



Does adding ketamine to morphine in a patient-controlled intravenous analgesia pump after orthopedic surgeries help better management of postoperative pain in obese patients? A double-blinded clinical trial

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Abstract

Introduction: Low doses of ketamine can cause an antagonistic effect on NMDA-receptors by blocking the magnesium-gated channels. Several studies demonstrated the effect of ketamine in improving the analgesia using opioids, however, obese people reported different reactions to this problem.

Objectives: This study seeks to answer the following question: Does adding ketamine to morphine in a patient-controlled intravenous analgesia pump (PCIA) after orthopedic surgeries help better management of postoperative pain in obese patients?

Patient and Methods: This double-blinded clinical trial involved 60 obese (body mass of higher than 30 kg/m²) lower limb orthopedic surgery candidates at Shohada hospital (Tabriz, Iran). The participants were randomly categorized into three groups. In group M, 20 mg morphine sulfate, in group MK1 100 mg ketamine + 20 mg morphine sulfate, and in group MK2 200 mg ketamine+10 mg morphine sulfate was added to the analgesia pump. Pain intensity (VAS), sedation score (Ramsay Scale), as well as nausea and vomiting (N&V score) were compared among different groups at 12, 24, 36, and 48 hours after the operation.

Results: Group M manifested a significantly higher pain intensity than two other groups during all examined times, and group MK2 demonstrated a significantly lower pain intensity than other groups. In the course of the research, the amount of opioid consumption in group MK2 was significantly lower than in the other groups.

Conclusion: The addition of a low dose of ketamine to morphine in the PCIA pump after orthopedic surgeries in obese patients results in proper postoperative pain management.

Trial Registration: The trial protocol was approved in the Iranian registry of clinical trial (identifier: IRCT2017101636822N1, <https://www.irct.ir/trial/27429>, ethical code; IR.TBZMED.REC.1400.820).

Keywords: Analgesia pump, Intravenous, Ketamine, Low dose, Orthopedics, Nausea and vomiting

Citation: Moradi A, Abedini N. Does adding ketamine to morphine in a patient-controlled intravenous analgesia pump after orthopedic surgeries help better management of postoperative pain in obese patients? A double-blinded clinical trial. J Ren Endocrinol. 2022;8:e17076. doi: 10.34172/jre.2022.17076.

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Introduction

The patient-controlled intravenous analgesia (PCIA) pump using opioids is a prevalent procedure to alleviate postoperative pain. Opioids cause analgesia through inhibiting substance P (SP) release in the spinal cord and the direct impact on the opioid receptors in the dorsal horn of the spinal cord (1). Adjuvant drugs are suggested by taking into account the side effects of opioids (nausea, respiratory depression, tolerance, and sedation), the necessity of decreasing their consumption, and improvement of the quality of analgesia. Ketamine, in low doses, has analgesic properties and when prescribed with opioids, it can have a synergistic effect (2, 3).

The NMDA-receptors are situated in the peripheral tissues and visceral pain pathways. They are crucially

important in receiving the feeling of pain (4). Activation of these receptors causes the spinal cord neurons to be more susceptible to stimuli and reduces the sensitivity of neurons to opioid agonists. Consequently, a less peripheral stimulus is required in response to pain in the central nervous system (5). The NMDA-receptor in patients leads to Allodynia (painful response in patients to non-painful stimuli). In addition, it produces intense painful responses to weak pain stimuli (6).

Ketamine blocks N-methyl-D-aspartate (NMDA). It decreases postoperative pain through the mechanism of preventing hypersensitivity to pain (hyperalgesia). Ketamine decreases the postoperative pain triggered by nerve injuries due to neuralgia in the peripheral nerves (7,8).

Implication for health policy/practice/research/medical education

In this double-blinded clinical trial 60 obese (body mass of higher than 30) lower limb orthopedic surgery candidates were randomly categorized into three groups. In group M, 20 mg morphine sulfate, in group MK1 100 mg ketamine + 20 mg morphine sulfate, and in group MK2 200 mg ketamine+10 mg morphine sulfate was added to the analgesia pump. Pain intensity (VAS), sedation score (Ramsay Scale), as well as nausea and vomiting (N and V score) were compared among different groups at 12, 24, 36, and 48 hours after the operation. Results show the addition of a low dose of ketamine to morphine in the PCA pump after orthopedic surgeries in obese patients results in proper postoperative pain management.

Low amounts of ketamine can cause an antagonistic effect on NMDA-receptors by blocking the magnesium-gated channels (9). Numerous studies reported the effect of ketamine in improving analgesia using opioids. Nevertheless, obese individuals demonstrated different reactions to this subject, which causes problems in the pain management of these patients. It is due to the fact that the dosage of consumption of analgesic drugs has an unknown relationship with the body fat percentage (10).

Objectives

This study seeks to answer the following question: Does adding ketamine to Morphine in the PCA pump after orthopedic surgeries facilitate the management of postoperative pain in obese patients?

Patients and Methods

Study design

This double-blinded clinical trial was carried out in 2020 at Shohada Hospital (Tabriz University of Medical Education) upon observing the inclusion/exclusion criteria. Sixty obese patients were selected through convenience sampling (Figure 1).

Inclusion/exclusion criteria

The inclusion criteria of the research included patients with the age ranging from 20 to 60 years old, ASA patients, i.e., Class I and II, who were orthopedic surgery candidates, with a body mass index (BMI) of above 30 kg/m². The exclusion criteria involved drugs contraindications, addiction, morbid obesity, records of seizures, records of neurological and psychological diseases, consumption of psychotropic drugs, daily substance abuse (more than

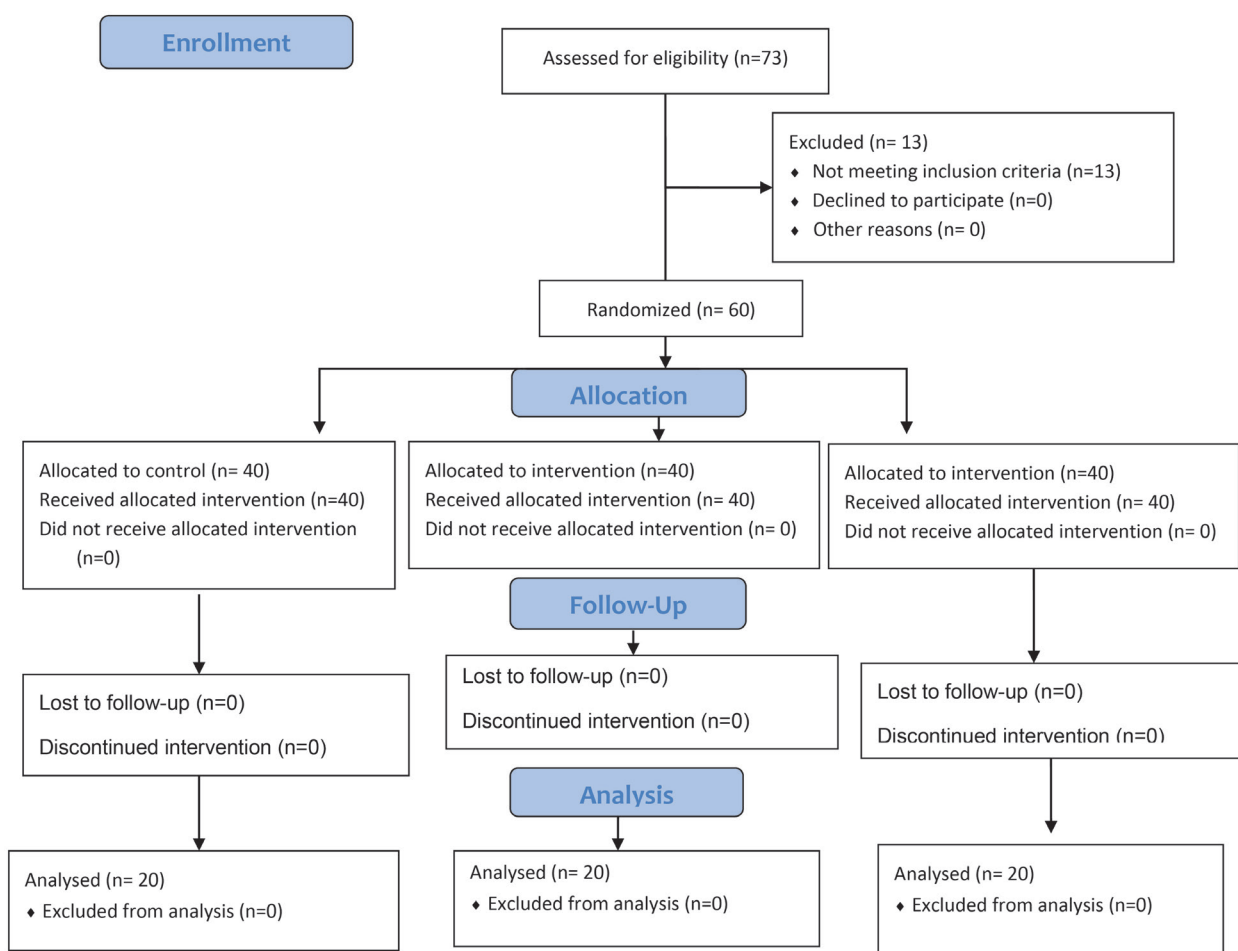


Figure 1. COSORT flowchart of the study.

once a week), lack of cooperation of the patient, chronic pain, and upper respiratory tract infection.

Random allocation and blinding

In this study, the random allocation was carried out using the randomized four-block design. The random allocation was performed by the statistical consultant of the group (other than the authors of the article). Anesthesiologists who performed the intervention and the individual who examined the outcomes were unaware of the classifications. A proficient nurse from the ward prepared the medications for each patient on the basis of their classification. When they were transferred to the operating room, the medications were handed over to the anesthesiologist, who was totally unaware of their content. The patients were categorized into three groups, i.e., M, MK1, and MK2 (n=20).

Methods

In group M, 20 mg morphine sulfate, in group MK1, 100 mg ketamine + 20 mg morphine sulfate, and in group MK2, 200 mg ketamine + 10 mg morphine sulfate were added to the analgesia pump. An autofuse pump, with a volume of 10 mL (bolus injection of 2 mg infusion, 5 mg per hour, and deprivation duration amounted to 60 minutes) was administered to patients in the recovery room. The pain score of patients was measured via the VAS scale (the score of zero signifies no pain, and 10 signifies intense and intolerable pain). The score of sedation was measured via Ramsay Scale (scores ranging from 0 to -5, i.e., the lowest score indicated a higher level of sedation), and nausea and vomiting were measured by the N&V score (scores ranging from 1 to 0.4, the highest score indicates more nausea and vomiting), and at hours 6 (6T), 12 (12T), 24 (24T), 36 (36T), and 48 (48T), and after administration of the pump. The results were recorded on forms provided in this regard. In case the visual analogue scale (VAS) score equaled or exceeded 3 or in case the sedation score equaled zero, the dosage of the medication was increased up to 20% and 2 mg morphine was administered via bolus injection. If VAS=0 or side effects of drugs (nausea, vomiting, other side effects, or sedation score of higher than 1), the dosage of the drug was decreased down to 20%. Metoclopramide was injected in case of nausea or vomiting. After two days from the start of administration of this drug, the dosage

of drugs was gradually decreased concerning the clinical conditions and satisfaction of patients, and then, they were stopped. All basic information (age, gender, anesthesia procedure, duration and region of surgery), VAS score of pain, a score of sedation, nausea and vomiting, and other side effects were recorded in the respective forms.

Statistical analysis

When the forms were completed, all information was imported into SPSS, version 21 (by the statistical consultant). The qualitative data were demonstrated through frequency (percentage)/mean and standard deviation. The one-way ANOVA was used to analyze the qualitative variables and chi-square was used for qualitative variables. The ANOVA and Tukey's post hoc test were used to compare the groups. The level of significance was considered less than 0.05.

Results

In this study, 60 patients who met the inclusion criteria of the study were categorized into three groups of medications. The orthopedic surgery was performed on the lower limb and via spinal anesthesia. The average age of the participants amounted to 4.96 ± 41.33 years old. The surgery lasted for 26.14 ± 143.88 minutes. The duration of anesthesia equaled 30.49 ± 176.14 minutes. The patients' BMI equaled 35.19 ± 3.22 kg/m². The patients had no significant difference in terms of age, gender, anesthesia duration, operation duration, and BMI (Table 1).

Group M manifested a significantly higher pain intensity than two other groups during all examined times, and group MK2 demonstrated a significantly lower pain intensity than other groups. In the course of the research, the amount of opioid consumption in group MK2 was significantly lower than in the other groups (Table 2).

The groups had no statistically significant difference in the occurrence of nausea and vomiting (the first group had the lowest and the second group had the highest score), and the score of sedation (the second group scored the highest).

Discussion

This study found that various doses of ketamine in combination with morphine in the PCIA pumps can reduce the score of postoperative pain of obese patients

Table 1. Basic characteristics of participants

Variable	Groups (N=60)			P value
	Group M (n=20)	Group MK1 (n=20)	Group MK2 (n=20)	
Age (y)	41.29±51.61	40.98±5.85	41.75±6.02	0.552 ^a
Gender (Male)	11 (55%)	12 (60%)	11 (55%)	0.893 ^b
Operation duration (min)	142.59±25.18	145.96±30.32	139.59±20.56	0.606 ^a
Anesthesia duration (min)	175.12±31.96	179.96±12.27	173.22±12.66	0.789 ^a
BMI (kg/m ²)	35.96±3.42	35.44±3.81	34.89±3.10	0.773 ^b

BMI, body mass index. ^aT test; ^bChi-square.

Table 2. Comparing the pain intensity and opioid consumption in the course of the research

Variable	Groups (N=60)			P value
	Group M (n=20)	Group MK1 (n=20)	Group MK2 (n=20)	
T 6	5.29±1.61	3.29±1.42	3.11±1.45	0.021 ^a
T 12	4.83±1.79	2.24±0.59	2.15±0.56	0.014 ^a
T 24	4.36±1.76	1.89±0.42	1.55±0.75	0.019 ^a
T 36	3.59±1.34	1.55±0.34	1.15±0.19	0.017 ^a
T 48	2.41±1.22	1.34±0.66	0.93±0.37	0.041 ^a
Pethidine consumption (mg)	42.75±5.29	15.36±3.85	10.49±2.24	0.001 ^a

^a T test.

after orthopedic surgeries and decrease the consumption of opioids (11). The addition of Ketamine significantly decreased the pain intensity and consumption of opioids. This reduction in the patients' postoperative pain score in the ketamine group might be on account of the analgesic properties of this drug, as well as strengthening the opioid effect, which is applied via cholinergic, and monoaminergic mechanisms (12).

On the other hand, ketamine prevents intense drug tolerance and hyperalgesia, which decreases morphine consumption. Moreover, the nociceptive stimulation can activate the NMDA-receptors, which is intensified by higher amounts of opioids and aggravates the postoperative pain. Adding ketamine might prevent this process. The results of this research correspond to several similar studies in this field (13,14). A study considered the consumption dose of ketamine to be 1.2 mg per hour. Adding ketamine manifested a considerable effect after the elective Microdiscectomy.

In another research, the mean consumption of ketamine during the first 24 hours after major abdominal surgery in obese patients amounted to 3.2 mg/h (15,16). However, no measurable impact was found. These different results might have been obtained due to the difference in the research methodology. A study on 30 obese patients and normal-weighted patients indicated that 10 mg ketamine per hour possesses a better decreasing effect on the consumption of opioids. Besides, when compared to thin patients, it reduces nausea after abdominal surgery in obese patients (17).

In this study, three groups had no significant difference concerning the side effects such as sedation, nausea, vomiting, hallucination, and sleep disorder. Even though the amount of sedation, nausea, vomiting, and sleep disorder was reported to be lower in the ketamine + opioid group, which is due to the decrease in the consumption of opioids, all of these disorders are included in the side effects of opioids. The hallucination in this group was higher due to the higher dose of ketamine. A study argued that the sedation score of the ketamine group was lower than the morphine group, and it had better analgesic properties on patients. These results did not match that of this research (18). Another study reported that the occurrence of nausea and vomiting was lower in the

ketamine group in comparison to the morphine group, which matches the results of this study. The hallucination and sleep disorder in this study was obtained to be higher in the ketamine group in comparison to the morphine-sole group. However, they had no statistically significant difference, which corresponds to the studies conducted in this regard (9,19,20).

Conclusion

Adding a low dose of ketamine to morphine in the PCIA pump after orthopedic surgeries in obese patients results in proper postoperative pain management.

Limitations of the study

Not paying attention to the body mass index in the combination of PCIA pump drugs was one of the weak points of our study, which should be paid attention to in future studies.

Acknowledgments

The Authors would like to thanks Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Sciences, Tabriz, Iran for kind supports.

Authors' contribution

Conceptualization; AM and NA. Methodology; AM. Validation; NA. Formal Analysis; NA. Investigation; AM and NA. Resources; AM and NA. Data Curation; AM and NA. Writing—Original Draft Preparation; AM and NA. Writing—Review and Editing; AM and NA. Visualization; NA. Supervision; NA. Project Administration; NA. Funding Acquisition; NA.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Tabriz University of Medical Sciences approved this study (#IR.TBZMED.REC.1400.820). Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT2017101636822N1, <https://www.irct.ir/trial/27429>). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study is sponsored by Tabriz University of Medical Sciences (Grant #67632).

References

- Dinges H-C, Otto S, Stay DK, Bäumllein S, Waldmann S, Kranke P, et al. Side effect rates of opioids in equianalgesic doses via intravenous patient-controlled analgesia: a systematic review and network meta-analysis. *Anesth Analg*. 2019;129:1153-62. doi: 10.1213/ANE.0000000000003887.
- Papa L, Maguire L, Bender M, Boyd M, Patel S, Samcam I. Patient controlled analgesia for the management of acute pain in the emergency department: A systematic review. *Am J Emerg Med*. 2022;51:228-38. doi: 10.1016/j.ajem.2021.10.042.
- Lawal OD, Mohanty M, Elder H, Skeer M, Erpelding N, Lanier R, et al. The nature, magnitude, and reporting compliance of device-related events for intravenous patient-controlled analgesia in the FDA Manufacturer and User Facility Device Experience (MAUDE) database. *Expert Opin Drug Saf*. 2018;17:347-57. doi: 10.1080/14740338.2018.1442431.
- Liu J, Chang L, Song Y, Li H, Wu Y. The role of NMDA receptors in Alzheimer's disease. *Front Neurosci*. 2019;13:43. doi: 10.3389/fnins.2019.00043.
- Wu QJ, Tymianski M. Targeting NMDA receptors in stroke: new hope in neuroprotection. *Mol Brain*. 2018;11:1-14. doi: 10.1186/s13041-018-0357-8.
- Franchini L, Carrano N, Di Luca M, Gardoni F. Synaptic GluN2A-containing NMDA receptors: from physiology to pathological synaptic plasticity. *Int J Mol Sci*. 2020;21:1538. doi: 10.3390/ijms21041538.
- Jelen LA, Young AH, Stone JM. Ketamine: a tale of two enantiomers. *J Psychopharmacol*. 2021;35:109-23. doi: 10.1177/0269881120959644.
- Zanos P, Gould T. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. 2018;23:801-11. doi: 10.1038/mp.2017.255
- Riddell JM, Trummel JM, Onakpoya IJ. Low-dose ketamine in painful orthopaedic surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2019;123:325-34. doi: 10.1016/j.bja.2019.05.043.
- Sattar Y, Wilson J, Khan AM, Adnan M, Larios DA, Shrestha S, et al. A review of the mechanism of antagonism of N-methyl-D-aspartate receptor by ketamine in treatment-resistant depression. *Cureus*. 2018;10:e2652. doi: 10.7759/cureus.2652.
- Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth*. 2021;68:110071. doi: 10.1016/j.jclinane.2020.110071.
- Meyer-Frießem CH, Lipke E, Weibel S, Kranke P, Reichl S, Pogatzki-Zahn EM, et al. Perioperative ketamine for postoperative pain management in patients with preoperative opioid intake: A systematic review and meta-analysis. *J Clin Anesth*. 2022;78:110652. doi: 10.1016/j.jclinane.2022.110652.
- Ma J-H, Wang S-Y, Yu H-Y, Li D-Y, Luo S-C, Zheng S-S, et al. Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section. *Psych Res*. 2019;279:252-8. doi: 10.1016/j.psychres.2019.03.026.
- Zhu T, Gao Y, Xu X, Fu S, Lin W, Sun J. Effect of ketamine added to ropivacaine in nerve block for postoperative pain management in patients undergoing anterior cruciate ligament reconstruction: a randomized trial. *Clin Ther*. 2020;42:882-91. doi: 10.1016/j.clinthera.2020.03.004.
- Shindyapina N, Marshalov D, Shifman E, Kuligin A. Clinical effects of low-dose intravenous ketamine in obstetrics: a systematic review. *Ann Crit Care*. 2020;2:104-21. doi: 10.21320/1818-474X-2020-2-104-121.
- Zhang X, Wang J, An X-H, Chao Y-C, Bian Y, Xu Z, et al. Optimum dose of spinal ropivacaine with or without single intravenous bolus of S-ketamine during elective cesarean delivery: a randomized, double-blind, sequential dose-finding study. *BMC Pregnancy Childbirth*. 2021;21:746. doi: 10.1186/s12884-021-04229-y.
- Liu P, Li P, Li Q, Yan H, Shi X, Liu C, et al. Effect of pretreatment of S-ketamine on postoperative depression for breast cancer patients. *J Invest Surg*. 2021;34:883-8. doi: 10.1080/08941939.2019.1710626.
- Hamburger J, Beilin Y. Systemic adjunct analgesics for cesarean delivery: a narrative review. *Int J Obstet Anesth*. 2019;40:101-18. doi: 10.1016/j.ijoa.2019.06.009.
- Li Q, Wang S, Mei X. A single intravenous administration of a sub-anesthetic ketamine dose during the perioperative period of cesarean section for preventing postpartum depression: A meta-analysis. *Psychiatry Res*. 2022;114396. doi: 10.1016/j.psychres.2022.114396
- Inoue S, Miyoshi H, Hieda K, Hayashi T, Tsutsumi YM, Teishima J. Postoperative around-the-clock administration of intravenous acetaminophen for pain control following robot-assisted radical prostatectomy. *Sci Rep*. 2021;11:1-7. doi: 10.1038/s41598-021-84866-7