The Effect of Intraoperative Ketamine and Magnesium Sulfate on Acute Pain and Opioid Consumption After Spine Surgery

Farhad Etezadi[1], Mansour Farzizadeh[1], Hamid Reza Sharifinia[1], Maysam Alimohammadi[2], Mohammad Reza Khajavi[1]

[1] *Department of Anesthesiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

Received: 28 Jan. 2020; Accepted: 28 May 2020

Abstract- Ketamine and magnesium in brain act as an *N*-methyl-D-aspartate receptor antagonist that has been shown to be useful in the reduction of acute postoperative pain and analgesic consumption in a variety of surgical interventions. We hypothesized that combination of low dose ketamine and magnesium would reduce early postoperative opiate consumption and analgesic requirement after 6 weeks. This was a randomized, prospective, controlled-placebo trial involving elective and eligible patients undergoing lumbar spine surgery. Seventy patients in the treatment group were administered 0.5 mg/kg intravenous ketamine and 1 gram of magnesium as an intravenous bolus slowly during 3 minute before incision and 0.25 mg/kg/hr ketamine and 0,5 g/hr magnesium intravenous infusion during surgery. Seventy patients in the placebo group received saline of equivalent volume. Patients were observed for48 h postoperatively and followed up at 6 weeks. The primary outcome was 48h morphine consumption. The severity of pain was lower in the intervention group than in the placebo group during 48 hr post-operatively, morphine consumption in this group also decreased significantly during this period. Intraoperative ketamine-magnesium reduces opiate consumption in the 48-h postoperative period. This combination may also reduce pain intensity throughout the postoperative period in this patient population.

Acta Med Iran 2020;58(5):221-224.

Keywords: Ketamine; Magnesium; Spine surgery; Preventive analgesia

Introduction

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that works by blocking the NMDA receptors in the central and peripheral nervous systems. Intraoperative subanesthetic doses of ketamine can possibly reduce hyperalgesia and postoperative acute and chronic pain by blocking the wind-up effect when blocking the NMDA receptors (1). Intraoperative use of preventative ketamine has been shown to generate a modest reduction in acute pain intensity and postoperative analgesic consumption after the surgical insult (2-3).

One of the complications of using ketamine during surgery is postoperative delirium. In Elsamadicy *et al.*, study the intraoperative use of ketamine increased the risk of postoperative delirium in comparison to no ketamine consumption (Ketamine-Use: 14.3% *vs.* No-Ketamine: 2.6%, *P*=0.047) (4).

Magnesium, like ketamine, is an N-Methyl-D-aspartate (NMDA) receptor antagonist that it's used in many studies for the reduction of postoperative pain and opioids consumption (5-6-7).

We, therefore, conducted a randomized controlled trial on patients hypothesizing that intraoperative ketamine and magnesium sulfate has immediate and short- term effects on analgesic consumption and pain after spine surgery.

Materials and Methods

After being approved by the Ethical Board Committee of Anesthesiology Department of Tehran University of Medical Sciences (TUMS), this interventional, randomized clinical controlled trial was conducted on 140 patients aged 20-65-year-old, candidates for elective lumbar spine surgery. After explaining different aspects of the procedure, written informed consent was obtained from all the participating patients. This trial was conducted in Sina Hospital

Corresponding Author: M.R. Khajavi
Department of Anesthesiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9123837096, Fax: +98 2166348551, E-mail address: khajavim@tums.ac.ir

affiliated with Tehran University of Medical Sciences.

Exclusion criteria were patients with a history of kidney, liver failure, opiate drug and alcohol use, psychological disorder, traumatic and metastatic spinal injury.

After standard monitoring, general anesthesia were performed for all patients using the same method: injecting fentanyl 2.0 µg/kg, midazolam 0.05 mg/kg, propofol 1.5-2 mg/kg, atracurium 0.5.0 mg/kg, and lidocaine 1.0 mg/kg. Anesthesia was maintained using isoflurane in an air/oxygen mixture and remifentanil infusion.

After induction, the patients were randomly allocated by using a computer-generated table into two following groups, for the intervention group, 0.5 mg/kg ketamine was administered intravenous bolus before incision and 0.25 mg/kg intravenous infusion during surgery. Patients in this group also received 1 gram of magnesium as an intravenous bolus slowly during 3 minutes before incision and 0,5 gram per hour as an intravenous infusion during surgery.

Patients in the control group received a placebo at the same rate. All patients were injected with the same anesthetic provider.

The amount of anesthetic and narcotic drugs and muscle relaxants used during surgery are recorded separately for each patient.

Intraoperative heart rate and blood pressure changes were recorded by the anesthesia providers on the standard anesthetic record, and postoperative opioid requirements were followed for 48 h by the principal investigator (s). Ketamine-related side effects during the perioperative period were systematically evaluated and recorded.

The severity of pain was evaluated by using Numeric rating scales (NRS) (0=no pain and 10=worst possible pain). The primary endpoints were the intensity of pain score and the total analgesic requirement for the first 48 hours in postoperative periods. The evaluations were performed q6hrs for the first 48 hr following the surgery. Rescue analgesia was given intravenously (titratable bolus doses of morphine) during the first 48 hours after the surgery upon each patient's demand for more pain control. Secondary outcomes included Numeric rating scales 6 wk after surgery.

Statistical and power analysis

Based on the results of Loftus *et al.*,'s a clinical trial (8) and using 95% of the confidence level, 90% of power, and at least one mean pain score difference between the two groups, the sample size was estimated to be 70 patients in each of the two groups.

We used the SPSS ver. 22.0 for Windows (SPSS, Chicago, IL, USA) for statistical analyses. Variables were tested for normal distribution, and the Students *t*-test and Mann–Whitney U test were applied as appropriate. Categorical data were analyzed using the *chi*-squared test or Fisher's exact test. $P<0.05$ were considered as statistically significant. A multivariate regression approach was then undertaken to assess the impact of potentially confounding covariates.

Results

One hundred forty eligible patients with chronic back pain scheduled for elective lumbar surgery were enrolled in this study from May 1, 2018, to 30 October 2019. The median age of patients was 51.5±10.8 years (23-61 yr). The demographic variables of patients are depicted in Table 1.

Table 1. Demographic data and perioperative outcome of patients

Variable	Intervention	Control	*P*
Gender(male/female)	38/32	40/30	0.1
Age(yr)	49.09±6.5	51.10±9.3	0.2
Duration of pain before operation (month)	14.56±6.8	13.39±5.9	0.2
The severity of pain before operation (NRS)	7.3±1.2	6.9±1.8	0.2
Weight (kg)	78.40±5.7	79.60±8.2	0.4
Duration of operation (min)	187.07±11.2	204.21 ±12.3	0.05
Atracurium dosage used during operation (mg)	10.8 ± 2.41	23.57 ±2.51	0.002*
Remifentanil dosage used during operation (mg)	3. 5± 1.2	4.8±1.6	0.005*

NRS= numeric rating scale
*= statistically significant

The range of hemodynamic changes during the procedure was less in the intervention group. Generally, the mean of mean arterial pressure was lower in the intervention compared to the control group (86.44 mmHg±12.34 vs, 100.83 mmHg±22.45 $P=0.001$). In terms of heart rate, the intervention group also had a

lower heart rate during the procedure (72.51±16.7 vs. 90.56±15.71 *P*=0.001).

In the intervention group anesthetic drug (muscle relaxant and remifentanil) has been used less than the control group during surgery (Table 1).

The severity of pain was lower in the intervention group than in the placebo group during 48 h post-operatively, morphine consumption in this group also decreased significantly during this period (Table 2).

Table 2. Postoperative mean severity of pain and morphine requirement

Variable	Intervention	Control	*P*
Ward NRS 6-hr,	3.27±1.2	4.12±	0.005*
Ward NRS 12-hr,	3.11±1.1	4.11±1.2	0.005*
Ward NRS 24-hr,	3.01±1.3	3.87±1.4	0.6
Ward NRS 48-hr,	3.11±1.3	3.67±1.1	0.5
Morphine ,total mg/48h	35±2.5	43±37	0.032*
NRS, 6 wk	2.39	3.76	0.001*

Data are presented as mean ± (SD)
SD = standard deviation
NRS= numeric rating scales
*=statistically significant

Discussion

In this clinical trial, we have demonstrated that patients, who received ketamine and magnesium sulfate during spine surgery, had reduced opioid consumption and pain score one month after surgery as compared to patients who received placebo. Opioids and anesthetic consumption was also reduced during surgery.

The severity of pain during 48 hours after surgery in ketamine group was reduced that is similar to Nielsen, *et al.*, study. They used intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 mg·kg/hr during spinal fusion surgery in chronic pain patients with opioid dependency andthey conclude that intraoperative ketamine significantly reduced morphine consumption 0 to 24 hours after surgery, the difference was that the patients in our study were not drug dependent (9). In another study they explored the effect of intraoperative S- ketamine on analgesic consumption and pain one year after spine surgery in chronic opioid-dependent patients undergoing spinal fusion surgery. Finally, they showed that intraoperative ketamine may reduce opioid use and pain and improve labour market attachment one year after spine surgery in an opioid-dependent population (10).

One of the complications of using ketamine during surgery is postoperative delirium. Aladine *et al.*, through a study showed the administration of a subanesthetic ketamine dose during surgery are not useful in preventing postoperative delirium or reducing postoperative pain and minimizing opioid consumption. Instead, the net effect of ketamine might be deleterious since it increases the incidence of postoperative nightmares and hallucinations (11).

We used small dose ketamine before incision and magnesium sulfate in bolus and continued infusion during surgery and we have not any hallucination or delirium post-operation. Our findings are partly in line with those in Oguzhan *et al.*, study. They give an initial infusion of 30 mg/kg (over 10 minutes) magnesium sulfate immediately after anesthesia and completed before intubation. The infusion was then continued at 10 mg/kg/hr throughout surgery. At the end they concluded, intraoperative magnesium administration significantly reduced muscle relaxant and opioid requirements; and it also reduced postoperative pain and opioid use (12). Magnesium causes a dose-dependent negative inotropic effect, and in humans, hemodynamic studies have shown that it has a peripheral (predominantly arteriolar) vasodilatory effect (13). After rapid infusion of 3 or 4 g of magnesium sulphate, systolic arterial pressure decreased in relation to decreased systemic vascular resistance. For this reason, the use of anesthetic and opiate medications may be reduced in patients in the intervention group.

Magnesium administration may have another benefit, that it potentiates neuromuscular block during general anesthesia. It has been shown that the basic mechanisms involve a reduction of the amount of acetylcholine released from motor nerve terminals and a decrease in the depolarizing action of acetylcholine at the motor endplate, or a depression of muscle fiber membrane excitability (14). For this reason, in our study, the use of muscle relaxant and anesthetic and opioid in patients that took magnesium and ketamine were reduced.

In conclusion, intraoperative low dose ketamine/magnesium sulfate may reduce analgesic use

and pain 48 hour and one month after spine surgery and improve analgesics free time in patients. These findings need further investigation of ketamine as an opioid-sparing analgesic for chronic pain.

The limitation of our study is that we did not evaluate the criteria for patient physical activity, and patients return to normal life or work.

Acknowledgments

The authors would like to thank statistics consultants of the Research Development Center of Sina Hospital for their technical assistance.

References

1. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. Spine 2018;43:E299-307.
2. Khajavi MR, Sabouri SM, Moharari RS, Pourfakhr P, Najafi A, Etezadi F, et al. Multimodal analgesia with ketamine or tramadol in combination with intravenous paracetamol after renal surgery. Nephrourol Mon 2016;8;e36491
3. Shariat Moharari R, Lajevardi M, Khajavi M, Najafi A, Shariat Moharari G, Etezadi F. Effects of Intra-Operative Ketamine Administration on Postoperative Catheter-Related Bladder Discomfort: A Double-Blind Clinical Trial. Pain Pract 2014;14:146-50.
4. Elsamadicy AA, Charalambous LT, Sergesketter AR, Drysdale N, Adil SM, Freedman IG, et al. Intraoperative ketamine may increase risk of post-operative delirium after complex spinal fusion for adult deformity correction. J Spine Surg 2019;5:79-87.
5. Kizilcik N, Koner O. Magnesium sulfate reduced opioid consumption in obese patients undergoing sleeve gastrectomy: a prospective, randomized clinical trial. Obes Surg 2018;28:2783-8.
6. Moharari RS, Motalebi M, Najafi A, Zamani MM, Imani F, Etezadi F, et al. Magnesium can decrease postoperative physiological ileus and postoperative pain in major non laparoscopic gastrointestinal surgeries: a randomized controlled trial. Anesth Pain Med 2014;4:e12750.
7. Etezadi F, Aklamli M, Najafi A, Khajavi M, Moharari RS, Mirrahimi B, et al. Evaluation of the anti-inflammatory effects of peri-operative infusion of magnesium sulfate on the microsurgical procedures for intracranial tumors. Anesth Pain Med 2014;4: e22379.
8. 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. J Am Soc Anesthesiol 2010;113:639-46.
9. Nielsen RV, Fomsgaard JS, Nikolajsen L, Dahl JB, Mathiesen O. Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. Eur J Pain 2019;23:455-60.
10. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain 2017;158:463-70.
11. Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PH E, Pryor KO, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet 2017;390:267-75.
12. Oguzhan N, Gunday I, Turan A. Effect of magnesium sulfate infusion on sevoflurane consumption, hemodynamics, and perioperative opioid consumption in lumbar disc surgery. J Opioid Manag 2008;4:105-10.
13. Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS, Do SH. IV infusion of magnesium sulphate during spinal anaesthesia improves postoperative analgesia. Br J Anaesth 2009;104:89-93.
14. Rodriguez-Rubio L, Nava E, del Pozo JS, Jordan J. Influence of the perioperative administration of magnesium sulfate on the total dose of anesthetics during general anesthesia. A systematic review and meta-analysis. J Clin Anesth 2017;39:129-38.