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Effect of Low-Dose Intravenous Ketamine on Prevention of Headache After Spinal Anesthesia in Patients Undergoing Elective Cesarean Section: A Double-Blind Clinical Trial Study

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Abstract

Background: Spinal anesthesia is the most commonly used method for elective cesarean section, which is a popular technique due to its simplicity, reliability, and speed to achieve adequate anesthesia. Headache following dura perforation is the most important delayed complication following spinal and epidural anesthesia.

Objectives: To evaluate the impact of low-dose intravenous ketamine in patients undergoing cesarean section under spinal anesthesia on the prevention of dura perforation headache (PDPH).

Methods: This clinical trial study was performed on 64 pregnant women undergoing cesarean section at Vali-e-Asr Hospital. The patients were divided into two groups. In the case group, 0.15 mg/kg body weight ketamine was injected intravenously and in the control group, normal saline was used as the placebo. The incidence of headache and its severity at one, 4, 12, and 24 hours postoperatively, nausea and its severity were also measured and compared. Independent *t*-test, Mann-Whitney U and chi-square tests were used. A P value < 0.05 was considered statistically significant.

Results: The data revealed that low dose intravenous ketamine significantly decreased patients' headaches ($P = 0.001$), the sensation of pruritus ($P = 0.009$), and the need for analgesic ($P = 0.001$). Furthermore, the sensation of postoperative nausea was less in the case group. The patients in the case and control groups had no significant difference in terms of hypertension or bradycardia ($P = 0.717$ and 0.939, respectively).

Conclusions: The injection of ketamine as a premedication in the cesarean section can reduce the severity of postoperative headache in mothers. Therefore, it is recommended to use ketamine as an anti-headache drug in pregnant women.

Keywords: Spinal Anesthesia, Headache, Cesarean Section, Ketamine

1. Background

Delivery is a completely natural process that requires preventive and supportive measures. Normal delivery applies to mothers who are unable to perform it, otherwise, a cesarean section may be used in cases where childbirth is not possible or if it may pose risks to the mother and infant (1). Over the past few decades, cesarean sections have increased dramatically around the world, causing concern for public health officials (2). According to the latest data from 150 countries, the cesarean delivery rate was 18.6% (3). The highest rates of cesarean delivery were related to Latin America and the Caribbean Sea (mean: 40.5%) and the lowest were reported on the African continent (mean: 7.5%) (3).

Cesarean delivery has many complications for the mother and baby. The most important maternal complications include bleeding, suture infection, endometritis, and increased hospitalization (4). On the other hand, the fetus is at risk for respiratory problems, low Apgar score and increased neonatal death (5). Besides, post-cesarean pain harms maternal activity and quality of life after delivery (6). One of the effective ways to reduce the severity of postoperative pain is to take preoperative treatment such as painkillers. Studies have shown that both local anesthesia and general anesthesia are acceptable methods of anesthesia care for good cesarean delivery. Regional anesthesia

is a more common and safer method than general anesthesia for delivery anesthesia (7). Also, in spinal anesthesia, the likelihood of maternal pulmonary aspiration and fetal distress is minimized (8).

Headache following Dura's perforation, the most important delayed event following spinal and epidural anesthesia, was first reported in 1889 (9). Headache caused by spinal anesthesia is a severe, vague headache that engages the front and back of the head and spreads to the neck and shoulder and sometimes causes a stiff neck. This headache gets worse with movement, sitting and standing, and gets better with sleeping (10). Methods of treatment for headache after spinal anesthesia can include non-narcotic pain killers, caffeine intake, reduction of fasting time before surgery to 8 hours, reduction of auditory and peripheral visual acuity, and if not responding to these treatments epidural blood transfusions can be used (11).

Ketamine is a derivative of phencyclidine and is one of the intravenous drugs used in general anesthesia. The high solubility of this drug in fat guarantees its rapid onset (12). Ketamine is the only intravenous anesthetic drug that has an analgesic effect. The analgesic effect of this drug is administered at low doses (0.1 - 0.8 mg/kg) by inhibiting NMDA receptors (N-methyl D aspartate), which inhibits CNS pain transfer, which may be effective in preventing dura perforation headache (13). Another effect of ketamine is a mild increase in intracranial pressure, so since post-dural puncture headache (PDPH) causes intracranial pressure depletion, ketamine may be effective in preventing PDPH by compensating this decrease in pressure (14).

2. Objectives

This study aimed to use low-dose intravenous ketamine (0.15 mg/kg) in patients undergoing cesarean section under spinal anesthesia to evaluate its effect on the prevention of PDPH.

3. Methods

This double-blind clinical trial was conducted at Vali-e-Asr Hospital affiliated with Birjand University of Medical Sciences, Birjand, Iran. The study population was pregnant women who were candidate for elective cesarean section with spinal anesthesia who referred to Vali-e-Asr Hospital in 2018. According to Behdad et al. (12) study, the minimum sample size for each group was about 29 people with a 95% level of confidence. Taking into account a 20% drop, our study sample size was 32 per group. Convenient sampling was used to select patients from those who met the inclusion criteria. Checklists were used to gather patients' information such as demographic data (age, weight, and height), length of the operation and duration of hospital stay. All information was gathered and recorded in the recovery section.

In both groups, the incidence of headache and its severity at one, 4, 12, and 24 hours postoperatively, nausea, and its severity were also recorded. The frequency of pruritus and meantime of the first analgesic application were also recorded for both groups. The severity of the headache and the severity of the nausea were measured using the visual analog scale (VAS) for pain, which was taught to the patients before the surgery. In case of a headache greater than or equal to 4, diclofenac 100 mg suppository was administered. Pregnant women who were candidate for elective cesarean section with spinal anesthesia who had ASA class 1 - 2, with no history of migraine or other types of headaches, psychological problems and seizures, coagulation disorders, and any drug addiction, were included in the study. The incidence of drug allergy, respiratory complications, severe bleeding, bronchospasm and laryngospasm, changes in anesthesia, and having more than once experience of spinal anesthesia were the exclusion criteria.

This study was approved by Birjand University of Medical Sciences Ethics Committee (code: ir.bums.REC.1397.330). This study was registered at the Iranian Registry of Clinical Trial (IRCT20190202042589N1). At the start of the study, all patients were informed about the goal of the study and informed consent was obtained from all participants. They were insured that their information remains confidential throughout the study. In this study, the patients were randomly divided into two case and control groups, each one consisted of 32 patients. It should be noted that the case group was similar to the control group at all stages of intervention except ketamine administration. The method of blinding was that patients were unaware of the type of the drug received, and the drugs were prepared in encoded uniform syringes by one of the operating room nurses who was not involved in the study.

Spinal anesthesia was performed by a single anesthetist using needle 25 gauge in intervertebral space between L4 - L5. After anesthesia preparation and injection of 2 cc lidocaine 2% with a gray needle (27G) as topical anesthesia, patients underwent spinal anesthesia with the injection of 10 mg marcaine drugs and 20 μg fentanyl in subarachnoid space. After anesthesia was stabilized at the T4 sensory level, and about 5 minutes before surgery, the case group was injected intravenously with 0.15 mg/kg ketamine and in the control group, normal saline was injected as placebo. If blood pressure dropped more than 20% the normal, 5 mg of ephedrine was injected into the

patient. Also, if the heart rate dropped to less than 50 times per minute, 0.5 mg atropine was injected. Cesarean section was then performed as usual in both groups.

Statistical analyses were performed using SPSS for Windows version 15 (SPSS Inc. Chicago, IL). The Kolmogorov-Smirnov test was used to examine normal distribution. Independent *t*-test, Mann-Whitney U, and chi-square tests were used to analyze the data. A $P < 0.05$ was considered statistically significant.

4. Results

Independent *t*-test showed no significant difference between the mean age, height, and body mass index (BMI) of the two groups (P = 0.812, 0.212, and 0.574, respectively). As in Table 1, results of Mann-Whitney U test showed that the mean of headache was different between the case and control groups immediately after the surgery (P = 0.001) and four hours after the surgery (P = 0.002); however, 12 and 24 hours after the surgery there was no significant difference between the groups.

Table 2 illustrates the comparison of itching between the two groups. The results of chi-square test showed that 18.75% of the case group and 50% of the control group had itching immediately after the surgery and this difference was statistically significant (P = 0.009). In contrast, 4 hours after the operation, there was no significant difference between the two groups in terms of itching (P = 0.672). Also, 12 and 24 hours after the surgery, none of the subjects in the case and control groups had itching. The nausea was less in the case group immediately after the surgery and 4 hours after that; however, Mann-Whitney U test showed that these differences were not significant (P = 0.056, and 0.074, respectively).

After examining the quantitative variable normality (time to request the first analgesic), using Kolmogorov-Smirnov test, it was found that this variable did not follow the normal distribution, and nonparametric Mann-Whitney test was performed for comparison of median in the case and control groups (Table 3). The results of Mann-Whitney test showed that there was a significant difference between the time of first analgesic administration in the case and control groups (P = 0.001). The data revealed that there was no significant difference considering bradycardia and hypertension induced by spinal anesthesia between the two groups (P = 0.717 and 0.939, respectively).

Table 1. Comparison of Mean Headache After Spinal Anesthesia in the Case and Control Groups

Headache Time, Group	Number	Average Rating	P Value
Immediately after surgery			0.001
Ketamine	32	22.73	
Normal saline	32	43.59	
4 hours			0.002
Ketamine	32	29	
Normal saline	32	37.13	
12 hours			0.528
Ketamine	32	32.47	
Normal saline	32	33.55	
24 hours			0.528
Ketamine	32	32.47	
Normal saline	32	33.55	

5. Discussion

Spinal anesthesia has been used in recent decades as a low-risk rapid method for semi-inferior body surgery. It has been nearly a century since the introduction of the headache following the puncture of dura mater. However, this complication is still one of the most prominent factors limiting the use of spinal anesthesia (15). According to the findings of the present study, the mean of headache in the case and control groups were significantly different immediately and four hours after surgery. However, there was no statistically significant difference between the two groups at 12 and 24 hours after the surgery.

Sen et al. also showed that the ketamine receiving group (0.15 mg/kg) had less discomfort and pain during spinal anesthesia in the first days after surgery (16). In the study of Behdad et al. aimed at investigating the effect of intravenous ketamine injection on pain relief of spinal anesthesia in pregnant women who underwent cesarean section by double-blind clinical trial, subjects were divided into two groups: ketamine and midazolam users. In accordance with our results, they indicated that the mean pain score in the first hours after the cesarean section was significantly lower in the ketamine group compared with the midazolam group (12).

The rate of headache after spinal anesthesia has been reported between 0.1 - 36%. This range of variation depends on several factors, such as the patient's condition, the technique of injection, and the method of study (17). In the study of Lowder et al., it was shown that administration of ketorolac is efficacious in reducing postoperative pain and the need for narcotics (18). El-Tahan et al. examined the prophylactic use of ketorolac in pregnant women who were candidates for cesarean section in their study and showed that the mean pain score in the first 2 hours after surgery was significantly lower in the ketorolac group than in the control group (19). Another study by Abbas et al. showed

Table 2. Comparison of Pruritus Ratio After Spinal Anesthesia in the Case and Control Groups[a]

Itching	Ketamine	Normal Saline	Total	P Value
Immediately after surgery				0.009
Yes	6 (18.75)	16 (50)	22	
No	26 (81.25)	16 (50)	42	
4 hours after surgery				0.672
Yes	2 (6.25)	3 (9.375)	5	
No	30 (93.75)	29 (90.625)	59	

[a]Values are expressed as No. (%).

Table 3. Comparison of Mean Time of First Request for the Analgesic in the Case and Control Groups

The Variable Under Study	Group	Number	Average Rating	Median (Q1 - Q3)	P Value
Time of taking the first dose of analgesic	Ketamine	32	45.15	600 (540 - 720)	0.001
	Normal saline	32	20.47	240 (180 - 655)	

that the administration of 30 mg of pre-operative ketorolac reduces postoperative pain severity in mothers (20). Contrary to the results of the aforementioned studies, a study by Roche et al. showed that the use of ketorolac was not significantly superior to placebo and was not effective in reducing post-cesarean pain (21). The inconsistency in the results may be due to differences in the method of administration of ketorolac in the investigated studies.

In addition, the results showed that there was no significant difference between the two groups in the mean severity of nausea in the case and control groups immediately, 4, 12, and 24 hours after surgery. Likewise, in the study of Behdad et al., there were no significant side effects in the ketamine user group and ketamine was tolerable for patients (12). Although in Subramaniam et al. study some side effects such as itching, urine suppression, hallucinations, nausea, and vomiting were seen in women, this difference was not statistically significant (22). Meer et al. also showed that the use of ketamine to relieve pain caused by spinal anesthesia had fewer side effects in the cesarean section (23). Bell et al. mentioned in a systematic review that ketamine is beneficial in reducing postoperative nausea and vomiting (24). A study by Song et al. showed that the use of ketamine in patients not only did not reduce the incidence of nausea and vomiting but also increased its prevalence and severity in patients (25). Nausea and vomiting cause stress for the patient, surgeon, and anesthesiologist and it causes distress, disgust, increased anxiety, and inefficiency in patients, and if continued, it leads to lowering blood pressure and lowers heart rate (26). Therefore, prevention and attention to this issue are of great importance.

According to the findings of the present study, there was a significant difference between the time of the first analgesia in the case and control groups. Also, in the study of Behdad et al., the duration of the first analgesia in the ketamine group was significantly longer than that of the midazolam group (12). In a study by Urban et al. on patients who underwent spinal fusion surgery, the use of ketamine resulted in a significant decrease in postoperative narcotic consumption (27). However, in a meta-analysis by Dahmani et al., it was mentioned that ketamine decreases postoperative care unit pain intensity but has no effect analgesic requirement 6 - 24h postoperatively (28).

Furthermore, the results of this study showed that there was no significant difference in blood pressure and bradycardia between the case and control groups. In accordance with our findings, in a study by Nesher et al, patients who received ketamine and morphine had better cardiovascular stability and better respiratory parameters than those who only received morphine (29).

The limitations of this study include the lack of measurement of confounding variables, such as the number of previous pregnancies in mothers, measurement of serum hemoglobin, hematocrit, and neonatal Apgar score. Therefore, we suggested that future studies consider and measure confounding variables, maternal and fetal characteristics, underlying diseases, and other factors that may impact postoperative headache.

5.1. Conclusions

The results of the present study showed that precesarean injection of ketamine significantly reduces postoperative headache in pregnant women. It was also observed that the incidence of pruritus and the time of the first analgesic in the ketamine group were lower from that

of the normal saline group. Therefore, we suggest the use of ketamine as a premedication in spinal anesthesia as it helps reduce the risk of complications, which results in a faster maternal and neonatal communication.

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Footnotes

Authors' Contribution: Malihe Zangoue and Amir Saber Tanha designed the study. Ali Nademi, Malihe Zangoue, and Amir Saber Tanha conducted the clinical trial. Amirsadra Zangouei, Seyed Ali Hossein Zahraei, and Zahra Golafshan wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

Clinical Trial Registration Code: This study was registered at the Iranian Registry of Clinical Trial (IRCT20190202042589N1).

Conflict of Interests: The authors declare that they have no conflict of interest.

Ethical Approval: This study was approved by the Birjand University of Medical Sciences Ethics committee (code: ir.bums.REC.1397.330).

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Patient Consent: Informed consent was obtained from all participants.

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