

# Effect of Using Low-Dose Ketamine after Spinal Anesthesia on the Severity of Postoperative Pain in Patients with Orthopedic Surgery

Alireza Rahat Dahmardeh<sup>1</sup>, Aliakbar Keykha<sup>2\*</sup>, Nabi Bamerian<sup>1</sup>

**Background:** Pain relief is one of the most important goals in patients undergoing surgery without using high-dose opioid analgesics due to their complications. The aim of this study was to evaluate the effect of using low-dose ketamine after spinal anesthesia on the severity of postoperative pain in the patients with orthopedic surgery.

**Methods:** The present double-blind clinical trial after obtaining approval was performed on 60 patients with lower limb fracture. The patients were selected by convenience sampling method and then divided into two equal (n=30) intervention and control groups using random number table. The patients in the intervention group after spinal anesthesia received 0.2mg/kg intravenous ketamine diluted with 10cc normal saline. The same amount of normal saline was injected intravenously in the control group. Then, the intensity of pain using VAS and the level of need for analgesics were measured in both groups at different times up to 24 hours after surgery.

**Results:** The intervention group included 21 males and 9 females with a mean age of  $30 \pm 1.2$  years and control group consisted of 19 males and 11 females with a mean age of  $29 \pm 4$  years. There was no significant difference between the age and sex of the patients in the intervention and control groups ( $P=0.677$ ), ( $P=0.589$ ). In the intervention group with the VAS, the lowest pain score was found at the first turn of the assessment ( $2.4 \pm 0.6$ ), and the highest pain at 24 h ( $4.3 \pm 2.6$ ). The control group had the lowest pain score at the first turn of the assessment ( $3.6 \pm 0.8$ ) and the maximum pain at the first turn of the assessment ( $5.2 \pm 1.7$ ). According to independent t-test, there was a significant difference between the two groups at all times, except for the first turn of the assessment. In the intervention group, 12 (40%) patients did not receive analgesics within 24 hours. In the control group, 2 (6.7%) had no analgesics. Chi-square showed a significant difference between the two groups ( $P=0.002$ ).

**Conclusion:** The present study showed that low-dose intravenous ketamine could relieve pain in patients and reduce postoperative analgesics.

**Keywords:** ketamine; postoperative pain; orthopedic surgery

Providing a proper pain relief after each surgery for the patient is one of the important responsibilities of the treatment team [1]. The cause of postoperative pain is tissue damage, inflammation, and activation of c-fibres as well as cytokine penetration [2]. Opioid analgesics are often used to relieve postoperative pain; fatal respiratory depression is one of the most worrisome complications [3]. Also, other complications such as the urinary retention syndrome, constipation, nausea and vomiting caused by these drugs suggest that it would be better to use a method with minimum opioid analgesics to relieve pain in the

patients [4]. A modern approach to postoperative pain management is the combination of opiates with other drugs. This technique reduces the amount of opioid consumption and prevents the associated complications. The use of regional anesthesia reduces postoperative pulmonary complications, and shortens the amount of taking analgesics and recovery time [5].

Intermittent use of opioid and non-opioid analgesics is one of the most effective methods for relieving pain in the patients [6]. One of the best medicines for intermittent use is ketamine that has a very good analgesic effect but does not suppress breathing, and after preoperative injection can relieve postoperative pain and reduce consumption rate of opioid analgesics [7-8]. Preoperative intravenous ketamine can prevent postoperative pain [9]. It has been reported that the use of low-dose ketamine can reduce the consumption rate of opiates as well as prolong the time of first use of narcotics [10]. Cyrus et al. applied intravenous ketamine to manage the pain associated with renal colic. They concluded that it has a very good effect on the control of pain, nausea and vomiting in these patients and is a proper drug for controlling the pain of these patients due to low side effects

From the <sup>1</sup>Department of Anesthesiology and Intensive Care Medicine Zahedan University of Medical Sciences, Zahedan, Iran.

<sup>2</sup>Community Nursing Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

Received: 14 Jun 2017, Revised: 6 July 2017, Accepted: 21 August 2017

The authors declare no conflicts of interest.

\*Corresponding author: Aliakbar Keykha, MSc. Community Nursing Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: aliakbar.keykha@gmail.com

Copyright © 2017 Tehran University of Medical Sciences

[11]. Marzban et al. examined the effects of ketamine versus placebo in controlling sore throat after tonsillectomy, and reported that ketamine controls postoperative sore throat well, and reduces the consumption rate of opioid analgesics; the rate of nausea and vomiting was not different in two groups [12]. Adequate control of postoperative pain, in addition to preventing chronic pain, can lead to early patient mobility and relaxation [13-14]. This issue is very important in patients with lower limb fractures to prevent the occurrence of immobile complications, such as deep vein thrombosis and dry joints. Therefore, the study was conducted to investigate the effect of using low-dose ketamine after spinal anesthesia on the severity of postoperative pain in patients with orthopedic surgery.

## Methods

The present double-blind clinical trial after obtaining approval from Deputy of Research and Technology of Zahedan University of Medical Sciences was conducted on patients with lower limb fracture. Sample size was considered 60 people according to previous studies [12, 15] and the formula for calculating sample size. The patients were selected by convenience sampling method and then divided into two equal (n=30) intervention and control groups using a random number table. They were unaware of their position in each of the groups.

Inclusion criteria for the study included age between 18-40 years, satisfaction to participate in the study, indication of spinal anesthesia, lack of chronic diseases such as diabetes and high blood pressure, malignant diseases, lack of drug abuse, no history of epilepsy and seizure, no known history of ketamine allergy, no reduction level of consciousness and head injury.

Exclusion criteria were dissatisfaction to continue participating in the study and intraoperative complication leading to the need for operation on the upcoming day.

The patients who met the inclusion criteria were under monitoring and pulse oximetry. Then, an anaesthesiologist who was unaware of the position of the patients in the control or the intervention groups performed spinal anesthesia with Marcain 0.5% (12.5-15.5 mg) for all patients. Sodium chloride (5cc/kg) serum infusion was continued for all patients. Immediately after spinal anesthesia and before surgery, the patients in the intervention group received 0.2mg/kg intravenous ketamine diluted with 10cc normal saline. The same amount of normal saline was injected intravenously in the control group. After the surgery, the patients were transferred to recovery and after the return of the sense and movement of the lower extremities were transferred to the orthopedic section.

During this period, a trained nurse who was unaware of the position of the patients in the control or intervention groups measured the pain level of patients using the visual analog scale (VAS). Transfer time to recovery was considered zero time. Then, this measurement was done in 1, 6, 12, 18 and 24 hours later as well. The nurse injected 0.5 mg/kg pethidine to the patients with the VAS score over three. At all stages, the nurse noted the data in a pre-designed form. Finally, pain intensity and consumption rate of analgesics were compared in two groups using SPSS software via independent t-test and Chi-square

## Results

The study patients (n=60) included 40 (67.7%) males and 20 (33.3%) females. The mean age of the patients was  $31.2 \pm 2.2$  years. The intervention group included 21 males and 9 females with a mean age of  $30 \pm 1.2$  years and control group consisted of 19 males and 11 females with a mean age of  $29 \pm 4$  years. There was no significant difference between the age and sex of the patients in the intervention and control groups ( $P=0.677$ ), ( $P=0.589$ ). In the intervention group with the VAS, the lowest pain score was found at the first turn of the assessment ( $2.4 \pm 0.6$ ), and the highest pain at 24 h ( $4.3 \pm 2.6$ ). The control group had the lowest pain score at the first turn of the assessment ( $3.6 \pm 0.8$ ) and the maximum pain at the first turn of the assessment ( $5.2 \pm 1.7$ ). According to independent t-test, there was a significant difference between the two groups at all times, except for the first turn of the assessment (Table 1).

**Table 1- The mean pain VAS scores in terms of assessment intervals in the two groups**

Assessment intervals	Groups		P-value
	Intervention (SD±mean)	Control (SD±mean)	
Zero	2.4±0.6	3.6±0.8	0.07
After 1 hour	2.6±1.2	4.1±0.9	0.03
After 6 hours	3.1±1.8	4.3±1.9	0.000
After 12 hours	3.6±2.2	4.9±0.2	0.000
After 18 hours	3.9±1.2	5.1±1.8	0.000
After 24 hours	4.3±2.4	5.0±1.7	0.000

The patients in the intervention group received analgesics in 32 turns, while in the control group received in 68 turns. In the intervention group, 12 (40%) patients did not receive analgesics within 24 hours. In the control group, 2 (6.7%) had no analgesics. Chi-square showed a significant difference between the two groups ( $P=0.002$ ) (Table 2).

**Table 2- Frequency of analgesics injections within 24 hours in terms of the number of patients in the two groups**

Number of analgesic injections	Number of patients in the intervention group	Number of patients in the control group	P-value
0	12 (40%)	2 (6.7%)	0.002
1	8 (26.7%)	4 (13.3%)	0.002
2	6 (20%)	13 (43.3%)	0.000
3	4 (13.3%)	6 (20%)	0.004
4	0	5 (16.7%)	0.000

## Discussion

The results showed that the preoperative use of low-dose intravenous ketamine significantly reduces postoperative pain intensity and reduces significantly the consumption rate of opioid analgesics. Consistent with the results of this study, Jendoubi et al. studied the effect of intravenous lidocaine and ketamine in comparison with placebo in patients with nephrectomy. They reported that pain was significantly lower in patients receiving lidocaine and ketamine and the morphine consumption rate was also significantly decreased. In the lidocaine group, the rate of postoperative nausea and vomiting was significantly reduced. There was no significant difference between the ketamine and placebo groups. The difference between the two studies was that the drugs in this study were injected as a controlled pump by the patients themselves after surgery, and intravenous morphine was injected if needed to analgesics due to the high VAS score. In this study, the drug was administered preoperatively and pethidine was injected to the patient to relieve pain if analgesics were required [15]. EL-Rahman et al. evaluated the effect of local ketamine wound instillation and intramuscular injection compared to placebo injection on the severity of pain and the morphine consumption rate of total thyroidectomy for patients with thyroid cancer. They reported that the total morphine consumption was reduced in both wound instillation and intramuscular injection groups versus placebo group. However, the first request of analgesia was delayed in the local ketamine wound instillation group [16]. Although their study method was not similar to our study, but their results are consistent with the findings of the present study in terms of the use of ketamine that can reduce the consumption rate of opioid analgesics and the pain severity in the patients. In line with the results of the current study, Marzban et al. investigated the effect of preoperative intravenous ketamine on the severity of postoperative sore throat in the patients with tonsillectomy, and reported that the use of ketamine can reduce the postoperative pain of these patients and facilitate the swallowing of the patients [12]. In another study, Krishna et al. investigated the effect of combination of low doses of intrathecal ketamine and midazolam with bupivacaine on pain and hemodynamic of patients with orthopedic surgery. They reported that the group receiving only ketamine had the least hemodynamic changes. The start time of the block and pain relief were the same in all three groups. However, it was longer in the group receiving ketamine and midazolam. The mean time that patients spent without pain was higher in the group receiving midazolam and ketamine, and then in the ketamine and bupivacaine groups respectively. Although the drug injection method in this study is not similar to the present study, but given that it has pointed out that ketamine injection in the subarachnoid space has beneficial effects in relieving pain and lowering hemodynamic changes, it might be proven that ketamine can be used safely to relieve pain [17]. In another study, Salama et al. by examining the effect of ketamine and hyoscine for the management of postoperative catheter-related bladder discomfort reported that both ketamine and hyoscine could control the catheter-related bladder discomfort, although hyoscine has a better effect in the first 30 minutes [18]. In line with the current results, Suzuki et al. assessed the low-dose intravenous ketamine (0.05 mg/kg) potentiates along with epidural morphine-ropivacaine on pain control in

patients after thoracotomy and reported that the patients receiving ketamine had less pain in comparison with the placebo group at 48 hours and one week, one month, and three months later [19].

## Conclusion

The use of preoperative low-dose intravenous ketamine has a significant effect on postoperative pain intensity. It also reduces the consumption of opioid analgesics and is recommended to be used as an adjuvant drug to relieve pain in patients.

## Acknowledgment

This article has been adopted from the dissertation in Resident of Anaesthesiology and Special Care, which was registered and funded by Deputy of Research and Technology of the Zahedan University of Medical Sciences. The researcher would like to thank and appreciate the deputy and staff of research and technology department of the university, the operating room and orthopedic department of Khatam-Al-Anbia hospital of Zahedan.

## References

- Brennan TJ, Kehlet H. Preventive analgesia to Reduce Wound Hyperalgesia and Persistent Postsurgical Pain Not an Easy Path. *Anesthesiology*. 2005; 103(4):681-3.
- Watkins LR, Wiertelak EP, Goehler LE, Smith KP, Martin D, Maier SF. Characterization of cytokine-induced hyperalgesia. *Brain Res*. 1994; 654(1):15-26.
- Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. *Pain physician*. 2008; 11(2 Suppl):S105-20.
- Manchikanti L, Manchikanti KN, Pampati V, Cash KA. Prevalence of side effects of prolonged low or moderate dose opioid therapy with concomitant benzodiazepine and/or antidepressant therapy in chronic non-cancer pain. *Pain Physician*. 2009; 12(1):259-67.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *The Lancet*. 2006; 367(9522):1618-25.
- Schwenk ES, Goldberg SF, Patel RD, Zhou J, Adams DR, Baratta JL, et al. Adverse drug effects and preoperative medication factors related to perioperative low-dose ketamine infusions. *Reg Anesth Pain Med*. 2016; 41(4):482-7.
- Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*. 2010; 113(3):639-46.
- Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth*. 2011; 58(10):911-23.
- McNicol E, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand*. 2014; 58(10):1199-213.
- Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. *Can J Anaesth*. 2016; 63(3):311-25.
- Sirous A, Pazouki S, Ghoudarzi D, Yavariy M, Babaei E, Pirasteh S. Evaluation of the effects of oral Ketamine as an adjuvant drug in treatment of renal colic. *Arak University of Medical Sciences*. 2008; 11(2):56-63.
- Marzban S, Hadadi S, Movahedi H, Parvizi A, Haghighi M. The effect of ketamine on sore throat after tonsillectomy. *Journal of Mazandaran University Of Medical Sciences*. 2007; 16(56):53-9.
- Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. *Anesthesiol Clin North America*. 2005; 23(1):185-202.
- Kehlet H, Holte K. Effect of postoperative analgesia on surgical

- outcome. *Br J Anaesth*. 2001 Jul;87(1):62-72.
15. Jendoubi A, Naceur IB, Bouzouita A, Trifa M, Ghedira S, Chebil M, et al. A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study. *Saudi J Anaesth*. 2017; 11(2):177-184.
  16. EL-Rahman AMA, El Sherif FA. Efficacy of Postoperative Analgesia of Local Ketamine Wound Instillation Following Total Thyroidectomy; A Randomized, Double-blind, Controlled-clinical Trial. *Clin J Pain*. 2017.
  17. Krishna TM, Panda N, Batra Y, Rajeev S. Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol*. 2008; 25(4):299-306.
  18. Salama AK. Comparison between ketamine and hyoscine for the management of postoperative catheter-related bladder discomfort: A randomized controlled double-blind study. *J Anaesthesiol Clin Pharmacol*. 2017; 33(1):76-80.
  19. Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology*. 2006; 105(1):111-9.