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Efficacy of pethidine 0.1 and 0.2 mg/kg body weight as an adjuvant of intrathecal bupivacaine 0.5% 10 mg in preventing shivering

Nur Hesti Kusumasari¹, IG Ngurah Rai Artika², Djayanti Sari²

¹Department of Anaesthesiology, Aisyiyah Diponegoro General Hospital, Ponorogo,

²Departement of Anaesthesiology, Faculty of Medicine/Dr. Sardjito General Hospital, Yogyakarta

ABSTRACT

Shivering related with spinal anesthesia commonly occurs in patients. It is not only uncomfortable for the patients, but also related to some complication. The efficacy of pethidine in the prevention of shivering is well known. The aim of this study was to compare the efficacy of intrathecal pethidine 0.1 mg/kg body weight (BW) and 0.2 mg/kg BW as shivering-prevention drug after spinal anesthesia. This was a randomized, double-blind controlled trial study involving 196 subjects between the age 18-40 years with ASA physical status I-II, gestational age 37-42 weeks, BW of 40-70 kg or Body Mass Index (BMI) < 30 kg/m², body height > 145 cm who underwent a caesarean delivery section with spinal anesthesia based of World Health Organization (WHO) procedure in cesarean delivery in Dr. Sardjito General Hospital, Yogyakarta and affiliated hospital. Subjects were divided into two groups with 98 subjects of each group. Group A was given an hyperbaric 0.5% bupivacaine 10 mg and pethidine 0.1 mg/kg BW, and Group B was given an hyperbaric 0.5% bupivacaine 10 mg and pethidine 0.2 mg/kg BW in the same volume (2.5 mL). The seubjects were observed for the incidence and severity of shivering and side effects of pehtidine. The results showed that the incidence of shivering in Group A (35.70%) was significantly greater than in Group B (22.44%) ($p < 0.05$). However, the onzet an duration of shivering were not significantly different in both groups ($p > 0.05$). Moreover, the incidence of nausea and vomiting in Group A (8.33%) was significantly lower than Group B (22.45%). In conclusion, pethidine 0.2 mg/kg BW is more effective to preven shivering than pethidine 0.1 mg/kg BW although the incidence of its side effects is more higher.

ABSTRAK

Shivering akibat tindakan anestesi spinal umum terjadi pada pasien. Kejadian ini tidak hanya membuat rasa tidak enak pasien tetapi juga berkaitan dengan berbagai komplikasi yang ditimbulkan. Efikasi petidin dalam mencegah sudah dikenal luas. Penelitian ini bertujuan untuk membandingkan daya guna petidin intratekal 0,1 mg/kg berat badan (BB) dengan 0,2 mg/kg BB sabagai obat untuk mencegah *shivering* setelah anestesi spinal. Penelitian ini merupakan uji klinik acak tersamar ganda yang melibatkan 196 subjek berumur antara 18-40 tahun, dengan status fisik ASA I-II, umur kehamilan 37-42 weeks, BB 40-70 kg atau Indeks Masa Tubuh (IMT) < 30 kg/m², tinggi badan > 145 cm yang menjalani bedah cesar dengan anestesi spinal sesuai dengan prosedur WHO. Subjek dibagi menjadi 2 kelompok dengan masing-masing kelompok 98 subjek. Kelompok A diberi 10 mg bupivakain 0,5% dan petidin 0,1 mg/kg BB dan Kelompok B diberi 10 mg bupivakain 0,5% dan petidin 0,2 mg/kg BB dengan volume sama (2,5 mL). Subject diamati terhadap kejadian dan keparahan terjadinya *shivering* dan efek samping akibat petidin. Hasil penelitian menunjukkan kejadian *shivering* pada Kelompok A (35,7%) secara nyata lebih tinggi dari pada Kelompok B (22,4%) ($p < 0.05$). Namun demikian onset dan lama terjadinya *shivering*

* corresponding author: hesty.kusumasari@gmail.com

tidak berbeda secara nyata antara kedua kelompok ($p > 0,05$). Selain itu, kejadian mual dan mutah pada Kelompok A (8,33%) lebih rendah dibandingkan Kelompok B (22,45%). Dapat disimpulkan bahwa petidin 0,2 mg/kg BB lebih berdaya guna dalam mencegah *shivering* daripada petidin 0,1 mg/kg BB meskipun kejadian efek sampingnya lebih tinggi.

Key words: shivering - intrathecal pethidine - spinal anesthesia - cesarean delivery -bupivacaine

INTRODUCTION

The incidence of shivering post regional anesthesia in section action caesarian is about 85%. Shivering is an event that can provide the adverse implications for patient.¹ Peripheral inhibition is a major cause of hypothermia during regional anesthesia.² Side effects are said to occur in the form of shivering when oxygen consumption increases by 400%, as well as the increase in blood pressure, intracranial pressure and intraocular pressure, cardiac output and minute ventilation and metabolic rate up to 200-500%, oxygen saturation of mixed vein reduction.³

Pharmacological approaches have implemented to prevent shivering. A wide range of drugs have been used to prevent shivering including pethidine. Intrathecal pethidine in varying dose of 10-50 mg has long been used to prevent and reduce shivering.^{1,4-7} At usual dose, pethidine does not cause severe side effects in both mothers and infants such as respiratory depression, however the incidence of nausea and vomiting remains occur. Booth *et al.*⁸ reported that although pethidine could potentially prolong analgesia during labor, it use was associated with a significant incidence of nausea or vomiting.

Prevention of shivering in patients undergoing caesarean surgery is important. Although pethidine is remarkably effective to prevent shivering, its side effect is often reported. The side effects of pethidine is usually dose-dependent.¹ In addition, this side effects are influenced by some factors including

physiological changes associated with pregnancy. This study was conducted to obtain the optimal dose of pethidine that effectively can prevent shivering with minimally side effects. The usual dose of pethidine which used as an adjuvant local anesthetic drug is 0.2 mg/kg BW. In this study, this pethidine dose of 0.2 mg/kg BW was compared to 0.1 mg/kg BW in 0.5% hyperbaric bupivacaine 10 mg in order to obtain the optimal efficacy with minimal side effects.

MATERIALS AND METHODS

Subjects

This was a randomized, double-blind controlled trial study involving 196 subjects between the age 18-40 years with ASA physical status I-II, gestational age 37-42 weeks, BW of 40-70 kg or Body Mass Index (BMI) < 30 kg/m², body height > 145 cm who underwent a caesarean delivery section with spinal anesthesia based of World Health Organization (WHO) procedure in caesarean delivery in Dr. Sardjito General Hospital, Yogyakarta and affiliated hospitals i.e. Dr. Soeradji General Hospital, Klaten, Banyumas District Hospital, Purworejo District Hospital, Cilacap District Hospital. Subjects were divided into two groups with 98 subjects of each group. Group A was given an hyperbaric 0.5% bupivacaine 10 mg and pethidine 0.1 mg/kg BW, and Group B was given an hyperbaric 0.5% bupivacaine 10 mg and pethidine 0.2 mg/kg BW in the same volume (2.5 mL). Exclusion criteria included patients or families refusing to participate in the study,

having a history of allergy to bupivacaine, pethidine, ketorolac, and metoclopramide, having initial body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, having a history of hypertension with systolic blood pressure (TDS)/diastolic blood pressure (TDD) $\geq 140/90$ mmHg, having a hepatic and renal dysfunction, drinking drugs inhibiting monoamine inhibitor, and having contraindication to spinal anesthesia. The study has been approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

Protocol of study

Preoperative visit and checkup were performed before surgery and characteristics of patients were taken. A detail operating procedure conducting was explained to all patients. The patients who met the inclusion and exclusion criteria and were willing to be involved in the study would signed an inform consent. The patient was then placed in the surgery preparation room and an intravenous line was installed using abbocath 18G on the dorsum manus vein of the hand and 500 mL of Ringer's lactate solution was infused at dosage of 2 cc/kg BW/hour for 30 minutes. Operating room temperature was maintained at $22\text{-}24^{\circ}\text{C}$. After shifting the patients to operation table, preoperative vital parameters like body temperature, blood pressure, mean arterial pressure (MAP), heart rate (HR) and SpO_2 rate were monitored and recorded prior to the anesthetic procedure. A few minutes before spinal anesthesia, pethidine 0.2 or 0.1 mg/kg BW was injected as an intravenous bolus injection. The patient was then placed in sitting position and spinal anesthesia was conducted at the lumbar intervertebral spaces 3-4 using 10 mg of 0.5% hyperbaric bupivacaine with a 25 G needle size spinoken under sterile technique. The patients were then placed in the

modified supine position with a pillow. The level of sensory blockade was evaluated using pinprick method at the second minute after spinal induction and continued in five-minute interval for 20 minutes. Standards for patient hemodynamic monitoring during anesthesia i.e. blood pressure, PR and respiratory rate (RR) was performed in two-minute interval until the baby born and continued in five-minute interval until the end of the operation. The incidence, severity, onzed and duration of shivering as well as the side effect of drugs were observed during surgery conducted until four hours after spinal anesthesia. The severity of shivering was measured as previous performed by Crossley and Mahajan⁹ with criteria as follow: Grade 0 if no shivering was observed; Grade 1 if subject experienced piloerection or peripheral vasoconstriction, shivering invisible; Grade 2 if subject experienced no muscle activity, but limited to one muscle group; Grade 3 if subject experience muscular activity occurring in more than one muscle group; Grade 4 if subject experienced shivering in the whole body. Subjects were considered to experience shivering if they have no shivering, whereas subjects were considered to experience shivering if they have shivering of Grade 1-4. Subjects who had shivering of Grade 1-2, non-pharmacological intervention (heating) would be conducted. Whereas, subjects who had shivering of Grade 3-4, pethidine 25 mg or other antishivering agents such as ketamine, tramadol or clonidine would be administered. Moreover, subjects who experienced an adverse effects due to spinal anesthesia or dugs administered, pharmacological intervention would be conducted. Intravenously ephedrine 10 mg would be given for hypotension, intravenously metoclopramide 10 mg for nausea and vomiting or other antiemetic agents if not cure with metoclopramide, naloxone $0.17\text{-}2\ \mu\text{g/kg BW/hour}$ for pruritus and oxygenation with naloxone 0.4-2 mg for respiratory depression.

Statistical analysis

Data were tabulated and presented as mean ± standard deviation (SD) or percent. Data of age, body weight, body height, BMI, body temperature, blood pressure, MAP, physical status, height of block, duration of operation, hemodynamic changes, operation room temperature were analyzed statistically using independent t-test or Mann-Whitney U test. Data of incidence and severity of shivering and the side effects of pethidine were analyzed statistically using Chi square test. A p value <0.05 was considered statistically significant.

RESULTS

The characteristics of patients of both groups are presented in TABLE 1. No significant difference was observed in terms of age, weight, BMI, body temperature, operation room temperature, diastolic blood pressure, MAP, physical status, height of block and duration of operation in both groups (p>0.05). However, significant difference was observed in body height and systolic blood pressure of both groups (p<0.05).

TABLE 1. Characteristics of subjects (mean ± SD or percent) in both group

| Variables | Group A (n = 98) | Group B (n = 98) | p |
|---------------------------------|---------------------|---------------------|--------|
| Age (years) | 28.56±6.06 | 28.88±6.36 | 0.529 |
| Body weight (kg) | 64.56±6.61 | 64.60±6.43 | 0.784 |
| Body height (m) | 1.53±0.54 | 1.55±0.55 | 0.008* |
| BMI (kg/m ²) | 27.30±2.07 | 26.57±2.37 | 0.320 |
| Body temperature (°C) | 36.70±0.12 | 36.68±0.11 | 0.149 |
| Operation room temperature (°C) | 22.11±2.00 | 22.40±0.80 | 0.349 |
| Blood pressure (mmHg) | | | |
| • Systolic | 120.55±11.17 | 119.9±8.77 | 0.014* |
| • Diastolic | 76.66±7.71 | 71.59±7.94 | 0.372 |
| MAP | 89.39±9.10 | 87.70±6.75 | 0.322 |
| Physical status | | | |
| • ASA I | 86 | 80 | 0.234 |
| • ASA II | 12 | 18 | |
| Height of block | T5 (T4-T6) | T5 (T4-T6) | 0.282 |
| Duration of operation (minute) | 67.60±15.35 | 65.93±13.41 | 0.379 |
| Hospital | | | |
| • Dr. Sardjito General Hospital | 11 (11.22%) | 11 (11.22%) | 0.400 |
| • Banyumas District Hospital | 26 (26.54%) | 28 (28.58%) | |
| • Purworejo District Hospital | 13 (13.26%) | 20 (20.41%) | |
| • Cilacap District Hospital | 17 (17.34%) | 19 (19.38%) | |
| • Dr. Soeradji General Hospital | 31 (31.64%) | 20 (20.41%) | |

Note: BMI=body mass index ; MAP = mean arterial pressure ; *significantly different (p<0.05).

Changes in MAP dan body temperature before, during and after spinal anesthesia as well as amount and types fluid used during surgey are presented in TABLE 2. No significant difference was observed in MAP and body

temperature before, during as well as after surgery ($p>0.05$). In addition, the number and type of fluid used during surgery were not also significantly different in both groups ($p>0.05$).

TABLE 2. Changes in MAP dan body temperature before, during and after spinal anesthesia and amount and types fluid used

| Variab les | Group A (n=98) | Group B (n=98) | P |
|------------------------------------|-------------------|-------------------|-------|
| MAP | | | |
| • Before surgery (T ₀) | 89.39±9.10 | 87.70±6.75 | 0.322 |
| • During surgery (T ₁) | 80.63.±5.88 | 78.20±5.55 | 0.463 |
| • After surgery (T ₂) | 82.30±6.58 | 82.76±6.11 | 0.556 |
| Body temperature | | | |
| • Before surgery (T ₀) | 36.70±0.12 | 36.68±0.11 | 0.149 |
| • During surgery (T ₁) | 36.20±0.14 | 36.21±0.13 | 0.807 |
| • After surgery (T ₂) | 36.44±0.12 | 36.43±0.11 | 0.412 |
| Amount of IV fluid (mL) | 1573.47±176.18 | 1558.16±188.82 | 0.598 |
| Types of fluid | | | |
| • Crystaloid | 1170.40±236.90 | 1165.30±245.83 | 0.923 |
| • Koloid | 459.30±137.52 | 469.51±120.37 | 0.609 |

Note: MAP=mean arterial pressure; *significantly different ($p<0.05$).

The incidence, severity, onzet and duration of shivering after spinal anesthesi in Group A compare to Group B are presented in TABLE 3. The incidence of shivering in Group A (35 incident or 35.70%) was significantly higher than in Group B (22 incident or 22.44%) ($p<0.05$). However, the onzet an duration of shivering were not significantly different in group ($p>0.05$). The onzet of shivering in Group A and B were 31.7±11.61 minutes and 34.31±8.76 minutes, respectively. While the duration of shivering in Group A and B were 3.97±1.10 minutes and 3.90±1.30 minutes,

respectively. Among 24 subjects who had experienced shivering in Grade 1-2 and provided non-pharmacological intervention with giving blankets, only 15 subjects could be cured. Nine subjects who no cure, intravenous bolus pethidine 25 mg were given. Whereas 33 subjects who had experienced shivering in Grade 3-4, non-pharmacological intervention as well as pharmacological intervention using intravenous bolus pethidine 25 mg or tramadol 25 were conducted. The incident of persistent shivering requiring the addition of other antishivering was not observed.

TABLE 3. Incidence, severity, onset and duration of shivering after spinal anesthesia in both groups

| Shivering | Group A (n=98) | Group B (n=98) | P |
|-------------------|-------------------|-------------------|--------|
| Incidence | 35 (35.71%) | 22 (22.44%) | 0.041* |
| Severity | | | |
| • 0 | 63 (64.29%) | 76 (77.55%) | |
| • 1 | 0 (0%) | 3 (3.06%) | |
| • 2 | 12 (12.24%) | 9 (9.18%) | 0.032* |
| • 3 | 21 (21.43%) | 10 (10.20%) | |
| • 4 | 2 (2.04%) | 0 (0%) | |
| Onset (minute) | 31.7±11.61 | 34.31±8.76 | 0.555 |
| Duration (minute) | 3.97±1.10 | 3.90±1.30 | 0.843 |

Note: significantly different (p<0.05)

The incidence of side effects after spinal anesthesia in both groups are presented in TABLE 4. The incidence of nausea and vomiting in Group A receiving pethidine 0.1 mg/kg BW (8.33%) was significantly lower than Group B

receiving pethidine 0.2 mg/kg BW (22.45%). The incident of pruritus and respiratory depression in both groups were not observed in both groups in this study.

TABLE 4. The incidence of side effects after spinal anesthesia in both groups

| Side effects | Group A (n=98) | Group B (n=98) | P |
|------------------------|-------------------|-------------------|--------|
| Nausea/vomiting | 8 (8.33%) | 22 (22.45%) | 0.005* |
| Pruritus | 0 (0%) | 0 (0%) | |
| Respiratory depression | 0 (0%) | 0 (0%) | |

Note: significantly different (p<0.05).

DISCUSSION

In general, the characteristics of subjects in both groups were not significantly different, except the body height which was shorter in Group A compare to Group B. The body height is one of the factors that influences the height of the block on spinal anesthesia.¹⁰ However, this

study showed the body height of subjects did not affect the height of the block that could lead to shivering. It was indicated that the subjects of the two groups were comparable. Some factors have been reported could influence the shivering. Operation room temperature and infusion rate at temperature of a cool room can

decrease of core temperature of the body. In addition, wide and duration of open exposure of operation site can increase heat loss of skin that causes the difference between core temperature and peripheral temperature of the body and leads to the shivering.¹¹ In this study, factors that contribute the incidence of shivering have been controlled. Gender, type of operation, height of block, operation room temperature, duration of operation, body temperature, and amount of liquid used that influence the shivering in the both group of this study were not significantly difference. Therefore, the incidence of shivering observed in this study was only influenced by the dose of pethidine administration.

The incidence of shivering in Group A who given the pethidine 0.1 mg/kg BW (35.71%) was significantly higher ($p < 0.05$) than Group B who given the pethidine 0.2 mg/kg BW (22.44%). The incidence of shivering in this study was lower that it was reported in the previous studies that range from 56-85%.^{4,1} The different in the incidence of shivering may be caused by the difference of the characteristics of subjects and research methods used. In the previous study, the operation room temperature was maintained between 21 to 23 °C, whereas in this study the temperature was maintained between 22 to 24 °C. In addition, the height of block achieved in previous study (T8-C2)¹ was relatively higher than this study (T4-6). The height of the block is directly associated with the decrease of shivering threshold. The higher the spinal block can decrease the shivering threshold.¹¹ Unfortunately, the liquid used during surgery that can influence the incidence of shivering was not reported in the previous study.¹

The effect of intrathecal pethidine in preventing shivering has been proven by some authors.^{1,4-7} However, its mechanism of action can not be clearly explained. The antishivering

effect of pethidine may due to its effects on spinal cord μ -opioid receptors and shivering threshold temperature. Nevertheless, these effects are almost impossible to achieve through the systemic absorption of intrathecal pethidine ingestion.^{2,1}

The pethidine plasma levels as anti-shivering ranges from 0.6 to 1.8 $\mu\text{g/mL}$ that achieved after intravenously administration.¹² In intrathecal administration, the pethidine plasma levels is lower due to systemic absorption effects. It could explain the high incidence of shivering after intrathecal pethidine administration at dose of 0.1 mg/kg BW. Pethidine plasma levels of $107 \pm 20 \text{ ng/mL}$ are achieved after intrathecal pethidine administration at dose of 1 mg/kg BW. This dose is five time higher than pethidine dose needed for prevention of shivering (0.2 mg/kg BW).^{13,1} The effects of antishivering obtained after intrathecal pethidine 0.1 and 0.2 mg/kg BW may due to stimulation of μ -opioid receptors on the spinal cord. The antishivering effect reduces with reduction of the pethidine dose from 0.2 to 0.1 mg/kg BW. In addition, pethidine plays role as *N*-methyl-*D*-aspartate (NMDA) receptor antagonist¹⁴ where the receptor can also be found in the spinal cord. Inhibition of the NMDA receptor increases antishivering effect of the pethidine.

This study found that the incidence of nausea and vomiting after intrathecal pethidine administration at dose of 0.1 mg/kg BW (8.33%) was significantly lower than at dose of 0.2 mg/kg BW (22.45%). This result is consistent with the previous studies that reported the incidence of nausea and vomiting ranged from 30-60% in the subjects who received intrathecal pethidine.^{4,7,15}

The incidence of nausea and vomiting are about 20% in subjects who underwent spinal anesthesia. The risk factors that are associated with nausea and vomiting including high of block

more than T5, hypotension, opioid administration, and history of motion sickness.¹⁶ Nausea and vomiting caused by intrathecal administration of opioid drugs due to distribution of the drug to selayang in cerebrospinal fluid lead to interaction with opioid receptors in the postrema area. Sensitization of vestibular system as well as slowing gastric emptying movement due to opioid drugs also plays a role in causing the nausea and vomiting.¹⁷ The nausea and vomiting observed in this study may be caused by the intrathecal pethidine administration. However, other risk factors may also contribute in the incidence of the nausea and vomiting. The side effects of pruritus and respiratory depression were not observed in this study. The respiratory depression has been reported in the previous study after intrathecal pethidine administration at doses more than 50 mg or doses for sedation.^{18,19} In this study, doses of pethidine is relatively small i.e. 0.1 and 0.2 mg/kg BW. Therefore, the adverse effects of respiratory depression have not been observed, yet.

The characteristics of operation room of the five hospitals where the study conducted was also different especially in the terms of area, number of personel in the operation room, lighting ect. However, the factors that influenced the clinical outcome such as the operation room temperature were controlled by maintaining the temperature between 22-24 °C.

CONCLUSION

In conclusion, intrathecal pethidine at doses of 0.2 mg/kg BW is more effective to prevent shivering in subjects who undergo spinal anesthesia than at dose of 0.1 mg/kg BW. However, the incidence of nausea and vomiting of the pethidine at dose of 0.2 mg/kg BW is more higher than at dose of 0.1 mg/kg BW. Further researchs are needed to obtain the

optimal doses of intrathecal pethidine to prevent shivering post spinal anesthesia.

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