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The Effect of Low-Dose Intravenous Ketamine on Postoperative Pain Following Cesarean Section with Spinal Anesthesia: A Randomized Clinical Trial

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ABSTRACT

Objectives: Low-dose ketamine has been considered a good substitute for opioids for controlling postoperative pain. The purpose of this study was to determine the effect of low-dose intravenous ketamine following cesarean section with spinal anesthesia on postoperative pain and its potential complications. ***Methods:*** One hundred and sixty pregnant women volunteered to participate in this randomized controlled trial. Participants were randomly divided into two groups (n=80 for each group). Five minutes after delivery, the experimental group received 0.25mg/kg ketamine while the control group received the same amount of normal saline. ***Results:*** There was a significant difference between the two groups in the severity of pain at one, two, six, and 12 hours following surgery. Postoperative pain was significantly less severe in the experimental group. Compared to the control group, the experimental group felt pain less frequently and therefore asked for analgesics less often. On average, the number of doses of analgesics used for the participants in the experimental group was significantly less than the number of doses used for the control group. Analgesic side effects (including nausea, itching, and headache) were not significantly different between the two groups. However, vomiting was significantly more prevalent in the control group and hallucination was more common in the experimental group. ***Conclusion:*** We conclude that administration of low doses of ketamine after spinal anesthesia reduces the need for analgesics and has fewer side effects than using opioids. Further studies are required to determine the proper dose of ketamine which offers maximum analgesic effect. Furthermore, administration of low-dose ketamine in combination with other medications in order to minimize its side effects warrants further investigation.

Everyday millions of people around the world undergo surgical operations and subsequently experience postoperative pain. Postoperative pain has numerous side effects, including (but not limited to) atelectasis, thrombosis, myocardial ischemia, cardiac arrhythmia, electrolyte imbalance, ileus, and urinary retention.[1-3] The aforementioned underscores the significance of effective control of postoperative pain. Cesarean section is one of the most common types of surgeries in the world.[4] Over the past century, cesarean section has significantly reduced the rate of neonatal deaths and has saved the lives of millions of new mothers.[5] Cesareans can negatively affect the physical domains of quality of life for a woman after delivery[6] and postoperative pain is one of the most significant side effects of cesarean section. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[5] Controlling postoperative pain and getting the new mother out of bed and moving as early as possible following the surgery will reduce the respiratory, cardiovascular, urinary, and digestive side effects of surgery. There are numerous medications for controlling postoperative pain. Based on the pros and cons of each medication, as well as the patient's preference, physicians choose the most suitable medication for each patient. Opioids, such as morphine and pethidine, are the most commonly used medications for postoperative pain. However,

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opioids have numerous side effects including addiction, respiratory depression, drug resistance, nausea, and vomiting. Therefore, surgeons generally prefer the use of non-opioid analgesics for reducing postoperative pain.[4]

Numerous studies have examined the effect of different doses of ketamine in combination with other medications in reducing postoperative pain.[4,7-17] However, the results have been contradictory. While some studies have shown that ketamine reduces the pain score and consequently the need for opioids following surgery[8,13,17] others have not found such results.[9,12] Spinal anesthesia can be done using different drug combinations including bupivacaine alone, bupivacaine and fentanyl, bupivacaine and fentanyl and morphine. The effect of ketamine on postoperative pain following spinal anesthesia using different drug combinations has also been investigated.[9]

In this study we examined the effect of low-dose intravenous ketamine on postoperative pain and the need for analgesics, including opioids, following cesarean section with spinal anesthesia using bupivacaine.

METHODS

One hundred and sixty pregnant women who were admitted to the Amiralmomenin Hospital in Semnan, Iran, between April 2013 and March 2014 for elective cesarean section volunteered to participate in this randomized controlled clinical trial (registry number IRCT2012100611019N1).

Women with singleton term pregnancy who were scheduled to undergo elective cesarean section were included in the study. Exclusion criteria were: history of drug abuse, chronic diseases such as diabetes, history of previous cesarean section or any other abdominal surgery, abnormal bleeding during and/or following the surgery, allergic reaction to ketamine, psychological disorders, high blood pressure, high intracranial pressure, history of seizure, and history of hallucination following taking ketamine. Women with contraindications to spinal anesthesia were also excluded from the study.

All participants were informed about the experimental procedure and the potential side effects of the medications used in the study before signing a consent form. All procedures were approved by the Office of Research Ethics of the Semnan University of Medical Sciences.

Participants were randomly divided into equal groups (n=80 in each group). All participants had spinal anesthesia using bupivacaine. The dose of the drug, as well as the method of injection was identical for all individuals; 12.5mg or 2.5cc 0.5% solution, in the L4-L5 space using needle 25, midline, with the patient in a sitting position. The duration of block was considered as the duration between inducing anesthesia at T4 level to back of sensation at umbilicus level. The upper dermatome level was T4 in all patients. Duration of surgery in all participants was recorded. Five minutes after delivery, women in the experimental group received 0.25mg/kg intravenous ketamine via bolus dose, while the control group received the same amount of normal saline. A researcher blind to the aforementioned grouping and the nature of treatment received by each group monitored the participants and recorded if and when the participants felt any pain and asked for sedatives. A numeric pain rating scale was used to record the participants' pain score at one, two, six, and 12 hours following surgery. Participants were asked to rate the intensity of their pain in the scale of one (no pain at all) to 10 (very intense and unimaginable pain). If the patient asked for analgesics, she was given a 100mg rectal diclofenac suppository. If the pain persisted the patient was given another 100mg rectal diclofenac suppository every six hours, with a maximum of four suppositories in 24 hours. In cases where the pain score was greater than five and the pain was persistent and could not be controlled by diclofenac suppositories, pethidine (50mg, intramuscular injection) was prescribed. A maximum of three doses of pethidine were prescribed during the first 24 hours following surgery, with a minimum six hour interval between the two consecutive injections. Participants were monitored for common side effects, such as nausea, vomiting, headache, hallucination, and itching, and the prevalence of such side effects was recorded.

The pain scores, time to first request for analgesia, and the number of diclofenac suppositories and pethidine injections used in the first 24 hours following the surgery were compared between the two groups using t-tests and Mann-Whitney U test. Chi-squared and Fisher's exact test were used to compare the frequency of side effects. The statistic software SPSS was used for all statistical analysis. For all analyses, a *p*-value of less than 0.050 was considered to be significant.

Table 1: Characteristics of participants for the control and experimental groups.

Characteristic	Control group (n=80)	Experimental group (n=80)	*p*-value
Age	27.6±4.4	27.4±4.8	0.700
Weight	77.7±10.8	78.5±11.9	0.600
Duration of surgery (minutes)	39.8±3.2	40.2±3.8	0.500

RESULTS

There was no significant difference between the experimental and control groups in participants' age (mean ± standard deviation (SD)=27.4 ±4.8 years and 27.6 ±4.4 years, respectively; p=0.700) and their weight (78.5±11.9 and 77.7±10.8; p=0.600). The mean ± SD for duration of surgery was 40.0±3.5 minutes (the minimum time was 35 minutes and the maximum time was 59 minutes) while there was no significant difference between the two groups in term of duration of surgery (p=0.500) [Table 1]. All of the participants were primigravida.

There was a significant difference between the two groups in pain scores at one, two, six, and 12 hours following surgery. The pain scores were significantly greater for the control group than the experimental group at all time intervals (p<0.001) [Table 2].

There were significant differences between the two groups in the time to first request for analgesia (p<0.001), time to the first use of diclofenac suppository (p<0.001), and time to the first pethidine injection (p<0.001). The time interval between the surgery and when the patient first complained of pain and requested analgesia was significantly longer for the experimental group than the control group. The time interval between surgery and the first use of diclofenac suppository, and the first pethidine injection were also significantly longer for the experimental group than the control group [Table 3].

Table 2: The mean and standard deviation of pain scores for the two groups of participants at one, two, six, and 12 hours following surgery.

Time interval	Control group (n=80)	Experimental group (n=80)	*p*-value
After one hour	4.95±1.2	3.55±0.31	<0.001
After two hours	5.38±1.06	3.92±1.33	<0.001
After six hours	6.16±0.27	3.90±1.7	<0.001
After 12 hours	4.64±0.47	3.19±0.67	<0.001

Table 3: The time interval (in hours) between the surgery and the first complaint of pain and request for and use of analgesia, and number of their use for the two groups of participants.

Time to (hours)	Control group (n=80)	Experimental group (n=80)	*p*-value
First request for analgesia**	1.36±0.48	2.76±1.28	<0.001
First diclofenac suppository use**	1.48±0.6	2.89±1.33	<0.001
Diclofenac use number***	3(1,4)	2(0,4)	<0.001*
First pethidine injection**	4.10±2.85	6.12±3.79	<0.001
Pethidine use number***	2(1,3)	0(0,2)	<0.001*

*Mann-Whitney U test; **mean±SD; ***median(range)*

There was a significant difference between the two groups in the mean number of doses of diclofenac (p<0.001) and pethidine (p<0.001) received. The mean ±SD of diclofenac received by the experimental and control group were 1.79±2 and 2.86±3, respectively. The mean ±SD of pethidine received by the experimental and control group were 0.44±0 and 1.62±2, respectively.

Everyone in the control group used diclofenac suppositories; however, four participants from the experimental group (5%) did not use diclofenac suppositories at all. The majority of the participants in the control group (n=45) required the first diclofenac suppository during the first hour following the surgery. On the contrary, the majority of the participants in the experimental group who used a suppository (n=23) took the first suppository during the second hour after surgery. This suggests that pain started later in the experimental group than in the control group.

Only one participant from the control group (1.2%) and 46 participants from the experimental group (57.5%) did not require pethidine. Participants in the control group who used pethidine (n=36) required their first injection during the first hour after surgery, whereas participants in the experimental group who required pethidine (n=17) received their first injection during the second hour after surgery. These results further indicate that the initiation of pain was delayed in the experimental group compared to the control group. In total,

Table 4: Frequency of side effects for the two groups of participants.

Side effect	Control group n(%)	Experimental group n(%)	*p*-value
Nausea	25 (31.2%)	26 (32.5%)	0.865
Vomiting*	28 (35.0%)	15 (18.8%)	0.020
Headache	27 (33.8%)	21 (26.6%)	0.301
Hallucination*	8 (10.0%)	18 (22.5%)	0.032
Itching	21 (26.2%)	12 (15.0%)	0.079

**indicates significant difference between the two groups.*

the experimental group received 143 diclofenac suppositories and 35 doses of pethidine, while the control group received 229 diclofenac suppositories and 130 doses of pethidine.

Table 4 summarizes the frequency of common side effects of surgery in the two groups. There was no significant difference between the two groups in the occurrence of nausea (p=0.865) and headache (p=0.301). Although itching was more common in the control group than the experimental group, the difference was not significant (p=0.079). Vomiting was significantly more common in the control group than the experimental group (p=0.020). There was a significant difference between the two groups in hallucination (p=0.032), which was more common in the experimental group than the control group.

DISCUSSION

Postoperative pain is one of the most significant side effects of cesarean section.[5] There are numerous methods for controlling postoperative pain. Opioids, such as morphine and pethidine, are the most commonly used medications; however, they usually cause multiple side effects.[4] In an attempt to avoid the side effects of opioids, many scientists[4,18,19] have examined the effectiveness of different doses of ketamine administered in a variety of methods as an alternative approach for controlling postoperative pain following cesarean section. We examined the effect of low-dose intravenous ketamine (0.25mg/kg) on postoperative pain in women undergoing caesarean section.

Our results showed that the pain scores were significantly greater for the control group than the experimental group at one, two, six, and 12 hours following surgery indicating that participants in the control group experienced a greater level of postoperative pain than those in the experimental group. This finding was similar to reports by Sen and colleagues[13] who showed that postoperative pain scores were significantly lower in elective cesarean section women who received low-dose intravenous ketamine (0.15mg/kg) than those who received an equal volume of normal saline intravenously (control group) and those who received intrathecal fentanyl. Arbabi and Ghazi-Saidi[15] also reported less severe pain in women who received low-dose ketamine for postoperative pain following caesarean section.

In our study, the initiation of pain was delayed in the experimental group, and therefore the time to first request for analgesia was significantly longer in this group than the control group. The longer time to first request for analgesia in women who had received low-dose intravenous ketamine has also been previously reported.[10,13,15] Furthermore, on average participants in the experimental group used fewer doses of analgesics than those in the control group. This finding is in agreement with reports by Arbabi and Ghazi-Saidi.[15]

Low-dose ketamine has been used to control postoperative pain following other types of surgeries too. Dahmani and colleagues[20] showed that local administration of ketamine during tonsillectomy decreases the intensity of postoperative pain and the need for analgesics. Adam et al,[14] examined the effect of low-dose intravenous ketamine in combination with continuous femoral nerve block on postoperative pain and rehabilitation following total knee arthroplasty. The ketamine group required significantly less analgesics than the control group. They also reached 90° of active knee flexion significantly sooner than the control group. The authors concluded that ketamine is a useful analgesic adjuvant in perioperative multimodal analgesia and could contribute to early knee mobilization.

Using a randomized, double-blind placebo-controlled design, Bauchat and colleagues[9] examined the effect of intravenous ketamine 10mg administered during spinal anesthesia for cesarean delivery on the incidence of breakthrough pain, the pain that required supplemental postoperative analgesia. Ketamine was used in addition to intrathecal morphine and intravenous ketorolac. The authors showed that the incidence of breakthrough pain in the first 24 hours following the surgery was not different between the

experimental and the control groups. Furthermore, the pain score in the first 24 hours and the number of analgesics (acetaminophen/hydrocodone tablets) administered during the first 24 or 72 hours following surgery were similar for the two groups. They concluded that low-dose ketamine offers no additional benefit during cesarean delivery in patients who received intrathecal morphine and intravenous ketorolac.[9] The difference between the results of our study and that of Bauchat et al, might be due to the differences in the dose of ketamine. While we used 0.25mg/kg ketamine, Bauchat et al, used 10mg. Furthermore, we used bupivacaine for spinal anesthesia. Bauchat et al, however, used a combination of bupivacaine, fentanyl, and morphine. The aforementioned may have contributed to the diverse findings of the two studies. Nonetheless, Bauchat et al, did report lower pain scores in the group who received ketamine compared to the control group at two weeks postpartum.

In a study by Moshiri and colleagues[11] administrating a low dose of ketamine (0.15mg/kg) did not affect the time to first request for analgesia following cesarean section. Therefore, the authors concluded that low-dose ketamine does not reduce the postoperative pain following cesarean section. Once again, the difference between the findings of our study and that of Moshiri et al, might be due to the differences in the dose of ketamine used, and the sample size. In comparison to our study, Moshiri et al, studied the effect of ketamine on a smaller group of participants (n=120 vs. n=160 in our study), and used a lower dose of ketamine (0.15mg/kg vs. 0.25mg/kg in our study).

The study performed by Kathirvel et al,[16] which evaluated the effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia, showed that the duration of motor blockade was shorter in the ketamine group. However, significantly more patients in the ketamine group had adverse events, including sedation, dizziness, nystagmus, strange feelings, and postoperative nausea and vomiting. They concluded that the central adverse effects of ketamine limited its spinal application. But in our study using low dose ketamine has only one limit in term of side effects, which was hallucination.

Reza and colleagues[12] also reported that low-dose ketamine has no effect on patients' pain scores at two, six, 12, and 24 hours following surgery or on the prevalence of side effects. However, in comparison with our study, they used a higher dose of ketamine (0.5mg/kg vs. 0.25mg/kg in our study) in a smaller sample (n=60 vs. n=160 in our study). Furthermore, while we used spinal anesthesia using bupivacaine, participants in their study underwent general anesthesia using thiopental and succinylcholine. The aforementioned differences might have contributed to the different findings of the two studies.

Our study showed that ketamine had no significant impact on the prevalence of side effects such as nausea, headache, and itching. Similar results were reported by Reza et al.[12] In our study, vomiting was significantly less common in patients that received ketamine. However, in the study by Reza et al, the occurrence of vomiting was similar between the experimental and control group. The different findings might be due to the fact that the participants in our study received smaller doses of pethidine.

In our study, although hallucination was more common in patients who received ketamine only 22.5% of these patients complained of hallucination. In contrast, Arbabi and Ghazi-Saidi[15] reported less prevalence of hallucination in individuals who received ketamine. The differences in the type of anesthesia, sample size, dose of ketamine, and the time ketamine was administered might have contributed to the different findings. Arbabi and Ghazi-Saidi studied the effects of 0.3mg/kg ketamine administered before general anesthesia in a group of 60 parturient women.[15] Sabzi and colleagues[21] reported that Midazolam effectively reduces ketamine-induced postoperative hallucination.

The inevitable use of analgesics would affect the pain score of patients and hide the presumptive effects of ketamine, especially in the later measurements, limiting the study.

CONCLUSION

We conclude that administration of low-dose intravenous ketamine following cesarean section with spinal anesthesia reduces postoperative pain and subsequently the need for analgesics. It also reduced the prevalence of side effects.

To fully understand the effect of ketamine in postoperative pain following cesarean section we recommend that future studies examine the effect of different doses of ketamine, alone and in combination with other medications to reduce

its inevitable side effects (e.g., benzodiazepine to control hallucination). Furthermore, we recommend future studies use larger sample sizes to increase their power in detecting the true differences between the experimental and control groups.

Disclosure
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References

1. Guyton AC, Hall JE. Somatic Sensation. Text Book of Medical Physiology. Saunders; 2000. p. 699-720.
2. Kirby RR. Pain management. Clinical Anesthesia Practice. Saunders; 2002. p. 1152-1159.
3. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001 Nov;48(10):1000-1010.
4. Madineh H, Rajaei M, Ghaheri H, Akhlaghi M, Ganji F. The Effect of Intravenous Low Dose Ketamine on Postoperative Pain. J Shahrekord Univ Med Sci 2005;7(2):29-34.
5. Walder B, Schafer M, Henzi I, Tramèr MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. Acta Anaesthesiol Scand 2001 Aug;45(7):795-804.
6. Mousavi SA, Mortazavi F, Chaman R, Khosravi A. Quality of life after cesarean and vaginal delivery. Oman Med J 2013 Jul;28(4):245-251.
7. Behdad S, Hajiesmaeili MR, Abbasi HR, Ayatollahi V, Khadiv Z, Sedaghat A. Analgesic Effects of Intravenous Ketamine during Spinal Anesthesia in Pregnant Women Undergone Caesarean Section; A Randomized Clinical Trial. Anesth Pain Med 2013 Sep;3(2):230-233.
8. Menkiti ID, Desalu I, Kushimo OT. Low-dose intravenous ketamine improves postoperative analgesia after caesarean delivery with spinal bupivacaine in African parturients. Int J Obstet Anesth 2012 Jul;21(3):217-221.
9. Bauchat JR, Higgins N, Wojciechowski KG, McCarthy RJ, Toledo P, Wong CA. Low-dose ketamine with multimodal postcesarean delivery analgesia: a randomized controlled trial. Int J Obstet Anesth 2011 Jan;20(1):3-9.
10. Ebong EJ, Mato CN, Fyneface-Ogan S. Pre-Incisional Intravenous Low-Dose Ketamine Does Not Cause Pre-Emptive Analgesic Effect Following Caesarean Section under Spinal Anaesthesia. J Anesthe Clinic Res 2011;138(2):100-103.
11. Moshiri E, Norozi A, Pazoki S, Gazerani N, Choghayi M. The effect of low dose Ketamine on postoperative pain after spinal anaesthesia in cesarean section. Arak University of Medical Sciences Journal 2011;14(2):81-88.
12. Reza FM, Zahra F, Esmaeel F, Hossein A. Preemptive analgesic effect of ketamine in patients undergoing elective cesarean section. Clin J Pain 2010 Mar-Apr;26(3):223-226.
13. Sen S, Ozmert G, Aydin ON, Baran N, Caliskan E. The persisting analgesic effect of low-dose intravenous ketamine after spinal anaesthesia for caesarean section. Eur J Anaesthesiol 2005 Jul;22(7):518-523.
14. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005 Feb;100(2):475-480.
15. Arbabi S, Ghazi-Saeidi K. The Preemptive Effect of Low Dose Ketamine on Postoperative Pain in Cesarean Section. Journal of Iranian Society Anaesthesiology and Intensive Care 2003;23(42):15-21.
16. Kathirvel S, Sadhasivam S, Saxena A, Kannan TR, Ganjoo P. Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia 2000 Sep;55(9):899-904.
17. Ngan Kee WD, Khaw KS, Ma ML, Mainland PA, Gin T. Postoperative analgesic requirement after cesarean section: a comparison of anesthetic induction with ketamine or thiopental. Anesth Analg 1997 Dec;85(6):1294-1298.
18. McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004 May;98(5):1385-1400.
19. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. J Pain Palliat Care Pharmacother 2002;16(3):27-35.
20. Dahmani S, Michelet D, Abback PS, Wood C, Brasher C, Nivoche Y, et al. Ketamine for perioperative pain management in children: a meta-analysis of published studies. Paediatr Anaesth 2011 Jun;21(6):636-652.
21. Sabzi F, Teimouri H, Nadri S. A comparison of effects of Diazepam and Midazolam on Ketamine induced postoperative Hallucination. Yafteh 2006;8(3):11-14.