Nalbuphine Vs Midazolam for Prevention of Shivering in Patients Undergoing Lower Limb Surgery under Spinal Anesthesia; Prospective, Randomized and Double Blinded Controlled Study

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ABSTRACT

Background: Shivering is an involuntary, repetitive contractions of skeletal muscles, which commonly occurred after spinal block and it is an uncomfortable problem to the patients and the anesthetists. Shivering is considered as a complication of anesthesia. Shivering has deleterious effects on the cardiac function especially in patients who have limited cardiopulmonary reserve and coronary disease, which could be explained by increased oxygen consumption, production of carbon dioxide and lactic acidosis caused by shivering.

Objective: Our study was aiming at evaluating the effect of intrathecal nalbuphine versus intrathecal midazolam in the prevention of shivering during subarachnoid block.

Patients and Methods: Ninety patients (ASA physical status I or II) scheduled for lower limb surgeries under spinal anesthesia were randomly allocated into three groups using sealed envelopes technique; Control group receiving mixture of bupivacaine and saline, Nalbuphine (N) group receiving nalbuphine and bupivacaine, and Midazolam group receiving midazolam and bupivacaine. Upon arrival to the operation room basic monitoring was applied and lactated ringer solution at room temperature was infused through peripheral venous catheter.

Results: Shivering occurred in 20 patients (66.7%) in control group, 7 patients in nalbuphine group (23.3%), and 10 in midazolam group (33.3%). The incidence of shivering and core temperature differed significantly between group N and the other two groups (P values in saline and midazolam groups > 0.05, while that of nalbuphine < 0.05).

Conclusion: Intrathecal nalbuphine is more effective than intrathecal midazolam in prevention of post-spinal shivering for patients undergoing lower limb surgery.

Keywords: Nalbuphine, Midazolam, Shivering, Lower limb surgery, Spinal anesthesia.

INTRODUCTION

Shivering is an unprompted, repetitive contractions of the muscles. Hypothermia may elicit these contractions as a physiologic response to warm the patient by enhancing heat production [1, 2]. Also, shivering occurs without hypothermia due to: decreased sympathetic activity, suppression of the spinal cord reflex, release of tissue pyrogens, and suppression of adrenal gland function. Many studies found that the incidence of shivering is high, approximately 40–50% of patients in their studies [3]. Hypothermia of patients in the theatre is due to cold environment of operating rooms, effect of general anesthesia on thermoregulation controlled by autonomic nervous system, and infusion of unwarmed intravenous fluids; this allows shivering to occur[3,4].

Shivering has deleterious effects on the cardiac function especially in patients who have limited cardiopulmonary reserve and coronary disease, which could be explained by increased oxygen consumption and production of carbon dioxide caused by shivering. Furthermore, shivering leads to increased intraocular pressure and intracranial pressure and may stretch the surgical wound leading to more pain, delayed healing and prolonged hospital stay [4,5]. Therefore, prevention of shivering is essential to avoid these unwanted effects [6].

Unfortunately, a standard guideline for management of shivering is deficit because the treatment by drugs have side effects and cannot be used to all patients. We can treat shivering pharmacologically or non-pharmacologically or combination of both methods. The non-pharmacological method is by providing heat externally to the patients by the use of air warmed blankets, and infusion of warm intravenous fluids. The American Society of Anesthesiologists (ASA) provided guideline recommending forced-air warming devices and administration of meperidine[7].

Other drugs are reported to be effective in treatment of shivering include clonidine, tramadol, dexmedetomidine and ketamine. Nalbuphine is a semisynthetic opioid and has a mixed agonist–antagonist effect on opioid receptors. It is not only having mu-opioid receptor antagonist effects but also proved to antagonize the kappa-opioid receptor. Analgesia produced by nalbuphine has the advantage of being free of μ opioid receptor agonist related adverse effects. As well as, nalbuphine decreases possibility and severity of the side effects related to the use of μ-agonist drugs such as respiratory depression, urinary retention, nausea, vomiting, sedation and pruritus[7-10]. Therefore, the analgesic effect mediated by κ and μ receptors can be achieved with a better side effects profile.

Received:20 /10 /2020
Accepted:9 /12/2020

The benzodiazepines are used primarily because of its favorable effects like sedation, amnesia and anxiolytic effect[11]. Analgesic effect of intrathecal benzodiazepines was explained after finding benzodiazepine receptors in the spinal cord[12]. Among these benzodiazepines midazolam have been used by several investigators to alleviate postoperative pain via intrathecal or epidural rout acting on spinal benzodiazepine receptors. Antinociceptive effects of midazolam have been demonstrated by several animal and human studies and it was fortunately not accompanied by sedative or neurotoxic as well as respiratory depressant effects[13]. Therefore, Midazolam have been shown to promote analgesia when added to intrathecal bupivacaine with a better side effect profile[14,15].

Our study conducted to compare the effect of intrathecal nalbuphine versus intrathecal midazolam on prevention of post spinal shivering in patients undergoing various lower limb surgery under spinal anesthesia.

PATIENTS AND METHODS

Ninety patients aged 18 to 60 years of both gender, American Society of Anesthesiology (ASA) I or II and scheduled for various lower limb surgeries under spinal anesthesia were included in this study. Patients did not take any opioids or benzodiazepines as preoperative medication. Patients who have allergy to the medications of the study, contraindication to spinal anesthesia or obese patients with body mass index (BMI) more than 30 were excluded from the study.

Patients were divided into three groups using sealed envelopes technique; Group S (Control group, n = 30), Group N (nalbuphine group, n = 30), and Group M (midazolam group, n = 30). Upon arrival to the operation room basic monitoring was applied and lactated ringer solution at room temperature was infused through peripheral venous catheter. Oxygen 5 L/min was administered via a face mask during anesthesia and patients were covered with drapes without any warming. Subarachnoid block was performed in the setting or lateral position at the L3–4 or L4–L5 levels by 25-gauge Quincke needle using hyperbaric bupivacaine 0.5 % 2.5 ml + normal saline 0.5 ml in group I, hyperbaric bupivacaine 0.5% 2.5ml + nalbuphine 400 μg (in 0.5 ml saline) in group II, and hyperbaric bupivacaine 0.5% 2.5ml +midazolam 2 mg (in 0.5 ml saline) in group III.

After injection, patients were put in supine position. Sensory block and level were assessed by pinprick and Bromage's scale was used to assess the motor blockade[16]. All patients were operated upon at the same operating room temperature of 25–27 °C. We prevented any method for warming the patients. Heart rate (HR), mean arterial pressure (MAP), arterial oxygen saturation (SPO_2), and core (tympanic) temperature were measured preoperatively then every 10 min after subarachnoid block till the end of surgery. All the above measurements were recorded, also the incidence of shivering and its severity were recorded both in the operation room and post-anesthesia care unit. Shivering Assessment Score (SAS) was used to assess shivering [17].

Table (1) Shivering Assessment Score [17]

Severity	Score	Shivering
None	0	Not palpated on masseter, neck or chest
Mild	1	Localized to neck and/or chest
Moderate	2	Involve neck, chest and gross upper limbs movements
Severe	3	Gross movement of trunk, upper and lower limbs

All patients were observed for occurrence of side effects including hypotension which was defined as mean arterial blood pressure 20% less than the preoperative baseline measurement and was treated with iv fluids and ephedrine 5 mg in increment intravenous boluses. Also 0.5 mg atropine intravenous bolus was used to treat bradycardia which was defined as heart rate decrease below 50 beat/minute.

Ethical approval:

After obtaining Ethics Committee approval from Sohag Faculty of Medicine, Sohag University, written informed consents were obtained from all patients.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 16 was used to analyze the data. Numerical data were presented as mean ± SD. Unpaired student's t test was used to compare values of the mean ± SD of the three groups. Non-numerical data were presented as percentage of the total number of patients and were compared by Chi^2 test. P-value < 0.05 was considered statistically significant.

RESULTS

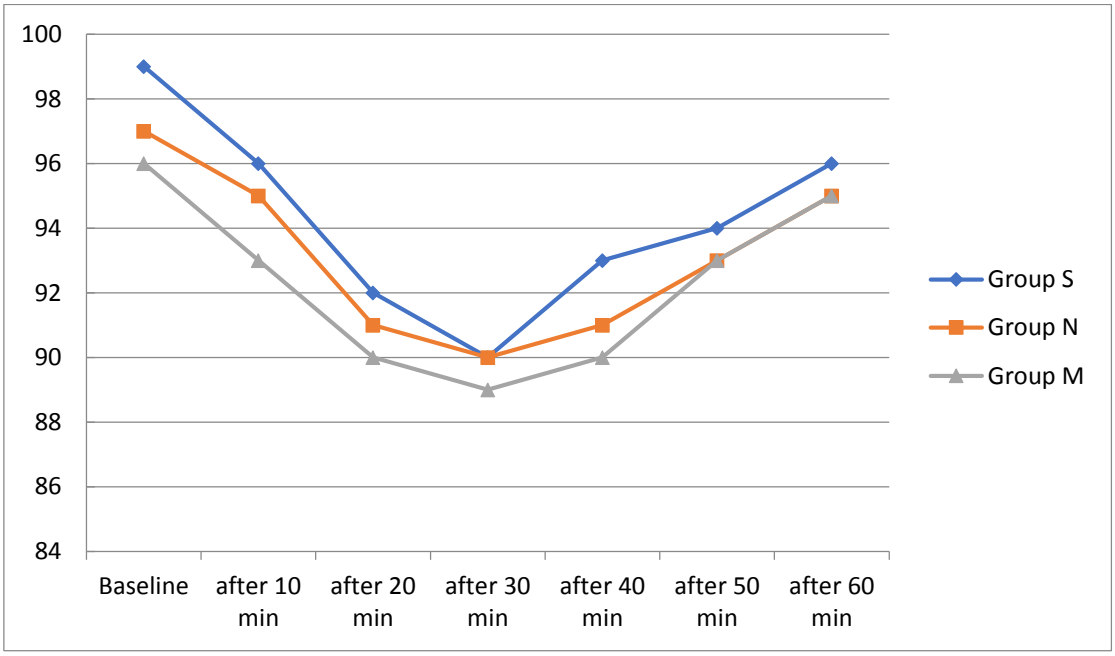
There were no significant differences between the three groups regarding demographic data (age, gender, height and weight) or surgery duration (Table 2).

Table (2): Demographic data and surgery duration

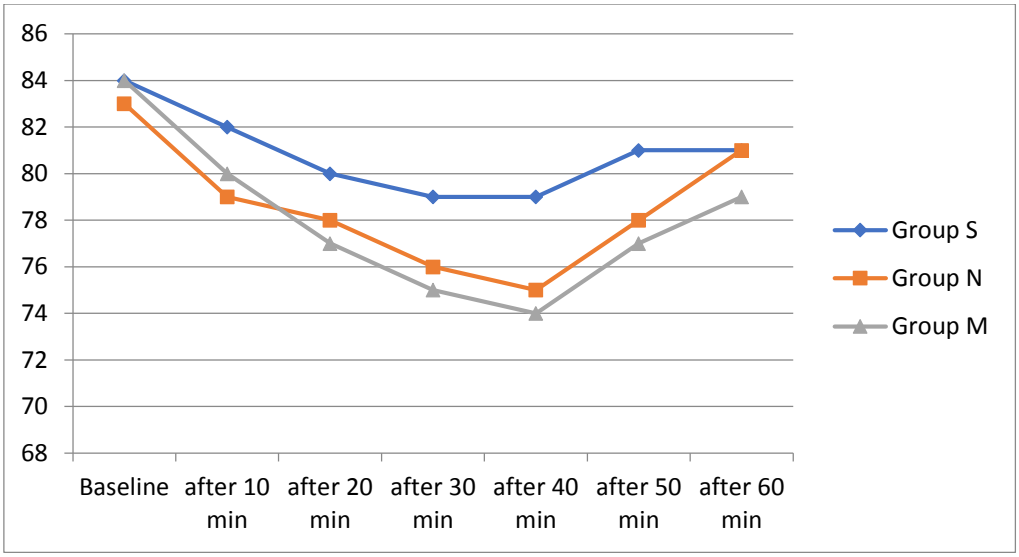
	Group S (n=30)	Group N (n=30)	Group M (n=30)	P value
Age (years)	46.54	47.63	44.78	0.312
Sex (f/m)	13/17	11/19	14/16	0.727
Weight (kg)	81.26 ± 9.72	84.47 ± 8.82	80.74 ± 9.18	0.683
Height (cm)	162.47±11.21	164.82±10.63	161.56±10.17	0.385
Duration of surgery (min)	50.27 ± 7.35	48.67 ± 8.47	47.83 ± 9.72	0.274

Data presented as Mean ± SD. Group S: saline group, Group N: nalbuphine group, and Group M: midazolam group, f: female, M: male, n= patients number.

MAP insignificantly decreased in the three groups from the baseline measurements (Figure 1). Also HR decreased from the baseline and the difference was statistically insignificant between the three groups (Figure 2).
Some patients needed vasoactive drugs and the numbers of patients were comparable in the three groups. Ephedrine was received by 4 patients in group S, 3 patients in group N and 4 patients in group M. Atropine was received by 3 patients in group S, 4 patients in group N and 5 patients in group M. Two patients received both ephedrine and atropine in group S.



Group S: saline group, Group N: nalbuphine group, and Group M: midazolam group.
Figure (1): Mean arterial blood pressure (MAP) of the studied patients



Group S: saline group, Group N: nalbuphine, and Group M: midazolam.

Figure (2): Heart rate (beat/min) of the studied patients

The three groups showed a reduction in body core temperature and the decrease was statistically significant ($P < 0.05$) in group N when compared to group S and group M (Table 3 and Figure 3).

Table (3): Core temperature of the studied patients before and during the operation

	Group S N=30	Group N N= 30	Group M N=30	P value
Baseline	37.13 ± 0.15	37.15 ± 0.16	37.1 ± 0.15	0.066
10 min	37.05 ± 0.17	36.93 ± 0.12	37.02 ± 0.17	0.074
20 min	36.8 ± 0.12	35.94 ± 0.17*	36.83 ± 0.12	< 0.05*
30 min	36.73 ± 0.11	35.33 ± 0.23*	36.73 ± 0.11	< 0.05*
40 min	36.72 ± 0.11	35.51 ± 0.18*	36.72 ± 0.11	< 0.05*
50 min	36.73 ± 0.12	35.69 ± 0.24	36.73 ± 0.12	0.084
60 min	36.92 ± 0.14	36.28 ± 0.21	36.95 ± 0.16	0.055

For the incidence of shivering (table 4 and figure 4) was significantly less in group N. SPO_2 was found more than 95% in all patients during the study times with statistically insignificant difference between the three groups.

Table (4): Shivering in the three groups

Shivering score	Group S (n =30)	Group N (n = 30)	Group M (n = 30)	P value
1	11(36.7%)	23 (76.7%)	12 (40%)	<0.003*
2	9 (30%)	3 (10%)	5 (20%)	0.131
3	7 (23.3%)	4 (13.3%)	4 (13.3%)	0.487
4	3 (10%)	0 (0%)	2 (6.7%)	0.227
Incidence of shivering	20 (66.7%)	7 (23.3)	10 (33.3%)	<0.002*

Group S: saline group, Group N: nalbuphine, and Group M: midazolam. Data were presented as Mean ± SD, n= number of patients (%). *: significant difference between the three groups.

Also we noticed that intrathecal nalbuphine provided good analgesia in the early postoperative period compared to midazolam and saline. Asking for analgesics was found to be earlier in group S compared to midazolam and nalbuphine, and also, the analgesic requirements.

Table (5): Incidence of intraoperative complications among three groups

Adverse effects	Group S	Group N	Group M
Hypotension	16 (53.3%)	18 (60%)	13 (43.3%)
Sedation	1 (3.3%)	3 (10%)	14 (16.7%)
Pruritus	-	2 (6.6%)	-

DISCUSSION

Several mechanisms have been proposed to explain post-spinal shivering including heat redistribution, increased heat loss from the blocked part of the body due to vasodilatation and impaired central thermoregulation[18-20].

Prophylaxis against shivering is very important to prevent its delirious effects, which might be harmful especially for vulnerable patients with low reserve, such as patients' discomfort, increased oxygen consumption, CO_2 production and lactic acidosis [21, 22].

Meperidine have been considered as the best choice to treat post-spinal shivering when administered intravenously in a dose of 20 to 30 mg[23]. Nalbuphine was administered intravenously for the same purpose as well[22-24]. However, nalbuphine was not well investigated as a prophylactic drug against post-spinal shivering especially when administered intrathecally, nowadays many studies going on with nalbuphine alone or combined with other drugs intrathecally for prevention of spinal shivering.

Our study showed that incidence and severity of shivering was successfully decreased when nalbuphine was added to intrathecal bupivacaine compared to midazolam in subarachnoid block; as intrathecal nalbuphine significantly decreased the incidence of shivering when compared with intrathecal midazolam.

This agrees with **Eskandr and Ebeid**[25] who reported that intrathecal nalbuphine effectively and safely prevented shivering during spinal anesthesia in patients undergoing knee arthroscopy. **Tiwari *et al.*** [26] found comparable effects in their study when used nalbuphine intravenously to control postoperative shivering. While using intrathecal nalbuphine for postoperative analgesia, its antishivering effect was significantly apparent[24]. **Eskandr and Ebeid**[25] study showed that (400 μg) of nalbuphine added to subarachnoid bupivacaine in comparable to placebo during subarachnoid block for knee arthroscopy decrease the incidence and severity of shivering with no significant hemodynamic changes, which was in agreement with the present study as we used similar dose of intrathecal nalbuphine. Also **Sun *et al.*** [27] study concluded that nalbuphine is very effective in preventing shivering after combined spinal-epidural anesthesia; significantly better than dexmedetomidine in reducing shivering and eliminating adverse reactions and can be used after combined spinal-epidural anesthesia for clinical prevention of shivering as the drug of choice.

Also, our findings are in agreement with a study done by **Pazuki *et al.*** [28]**,** who found that intrathecal midazolam is more effective than placebo in prevention of shivering. **Honarmand and his coworkers**[29] evaluated hundred and twenty patients scheduled for orthopedic surgery for post-spinal shivering after administration of intravenous ketamine, midazolam or combination of both drugs. They reported that the lowest incidence of shivering was achieved with the combination of ketamine and midazolam (3.3%), on the other hand the highest incidence was achieved in the control group (60%). The incidence of shivering was 50% in midazolam group and 23.3% in ketamine group. Furthermore, control group achieved significantly higher number of patients with a shivering score less than 3 when compared to other study groups. **Abdelrahman *et al.*** [30] who studied the effect of tramadol, tramadol plus ketamine, midazolam and midazolam plus ketamine as bolus iv injection in protection from shivering during regional anesthesia and concluded that midazolam (37.5 μg/Kg) plus ketamine (0.25 mg/Kg) is bitter than tramadol (0.25 mg/Kg) plus ketamine (0.25 mg/Kg) and both are better than midazolam (75 μg/Kg) alone or tramadol (0.5 mg/Kg) alone for protection from post spinal shivering.

In agreement with our study; where there was a significant decrease in the core temperature in nalbuphine group more than the other two groups, many studies recorded the same effect [31-34].

Hypotension and bradycardia were not statistically significant between the groups in our study. This shows that both the nalbuphine and midazolam did not have any significant sympatholytic activity and rather enhanced the anti-nociception in the spinal cord. Several investigators agreed with our results as regard to the non significant change in MAP including **Fournier *et al.*** [24]**, Roy *et al.*** [31]**, and Chaney** [35]**.** In **Tiwari *et al.*** [26] study where combination of bupivacaine with nalbuphine was compared with plain bupivacaine, showed that the incidence of hypotension and bradycardia were lesser in adjuvant groups than compared to plain bupivacaine.

Limitations of this work were a lack of trusted and objective way for detection and assessment of shivering, the need for large sample size and multi centers study.

CONCLUSION

Supplementation of nalbuphine (400 ug) to bupivacaine during spinal anesthesia is more effective in the prophylaxis from post spinal shivering when compared with intrathecal midazolam (2 mg), which in turn provides better prophylaxis from post spinal shivering than control group in patients undergoing lower limb surgery.

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