivering occured) ……..ml.

Indication: ……Time of spinal block: ……

Time of admission to postanesthetic care unit.……..

Recovery room temperature ……^{0}C

Vital sign: T= ……^{0}C RR=……/min HR=……../min BP=……mmHg. O_2 sat= ..……%

APGAR score: at 1 min…… at 5 min …… ASA …….

Selection of subjects

Inclusion criteria: Each subject must fulfill all of the following criteria for entrance into study.

Criteria	yes	no
1. post cesarean section patients of ASA physical status 1 or 2	☐	☐
2. Scheduled to have the cesarean section under spinal anesthesia with intrathecal morphine.	☐	☐

Note: A "NO" for any inclusion criteria is sufficient to exclude the subject.

Exclusion criteria

Fulfillment of any of the following criteria will exclude the subject from the study.

Criteria	yes	no
1.Contraindication for regional anesthesia.	☐	☐
2.History of allergy to nalbuphine, tramadol, ondansetron or morphine.	☐	☐
3.History of any disease associated with shivering such as Malaria, Thyroid, Epilepsy, and etc.	☐	☐
4.History of any disease associated with neurobehavioral.	☐	☐
5. Patient who does not agree to participate in the study.	☐	☐
6. Patient who is unable to understand how to rate the measurement scale such as verbal numeric pain scale.	☐	☐

Note: A "YES" for any exclusion criteria is sufficient to exclude the subject.

Data collection from for postanesthetic shivering after intrathecal morphine for cesarean section patients.

Code .....

Events (shivering)

Time of shivering .....

Time of treatment .....

Time of successful treatment .....

Event	Pretreatment score	Post treatment score	Remarks
Shivering			
Pruritus			
Nausea and vomiting			
Sedation			
Pain			

Recurrent of shivering grade 3 or 4: with in 4 hours after first successful treatment

☐ **Yes, at time** .....

☐ **No**

Other side effects:

- Dizziness ☐ No ☐ Yes, at time.....
- Extrapyramidal effects ☐ No ☐ Yes, at time.....
- Respiratory depression
  (Respiratory rate < 10 t/min) ☐ No ☐ Yes, at time.....
- others:.....
  .....

Shivering	sedation	pruritus	Nausea/vomiting
1=no shivering	1=fully awake	1=no pruritus	1=no nausea/vomiting
2=mild shivering	2=somnolent,responds to call	2=minimal pruritus	2=queasy
3=moderate shivering	3=somnolent,responds to tactile	3=moderate pruritus	3=severe nausea
4=severe shivering	4=asleep,responds to pain	4=severe pruritus	4=vomiting

APPENDIX 5

Satisfaction scale (Thai Version)

แบบสอบถามความพึงพอใจในการได้รับบริการทางวิสัญญีในผู้ป่วยผ่าตัดทำคลอดทางหน้าท้อง

Code ……..

คำชี้แจง: ให้ใส่เครื่องหมาย ✓ในช่องที่ท่านเห็นด้วยมากที่สุด

ข้อคำถาม	มากที่สุด (5)	มาก (4)	ปานกลาง (3)	น้อย (2)	น้อยที่สุด (1)
1.ท่านรู้สึกพึงพอใจในการให้ยาระงับความรู้สึกทางช่องไขสันหลัง					
2. ท่านรู้สึกพึงพอใจต่อการบรรเทาความเจ็บปวดหลังการผ่าตัด					
3.ท่านรู้สึกพึงพอใจในการให้ยารักษาอาการสั่นหลังการผ่าตัด					
4. ท่านรู้สึกพึงพอใจต่อการรักษาอาการข้างเคียงอื่นๆหลังการผ่าตัด					
5. ท่านรู้สึกพึงพอใจต่อการให้บริการของแผนกวิสัญญี					

APPENDIX 6

Satisfaction scale (English Version)

Questionnaires on patient satisfaction with anesthesia service

The following questions are questionnaires about your satisfaction with anesthesia service. Please mark ✓ the appropriate choice.

Items	Very satisfied (5)	Some-what satisfied (4)	Neither satisfied nor dissatisfied (3)	Some-what dissatisfied (2)	Very dissatisfied (1)
1. How satisfied were you with the spinal anesthetics?					
2. How satisfied were you with postoperative analgesia?					
3. How satisfied were you with postanesthetic shivering therapy?					
4. How satisfied were you with treatment of other postanesthetic side effects?					
5. How satisfied were you with the care provided by the department of anesthesia in general?					

VITAE

Mr. Decha Tamdee was born on February 1, 1971 in Phayao, Thailand. He got his Bachelor degree of Nursing Science (Nursing and midwifery) from Faculty of Nursing, Chiang Mai University in 1994, and Certificate of Occupational Health Nursing Department of Public health Nursing, Faculty of Nursing, Chiang Mai University, in 2000.

Since June 2001, he has been admitted in the Master degree Program of Health Development in Thai-CERTC, Faculty of Medicine, Chulalongkorn University, as funded by the Faculty of Nursing Chiang Mai University. During this course, he has conducted a clinical trial comparison the efficacy of nalbuphine, ondansetron, and tramadol in treatment of postanesthetic shivering after intrathecal morphine for cesarean delivery patients.

Presently, he has been working as the instructor in the Department of public Health Nursing, Faculty of Nursing, Chiang Mai University.