The Effect of Intrathecal Meperidine on Shivering during Knee Arthroscopic Meniscectomy under Spinal Anesthesia

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INTRODUCTION

Most patients who undergo surgery experience intraoperative and postoperative hypothermia because of misregulated body temperature due to anesthesia as well as the cold temperature of the operation room.(1) In addition to perioperative hypothermia, shivering is a common complication that may occur in patients.(2) Although the reported incidence of shivering varies depending on the study, the incidence is estimated to be 56.7%.(3)

Perioperative shivering causes patient discomfort because of severe muscle movements, and it also induces elevated blood pressure and tachycardia. This eventually leads to increased oxygen consumption, increased carbon dioxide synthesis that results in an increased pulmonary ventilation capacity and cardiac workload, and an increase in the metabolic rate by up to 400%. (4)

Spinal anesthesia can be simply and quickly induced and is more advantageous than general anesthesia because it causes fewer systemic complications. Therefore, spinal anesthesia is widely used for knee arthroscopic meniscectomy.

In spinal anesthesia for knee arthroscopic meniscectomy, the anesthetized area, i.e., the sympathetic nerve innervated in the lower limbs, is blocked. This blockade re-distributes the body heat from the center of the body to the periphery. As a result, the afferent temperature signal in the anesthetized area is not transmitted to the thermoregulation center located in the hypothalamus. This causes a disruption of normal temperature regulation, resulting in a decreased core temperature and increased shivering.(5-7)

Various methods have been used to prevent and treat shivering in patients who receive spinal anesthesia.(8) Of these, meperidine appears to be the most effective treatment agent for perioperative shivering. (9) Meperidine, an opioid \( \mu \) (Mu)-receptor and \( \kappa \) (Kappa)-receptor agonist that lowers the threshold for vascular constriction, is known to effectively prevent and treat shivering. (10)

Given this background, we concomitantly administered an intravenous infusion of meperidine with a local anesthetic for spinal anesthesia in patients who were undergoing knee arthroscopy (meniscectomy). Then, we examined the effects of this treatment regi-
men on the inhibition of shivering in patients under spinal anesthesia.

METHODS

1. Patients

We examined 40 adults who were scheduled to undergo knee arthroscopic meniscectomy under spinal anesthesia and who met the ASA physical status I or II. We excluded patients with a past history of illness, patients with cardiovascular diseases including coronary artery disease or ECG abnormality, and patients who were not undergoing regional anesthesia.

2. Anesthesia & Evaluation

The spinal anesthesia was performed after drainage of cerebrospinal fluid was confirmed by a lumbar puncture using a 26-gauge Quincke needle between L4 and L5 in the lateral decubitus, which is ipsilateral to the surgical site. For all patients, written informed consent was obtained for anesthesia. For pre-anesthetic treatment, an intramuscular infusion of midazolam (0.05 mg/kg) was made approximately 30 minutes prior to spinal anesthesia. Using a patient monitor (M3046A, Philips, Germany), blood pressure and heart rate were measured three times at 5-minute intervals for 15 minutes prior to anesthesia. These measurements were averaged to determine the mean blood pressure and heart rate prior to anesthesia. The temperature and humidity of the operation room were maintained at 20 ±2°C and about 60%, respectively.

Our patients were randomly assigned to two groups of 20 patients each (Groups M and N). In the M group, we used a 0.5% high specific volume bupivacaine (Marcaine®, AstraZeneca, Sweden) (10 mg) plus meperidine (Pethidine®, Hana Pharmaceutical Corp, Korea; no preservative) (0.2 mg/kg) as the spinal anesthetic agent. In the C group, we used 0.5% bupivacaine (10 mg) plus saline (0.004 ml/kg). Following the administration of the medication, the puncture needle was removed. The patient was immediately moved to the horizontal supine position. The patients then received an infusion of 5 ml/kg of Hartman’s solution for approximately 30 minutes. From then on, blood pressure and heart rate were measured five times at 2-minute intervals and thereafter for 60 minutes at 10-minute intervals. In cases where the systolic pressure was lower than 90 mmHg or had decreased by more than 20% compared to baseline, a vasopressor ephedrine was intravenously infused to control the blood pressure. The body temperature was measured for 30 minutes at 5-minute intervals using a Thermoscan® (Instant Thermometer HM3, Braun, San Diego, USA) on the tympanic membrane.

Following the induction of anesthesia, the range of the sensory block was measured by a cold test using an alcohol-soaked cotton at 1-minute intervals, and the maximum height of the sensory block was determined. To more objectively assess the occurrence of shivering following spinal anesthesia, observers were blinded to the type of drug administered. The occurrence of shivering was assessed at 5-minute intervals for 30 minutes following anesthesia and then 45 and 60 minutes later.

3. Statistical Analysis

The presence and extent of shivering in the patients were classified by observers according to the criteria by Singh et al.,(2) as shown in Table 1. We also noted if there were other side effects, such as nausea, vomiting, or headache. In cases of nausea or vomiting, 4mg ondansetron was administered. All the results were recorded as the mean ± standard deviation. Statistical analysis was performed using SPSS 12.0.

Demographic data, the incidence of shivering, the
### RESULTS

There were no significant differences in age, height, weight, surgical time, height of sensory block, or body temperature between the two groups prior to anesthesia (Table 2).

Prior to spinal anesthesia, the mean arterial pressure was 96.4±9.8 in the M group and 97.2±8.5 in the C group. Following spinal anesthesia, however, the mean arterial pressure significantly decreased relative to the baseline in both groups (P<0.05); 86.9±8.3 at 4 minutes and 88.1±9.9 at 6 minutes in the M group and 87.5±8.9 at 4 minutes and 87.9±9.2 at 6 minutes in the C group. There were two patients in group M and two patients in group C who were given ephedrine (Table 3). Thereafter, their mean arterial pressure did not significantly decrease (Fig. 1).

The heart rate also decreased to some extent following spinal anesthesia, but this was not statistically significant because no bradycardia or tachycardia were identified. There was no significant difference in heart rate between the two groups (Fig. 2).

Following spinal anesthesia, shivering was noted in seven patients from the M group and 16 patients from the C group. This showed that there was a significant difference in the incidence of shivering between the two groups (P<0.05) (Fig. 3). With regard to the grade of shivering, of the seven patients of the M group who

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Table 1. Classification of Shivering

<table>
<thead>
<tr>
<th>Grade</th>
<th>Signs</th>
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<tbody>
<tr>
<td>0</td>
<td>No shivering</td>
</tr>
<tr>
<td>1</td>
<td>One or more of piloerection, peripheral cyanosis without other cause, but without visible muscular activity</td>
</tr>
<tr>
<td>2</td>
<td>Visible muscular activity confined to one muscle group</td>
</tr>
<tr>
<td>3</td>
<td>Visible muscular activity in more than one muscle group</td>
</tr>
<tr>
<td>4</td>
<td>Gross muscular activity involving entire body</td>
</tr>
</tbody>
</table>

Table 2. Demographic Data and Baseline Variables (Data are expressed as mean±SD.)

<table>
<thead>
<tr>
<th></th>
<th>Group M (n=20)</th>
<th>Group C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.9±8.2</td>
<td>31.5±7.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.1±9.7</td>
<td>175.4±8.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.3±7.2</td>
<td>69.9±5.9</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>61.4±3.5</td>
<td>64.4±4.1</td>
</tr>
<tr>
<td>Highest segment blocked, median (range)</td>
<td>T9 (T8 to T10)</td>
<td>T9 (T7 to T10)</td>
</tr>
<tr>
<td>Baseline temperature (°C)</td>
<td>36.2±0.4</td>
<td>36.3±0.3</td>
</tr>
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</table>

Table 3. Incidences of nausea and vomiting, and requirement of ephedrine for hypotension after spinal anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Group M (n=20)</th>
<th>Group C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ephedrine requirements</td>
<td>6</td>
<td>6</td>
</tr>
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</table>
Fig. 1. The changes in mean arterial pressure between groups M and C. Filled circles represent group M, simple circles represent group C, and each bar represents the mean±SD. Group C (n=20) received spinal anesthesia that consisted of hyperbaric bupivacaine (0.5%; 10 mg) and normal saline (0.004 ml/kg). Group M (n=20) received spinal anesthesia that consisted of hyperbaric bupivacaine (0.5%; 10 mg) and meperidine (0.2 mg/kg). There were no significant differences between groups M and C.

*P<0.05: Compared to pre-op values within each group.

Fig. 2. The changes in heart rate between groups M and C. Filled circles represent group M, simple circles represent group C, and each bar represents the mean±SD. Group C (n=20) received spinal anesthesia that consisted of hyperbaric bupivacaine (0.5%; 10 mg) and normal saline (0.004 ml/kg). Group M (n=20) received spinal anesthesia that consisted of hyperbaric bupivacaine (0.5%; 10 mg) and meperidine (0.2 mg/kg). There were no significant differences between groups M and C.

presented with shivering, four were Grade 1, two were Grade 2 and one was Grade 3 and no patients were Grade 4. Of the 16 patients in C group who presented with shivering, four were Grade 1, six were Grade 2, five were Grade 5 and one was Grade 1 (Fig. 4). These results illustrate that there is a significant difference in the intensity of shivering between the two groups (P<0.05). No significant changes were noted in body temperature, which was slightly decreased for 5~10 minutes following spinal anesthesia. However, the intra-group and inter-group differences did not reach statistical significance.

The occurrence of nausea, which is another side effect, was not significant; it was seen in two patients from C group and in one patient from M group (Table 3).

DISCUSSION

In the field of orthopedic surgery, for short surgeries of approximately an hour, such as a knee arthroplasty or surgery of the region below the knee, a prompt recovery from anesthesia, early discharge, and stabilization of the cardiovascular system are required. Spinal anesthesia is therefore widely used for these surgeries. Spinal anesthesia causes well-established side effects such as nausea, vomiting, headache, and dyseria, for which treatment has been extensively examined. Another side effect is shivering, defined as the involuntary movement of muscles, which can cause discomfort in patients. Postoperative pain may promote the development of shivering in some cases.(11) Perioperative monitoring of vital signs including body
temperature is essential for the safety of patients. In particular, the management of body temperature following anesthesia is closely associated with the postoperative outcome and patient status. The perioperative occurrence of shivering may complicate the use of a monitor,(12,13) and may increase the intraocular pressure,(14) intracranial pressure,(15) oxygen consumption, and synthesis of carbon dioxide by two- or three-fold. The resulting increase in metabolic demand causes difficulties in patients with a fixed cardiac output, limited pulmonary capacity, and intrapulmonary compartments.(4,16)

The mechanisms by which shivering develops remain unclear. The etiology of shivering is assumed to be heat loss during surgery and anesthesia. But there is significant controversy surrounding the occurrence of hypothermia due to heat loss. Jones and McLaren(17) reported that the incidence of postoperative shivering was associated with the decrease in body temperature as measured through the esophagus. But Pflug et al. contradicted the reports of Jones and McLaren. Pflug et al.(8) noted that there was no significant difference in core temperature between patients who presented with shivering and those who did not. In the present study, we measured the core temperature at the tympanic membrane and found no significant differences in temperature between shivering and non-shivering patients.

Several hypotheses have been proposed to explain the occurrence of postoperative shivering,(5-7) including: (1) re-distribution of heat or body temperature, where core temperature and peripheral temperature are generated due to the re-distribution of heat from the center to the periphery because of the temperature difference; (2) loss of thermo-regulatory vasoconstriction below the level of the anesthetized area, resulting in increased heat loss from the body surface due to the excessive thermogenesis; and (3) altered thermoregulation due to a slight decrease of vasoconstriction and a mild increase in the sweat threshold.

As described above, the etiology of shivering has not been fully elucidated, but it is likely there are various...
etiolgies. While there have been a number of studies on shivering, the treatment regimen for shivering have not been established. The conventional treatment regimen for shivering include elevating the temperature of the operation room, warming the body temperature, and using drugs such as meperidine, clonidine, morphine, fentanyl, nalbuphine, butophanol, taurine, doxapram, and ketanserin.\(^{(18,19)}\)

Clonidine is an alpha-2 receptor agonist that acts on the \(\alpha-2\) receptor located in the presynaptic axon terminal. It inhibits the release of noradrenaline, which suppresses the hypothalamus\(^{(20)}\) and inhibits afferent conduction in the area of spinal cord, which lowers the threshold for thermoregulation of CNS. Further, it suppresses the efferent pathway that responds to shivering. Therefore, clonidine is effective in the treatment of shivering. It is noteworthy, however, that the effectiveness of clonidine is related to the administration time, dose, and administration period. The side effects of clonidine include hypotension, bradycardia, and excessive sedation.\(^{(21,22)}\)

Ketanserin is an alpha receptor antagonist that is effective at elevating body temperature, but it has a later onset time than clonidine.\(^{(23)}\)

In a clinical setting, doxapram is used to reduce the postoperative occurrence of pulmonary complications and alleviate lesions in cases of pulmonary complications.\(^{(24)}\) Doxapram acts on a chemoreceptor in the peripheral carotid artery and it indirectly stimulates the respiratory center in the medulla oblongata, thereby promoting respiration. Sarm and Fry\(^{(25)}\) and Singh et al.\(^{(12)}\) reported that doxapram was noticeably effective in treating the occurrence of shivering following anesthesia. However, doxapram may cause hypertension, tachycardia, and vomiting as a result of CNS stimulation.\(^{(26)}\)

In addition, opioids have been used as treatment agents for shivering. The opioid, fentanyl, is known to affect the normal physiologic response to hypothermia, thus reducing the occurrence of shivering.\(^{(18)}\)

Of the above-mentioned treatment regimens, an intravenous infusion of meperidine is considered the gold standard. Compared to other opioids, meperidine has a marked anti-shivering effect and is therefore most widely used to treat and to prevent shivering.\(^{(26)}\) Meperidine is an opioid receptor antagonist that shows the greatest affinity for the \(\mu\)-receptor and has a moderate degree of affinity for the \(\kappa\)- and \(\mu\)-receptors.

Many studies have reported that meperidine shows a greater anti-shivering effect than a similar dose of morphine or fentanyl, with have affinity for the \(\mu\)-receptor. It can therefore be inferred that meperidine has a greater anti-shivering effect than other opioid analgesic drugs due to its affinity for the \(\kappa\)-receptor. The exact mechanism by which meperidine mediates its anti-shivering effect has not been elucidated. According to some clinical studies, however, meperidine significantly decreases the threshold for vasoconstriction, slightly increases the threshold for sweating, and reduces the threshold for shivering.\(^{(27)}\)

The anti-shivering effect of meperidine is persistently maintained by administration of the general opioid reversal agent, naloxone, at a dose of 0.5 \(\mu g/kg/min\). It has been reported that an approximately 10-fold increase in dose of naloxone abolishes the anti-shivering effect of meperidine. This suggests that the anti-shivering effect of meperidine is mediated through the \(\kappa\)-receptor rather than the \(\mu\)-receptor.\(^{(11,28)}\)

As described here, an intravenous infusion of meperidine causes no pain unlike its intramuscular infusion, and it is very effective in the prevention and treatment of shivering. But an intravenous infusion of meperidine may produce unexpected side effects such as nausea, vomiting, pruritus, hypotension, bronchospasm, bradycardia, and respiratory insufficiency. However, these side effects can be minimized by an
intrathecal infusion of meperidine.

It should be noted, however, that a single use (0.5~1.8 mg/kg) of meperidine for spinal anesthesia has a powerful effect as a local anesthetic and it has also been reported that a higher dose (50 mg) of meperidine causes respiratory depression in a dose-dependent manner. In the present study, however, the dose of meperidine was fairly low (0.2 mg/kg), so respiratory depression did not occur. Further, in a comparison of the maximum height of the sensory block, there was no significant difference between the two groups. This indicates that an intrathecal infusion of a minimal dose of meperidine contained in a local anesthetic prevents the occurrence of shivering, does not affect the height of the sensory block, and minimizes the occurrence of side effects associated with an intravenous infusion of meperidine.

CONCLUSIONS

In conclusion, when meperidine (0.2 mg/kg) is added to a local anesthetic for spinal anesthesia, the occurrence and intensity of shivering can be effectively reduced, but not completely eliminated. Further studies are warranted to determine the optimal dose of meperidine for clinical use.

ABSTRACT

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REFERENCES


