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COMPARISON OF EFFICACY BETWEEN 20 MG PROPOFOL AND 3 MG NALBUPHINE IN TREATMENT OF INTRATHECAL MORPHINE INDUCED PRURITUS IN CAESAREAN-SECTION PATIENTS

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วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิผลของการใช้ยาพรอโพฟอล 20 มิลลิกรัม กับยานาลบูฟีน 3 มิลลิกรัม ฉีดเข้าเส้นเลือดในการรักษาอาการคัน ซึ่งเกิดขึ้นจากการฉีดมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดคลอดเด็กทางหน้าท้อง

รูปแบบการทดลอง : การทดลองทางคลีนิคแบบสุ่มทดลองโดยมีกลุ่มเปรียบเทียบ

สถานที่ทำการวิจัย : โรงพยาบาลจุฬาลงกรณ์ ซึ่งเป็นโรงพยาบาลระดับตติยภูมิ

วิธีการศึกษา : ผู้ป่วยหลังการผ่าตัดคลอดเด็กทางหน้าท้อง ซึ่งเกิดอาการคันจากการฉีดมอร์ฟีนเข้าชั้นไขสันหลัง 181 คน ได้รับการสุ่มแบ่งกลุ่มด้วยการสุ่มแบบธรรมดาเป็น 2 กลุ่ม กลุ่มแรกได้ยา พรอโพฟอล 20 มล. กลุ่มที่ 2 ได้ยานาลบูฟีน 3 มก. ฉีดเข้าหลอดเลือดดำ ประเมินผลการรักษาอาการคันและผลข้างเคียงอื่น ๆ ที่ 10 นาที ภายหลังการบริหารยา

ผลการศึกษา : การฉีดยานาลบูฟีนได้ผลในอัตราสูงกว่าพรอโพฟอล (83.5 % ต่อ 61.1 %, P = 0.0008) โดยมีอัตราการเกิดอาการคันซ้ำภายใน 4 ชั่วโมง หลังการรักษาครั้งแรกสำเร็จไม่แตกต่างกัน (นาลบูฟีน 9.2 % ขณะที่พรอโพฟอล 7.3 %, P = 0.7603) สำหรับอัตราการเกิดอาการข้างเคียงอื่น ๆ ได้แก่ การเปลี่ยนแปลงระดับความเจ็บปวด อาการคลื่นไส้ อาเจียน อาการง่วงซึม อาการปวดขณะฉีดยาหรืออาการมึนงงหลังการฉีดยาไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุป : นาลบูฟีน 3 มก. ฉีดเข้าหลอดเลือดดำมีประสิทธิผลสูงกว่าพรอโพฟอล 20 มก. ในการรักษาอาการคันซึ่งเกิดจากการฉีดมอร์ฟีนเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดคลอดเด็กทางหน้าท้อง โดยเกิดอาการข้างเคียงในอัตราต่ำและไม่รุนแรง

ภาควิชา ..การพัฒนาสุขภาพ.. ลายมือชื่อนิสิต ..Somrat Charuluxananan..

สาขาวิชา ..การพัฒนาสุขภาพ.. ลายมือชื่ออาจารย์ที่ปรึกษา ..Okyokang..

ปีการศึกษา ..2542.. ลายมือชื่ออาจารย์ที่ปรึกษาร่วม ..Somrat Lertmaharit..

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SOMRAT CHARULUXANANAN : COMPARISON OF EFFICACY BETWEEN 20 MG PROPOFOL AND 3 MG NALBUPHINE IN TREATMENT OF INTRATHECAL MORPHINE INDUCED PRURITUS IN CAESAREAN-SECTION PATIENTS. THESIS ADVISOR : ASSOC.PROF. ORANUCH KYOKONG, M.D., M.Sc., THESIS CO-ADVISOR : ASSIST.PROF.SOMRAT LERTMAHARIT, M.Sc., M.Med.Stat. 41 pp. ISBN 974-333-495-5

Objective : To compare the efficacy of 20 mg propofol and 3 mg nalbuphine in treatment of intrathecal morphine induced pruritus in caesarean-section patients.

Design : Randomized double-blind controlled trial.

Setting : Chulalongkorn University Hospital which is the tertiary care center.

Methods : One hundred eighty one parturients who developed moderate to severe pruritus caused by intrathecal morphine were randomly allocated into 2 groups with simple randomization. One group received 20 mg propofol while the other one received 3 mg nalbuphine. The improvement of pruritus and other adverse effects were determined at 10 minute after study drug administration.

Results : The treatment success rate was higher in nalbuphine group than in propofol group (83.5 % VS 61.1 %, p = 0.0008). Among the successfully treated patients, the recurrence rates of moderate to severe pruritus within 4 hours were not significantly different (nalbuphine 9.2 % VS propofol 7.3 %, P = 0.7603). Other side effects such as decreased analgesia, decreased nausea, vomiting, increased sedation, pain on injection, dizziness were not significantly different.

Conclusion : Three milligrams of nalbuphine is more efficacious than 20 mg propofol in treatment of intrathecal morphine induced pruritus in caesarean-section patients with few and minor side effects.

ภาควิชา .....การพัฒนาสุขภาพ..... ลายมือชื่อนิสิต Somrat Charuluxananan

สาขาวิชา .....การพัฒนาสุขภาพ..... ลายมือชื่ออาจารย์ที่ปรึกษา A Kyokong

ปีการศึกษา .....2542..... ลายมือชื่ออาจารย์ที่ปรึกษาร่วม Somrat Lertmaharit

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CHAPTER 1

INTRODUCTION

Opioids are perhaps the oldest and most studied of drugs. Opium use, for its euphoric effects, can be traced back over 4000 years and its respiratory depressant effects were first noted approximately 600 years ago. It was not until 1971 that highly specific opioid receptors were discovered.[1] In 1973, opioids receptors were localized in mammalian brain[2] and in 1976 they were found to exist in primate spinal cord.[3]

Pure antinociception without side effects has long been an elusive goal. In the 1970s, the discovery of highly specific opioid receptors in the central nervous system, created new enthusiasm for the possible realization of this goal. Subsequent demonstration that small amounts of intrathecal or epidural opioids produced profound antinociception only heightened enthusiasm. However, with increasing universal application of the technique in humans in the 1980s, a wide variety of clinically relevant non-nociceptive side effects have been reported.[4,5]

Side effects of intrathecal and epidural opioids are caused by presence of the drug in either cerebrospinal fluid or blood. Therefore, following administration of intrathecal opioids, side effects will be profoundly affected by their pharmacokinetic behaviour. Fentanyl and sufentanil are, respectively,

approximately 800 and 1600 times as lipid-soluble as morphine. When administered intrathecally, therefore, morphine will exhibit slower onset and longer duration of antinociception and a higher incidence of some side effects. The four classic side effects are pruritus, nausea, vomiting, urinary retention and respiratory depression. Numerous other side effects have also been described.[6]

The post-caesarean section patient differs from others recovering from general surgery in that her overall satisfaction with postoperative analgesia is influenced by her desire and ability to interact with her newborn. Thus modalities capable of providing superior analgesia with minimal sedation would appear most useful in this setting. The addition of preservative-free morphine to intrathecally injected local anesthetic provides effective, long-lasting postoperative analgesia following caesarean section under spinal anesthesia.[7,8] However, a common side-effect of intrathecal morphine administration has been the development of pruritus, occuring in up to 80 % of patients.[4,9,10]

Pruritus or itch is a subjective, unpleasant and irritating sensation arising from the superficial layers of skin that provokes an urge to scratch. It is usually localized to facial areas innervated by the trigeminal nerve. Although often mild, symptoms may cause the patient considerable distress and even necessitate termination of opioid analgesia. Therefore, treatment of intrathecal morphine induced pruritus would improve postoperative condition and strengthen advantage of neuraxial opioids.

CHAPTER 2

LITERATURE REVIEW

2.1 *Literature search strategy*

The literature search strategy used to locate the information in this review is the MEDLINE reference database and additionally by going through the reference lists of other articles and institutional database. The keywords used were complication, intrathecal, morphine, opioids, pruritus and caesarean section. The year covered by the search was from 1985-1999.

2.2 *Anesthesia for caesarean section*

In obstetric anesthesia, anesthesiologists are responsible for two or more patients. 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. Neurobehavioural scores, for what they are worth, tend to be better in newborns of patients receiving regional anesthesia. Neurobehavioural

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 neurobehavioural 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 a long lasting effects.[11]

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.[12] Maternal mortality at caesarean section is quoted to be about 20 times that for vaginal delivery. Anesthesia is responsible for about ten percent of all maternal deaths.[12] 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.[12]

Spinal anesthesia is an increasingly popular technique for elective caesarean section[11,13] because of its rapid onset, using low dose of local anesthetic and postoperative analgesia provided by intrathecal morphine.

2.3 ***Intrathecal morphine induced pruritus***

The most common side effect of intrathecal or epidural morphine is pruritus. It may be generalized but is more likely to be localized to the face, neck, or upper thorax.[4] Pruritus usually occurs within a few hours of injection and may precede the onset of antinociception.[14,15] The incidence may[16] or may

not[14] be related to the dose of opioids administered. Pruritus is more likely to occur in obstetric patients[16] which may result from an interaction of oestrogen with opioid receptors.[17]

2.4 *Clinical studies*

The mechanism of pruritus following opioid analgesia particularly its spinal administration is not fully understood.[6] Many drugs have been used to treat intrathecal opioid induced pruritus. Although not histamine mediated, the sedating antihistamines may reduce pruritus in situations where itch is not due to histamine release whereas the non-sedating antihistamine may not.[18] Droperidol has also been reported to reduce epidural morphine induced pruritus which its mode of action is likely to be due to sedation.[19] Complete μ-receptor antagonist such as naloxone is the most successful treatment but has been associated in certain cases with a concomitant reduction in analgesia[20] and because of its short duration of action has generally required continuous infusion.[21] Nalbuphine, a partial agonist at the Kappa-receptor and antagonist at μ-receptor, has been shown to reverse epidural morphine-induced pruritus.[22] In our recent study, treatment of intrathecal morphine induced pruritus in obstetric population was 86 % effective by intravenous administration of 3 mg nalbuphine with slightly decreased analgesia.[23] Antagonist to μ-receptor can reverse pruritus and analgesia whereas agonist to Kappa-receptor can cause analgesia and sedation.[22] There is another hypothesis postulates that

intrathecal morphine induced pruritus is the result of local, particularly spinal cord stimulation due to excitatory effects of high morphine concentration.[24] Propofol, (2-6, di-isopropylphenol), an intravenous anesthetics can exert its antipruritic action through the inhibition of posterior horn transmission.[25] Borgeat et al first reported the successful use of 10 mg propofol to reduce pruritus following spinal morphine in two patients and later confirmed their uncontrolled findings in a placebo-controlled study with 84 % success rate.[25,26] Warwick et al demonstrated that subhypnotic dose (10-20 mg) of propofol given intravenously during spinal anesthesia could not prevent intrathecal morphine induced pruritus.[27] But Torn et al found that bolus dose of 10 mg propofol followed by an infusion of 30 mg. 24 h^{-1} offered significant protection against itching and a modest effect on postoperative nausea and vomiting following the administration of spinal morphine in patients undergoing orthopaedic surgery.[28] In conclusion, both nalbuphine with its analgesic through Kappa receptor agonist and propofol with its analgesic, antiemetic and sedative properties seem to be logical agents for treatment of intrathecal morphine induced pruritus. However, no study has been carried out to compare the efficacy of these two agents.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Questions and Objectives

3.1.1 *Research Questions*

3.1.1.1 Primary research question

Is 20 mg propofol 25 % more efficacious than 3 mg nalbuphine in treatment of intrathecal morphine induced pruritus in caesarean-section patients ?

3.1.1.2 Secondary research questions

Are there any differences in adverse effects ? (i.e. decreased analgesic effect, nausea, vomiting, sedation, respiratory depression.)

3.1.2 *Research Objectives*

3.1.2.1 To compare the efficacy of 20 mg propofol and 3 mg nalbuphine in treatment of intrathecal morphine-induced pruritus in caesarean-section patients.

3.1.2.2 To compare the event rate of adverse effects, (decreased

analgesic effect, nausea, vomiting, sedation, respiratory depression etc.) between patients treated with 20 mg propofol and 3 mg nalbuphine.

3.1.3 *Research Hypothesis*

Twenty milligram of propofol is 25 % more efficacious than 3 mg nalbuphine in treatment of intrathecal morphine induced pruritus in caesarean-section patients.

3.2 Conceptual Framework

Pruritus associated with spinal opioids is not fully understood.[6] From literature review, intrathecal morphine-induced pruritus is thought to be result from imbalance of sensory modulation secondary to spread of opioid to the medulla or fourth ventricle[29,30] as illustrated in Figure 1. Treatment of this annoying symptom has also been demonstrated.

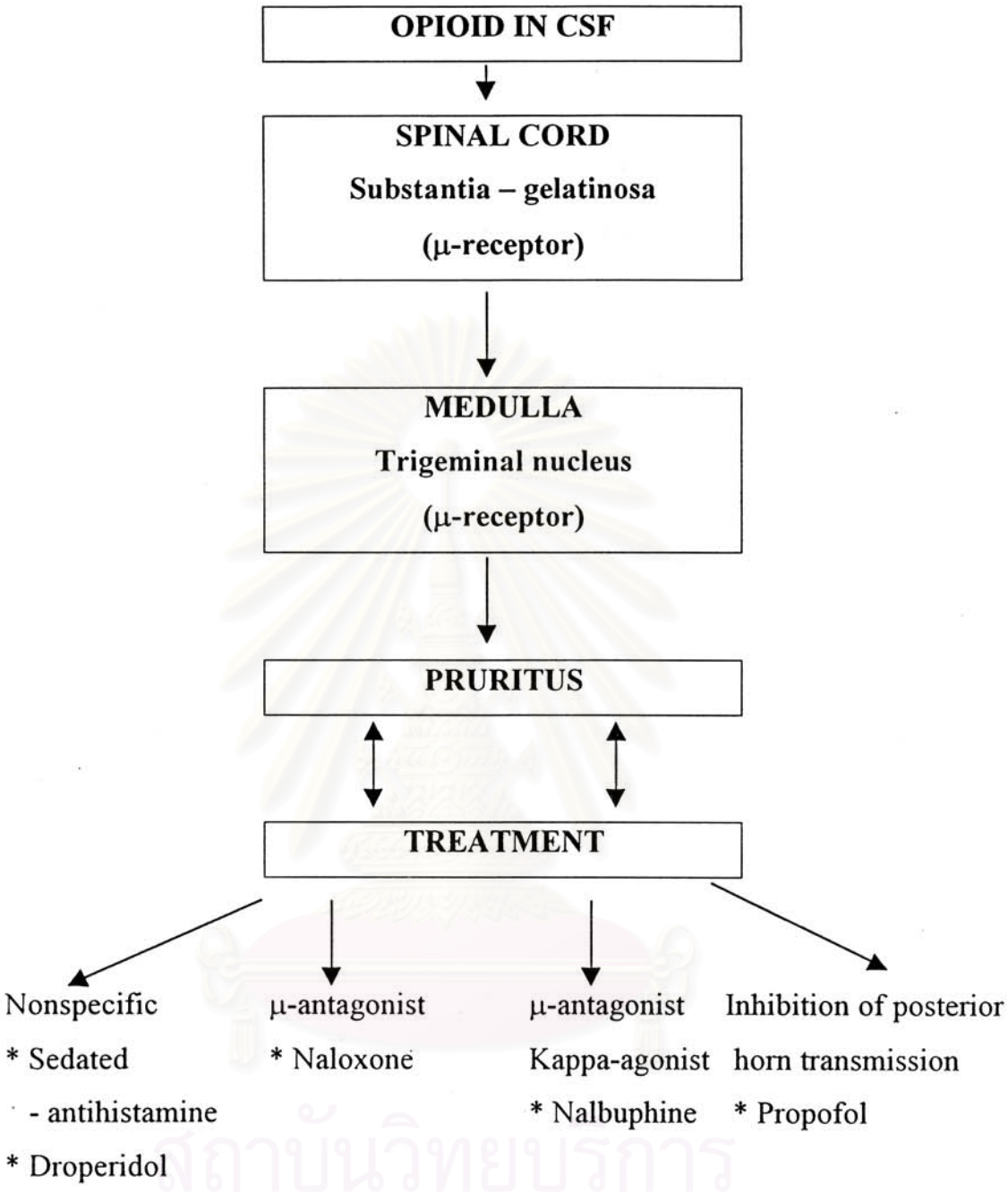
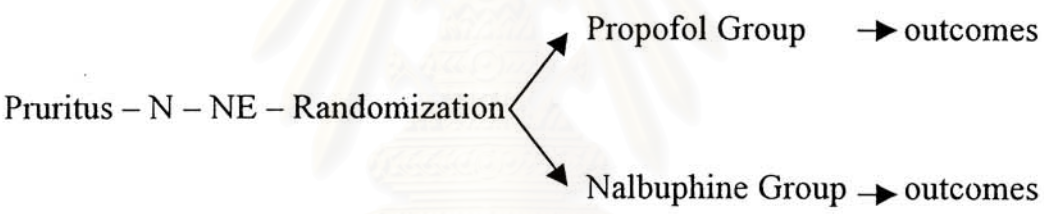


Figure 1 Proposed mechanism and treatment of intrathecal morphine-induced pruritus

3.3 Research Design

This study was carried out as a randomized double-blind controlled trial. Since pruritus, analgesia, nausea, vomiting are soft subjective outcomes, they should be evaluated blindly. The randomization can avoid allocation bias, tends to produce comparable groups and assures the validity of statistical tests of significance.

3.3.1 *Research Design Model*



N : Target population

NE : Eligible subjects

3.4 The Sample

3.4.1 *Target Population*

Post caesarean-section patients who suffer from intrathecal morphine induced pruritus.

3.4.2 *Sampled Population*

Post caesarean-section patients at King Chulalongkorn Memorial Hospital who suffer from intrathecal morphine induced pruritus and meet the following criteria.

3.4.2.1 Inclusion criteria

1. Patients who are classified as physical status 1 or 2 according to the American Society of Anesthesiologists. (Appendix C).
2. Able to understand how to rate verbal numerical pain scale.

3.4.2.2 Exclusion criteria

1. History of allergy to propofol or intralipid or nalbuphine.
2. History of any other diseases associated with pruritus or having a complaint of pruritus prior to caesarean-section or pre-existing pruritus due to pregnancy or a coexisting skin disorder.
3. Not agree to participate in the study.

3.4.3 Randomization Procedure

Simple randomization was conducted in the study. The patients who meet the selection criteria were randomly divided into propofol and nalbuphine groups according to random number table. The random number was written in a paper and enclosed

in a sealed envelope. The number compatible with number in sealed envelope was on package of syringes of intervention agents and placebo. The code was kept in the operating room without broken until the patients were discharged and all data were collected or in case of side effects occurred and interim analysis might be necessary.

3.5 Experimental maneuver

3.5.1 *Preanaesthetic period*

The patient who meet the eligible criteria was admitted for caesarean-section. The routine preoperative preparation was done. The patient was explained about detail of the protocol, how to rate verbal numerical pain scale. No premedication was given.

3.5.2 *Anesthesia and operative period*

After starting intravenous fluid and urinary catheterization, all patients were placed in left lateral position and received spinal anesthetic consisting of 2.2 ml of hyperbaric bupivacaine with 0.2 ml (0.2 mg) of morphine. Intravenous fluid and ephedrine were administered as appropriate to maintain the decreasing of systolic arterial blood pressure not more than 30 % of its pre-operative value or to be more than 100 mmHg. After testing for

a satisfactory spinal block by using loss of pinprick sensation, the caesarean-section was performed in the usual way.

3.5.3 *Postanesthetic period*

After the caesarean-section, women who spontaneously complained of pruritus while in the postanesthesia care unit (PACU) (approximately 3-4 hours after completion of the caesarean-section) were evaluated by one anesthesiologist (the author). The patients whose pruritus score $\geq$ 3 (1 = no pruritus ; 2 = minimal pruritus, treatment not necessary ; 3 = moderate pruritus, treatment desirable ; 4 = severe pruritus and scratching, treatment necessary) as determined by anesthesiologist were randomly assigned to receive 1 ml. of 2 % lidocaine and 2 syringes of intervention agent (either 20 mg propofol or 3 mg nalbuphine with double dummy technique). Ten minutes after treatment, pruritus was reevaluated by the same anesthesiologist who did not aware of which drug the patient received. In the absence of a positive response (pruritus score remained $\geq$ 3) the result was considered failure of treatment and pruritus was treated by 0.4 mg naloxone intravenous injection by titration method. If the treatment was successful, the patient had been evaluated for 4 hours to determine whether the patient needed more antipruritic drug, number of patients who develop pruritus score $\geq$ 3 were recorded.

At the same time that the patient was evaluated for pruritus, her level of sedation was assessed using a 4-point sedation rating scale ; the pain level was assessed by verbal numeric pain scale (with 0 representing no pain and 10 representing the worst imaginable pain), nausea and vomiting was assessed by 4-point rating scale. Metoclopramide 10 mg intravenously was prescribed for nausea and vomiting as required.

After each drug administration, pain on injection, dizziness, mood changes or hallucination were also recorded.

3.5.4 *Blindness*

Since this is a double-blind study, the patient and the investigator do not know which intervention agents (either propofol or nalbuphine) each patient received. We used double dummy technique to assure blindness because nalbuphine is clear colorless and propofol is milklike white. The patient in propofol group received one white syringe (20 mg propofol) and one clear colorless syringe (2 ml of normal saline), while patient in nalbuphine group received one white syringe (2 ml of intralipid) as placebo and one clear colorless syringe (3 mg of nalbuphine adding distilled water to 2 ml). Before injection of intervention agent, 1 ml of 2 % lidocaine was administered to prevent pain on injection which possibly occurs with propofol to assure the blindness.

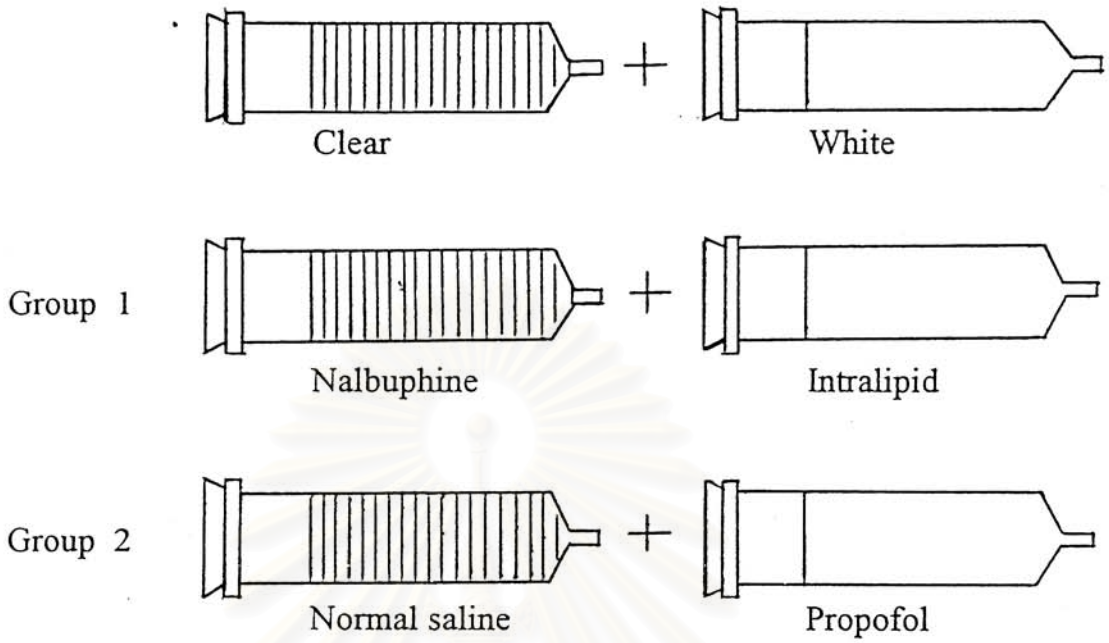


Figure 2 Double dummy technique

3.5.5 *Intervention agents*

The intervention agents were prepared by one assigned nurse anesthetist not involved in the study according to random number. Syringes of intervention agent and placebo were enclosed in envelop or package together with the random number to ensure concealed allocation randomization technique.

3.6 Measurement

The variables being measured were as followed :

3.6.1 *Demographic Variables*

1. Age (years)
2. Weight (kilograms)
3. Height (centimetres)

3.6.2 *Outcome Variables*

1. Pruritus

   4 – point rating scale for pruritus

   1 = no pruritus

   2 = minimal pruritus, treatment not necessary

   3 = moderate pruritus, treatment desirable

   4 = severe pruritus and scratching, treatment necessary

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

2. The level of pain

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

   The result was divided into 2 categories : increased pain (pain score increases ≥ 2) and not increased pain (pain score does not change or increases < 2)

3. Sedation

   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

4. Nausea and vomiting

4 – point rating scale

1 = no nausea or vomiting

2 = queasy

3 = severe nausea

4 = vomiting

3.7 Sample Size Estimation

Since the primary outcome is proportion of successful treatment of patients in each group, the sample size formula for comparing two proportion of two independent groups was used.[31]

$$n/group = \frac{2\,(Z_\alpha + Z_\beta)^2 \bullet \bar{P}\bar{Q}}{(P_t - P_c)^2}$$

where α = 0.05

Z_α = 1.96 (two – tailed)

Z_β = 1.28 (power = 90 %)

P_t = proportion of successful treatment of pruritus in propofol group

P_c = proportion of successful treatment of pruritus in nalbuphine group

$\bar{P} = \frac{P_t + P_c}{2}$

$\bar{Q} = 1 - P$

From pilot study of 10 patients in each group ;

$P_t = 0.9$,

$P_c = 0.7$;

n/group = 83.9 ~ 84

The total estimated sample size will be 90 patients per group.

3.8 Data Collection

The data was collected in a data collection form (Appendix A). The pruritus rating scale, verbal numeric pain scale and other side effects were recorded by one anesthesiologist (the author)blinded to intervention agents and placebo.

3.9 Data analysis

3.9.1 *Demographic and Baseline Variables*

Demographic and baseline data were compared between groups. Age, weight and height were quantitative data, range, mean and standard deviation were demonstrated as summarized (Table 1).

Table 1 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.

3.9.2 *Outcome Variables*

The outcome variables were described and compared between groups using the appropriate inferential statistics (Table 2).

Table 2 Inferential statistics used to compare outcome variables

Variables	Data summary	Statistics
1. Pruritus rating scale - Treatment success	proportion	z test 95% CI of P_1-P_2
2. Verbal numeric pain scale - Increased pain score $\geq$ 2, - Number of patient require analgesics	proportion	Chi-square*
3. Nausea, vomiting rating scale - Decreased rating score	proportion	Chi-square*
4. Sedation rating scale - Increased rating score	proportion	Chi-square*
5. Other side effects : pain on injection, dizziness, mood change, hallucination	proportion	Chi-square*
6. Number of patients who need more antipruritic agents within 4 hours after first dose of successful treatment	proportion	Chi-square*

* Fisher's exact test if necessary (expected value in 2 x 2 table < 5)

Differences are considered significant at $P < 0.05$

Analysis was performed by using "intention-to-treat" approach. Proposal violators was included as long as they had measurements both at baseline and on treatment, Statistical tests are 2-tailed with significant level taken at 0.05. All data analysis was performed by using SPSS version 6.0 and STATA version 5.0 program.

3.10 Ethical Consideration

The study protocol was explained to the patient and written informed consent had been 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, nalaxone was used as a rescue drug. If any serious complication occurred the code would have been broken to search for actual cause and prompt treatment. Therefore the intervention would provide more benefit than harm.

3.11 Limitation and Obstacles

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 no problem of loss to follow up. Rating of the verbal numeric pain scale, needs intelligence and cooperation of the patients.

If the patient can not understand how to rate the verbal numeric pain scale, she should be excluded from the study. All patients had been informed about the protocol and adviced thoroughly to prevent contamination.

The generalizability of this study is limited to obstetric patients with intrathecal morphine induced pruritus. Further study is required to determine the efficacy of drugs in nonobstetric patients.

3.12 Expected Benefit and Application

If propofol is more efficacious in treatment of intrathecal morphine induced pruritus, it should be recommended to treat itching in caesarean-section patients since propofol itself does not antagonize the analgesic effect of intrathecal morphine. Moreover, the antiemetic effect of propofol would add more benefit in reducing nausea and vomiting associated with intrathecal morphine.

CHAPTER 4

RESULTS

4.1 Basic characteristics of patients and baseline data

Five hundred eleven parturients undergoing cesarean-section under spinal anesthesia gave an incidence of intrathecal morphine induced pruritus of 61.84 %. Among 316 cases of intrathecal morphine induced pruritus, 181 cases with moderate to severe pruritus (pruritus score $\geq$ 3) were allocated to the nalbuphine group (n = 91) and propofol group (n = 90). Both groups were comparable, regarding demographic characteristics and onset of intrathecal morphine induced pruritus as shown in Table 3. The onset of pruritus appeared 25-180 minutes after neuraxial administration of morphine.

Table 3 Demographic characteristics and onset of pruritus

	Nalbuphine group N = 91	Propofol group N = 90	P value
Age (yr)	29.8 (6.2) [17.0, 57.0]	30.0 (4.6) [18.0, 39.0]	0.883
Weight (kg)	67.6 (9.9) [41.3, 102.0]	68.6 (11.2) [52.0, 102.2]	0.544
Height (cm)	155.0 (5.7) [142.0, 168.0]	156.0 (5.8) [135.0, 175.0]	0.243
Onset of pruritus (min)	92.0(30.3) [25, 175]	92.1 (27.4) [25, 180]	0.987

Values are expressed in mean (S.D.) and [min, max]

4.2 Primary Outcome Analysis

4.2.1 *Treatment Success Rate*

The treatment success rate for moderate to severe intrathecal morphine-induced pruritus were 83.5 % (76 in 91 patients) and 61.1 % (55 in 90 patients) in nalbuphine and propofol groups respectively. The result was considered statistically significant

(p value = 0.0008) with difference of success rate equaled to 22.4 %, 95 % CI (9.4, 35.4).

4.3 Secondary outcome analysis

4.3.1 *Verbal Numeric Pain Scale*

4.3.1.1 Number of patients with increased pain score ≥ 2 were 4 and 2 after administration of nalbuphine and propofol respectively, which was considered statistically nonsignificant (p value = 0.653).

4.3.1.2 Number of patients with decreased pain score ≥ 2 were 5 and 2 after administration of nalbuphine and propofol respectively, which was considered statistically nonsignificant (p value = 0.449).

4.3.2 *Nausea, Vomiting Rating Scale*

4.3.2.1 Number of patients with decreased nausea, vomiting score were 8 and 9 after administration of nalbuphine and propofol respectively, which was considered statistically nonsignificant (p value = 0.981).

4.3.2.2 Number of patients with increased nausea, vomiting score were 1 and 3 after administration of nalbuphine and propofol respectively. The result was considered statistically nonsignificant (p value = 0.368).

4.3.3 *Sedation Rating Scale*

4.3.3.1 Number of patients with increased sedation score were 37 and 25 after administration of nalbuphine and propofol respectively. The result was considered statistically nonsignificant (p value = 0.095).

4.3.3.2 Number of patients with decreased sedation score was 1 and 0 after administration of nalbuphine and propofol group respectively.

4.3.4 *Other side effects*

4.3.4.1 The number of patients who had painful sensation during nalbuphine and propofol injection were 20 and 20 respectively, which was considered statistically nonsignificant (p value = 0.889).

4.3.4.2 The number of patients who had dizziness after administration of nalbuphine and propofol were 3 and 10 respectively. The result was considered statistically nonsignificant (p value = 0.08).

4.3.4.3 There was no hallucination, mood change or respiratory depression observed in both groups of patients.

4.3.5 *Recurrence rate*

4.3.5.1 The number of patients who need more antipruritic agents within 4 hours after first successful treatment by either of intravenous nalbuphine and propofol were 7 and 4

respectively. The result was considered statistically nonsignificant (p value = 0.7603).

4.4 Summary of result

The primary outcome variables and recurrence rate of moderate to severe pruritus within 4 hours after successful treatment of intervention agents were summarized in Table 4. The secondary outcome variables were summarized in Table 5.

Table 4 Success rate and recurrence rate of moderate to severe pruritus

	Nalbuphine	**Propofol**	**P value**
Treatment success (%)* [n]	76 (83.5 %) [91]	55 (61.1 %) [90]	0.0008
Recurrence within 4 hr. after successful treatment [n]	7 (9.2 %) [76]	4 (7.3 %) [55]	0.7603

* Difference of success rate = 22.4 %, 95 % CI (9.4, 35.4)

Table 5 Frequency and percentage of side effects

	Nalbuphine n = 91	Propofol n = 90	P value*
Increased pain score ≥ 2	3 (3.3%)	3 (3.3%)	0.653
Decreased pain score ≥ 2	5 (5.5%)	2 (2.2%)	0.449
Increased nausea, vomiting score	1 (1.1%)	3 (3.3%)	0.368
Decreased nausea, vomiting score	8 (8.8%)	9 (10.0%)	0.981
Increased sedation score	37 (40.7%)	25 (27.8%)	0.095
Decreased sedation score	1 (1.1%)	0 (0.0%)	--
Dizziness	3 (3.3%)	10 (11.1%)	0.08
Pain on injection	22 (22.0%)	20 (22.2%)	0.889

* By Chi-square test (Fisher's exact test when appropriate)

CHAPTER 5

DISCUSSION

In obstetric patients, the incidence of pruritus after epidural or intrathecal administration of opioids particularly hydrophilic agents such as morphine is high and may limit its beneficial application.[16,32,33,34] This vulnerability to the pruritic effect and the altered binding of opioids at receptor sites is due to competition by oestrogens.[35] The greater cephalad spread of spinally administered drugs in the women at term as compared to the general population may also play a role.[27] This study showed a 61.84 % incidence of intrathecal morphine induced pruritus with 35.42 % of pruritus requiring treatment (pruritus score $\geq$ 3), confirming previous studies. Since pruritus usually occurred within a few hours of intrathecal morphine injection,[14,15] therefore we observed the patients for 4 hours in the postanesthesia care unit to enroll all patients with intrathecal morphine induced pruritus. The range of onset of pruritus in our study was 25-180 minutes. The numbers of nalbuphine group (n = 91) and propofol (n = 90) were not equal because simple randomization could not guarantee the equal number in each group.

In the study, we were able to demonstrate that the success rate of treatment with 3 mg nalbuphine was significantly greater than with 20 mg propofol ; 83.5 % VS 61.1 % (p = 0.0008). The result was confirmed by

difference of success rate equaled to 22.4 % with 95 % confidence interval of 9.4 to 35.4. When we calculated Z_β from the result of this study, we found that Z_β was 1.4, therefore the power of this study was 91.92 %. The low recurrence rates after successful treatment by nalbuphine and propofol were not significantly different and showed considerable long duration of antipruritic effect. There was no evidence that both agents had a deleterious effect on the analgesia. Nor was there evidence that both agents altered the incidence of nausea, vomiting. Our findings are consistent with those of Cohen[25] and Borgeat[36,37] that nalbuphine and propofol were effective in treatment of pruritus and nausea, vomiting in patients receiving neuraxial opioids. However, Borgeat reported 84 % success rate of propofol in treatment of pruritus induced by epidural and intrathecal morphine[25] which is higher than 61.1 % success rate in this study which confinded to obstetric patients receiving only intrathecal morphine. Nalbuphine, a mixed antagonist-agonist, is an antagonist at the μ receptor and reverses pruritus, nausea and respiratory depression caused by intravenous and neuraxial opioid. It is a weak Kappa-agonist, resulting in analgesia and sedation. Propofol has been shown to produce marked spinal depression and probably exerts its antipruritic action through inhibition of posterior horn transmission and antiemetic on action partly from its significant brain depressant effects.[38]

Other side effects such as sedative effect, dizziness and pain on injection were not significantly different between groups. However sedative

effect and pain on injection occurred more common than other side effects. With 1 cc of 2 % lidocaine intravenous administration prior to intervention agent, both agents could produce pain on injection. Therefore further study concerning sedative effect and pain on injection should be considered. Another aspect to compare these two agents was economics. With assumption of using one ampule of either nalbuphine or propofol per one time of administration. The cost of nalbuphine was cheaper than propofol ; 60 Baht VS 350 Baht (Data from Department of Pharmacy, King Chulalongkorn Memorial Hospital, 1999). Therefore in term of cost minimization, nalbuphine was certainly preferable.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

This study showed that 3 mg nalbuphine is superior to 20 mg propofol for the treatment of pruritus caused by intrathecal morphine in caesarean-section patients without interfering the quality of analgesia. The side effects were not significantly different between groups. Moreover, in term of cost minimization the cost of nalbuphine is lower than propofol.

6.2 Recommendation

The author would recommend that 3 mg nalbuphine administered intravenously is suitable for treatment of intrathecal morphine induced pruritus after caesarean-section. Further study about sedative effect and pain on injection should be considered.

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APPENDIXS

APPENDIX A

DATA COLLECTION FORM

INTRATHECAL MORPHINE INDUCED PRURITUS

Number ..... Code .....

Date .....

Name ..... Family name ..... HN .....

Age ..... yr., Weight ..... kg., Height ..... cm.

Indication .....

Time (spinal anesthesia) ..... Time (discharge) .....

Time (pruritus begin) .....

	BEFORE	AFTER
PRURITUS		
1. no pruritus	[ ]	[ ]
2. mild pruritus	[ ]	[ ]
3. moderate pruritus treatment desirable	[ ]	[ ]
4. severe pruritus and scratching treatment necessary	[ ]	[ ]

	BEFORE	AFTER
Verbal numeric pain (0-10)	.....	.....
Sedation 1, 2, 3, 4	.....	.....
Nausea/Vomiting 1, 2, 3, 4	.....	.....

Other side effect : [ ] pain on injection, [ ] dizziness, etc : .....

[ ] respiratory depression, etc : .....

Recurrence of pruritus ≥ 3 (within 4 hr. after first successful treatment)

[ ] No [ ] Yes

Sedation grading	Nausea/vomiting grading
1. fully awake	1. No nausea or vomiting
2. somnolent, responds to call	2. Queasy
3. somnolent, responds to tactile	3. Severe nausea
4. asleep, responds to pain	4. vomiting

APPENDIX B

CONSENT FORM

ใบยินยอมของผู้เข้าร่วมโครงการวิจัย

ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ได้ทำการศึกษายา propofol โดยมีวัตถุประสงค์ เพื่อเปรียบเทียบประสิทธิผลการรักษาอาการคัน ซึ่งเกิดจากการผสมมอร์ฟีนในยาชาฉีดเข้าไขสันหลัง สำหรับการผ่าตัดคลอดเด็กทางหน้าท้อง ซึ่งช่วยระงับปวดหลังผ่าตัดได้ 36-48 ชั่วโมงเทียบกับ nalbuphine ซึ่งเป็นยาที่ใช้อยู่เดิม

ยา propofol เป็นยาระงับความรู้สึกสำหรับฉีดเข้าเส้น ซึ่งเป็นที่รู้จักและใช้กันแพร่หลายอยู่แล้ว ทางด้านวิสัญญีในการศึกษานี้ผู้ป่วยจะได้รับการฉีด propofol 20 มก. หรือ nalbuphine 3 มก. ซึ่งเป็นยาที่ใช้อยู่เดิม

ทางภาควิชาวิสัญญีวิทยา ขอเชิญท่านเข้าร่วมโครงการวิจัยนี้ โดยความ**สมัครใจ**ของตัวท่านเอง

ถ้าท่านตกลงเข้าร่วมโครงการ ท่านจะได้รับการดูแลตามปกติที่ได้รับจากโรงพยาบาล-จุฬาลงกรณ์ โดยไม่มีค่าใช้จ่ายเพิ่มเติม

ถ้าท่านไม่เข้าร่วมโครงการ ท่านยังคงได้รับการดูแลตามปกติที่ได้รับจากโรงพยาบาลจุฬา-ลงกรณ์เช่นเดิม

ท่านสามารถตัดสินใจเข้าร่วมโครงการหรือไม่ก็ได้ โดยความสมัครใจ โดยจะไม่มีผลกระทบใด ๆ ต่อการดูแลด้านการแพทย์ของโรงพยาบาล

ข้าพเจ้าได้อ่านข้อมูลด้านบนแล้ว และได้รับการอธิบายจากคณะผู้ทำวิจัย และสมัครใจเข้าร่วมโครงการ

.....	.....	.....
(ชื่อผู้ป่วย)	(ลายเซ็น)	(วันที่)
.....	.....	.....
(แพทย์ในโครงการวิจัย)	(ลายเซ็น)	(วันที่)
.....	.....	.....
(ชื่อพยาน)	(ลายเซ็น)	(วันที่)

APPENDIX C

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 patient 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 operations, add that letter E before classification.

VITAE

Dr.Somrat Churuluxananan was born on August 17, 1959 in Bangkok, Thailand. He graduated form Chulalongkorn University in 1985 after accomplishment of a six-year course and earned the degree of Bachelor of Science (B.Sc.) and Doctor of Medicine (M.D.). He completed one-year internship in a regional hospital at Haadyai, Songkhla and then worked as staff at Southern Regional Tuberculosis Centre in Yala province for 2 years. After completed tree-year residency training in Department of Anesthesiology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, he had served fellowship in Anesthesia at Toranomon Hospital, Tokyo, Japan in 1992 and visiting researcher at University of California at San Francisco, U.S.A. in 1994.

Since June 1998, he has been admitted in the Master Degree Program of Health Development in Faculty of Medicine of Chulalongkorn University. He had principal research interest in postoperative pain management and complication of neuraxial opioid. During this course, he has conducted a clinical trial comparing the efficacy of propofol and nalbuphine in treatment of intrathecal morphine induced pruritus after cesarean section.

Presently, he has been working as the instructor in the Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University.