

Comparison of preemptive effect of intravenous ketorolac versus meperidine on postoperative shivering and pain in patients undergoing cesarean section under spinal anesthesia: A prospective, randomized, double-blind study

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Abstract

Background: Pain and shivering are two unpleasant problems in postoperative period. Various techniques are used to alleviate the postoperative shivering and pain. We compared the preemptive prescription of a single dose of intravenous meperidine and ketorolac on postoperative pain and shivering in patients undergoing cesarean section with spinal anesthesia.

Methods: One hundred and fifty patients who were scheduled for elective cesarean section under spinal anesthesia were randomly allocated to one of three study groups to receive intravenous ketorolac (group K), meperidine (group M) or normal saline (group P). Time to first analgesic request, analgesic requirement in the first 24 hours after surgery, body tympanic temperature, hemodynamic variables and incidence of shivering were assessed as outcome variables.

Results: There was no significant difference between meperidine and ketorolac groups in terms of prevalence of shivering, although both groups were different from the placebo group ($p < 0.04$). The mean time to first analgesic request was longer in group k (3.8 ± 1.4) and groups M (3.3 ± 1.2) than in group P (2.1 ± 0.8) hours ($p < 0.001$).

Conclusions: The preemptive prescription of a single dose of intravenous meperidine and ketorolac can provide a satisfying analgesia immediately after surgery and decrease shivering prevalence without any serious side effects.

Keywords: Shivering, Ketorolac, Meperidine, Spinal anesthesia, Cesarean section

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Postoperative pain and postanesthetic shivering remain two common problems after surgery. These problems should be managed to improve the outcome and satisfaction of patients. In a review of 21 studies, median incidence of shivering related to regional anesthesia was reported as 55% (1, 2). Shivering may increase cardiac output, circulating catecholamine's, intracranial and intraocular pressures, and blood pressure (3,4). Furthermore, it is considered as a responsible factor for exacerbating postoperative pain and patient discomfort (5, 6). Pain control after cesarean section improves breastfeeding and mother satisfaction. In addition, postoperative pain is associated with neuroendocrine responses (6). It is believed that central sensitization is one of the mechanisms implicated in chronic postoperative pain (7, 8). Postoperative pain could be a provocative factor for postoperative shivering and its appropriate treatment prevents non-thermoregulatory tremors (9-11). Shivering also causes aggravating of postoperative pain by stretching of sutures. Painful stimulation slightly increases the vasoconstriction threshold anesthesia (11). Several techniques are used for the prevention and treatment of postoperative pain and shivering, such as administration of meperidine, buspirone, nefopam, clonidine, alfentanil, dolasetron, ketanserin, doxapram, and dexmedetomidine (12-15).

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Meperidine is widely used to treat postoperative shivering and pain (4, 12, 13). Although its mechanism of action is not completely clear, meperidine probably acts directly on the thermoregulatory center or via agonistic effect on μ and κ -opioid receptors (4, 16, 17). Like many other narcotics, meperidine has various side-effects such as respiratory depression, hypotension, tachycardia, nausea, vomiting, itching, decreased gastrointestinal (GI) motility, and physical dependency (17). Furthermore, it is reported that only a single administration of an opioid may also induce a long-lasting reduction of threshold of pain sensitivity, which leads to delayed hyperalgesia and somewhat increased incidence of postoperative shivering (18-21). Therefore, the potential clinical advantages of new drugs in this setting need to be evaluated.

It is proposed that steroidal and non-steroidal anti-inflammatory agents (NSAIDs) prevent postoperative shivering through either reduction of postoperative pain or inhibition of releasing vasoconstrictor and pyrogenic cytokines (6, 22-26). Ketorolac (NSAIDs category) has analgesic properties through direct anti-inflammatory effects. Moreover, ketorolac neither causes respiratory depression, nor other side-effects such as vomiting, itching, hyperalgesia effect, and hemodynamic instability, although, it has some gastrointestinal and antiplatelet effects (27). We hypothesized that ketorolac may relieve pain and shivering after cesarean section without pruritus, respiratory depression, hemodynamic instability, or hyperalgesia, (at least as much as meperidine). In order to test our hypothesis, we designed a randomized, double-blind, placebo-controlled study to compare the postoperative analgesic and anti-shivering effects of ketorolac and pethidine in patients undergoing cesarean section under spinal anesthesia.

Methods

This trial has been registered in Iranian Clinical Trial Registry (IRCT201104073051N4). Following approval of ethics committee and informed patient's consent, a randomized study was started with one hundred and fifty adult patients. All patients had physical status I and II according to American Society of Anesthesiologists (ASA) aged 18 to 40 years. They were also scheduled from October 2014 to November 2015 for elective cesarean section under spinal anesthesia at Kowsar Hospital which is a referral Obstetrics/Gynecology center in Qazvin, Iran. Patients with

ASA physical status III or IV, cardiac arrhythmias, myocardial insufficiency, body temperature $>37.5^{\circ}\text{C}$, muscle diseases, Parkinson disease, administration of opioids for long term treatment, history of hypersensitivity to nonsteroidal and steroidal anti-inflammatory agents and peptic ulcer were excluded. Randomization was undertaken by means of computer generated random number in sealed opaque envelopes. Blinding was achieved using equal amounts of drugs (2 mL), while each syringe was labeled as A, B, and C per its content. Identical coded syringes prepared by the personnel (who were not involved in the study) were randomly handed to the anesthetists, who were unaware of the identity of the drug formulations. The patients were randomly divided into three groups of 50 each. Ten minutes before the spinal anesthesia, group K received 30 mg ketorolac, group M received 50 mg meperidine and group P received 2 ml normal saline intravenously.

Thermometry from tympanic membrane was done 10 min before anesthesia and every 30 minutes after surgery up to an hour. Temperature of operating room was approximately 22°C . All patients received 5-7 ml/kg lactated Ringer's solution before spinal anesthesia. After using an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via a midline approach into the L4-5 interspaces, while the patient was in a sitting position with 2.5 ml bupivacaine 0.5% in all three groups. The primary outcomes were to evaluate the time to first requirement of analgesic supplement, total analgesic consumption in the first 24 hours after surgery, and incidence and severity of postoperative shivering. Postoperative analgesia was defined as the time from intrathecal injection of the anesthetic solution to the first request for analgesics. Patients were trained preoperatively for the use of the visual analogue scale (VAS) of pain from zero to 10 (0 no pain, 10 maximum imaginable pain) for pain assessment.

If the VAS exceeded four and the patient needed a supplement analgesic, apotel 500 mg was given intravenously as postoperative pain relief. Shivering was classified as mild (muscular activity in only one muscle group), moderate (muscular activity in more than one muscle group but not generalized) and severe (shivering involving whole body). After the end of any surgery, shivering scores were assessed by an anesthesiologist resident who was unaware of the patients' assignment in the PACU (Post Anesthesia Care Unit) for a minimum of 60 minutes for observation. If shivering was severe, 8 mg of ondansetron

was given intravenously (IV). The secondary outcomes included hemodynamic variables.

To calculate the sample size, data from previous similar studies were taken into consideration (2, 6). A sample size of 40 patients per group were required to provide 90% power to detect a reduction of the incidence of post-anesthetic shivering from 50% to 25%. To compensate for dropout cases and shifting from normality in data distribution, 50 cases were recruited in each group. Normal distribution of the data was tested by Kolmogorov-Smirnov test. Normally, distributed data were expressed as means and standard deviations (SD). Analysis of variance (ANOVA) and repeated measure analysis were used for continuous

parametric variables. Within groups, comparisons were made using the *Tukey's* post-hoc analysis. Chi-square test was used for comparing the incidence of shivering between the groups. A $p < 0.05$ was considered as statistically significant. Statistical analysis was carried out using SPSS Version 16 for Windows (SPSS, Chicago, IL).

Results

One hundred and sixty patients were screened and 150 who met the eligibility criteria were enrolled, consented and randomized.

All enrolled patients completed the trial (figure 1).

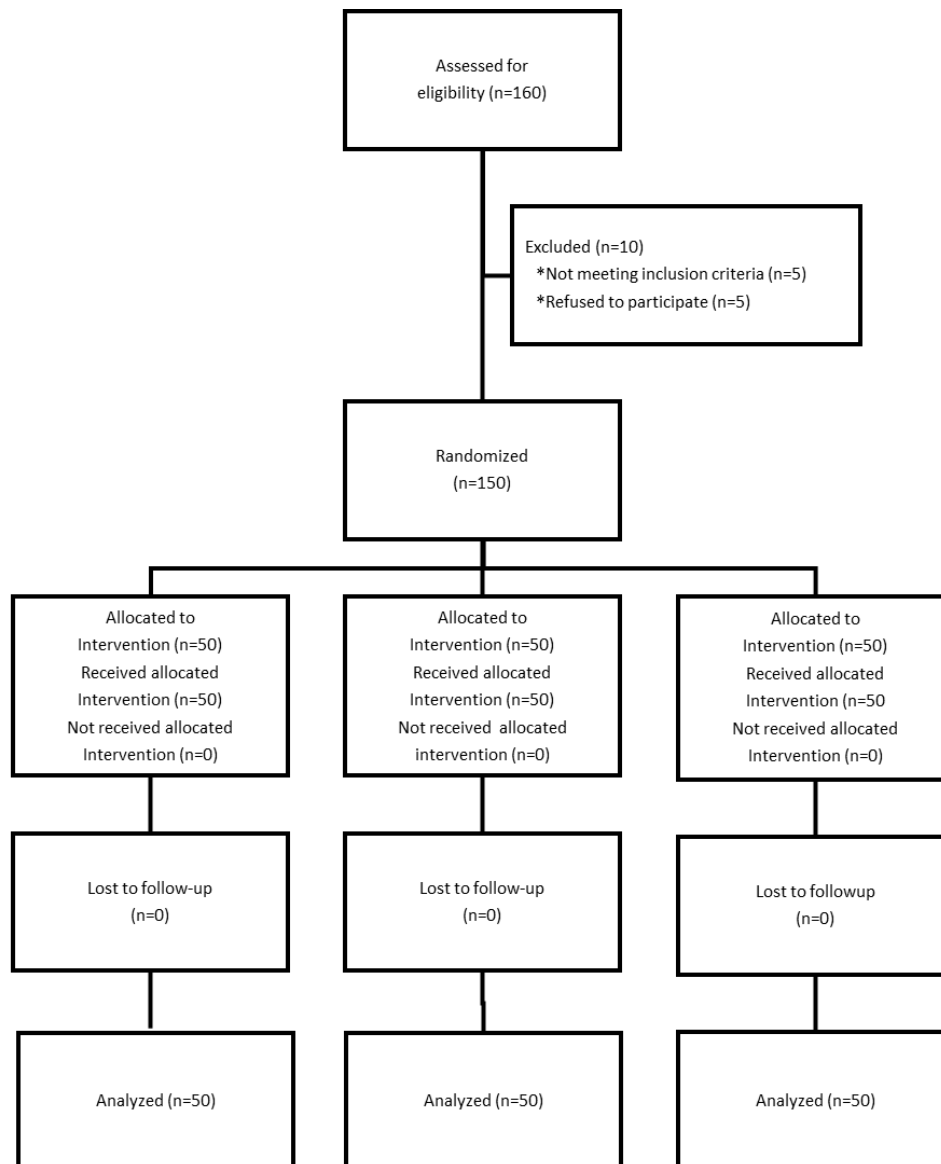


Figure 1. Consort flow diagram

Three groups were similar in terms of age, weight, height, ASA physical status and duration of surgery (table 1). None of the patients received transfusion. As shown in table 2, there was a significant difference between three groups in the overall incidence of shivering for patients sixty minutes after surgery ($P=0.041$). The incidence of shivering after sixty minutes of surgery was 60% in group K, 66% in

group M and 82% in group P. Meanwhile there was a significant difference between the three groups in the severity of shivering during the first sixty minutes after the end of surgery ($P=0.012$). The mean temperature changes in the groups K, M and P were ($0.31\pm 0.11C$), ($0.67\pm 0.09C$) and ($0.71\pm 0.01C$), respectively. This difference was found to be significant among all three groups ($P<0.001$).

Table 1. Demographic data associated with the study

Groups	Ketorolac(N=50)	Meperidine(N=50)	Placebo(N=50)	P-value
	Mean±SD	Mean±SD	Mean±SD	
Weight(kg)	75.21±5.96	72.45±6.59	74.75±6.88	0.169
Height(cm)	160.98±2.9	1.9±160.1	2.1±160.56	0.409
Age(years)	6.9±27.4	6.1±27.9	7.8±28.3	0.801
Duration of surgery(min)	85.63±15.70	79.16±20.11	81.70±18.76	0.840

Table 2. Incidence and severity of shivering

Shivering	Ketorolac N=50	Meperidine N=50	Placebo N=50	P value
Incidence, n (%)	30(%60)	33(%66)	41(%82)	0.041
Severity (a, b, c,)	4,8,18	8,12,13	2,10,29	0.012
Treatment (Ondansetron)requirement	18(%60)	13(%39.4)	29(%70.7)	0.042

Values are number (percent age) of patients. a) mild shivering, b) moderate shivering, c) severe shivering.

As shown in figure 2, the mean time to first analgesic request was significantly longer in groups K (3.8 ± 1.4) and M (3.3 ± 1.2) compared to group P (2.1 ± 0.8 hours) ($p<0.001$ for both comparisons). However, the difference between groups K and M was insignificant ($P=0.06$) through *Tukey's* post hoc test. The total analgesic consumption by patients during the first 24 hours after surgery in ketorolac and meperidine groups was significantly smaller than in control group ($P<0.001$) while we failed to find a significant difference between K and M groups ($P=0.41$). There was no respiratory depression, excessive blood loss, and urinary retention in our patients and the SPO₂ was in the normal range.

Figure 3 shows that the mean arterial pressure (MAP) variation between three groups was significant ($P=0.001$), while the difference between ketorolac and meperidine groups was insignificant ($P=0.42$). The mean difference of heart rate (HR) variation was also significant between three groups ($P=0.001$). Neither gastrointestinal problems, respiratory complication nor postoperative hemorrhage (due

to platelet aggregation disturbances) were reported in patients.

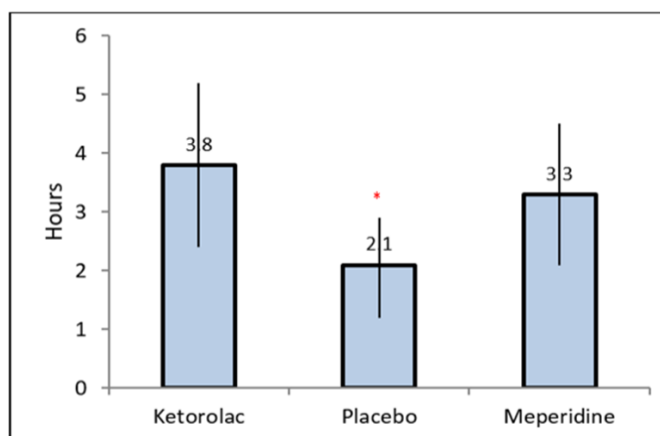


Figure 2. Comparison of analgesic duration in three study groups

Data were expressed as mean and error bars representing SD deviation values. *Significant difference between the three groups.

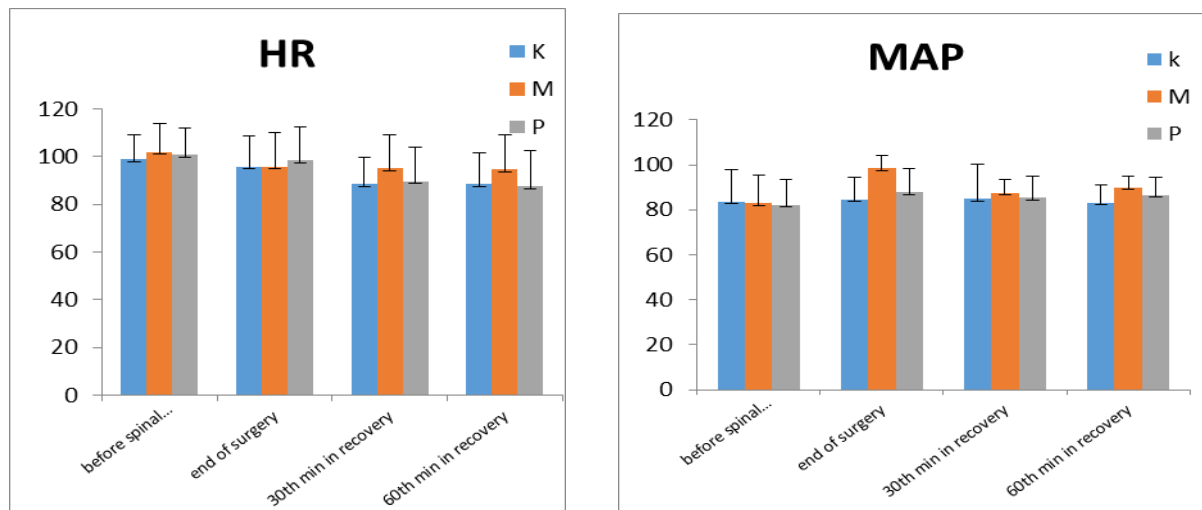


Figure 3. Hemodynamic changes including heart rate (bpm) (HR) and mean arterial blood pressure (mmHg) (MAP)
K=Ketorolac, M= Meperidine, P=Placebo. Data are expressed as mean and error bars representing standard deviation.

Discussion

Based on the results, ketorolac and meperidine were equally effective in reducing shivering incidence and pain control after cesarean section. To the best of our knowledge, this is the first study in which the effect of ketorolac on postoperative shivering has been evaluated. Our findings support the effect of ketorolac on shivering that was indirectly proposed by several other studies. Those reports showed that steroidal and non-steroidal anti-inflammatory agents prevent postoperative shivering through either inhibition of vasoconstrictor and pyrogenic cytokine release or reduction of postoperative pain (6, 22-26).

Our findings report comparable incidence of shivering when using ketorolac or pethidine intravenously. The overall results of the current study are almost consistent with that of other studies (5, 22-23), however, the overall incidence of shivering in all three groups of our study is higher than what others have reported. This difference may be due to different methods of anesthesia, populations, and methodologies of shivering assessment. Though hypothalamic thermoregulation remains intact during regional anesthesia, it is associated with greater heat loss than general anesthesia which can be attributable to abnormal heat loss (due to vasodilatation), impairment of shivering in the area of block, and rapid intravenous (IV) infusion of cold fluids (28, 29). There might be few possible explanations for the effect of ketorolac on the prevalence of postanesthetic shivering.

Firstly, suppression of the inflammatory response and activity of pyrogenic cytokines may lead to a reduction in the incidence of shivering. This effect is similar to other anti-inflammatory agents; as they reported a lower incidence of shivering by dexamethasone, hydrocortisone and sodium diclofenac in the previous studies (6, 22-26). The results of the present study support the role of the inflammation process in the etiology of shivering. Another explanation could be the role of postoperative pain that is reported to stimulate shivering. Sufficient postoperative pain treatment prevents non thermoregulatory tremors; therefore, it could be concluded that the administration of ketorolac causes a decline in postoperative shivering through reduction of pain. In agreement with this idea, Horn et al. also declared that the incidence of shivering was high in the patients who did not receive intra-articular lidocaine, and it was suggested that pain is an important provocateur for shivering (9). This result is also consistent with the observation in patients who have shivering like tremor during labor (10).

The other considerable observation is that the mean temperature change in the ketorolac group was smaller than the others, while shivering incidence in both meperidine and ketorolac groups was similar. This finding is in agreement with the idea that suggests both steroids and non-steroidal agents reduce the temperature gradient between skin and core temperature. It also

supports the hypothesis that shivering is not a phenomenon induced only by intraoperative hypothermia and thermoregulatory mechanisms (6, 22-26, 28, 29).

Another observation that should be noted is that ketorolac and meperidine were equally effective in reducing the analgesic use after cesarean section. This finding is consistent with the results of some other studies which indicate that preemptive intravenous prescription of single dose non-steroidal anti-inflammatory agents can effectively reduce severity of pain (22, 30).

We selected a dose of 30 mg ketorolac which is within the common dose range used by other studies for postoperative pain relief. This dose of ketorolac is a reasonable compromise between efficacy and toxicity (30).

The other finding which should be taken into account is hemodynamic changes with the use of ketorolac or meperidine was statistically lower than placebo. The possible explanation for the hemodynamic stability is that these drugs can prevent high blood pressure and tachycardia by decreasing anxiety, fear and pain. However, our study had some limitations; we did not evaluate the dose-response or the effect of multiple dose therapy. Good pain control after surgery is important to prevent persistent postsurgical pain (7, 30). Further studies are required to evaluate the effect of multiple dose administration of ketorolac to find methods to *prevent* the shivering and postsurgical pain.

In conclusion based on the results of the study, we concluded that the analgesic and anti-shivering effects of 30 mg ketorolac did not have significant difference with 50 mg IV meperidine and therefore, ketorolac could be considered as a good substitution to control postoperative pain and shivering for the patients who have problems with the administration of opioids like meperidine.

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Conflict of Interest: The authors of this paper have not declared any conflict of interest.

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