Comparison between Tramadol and Nalbuphine As an Adjunct to Midazolam for Control of Shivering after Intrathecal Anesthesia

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Abstract:
Background: Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under regional anesthesia. Post-anesthetic shivering is spontaneous, involuntary, rhythmic, oscillating and tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia. The aim of this study was to evaluate the efficacy, potency and side effects of tramadol plus midazolam as compared to nalbuphine plus midazolam in control of shivering after intrathecal anesthesia.

Patients And Methods: 60 American Society of anesthesiologists grade I, II (ASA physical status I or II) patients of either sex aged 18 to 60 years who were scheduled for lower abdominal or lower limb surgery, under intrathecal block, were included in this prospective double-blind randomized study. These patients were allocated by closed envelop technique to two groups: Group T (n=30) received tramadol 0.5mg/kg plus midazolam 0.05mg/kg (intravenously) IV, and Group N (n=30) received nalbuphine 0.1mg/kg plus midazolam 0.05mg/kg IV. Heart rate, respiratory rate, non-invasive arterial blood pressure, peripheral oxygen saturation (SpO2) and body temperature were recorded at 5 minutes intervals during the pre-and the post anesthesia period. After intrathecal injection the degree of sensory and motor block was assessed every 5 minutes in the first 20 minutes after intrathecal injection. The time in minutes at which shivering started, severity of shivering, time of disappearance of shivering and response rate were recorded. Recurrence of shivering was also noticed until the patient left the operation theatre. The degree of sedation was also assessed. Side effects were recorded and properly treated.

Results: No drug showed any statistically significant advantage over the other. No major hemodynamic changes were seen in the two study groups, except that the respiratory rate at 10, 15, 25, 30, 120 minutes was higher in tramadol group than nalbuphine group, body temperature at 90, 120 minutes was higher in tramadol group than nalbuphine group.

Conclusion: Both tramadol (0.5mg/kg) plus midazolam(0.05mg/kg) and nalbuphine(0.1mg/kg) plus midazolam(0.05mg/kg) had the same effect in the treatment of post spinal anesthesia shivering, with no statistically significant difference between them.

Key words: Tramadol, Nalbuphine, Midazolam, Shivering, anesthesia

I. Introduction:

Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under regional anesthesia.\(^1\)\(^2\) Post-anesthetic shivering is spontaneous involuntary, rhythmic, oscillating, tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia.\(^3\) Post-anesthetic shivering may cause discomfort to patients, and aggravate wound pain by stretching incisions and increase intracranial\(^4\) and intraocular\(^5\) pressure. Various methods are available for control of shivering; these may be non pharmacological or pharmacological methods using drugs which have anti-shivering properties. Tramadol (0.5 mg/kg) was found to be an effective treatment for shivering after intrathecal block.\(^6\) The intravenous (IV) administration of nalbuphine (0.08mg/kg) provides a rapid and potent anti-shivering effect on post anesthesia shivering.\(^7\) Midazolam is one of the benzodiazepines. It was found that it may decrease the incidence of shivering.\(^8\) The aim of this study was to evaluate the efficacy, potency and side effects of tramadol plus midazolam as compared to nalbuphine plus midazolam in control of shivering after intrathecal anesthesia.
II. Patients and methods:

After obtaining institutional ethical committee approval of Fayoum University and written informed consent from all patients, 60 American Society of Anesthesiologists (ASA) grade I and II of either sex, their ages ranged between 18 and 60 years who were scheduled for lower abdominal or lower limb surgery, under intrathecal block.

Patients with known hypersensitivity to tramadol, nalbuphine and midazolam, known history of alcohol or substance abuse, cardiopulmonary diseases, uncontrolled hypertension, coagulation defect, thyroid diseases, neuromuscular diseases, psychological disorders, uncontrolled diabetes, patients with recent history of febrile illness and those with history of malignant hyperthermia were excluded from the study.

All patients were evaluated initially by medical history, a complete physical examination and laboratory investigations. In the preparation room, all patients received IV midazolam (0.01-0.1mg/kg) as a premedication after insertion of 18G intravenous line. IV fluids in the form of lactated Ringer’s solution were infused at a rate of 10 ml/Kg over 30 minutes before spinal anesthesia then the rate was reduced to 6 ml/Kg/h. Fluid’s temperature were at room temperature. The ambient temperature was maintained at 22-24°C.

On arrival to the operating theatre patients were monitored by pulse oximetry, ECG, and non invasive blood pressure (NIBP). Body temperature (axillary) was recorded before the intrathecal block and every 5 minutes after the block using mercury thermometer. With the patient in the sitting position lumbar puncture was performed at L3-L4 or L4-L5 interspace (with a 22G Quincke’s needle) where 10-20mg hyperbaric bupivacaine 0.5% and fentanyl 0.25µg/kg were injected under complete aseptic conditions. Supplemental Oxygen was given via a face mask at a rate of 2L/min throughout the procedure. All patients were covered with one layer of surgical drapes over the chest, thighs and calves during the operation and one cotton blanket over the entire body after the operation. After intrathecal injection the degree of sensory(with pinprick test) and motor block according to Bromage\(^9\) score(Table 1) were assessed every 5 minutes in the first 20 minutes after intrathecal injection.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
<th>Degree of block</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Free movement of legs and feet</td>
<td>Nil (0%)</td>
</tr>
<tr>
<td>II</td>
<td>Just able to flex knees with free movement of feet</td>
<td>Partial (33%)</td>
</tr>
<tr>
<td>III</td>
<td>Unable to flex knees, but with free movement of feet</td>
<td>Almost complete (66%)</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to move legs or feet</td>
<td>Complete (100%)</td>
</tr>
</tbody>
</table>

Table 1: Bromage score

Measured parameters: When spinal anesthesia was established, the presence of shivering was observed and graded by using a scale similar to that validated by Tsai and Chu\(^10\) (Table 2):

Table 2: Shivering score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No shivering.</td>
</tr>
<tr>
<td>1</td>
<td>Piloerection or peripheral vasoconstriction but no visible shivering</td>
</tr>
<tr>
<td>2</td>
<td>Muscular activity in only one muscle group.</td>
</tr>
<tr>
<td>3</td>
<td>Muscular activity in more than one muscle group but not generalized.</td>
</tr>
<tr>
<td>4</td>
<td>Shivering all over the body.</td>
</tr>
</tbody>
</table>

Patients who developed either grade 3 or 4 were included in this prospective double-blind randomized study. These patients were randomly allocated into two equal groups:

**Group T:** received tramadol 0.5mg/kg plus midazolam 0.05mg/kg IV.

**Group N:** received nalbuphine 0.1mg/kg plus midazolam 0.05mg/kg IV.

Anesthesiology personnel who were involved in the study made the trial preparations and recorded group randomization separately. The anesthesiologists conducting the case and recording the data were unaware of the preparation. The time in minutes at which shivering started (onset of shivering), severity of shivering, time of disappearance of shivering (the time elapsed between the end of giving the test drugs till the cessation of shivering) and response rate (complete cessation of shivering after treatment) were recorded. If the shivering did not subside by 15 minutes, the treatment was considered to be not effective. Recurrence of shivering was also noticed until the patient left the operating theatre. Patients who did not respond or in whom recurrence of shivering occurred were treated with additional dose (the same initial dose of nalbuphine and tramadol without midazolam).
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HR, respiratory rate, non-invasive arterial blood pressure, peripheral oxygen saturation (SpO2) were recorded at 5 minutes intervals during the pre-and the post anesthesia period. The degree of sedation was assessed according to a five-point scale (Table 3).

Table 3: The degree of sedation according to a five-point scale

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fully awake and oriented.</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy.</td>
</tr>
<tr>
<td>3</td>
<td>Eye closed but responds to commands.</td>
</tr>
<tr>
<td>4</td>
<td>Eye closed but responds to mild physical stimulation.</td>
</tr>
<tr>
<td>5</td>
<td>Eye closed and not responding to mild physical stimulation.</td>
</tr>
</tbody>
</table>

Any other side effects were recorded and properly treated e.g. hypotension, nausea, vomiting and bradycardia.

III. Statistical Analysis:
- Data were collected, coded, and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Quantitative parametric data were presented as mean and standard deviation and were analyzed by student t-test.
- Qualitative data were presented as numbers and percentages and were analyzed by Chi square test.
- p- Value ≤ 0.05 was considered statistically significant while p- value ≤ 0.01 was considered statistically highly significant.

IV. Results:
There was no statistically significant difference between groups as regarding the demographic characteristic. (Table 4)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (T)</th>
<th>Group 2 (N)</th>
<th>p-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.3±12.2</td>
<td>32.1±12.3</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73.1±11.2</td>
<td>72.6±9.6</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169±7.1</td>
<td>169±7.8</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>♂</td>
<td>18 (60%)</td>
<td>23 (76.7%)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>♀</td>
<td>12 (40%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
</tbody>
</table>

NS= Non significant

There was no statistically significant difference between groups as regarding the level of intrathecal block (sensory, motor) after 15 minutes. (Figures 1 & 2)

Fig. 1: level of sensory block

Fig. 2: level of motor block
Regarding the body temperature before, during and after surgery, there was no statistically significant difference between groups except after 90, 120 minutes there was statistically significant difference between them. (Figure 3)

There was no statistically significant difference between groups as regarding the respiratory rate before; during and after surgery except after 10, 15, 25, 30, 120 minutes there was statistically significant difference between them. (Figure 4)
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There was no statistically significant difference between groups as regarding the heart rate, peripheral oxygen saturation and the mean arterial blood pressure before, during and after surgery. (Figures 5, 6, 7)

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Fig. 4: Respiratory rate

* = significant

Fig. 5: Heart rate.

Fig. 6: Peripheral oxygen saturation.
There was also no statistically significant difference when comparing intergroup frequent measurement. There was no statistically significant difference between groups as regarding the time of occurrence, the time of disappearance, the time of recurrence of shivering and the response to treatment. (Figures 8, 9)
There was no statistically significant difference between groups as regarding the severity of shivering, the degree of sedation, the need for additional dose and the recurrence of shivering. *(Figures 10, 11, 12, 13 & 14)*

![Fig.10: The degree of shivering in the two study groups](image)

![Fig.11: The degree of the recurrent shivering in the two study groups](image)

![Fig.12: The degree of sedation the two study groups](image)
Discussion:

There are various methods available to control shivering during anesthesia, which include non-pharmacological methods and pharmacological methods using drugs which have anti-shivering properties. In the present study, we compared the efficacy, potency and side effects of tramadol plus midazolam to nalbuphine plus midazolam in control of shivering after intrathecal block. Tramadol is a centrally acting analgesic that has weak opioid agonist properties. It also inhibits serotonin and norepinephrine uptake in the spinal cord and it is effective in the treatment of post operative shivering after regional and general anesthesia. (6) κ-opioid receptors may play a more important role than μ-opioid receptors in the treatment of post spinal anesthesia shivering. Nalbuphine, a semisynthetic opioid related to both naloxone and oxymorphone, has the characteristics of μ-antagonist and κ-agonist activities. It has a high affinity for κ-opioid receptors in the central nervous system. Theoretically, nalbuphine may have a significant effect on post spinal anesthesia shivering. Meperidine, which binds to both μ- and κ-opioid receptors, is frequently recommended for the treatment of post spinal anesthesia shivering. Although meperidine’s mechanism of action has yet to be fully elucidated, much evidence suggests that the drug’s special anti-shivering effect is mediated by its κ-receptor activity. (7)

The hemodynamic variables (HR, MAP & SPO2) in both groups were readily comparable. As regarding surface body temperature, readings were comparable between the two groups except after 90 minutes where temperature in (N) group was (36.7°C ± 0.4) and in (T) group was (36.9°C ± 0.2) with p-value 0.03 but this data may be irrelevant as this occurred twice during 120 minutes. There were significant decrease in respiratory rates in (N) group in five separated times at 10, 15, 25, 30 and 120 minutes. This could be attributed to κ-opioid receptors agonistic effect of nalbuphine. Duration of surgery in group (T) was (84.2 min ± 17.8) and (80.8 min ± 22.9) in group (N) with no statistically significant changes between both groups. Sensory block level after 15 minutes was T6-T8 in 73.4% of patients in (T) group and 76.7% of patients in (N) group and that was not statistically significant. Group (T) patients have 100% (n=30) initial response to tramadol with recurrence of shivering in 9 patients (30%). In group (N) patients there was initial response 100% (n=30) with recurrence of shivering in 8 patients (26%), there was no statistically significant difference between both groups as regarding: onset, severity and disappearance of shivering, also the response rate and the degree of sedation after the initial dose were not statistically significant between the two groups. As regarding recurrent shivering onset, severity, disappearance, response rate and the degree of sedation after the second dose there was no statistically significant difference between both groups. The number of patients who developed any side effect from the two drugs in both groups was only one patient in (T) tramadol group who had hypotension. We found that tramadol...
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(0.5mg/kg) plus midazolam (0.05mg/kg) and nalbuphine (0.1mg/kg) plus midazolam (0.05mg/kg) had the same effect in the treatment of post spinal anesthesia shivering as regard the efficacy, potency and side effects.

Kyo Kong O, et al. (13) who studied the efficacy of nalbuphine, tramadol, ondansetron and placebo in the treatment of post spinal anesthesia shivering (that was restricted to cesarean delivery, and in which morphine was injected intrathecally) had the same results of our study that tramadol and nalbuphine were efficacious in the treatment of post spinal anesthesia shivering with no statistical difference in response between them. They also found that the recurrence rates of post spinal anesthesia shivering within 4 hours after successful treatment of all groups were not significantly different.

Wason et al. (12) studied the prophylactic effect of ketamine, clonidine and tramadol in the control of shivering under neuraxial anesthesia and reported that tramadol was effective in decreasing the incidence of shivering after spinal anesthesia and the side effects were not significantly different between tramadol group and placebo group.

Joshi (14) et al, who studied the effect of butrophanol, ondansetron and tramadol in the control of shivering during regional anesthesia, also reported that tramadol 1mg/kg was effective in controlling of shivering under regional anesthesia.

On the other hand, Gangopadhyay et al. (15) studied the effect of ketamine, tramadol and pethidine in prophylaxis of shivering during spinal anesthesia and reported a significant number of cases (20/30) of nausea and vomiting with tramadol this high number of cases could be explained by the fact that they used tramadol at 1mg/kg as compared with 0.5mg/kg in our study.

Reddy et al. (16) studied the effect of clonidine and tramadol in control of post spinal anesthesia shivering during caesarean section and reported that there was a higher incidence of side effects with tramadol (nausea, vomiting, sedation and headache) than clonidine. Shukla et al. (17) studied the effect of clonidine and tramadol on post spinal anesthesia shivering and also reported that the complications were found to be higher in case of tramadol (nausea, vomiting and dizziness) compared to clonidine.

Abdelrahman (8) studied the effect of midazolam, midazolam plus ketamine, tramadol and tramadol plus ketamine in prevention of shivering during regional anesthesia and reported that tramadol (0.25mg/Kg) plus ketamine (0.25mg/Kg) is better than midazolam (75μg/Kg) alone or tramadol (0.5 mg/Kg) alone for prophylaxis of post spinal shivering.

A limitation of this study is that we could not measure the core body temperature. For measurement of core body temperature, the probe needs to be put in the esophagus, near the tympanic membrane, in the nasopharynx, or in the rectum that considered uncomfortable and unacceptable to patients who have been given spinal anesthesia. Other limitations in our study include a relatively small sample size in proportion to the burden of this perioperative problem, and short time of monitoring patients postoperatively.

VI. Conclusion:

In conclusion tramadol (0.5mg/kg) plus midazolam (0.05mg/kg) and nalbuphine (0.1mg/kg) plus midazolam (0.05mg/kg) had the same effect in the treatment of post spinal anesthesia shivering, with no statistically significant difference between them.

We recommend further studies with a large number of patients, and with measurement of core temperature with the same drugs or with other drugs to detect their effect in the treatment of post spinal anesthesia shivering.

References:

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