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Comparison of the Effects of Intrathecal Midazolam and Tramadol with the Conventional Method of Postoperative Pain and Shivering Control after Elective Cesarean Section

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ABSTRACT

Pain is a complex medical issue. Lack of postoperative pain relief adversely affects the physiological, metabolic and mental conditions of patients. Duration of analgesia could increase by using additional supplements. This study aimed to compare the effects of intrathecal midazolam and tramadol with the conventional method of postoperative pain and shivering control after elective cesarean section. This double-blind randomized clinical trial was conducted on 210 women aged 20-35 years with ASA class I and II who were candidates for elective cesarean section. Subjects were randomly divided into three groups of midazolam, tramadol and control to receive hyperbaric lidocaine and midazolam (2 mg), tramadol (25 mg), and normal saline (5 cc), respectively. Using the visual analogue scale (VAS), postoperative pain score and analgesia duration were assessed and compared between the groups. Moreover, scores of shivering during and after the surgery were compared between the groups. According to the results of Kruskal-Wallis, mean score of postoperative analgesia duration was significantly higher in the tramadol group compared to the other groups, while it was higher in the midazolam group compared to control subjects ($P<0.001$). Moreover, mean consumed dose of analgesics at 24 hours after surgery was significantly lower in the tramadol group compared to the other groups, while it was significantly lower in the midazolam group compared to control subjects ($P<0.001$). At different time intervals, postoperative shivering was significantly lower in the tramadol group compared to the other groups, while it was significantly lower in the midazolam group compared to control subjects ($P<0.01$). According to the results of this study, intrathecal midazolam and tramadol supplementary to lidocaine 5% could increase analgesia duration and reduce postoperative shivering after cesarean section, and midazolam was more effective than tramadol in this regard.

Keywords: Midazolam, Postoperative complications, Spinal anesthesia, Tramadol.

INTRODUCTION

Pain is a common postoperative complication, and anesthesiologists primarily aim at the reduction and control of pain after surgical operations[1]. Despite the importance of pain control during surgery, new methods of analgesia for postoperative pain relief have attracted the attention of many researchers. Effective postoperative pain control results in patient satisfaction, decreased length of hospital stay, and reduction of treatment costs[2].

Cesarean section is a freqeunt surgery among women, and postoperative analgesia is an important issue for both patients and surgeons.

Statistics suggest that general anesthesia after cesarean section is associated with a higher risk of mortality compared to local ansthesia[1]. Therefore, local anesthesia is preferable for maintaining the health of the mother and infant.

Today, various techniques are availabe for local ansthesia, the effectiveness of which has been confirmed in pain relief after cesarean section[2,3]. As such, use of these techniques is on the rise due to their easy application and high efficacy[2].

Some of the common complications of anesthesia are pain and shivering, respiratory depression in mother and infant, and nausea and vomiting. Given the importance of infant care by the mother immediately after recovery, use of analgesic drugs with limited side effects and effective anesthetic methods must be priritized in these women[4].

Pain is a complex and multifaceted phenomenon, which is infleunced by various parameters[4,5]. Duration of analgesia could increase through the use of additive compounds (e.g., epinephrine, opioids, neostigmine, midazolam and clonidine) in local anesthetics. Furhermore, these compounds are able to diminish other postoperative complications, such as shivering[6,7].

According to the literature, interathecal administration of midazolam with local anesthetics is effective in regional and neuraxial anesthesia for postoperative pain control. Midazolam has been shown to have remarkable analgesic effects with limited side effects[4]. On the other hand, tramadol, which is an atypical synthetic drug, exerts central analgesic effects, while its intrathecal administration could reduce postoperative pain and shivering[8].

This study aimed to compare the effects of intrathecal midazolam and tramadol with the conventional method of postoperative pain and shivering control after elective cesarean section.

MATERIALS AND METHODS

This interventional, double-blind randomized clinical trial was conducted on 210 women aged 20-35 years with the American Society of Anesthesiologists (*ASA*) physical status class I and II, who were candidates for elective cesarean section.

Sample population consisted of 210 participants who were randomly divided into three groups of midazolam, tramadol and control. An anesthesiologist examined candidates for non-emergency cesarean section referring to Taleghani Hospital of Arak, Iran. After explaining the objectives of the study and obtaining informed consent, eligible women were enrolled in the study.

Random allocation of the participants was performed using a random number table. Estimation of the level of pain was based on a numerical rating scale using the 10-centimeter spectrum of the visual analogue scale (VAS). Patients were asked to mark number 10 in case of severe pain and zero to indicate the absence of pain, while other numbers were marked depending on the intensity of postoperative pain.

Inclusion criteria of the study were as follows: 1) age of 20-35 years; 2) ASA class I and II; 3) no drug addiction; 4) lack of cardiac, renal and liver diseases; 5) no allergies to local anesthetics and 6) consent to receive spinal anesthesia. Exclusion criteria were the patients in whom spinal anesthesia failed and was replaced with general anesthesia, those undergoing spinal anesthesia more than twice, and patients with surgery duration of more than 90 minutes.

Initially, participants were divided into three groups based on the random number table. Candidates aged 35-55 years were administered with crystalloid (3-5 ml per kilogram of body weight) as the compensatory volume expansion. Following that, while patients were in a sitting position, spinal anesthesia was induced by a resident under sterile conditions through injection with a 25-gauge spinal needle between L5-L4 or S1-L5 lumbar regions using 75 mg of *hyperbaric* spinal *lidocaine* 5% (Rion Pharma, manufacturing number: 1295235).

Patients were equally divided into three groups of midazolam (2 mg=0.5 cc), tramadol (25 mg=0.5 cc) and control (0.5 cc normal saline) (70 subjects per

each group). In this study, 2 cc of the solution was injected into the intrathecal space, and surgical operation was performed five minutes after spinal anesthesia reached a T4 level. During the surgery, oxygen flow was set at the speed of 5-6 lit/min thorough a mask, and vital signs of the patients were measured and recorded simultaneously, including blood pressure, heart rate and arterial blood oxygen saturation.

Pain intensity scores of all the patients were evaluated based on VAS during recovery, as well as 4, 12 and 24 hours after the surgery. Moreover, trained nurses who were blinded to the medication use of patients verified the mean prescribed dose of analgesics within 24 hours after the surgery. Additionally, intensity of shivering during the surgery, recovery and four hours after the surgery was recorded in prepared checklists.

This study was performed using a double-blind design, so that patients were justified on their random allocation to each study group. Furthermore, they were assured that none of the medications would cause inconvenience or side effects, and the participants were blinded to the type of the injected anesthetics as well.

A resident performed the administration of spinal anesthesia, and an intern determined the level and score of postoperative pain and mean dose of the consumed analgesics. These individuals were blinded to the type of intrathecal anesthetics. Before injection, researchers and anesthesiologists prepared the anesthetics, and a resident who was unaware of the type of drugs carried out the intrathecal injection.

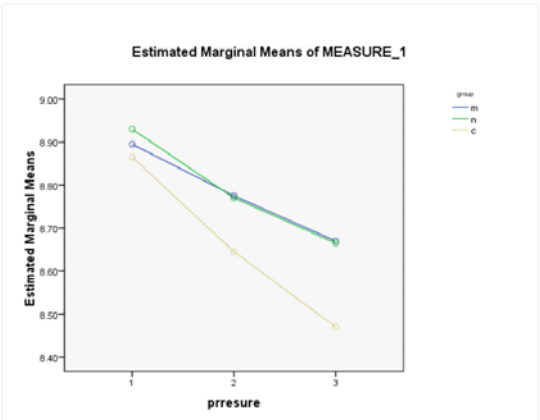

Fig. 1: Mean blood pressure of patients in tramadol, midazolam and control groups before spinal anesthesia

Furthermore, residents who were blinded to the type of anesthetics completed the questionnaires, which consisted of data on the pain intensity score, vital sign chages, mean dose of the consumed analgesics within 24 hours after the surgery, and duration of analgesia.

Data analysis was performed in SPSS version 16 using the Kruskal-Wallis test and analysis of variance (ANOVA). Sample size was determined at 210 subjects selected via simple random sampling, who were equally classified into three groups (70 women per each group). Using random number tables, participants were matched in terms of age, type of surgery, same surgeon in all operations, gender (all female), and no history of previous gynecological surgery. It is noteworthy that our participants had the same surgeon, and duration of surgery was similar in all the subjects according to the exclusion criteria of the study.

Ethical considerations

This study was performed in compliance with the principles and ethical codes of Arak University of Medical Sciences in all the stages. Study procedures and requirements were explained to the patients, and written informed contest was obtained prior to participation.

Tramadol and midazolam have been widely used as complementary drugs for spinal anesthesia, and no spinal complications have been reported in this regard. This article was extracted from a research project.

RESULT

Mean age of the participants in this study was 25.05±5.9 years, which was similar in all the groups. According to within-subjects test, there was no significant difference between the groups in terms of age (P>0.05). Mean arterial pressure before spinal anesthesia was estimated at 82.2±1.4

mmHg in all the groups, which was indicative of no significant difference in this regard (P>0.05).

Before spinal anesthesia, mean heart rate was calculated at 104.5±7.2 bpm in all the groups, which was indicative of no significant difference in this regard (P>0.05). According to our findings, mean duration of analgesia in patients of the tramadol, midazolam and control groups was 192.5±12.2, 111.3±16.6 and 86.1±9.9 minutes, respectively. According to the results of Kruskal-Wallis test, study groups had a significant difference in terms of the duration of analgesia. As such, postoperative analgesia duration was significantly longer in the tramadol group compared to the other two groups, while it was longer in the midazolam group compared to placebo subjects (P<0.001).

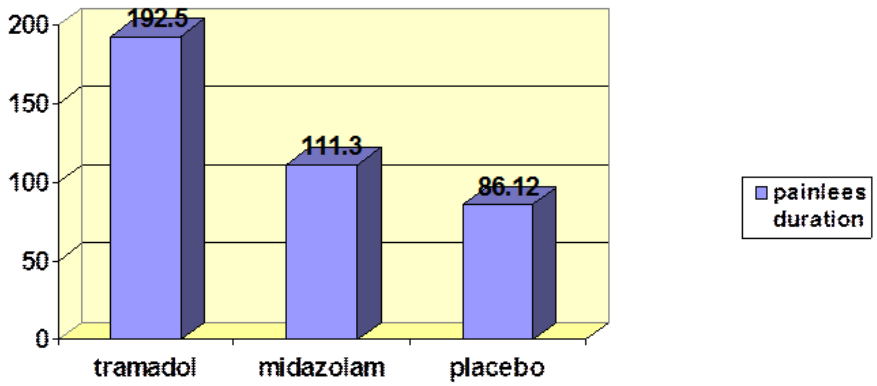

Fig. 2: Mean postoperative analgesia duration in patients of tramadol, midazolam and control groups (min)

Table 1: Pain scores of patients in tramadol, midazolam and control groups during recovery

Time	Groups	Pain score	Statistical test/ P-value
Recovery	Tramadol	0.65±0.23	Kruskal-Wallis ≤0.01
	Midazolam	1.4±0.81	
	Placebo	2.72±0.95	

Table 2: Pain scores of patients in tramadol, midazolam and control groups (4 hours after surgery)

Time	Groups	Pain score	Statistical test/ P-value
4 hours postoperative	Tramadol	3.5±1.1	Kruskal-Wallis ≤0.02
	Midazolam	3.7±1.2	
	Placebo	7.3±2.7	

At 24 hours after the surgery, results of Kruskal-Wallis test indicated that mean dose of

Table 3: Pain scores of patients in tramadol, midazolam and control groups (12 hours after surgery)

Time	Groups	Pain score	Statistical test/ P-value
12 hours postoperative	Tramadol	2.6±4.5	Kruskal-Wallis ≤0.01
	Midazolam	2.9±3.6	
	Placebo	4.8±6.6	

consumed analgesics was significantly lower in the tramadol group compared to the other groups, while it was lower in the midazolam group compared to placebo subjects (P<0.01). In patients of the tramadol group, mean dose of diclofenac suppository was 8.2±2.4, while it was 9.9±2.7 in the midazolam group and 11.2±3.3 in control subjects.

According to the results of ANOVA, mean score of postoperative pain during recovery and 4, 12 and 24 hours after the surgery was significantly lower in the tramadol group compared to the other two groups, while it was significantly lower in the midazolam group compared to control subjects (P<0.01).

With regard to postoperative shivering, study groups had a significant difference, as the mean score of shivering during surgery was lower in patients of the tramadol group compared to the other two groups, while it was lower in the midazolam group compared to control subjects (P<0.01). However, this was not observed during recovery and four hours after the surgery (P<0.02). On the other hand, nausea and vomiting were more prevalent among the patients of tramadol and midazolam groups compared to placebo subjects, which required special care and attention.

DISCUSSION

Findings of this study were indicative of a significant difference in the pain scores of patients in the three groups at 4, 12 and 24 hours after the surgery. Correspondingly, pain score of the tramadol group was significantly lower compared to the other two groups, while the pain score of patients in the midazolam group was significantly lower compared to control subjects.

According to the results of the present study, addition of midazolam or tramadol to lidocaine 5% for postoperative pain control in spinal anaesthesia could result in the discovery of alternative medications with fewer side effects to increase the analgesia duration and decrease pain intensity after caesarean section. This has been a major concern among anaesthesiologists.

Increasing the duration of analgesia prevents several postoperative complications, such as atelectasis, urinary retention, prolonged hospital stay and increased healthcare costs. Therefore, replacement of conventional analgesic methods with new pain-relieving compounds is of paramount importance. Some of the most effective drugs used in previous studies in this regard are ketamine, midazolam, neostigmine and tramadol.

In the current study, patients in the three groups had no significant difference in terms of age, and mean age of the participants was 24.05±5.9 years. With respect to the duration of postoperative analgesia, a significant difference was observed between the groups, as the duration of analgesia was significantly longer in the tramadol group compared to the other two groups, while it was longer in the midazolam group compared to placebo subjects.

Furthermore, mean dose of consumed analgesics at 24 hours after surgery was significantly lower in the tramadol group compared to the other two groups, while it was lower in patients of the midazolam group compared to control

Table 4: Pain scores of patients in tramadol, midazolam and control groups (24 hours after surgery)

Time	Groups	Pain score	Statistical test/ P-value
24 hours postoperative	Tramadol	0.95±0.78	Kruskal-Wallis ≤0.02x
	Midazolam	1.1±2.1	
	Placebo	3.3±3.8	

subjects. In women of the tramadol, midazolam and control groups, mean dose of diclofenac suppository at 24 hours after surgery was 2.4±8.2, 2.7±9.9 and 3.3±11.2, respectively.

Mean score of pain intensity during recovery and at 4, 12 and 24 hours after surgery was significantly lower in the tramadol group compared to the other two grous, while it was lower in the midazolam group compared to control subjects.

Similar studies have also suggested that intrathecal addition of midazolam and tramadol to lidocaine 5% could effectively increase the duration of postoperative analgesia and reduce pain intensity. For instance, in a research conducted in India, Sen A et al. (2001) evaluated the effects of midazolam (2 mg) on postoperative pain control, vital signs of the mother and one- and five-minute Apgar scores of infants in 40 women.

In the mentioned study, all the subjects received 1.5 cc of *lidocaine* 5% and *intrathecal* midazolam (2 mg). According to the results, *intrathecal* administration of midazolam could effectively control the pain after cesarean section, while exerting anti-nausea and tranquilizing effects[31].

In a clinical trial performed by Prakash et al. (2006), 60 pregnant women undergoing elective cesarean section receiving spinal anesthesia were examined. All the patients received 2 cc of bupivacaine 0.5%; the first group received 1 mg of midazolam in addition to bupivacaine, and the second group received 2 mg of midazolam.

According to the results of the mentioned research, mean duration of postoperative analgesia in the control group and experimental groups one and two was 3.8±0.5, 4.3±0.7 and 6.1±1.0 hours, respectively (P<0.001). Moreover, need for diclofenac administration was significantly lower in the second group compared to the first group and control subjects.

On the other hand, nausea and vomiting was significantly higher in the control group. As stated by the researchers, 2 mg of midazolam could induce an average local anesthesia duration and be used as an adjuvant therapy to control nausea and vomiting after cesarean section[33]. These findings are in congruence with the results of the present study. However, frequency of nausea and vomiting was observed to be higher in patients of the tramadol and midazolam groups compared to control subjects in our research, which might be due to the differences in the type of drugs and manufacturers.

Other studies in this regard have also mentioned the higher frequency of nausea and vomiting after surgery in experimental groups compared to control subjects. For instance, Shukla U et al. (2011) compared the effects of clonidine and tramadol on the management of postoperative shivering after spinal anesthesia. Researchers examined 80 patients and reported that clonidine was more effective than tramadol in controlling postoperative shivering. In the mentioned study, complete remission of shivering symptoms in clonidine and tramadol groups occurred at 2.54±0.76 and 5.01±1.02 hours, respectively. Furthermore, response rate was estimated at 97.5% in the clonidine group and 92.5% in the tramadol group (P=NS) (34).

In another study in this regard, Mohata M et al. (2009) compared the effects of three different doses of tramadol (1, 2 and 3 mg/kg), pethidine (0.5 mg/kg) and normal saline on the control of postoperative shivering in patients undergoing elective abdominal surgery with general anesthesia. According to the findings, all tramadol doses were effective in the control of postoperative shivering with no side effects. Therefore, use of this analgesic drug was recommended for the alleviation of postoperative shivering[14].

Another research in this regard was conducted by Honarmand et al. (2008) in Isfahan University (Iran) to compare the effects of prophylactic midazolam, ketamine and combination of both drugs on the control of shivering after spinal anesthesia in 120 orthopedic patients.

According to the results, level of postoperative shivering was 60% in the control

group, 50% in the midazolam group, 23.3% in the ketamine group, and 3.3% in patients administered with both ketamine and midazolam. Evidently, frequency of postoperative shivering was significantly lower in the last group compared to the other patients. Moreover, number of patients with shivering score of lower than three was significantly higher in the control group compared to the other groups[6].

Based on the findings of the aforementioned studies, it could be inferred that tramadol and midazolam increase the duration of analgesia and decrease the level of pain and shivering postoperatively, which is consistent with the results of the present study. It should be noted that none of the mentioned studies compared the effects of these drugs, while in our research, we compared the effects of additive tramadol and midazolam to lidocaine 5%. Our findings were indicative of the higher effectiveness of tramadol in controlling postoperative pain and shivering.

In conclusion, it is recommended that similar studies in this regard be conducted on larger sample sizes to confirm our findings. Moreover, it is suggested that postoperative nausea and vomiting due to the use of these drugs be further investigated.

Limitations of the study

One of the limitations of the present study was the disagreement of some patients with spinal anesthesia or addition of complementary drugs to their regimen; these individuals were excluded from further experimentation. The only postoperative complication in the current study was the slight reduction of the blood pressure in patients of the midazolam and tramadol groups. This was followed by the higher mean heart rate of the participants in these groups due to the higher ephedrine dose. This complication could be controlled through the adequate hydration of patients before surgery.

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