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ORIGINAL INVESTIGATION

Effect of magnesium sulfate with ketamine infusions on intraoperative and postoperative analgesia in cancer breast surgeries: a randomized double-blind trial☆

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KEYWORDS
Magnesium sulfate;
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Abstract
Background: Opioids are the cornerstone in managing postoperative pain; however, they have many side effects. Ketamine and Magnesium (Mg) are NMDA receptor antagonists used as adjuvant analgesics to decrease postoperative opioid consumption.
Objective: We assumed that adding Mg to ketamine infusion can improve the intraoperative and postoperative analgesic efficacy of ketamine infusion alone in cancer breast surgeries.
Methods: Ninety patients aged between 18 and 65 years and undergoing elective cancer breast surgery were included in this prospective randomized, double-blind study. Group K received ketamine 0.5 $mg.kg^{-1}$ bolus then 0.12 $mg.kg^{-1}.h^{-1}$ infusion for the first 24 hours postoperatively. Group KM: received ketamine 0.5 $mg.kg^{-1}$ and Mg sulfate 50 $mg.kg^{-1}$, then ketamine 0.12 $mg.kg^{-1}.h^{-1}$ and Mg sulfate 8 $mg.kg^{-1}.h^{-1}$ infusions for the first 24 hours postoperative. The primary outcome was the morphine consumption in the first 24 hours postoperative, while the secondary outcomes were: intraoperative fentanyl consumption, NRS, side effects, and chronic postoperative pain.
Results: Group KM had less postoperative opioid consumption (14.12 ± 5.11 mg) than Group K (19.43 ± 6.8 mg). Also, Group KM had less intraoperative fentanyl consumption. Both groups were similar in postoperative NRS scores, the incidence of side effects related to opioids, and chronic neuropathic pain.
Conclusion: Adding Mg to ketamine infusion can safely improve intraoperative and postoperative analgesia with opioid-sparing effect in cancer breast surgery.
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Introduction

Acute postoperative pain is the main complaint in 40% of patients undergoing Breast Cancer (BC) surgery. Inadequate analgesia can result in many adverse events (e.g., myocardial infarction, poor wound healing, and chronic pain development).[1,2]

Opioids are the cornerstone in managing postoperative pain; however, they are associated with many adverse events (e.g., Postoperative Nausea and Vomiting [PONV], urine retention, pruritis, and respiratory depression).[3]

Non-opioid analgesics can be beneficial in reducing opioid consumption during the postoperative period so that they can decrease the side effects of postoperative opioids.[4]

N-Methyl D-Aspartate (NMDA) receptors had a role in the pathogenesis of acute and chronic postoperative pain. Inhibition of NMDA receptors can prevent central sensitization and wind-up phenomenon produced in response to peripheral painful stimuli.[5] Therefore, NMDA receptor antagonists showed efficacy in reducing both intensity and period of postoperative pain.[6,7]

Ketamine is a non-competitive antagonist for NMDA receptors. Ketamine in low doses decreases the consumption of postoperative opioids in many surgeries.[8–10] Magnesium (Mg) sulfate is also an antagonist for NMDA receptor that has been evaluated in several studies and showed that Mg sulfate decreased consumption of postoperative opioids.[11–13]

Ketamine and Mg sulfate have different sites of action on NMDA receptors, so their combination may produce a synergistic effect on NMDA receptors, resulting in more control of postoperative pain and more sparing of consumption of opioids.[14]

We assumed that adding Mg sulfate to ketamine infusion can improve the intraoperative and postoperative analgesic efficacy of the ketamine infusion alone in the form of reducing opioid consumption in BC surgeries.

Methods

After approval from the local ethical committee and the institutional review board, 90 female patients aged between 18 and 65 years, American Society of Anesthesiologists (ASA) physical status class II, undergoing elective BC surgery (conservative mastectomy or modified radical mastectomy) were included in our randomized, double-blind trial. The trial was conducted between November 2019 and June 2020 after recording at ClinicalTrials.gov (ID: NCT04111848). Each patient had signed informed consent. The study complied with the Declaration of Helsinki (2013) and relevant national laws and regulations.

Exclusion criteria were refusal of the patient, patients unable to utilize Patient-Controlled Analgesia (PCA) devices, allergy to any drug used in the trial, diabetes, uncontrolled hypertension, cardiac impairment (ejection fraction less than 45%), any heart block, renal impairment (serum creatinine greater than 2 $mg.dL^{-1}$), hepatic impairment (transaminases greater than double the normal values), glaucoma, psychiatric or neurological disorders, difficulty in communication, pregnancy, and preoperative use of calcium channel blockers or narcotic drugs.

In the preoperative assessment, all cases were learned how to report pain intensity on the 11-points Numerical Rating Scale (NRS); point 0 represents no pain and point 10 represents the worst imaginable pain. Also, all patients were instructed about the usage of the PCA device.

Patients were randomly allocated into two groups in a parallel design by using a computer-generated randomization program (permuted block technique) by a statistician. The random allocation numbers were put in closed, sealed opaque envelopes that were opened on the day before surgery.

The patients were allocated into two equal groups (45 patients in each one).

Group K (Ketamine group): patients received ketamine 0.5 $mg.kg^{-1}$ bolus (diluted in 100 mL normal saline over 30 minutes) with anesthesia induction, then 0.12 $mg.kg^{-1}.h^{-1}$ ketamine infusion for the 1st postoperative 24 hours (the infusion concentration was 0.6 $mg.mL^{-1}$, and the infusion rate was 0.2 $mL.kg^{-1}.h^{-1}$). An infusion of NaCl 0.9% (placebo) was used with the same infusion rate as Mg infusion in Group KM.

Group KM (ketamine and Mg group): patients received 0.5 $mg.kg^{-1}$ ketamine and 50 $mg.kg^{-1}$ Mg sulfate (diluted in 100 mL normal saline over 30 minutes) boluses with anesthesia induction, then 0.12 $mg.kg^{-1}.h^{-1}$ ketamine and 8 $mg.kg^{-1}.h^{-1}$ Mg sulfate infusions for the 1st postoperative 24 hours (the infusion concentration was 0.6 mg ketamine and 40 mg Mg for each mL and the infusion rate was 0.2 $mL.kg^{-1}.h^{-1}$).

A pharmacist, who did not participate in managing patients or collecting data, prepared the medications of our trial. To warrant double blinding in our trial, administered drugs were given to each patient at equal rates and equal volumes. Group allocation was masked for both patients and investigators included in the management of patients.

For every patient, the same anesthetic techniques were done. Pulse oximetry, Electrocardiogram (ECG), noninvasive blood pressure, temperature probe, and capnography were used for standard continuous monitoring. After premedication with midazolam (0.03 $mg.kg^{-1}$), induction of anesthesia was carried out by giving intravenous (IV) propofol (2 $mg.kg^{-1}$) and IV fentanyl (2 $\mu g.kg^{-1}$), and IV rocuronium (0.6 $mg.kg^{-1}$) was given to facilitate endotracheal intubation. Anesthesia was maintained by inhalation of sevoflurane with minimum alveolar concentration (MAC) at 2–2.5%. To maintain muscle relaxation, IV rocuronium (0.1 $mg.kg^{-1}$) boluses were given when required. Ventilatory settings (tidal volume and respiratory rate) were modified to maintain end-tidal CO_2 between 35 and 40 mmHg. Fentanyl 0.5 $\mu g.kg^{-1}$ IV boluses were added to keep Mean Arterial blood Pressure (MAP) and Heart Rate (HR) within 20% of their baseline preoperative values after exclusion of other causes (e.g., tachycardia and hypotension due to blood loss). After wound closure, the reversal of neuromuscular block was by IV neostigmine (0.05 $mg.kg^{-1}$) and IV atropine (0.02 $mg.kg^{-1}$). Fully awake extubation was done after complete recovery from anesthesia.

After patient transfer to Post-Anesthesia Care Unit (PACU), a PCA device filled by 1 $mg.mL^{-1}$ morphine solution, was connected to the IV access in every case. The device was set to administer 1 mL with a 15-minute lockout interval and with no continuous infusion.

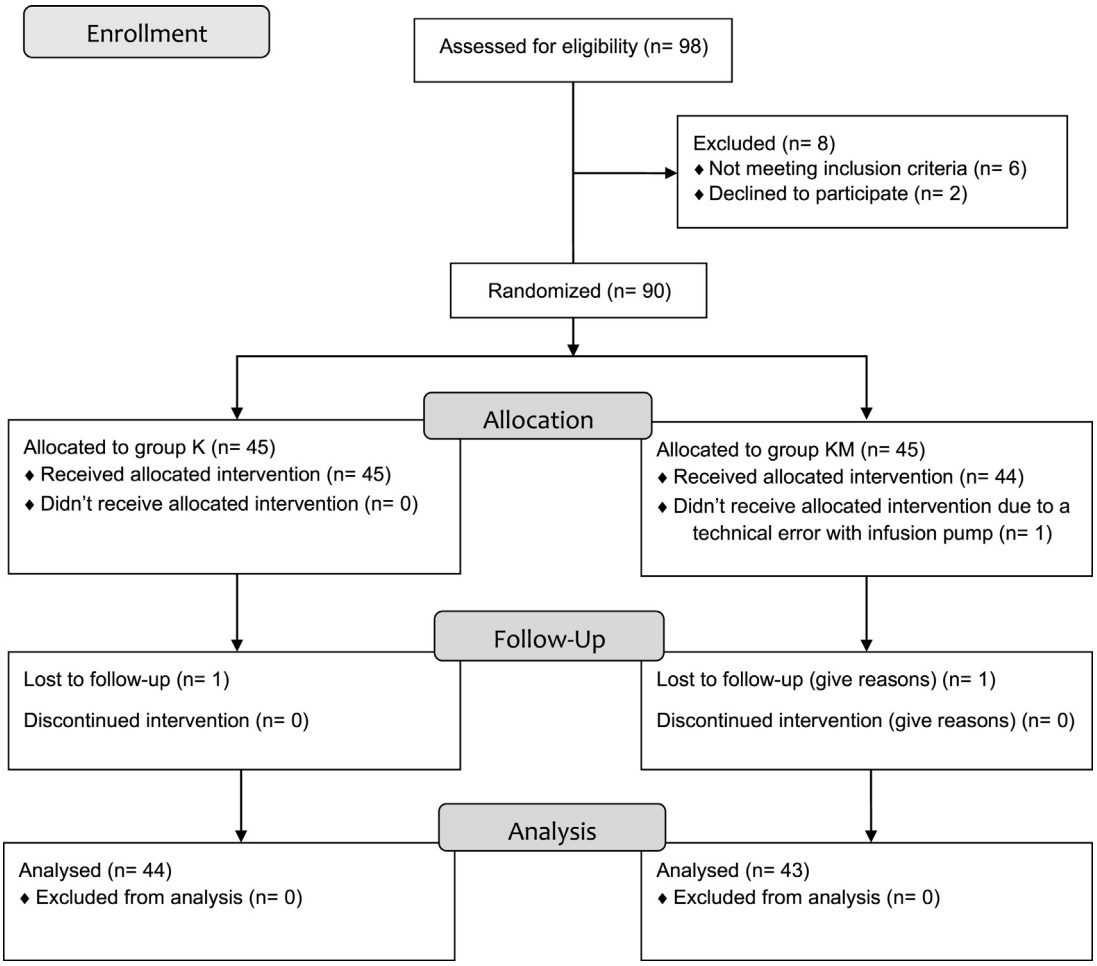

Fig. 1 CONSORT flow diagram of the participants through each stage of the trial.

The primary outcome was the morphine consumption in the first postoperative 24 hours, while the secondary outcomes were: the intraoperative fentanyl consumption, NRS scores (during rest and with shoulder movement at 0, 4, 8, 12, and 24 hours postoperative), and the incidence of side effects of postoperative morphine (e.g., PONV and pruritis), and of ketamine (e.g., nightmares and hallucination). All these side effects were managed and recorded. Sedation scores were evaluated using Ramsay Agitation Sedation Scale (RASS) during the first postoperative 24 hours; RASS > 2 was recorded.[15]

Chronic pain was assessed after three months during their visit in outpatient follow-up. Neuropathic pain was considered if Douleur Neuropathique 4 (DN4) questionnaire score more than or equal 4.[16]

G Power 3.1.9.7 program (Universitat Kiel, Germany) was used to calculate the sample size. A previous study done by Jabbour et al.[17] demonstrated that the mean consumption of morphine in the first 24 hours postoperatively for ketamine group was 44.68 ± 19.79 mg and of ketamine and Mg combination group was 32.02 ± 14.56 mg. To detect this difference, at least 41 patients per group were needed, taking into consideration that power (1-β) was 90% and significance (α) was 0.05. To override possible dropouts, the sample size was increased to be 45 patients in each group.

SPSS for Windows, version 23.0 (Armonk, NY: IBM Corp) was used for statistical analysis. The normality of data was checked with Shapiro-Wilk test and histograms. Quantitative parametric variables were described as mean and standard deviation (SD) and were compared by unpaired Student *t*-test. Quantitative non-parametric variables were described as median and Interquartile Range (IQR) and were compared by Mann Whitney test. Categorical variables were presented as frequency (and percent) and were analysed by the Chi-square or Fisher's Exact tests. A two-tailed p-value < 0.05 was considered statistically significant.

Results

In our study, assessment for eligibility was done in 98 cases. Two cases refused to participate, and six cases were excluded due to exclusion criteria. So, 90 cases were allocated into two groups (each of 45). During the study, three patients were excluded. One patient in group KM did not complete the study due to a technical error with his infusion pump, and two patients were lost during the 3-month follow-up (one in each group). Only 44 patients in Group K and 43 patients in group KM were statistically analyzed (Fig. 1).

Table 1 Demographic data of both groups.

		Group K (n = 44)	Group KM (n = 43)	*p*
Age (years)		50.14 ± 9.04	50.91 ± 8.68	0.686
Weight (kg)		75.59 ± 7.80	74.28 ± 6.99	0.411
Height (cm)		162.00 ± 5.20	161.26 ± 4.86	0.492
Type of surgery	Conservative mastectomy	21 (47.7%)	23 (53.5%)	0.591
	Modified radical mastectomy	23 (52.3%)	20 (46.5%)	
Duration of surgery (min)		103 ± 16	100 ± 15	0.351

Data are presented as mean ± SD or frequency (and percent).

Table 2 Total amount of intraoperative fentanyl and postoperative morphine consumptions and incidence of postoperative sedation and chronic pain.

	Group K (n = 44)	Group KM (n = 43)	*p*
Total amount of intraoperative fentanyl (μg) consumption	222.27 ± 56.19	195.58 ± 42.95	0.015
Total amount of morphine (mg) required during the 1st postoperative 24 hours	19.43 ± 6.8	14.12 ± 5.11	<0.001
Postoperative sedation	2 (4.5%)	2 (4.7%)	1
Chronic pain	9 (20.5%)	7 (16.3%)	0.615

Data are presented as mean ± SD.

Table 3 Numerical Rating Scale (NRS) during rest in the first 24 hours.

	Group K (n = 44)	Group KM (n = 43)	*p*
0 h	4 (3–4)	4 (3–4)	0.325
4 h	3 (2–3)	2 (2–3)	0.437
8 h	2 (2–3)	2 (2–3)	0.686
12 h	4 (3–4)	2 (1–2)	0.482
24 h	1 (1–2)	1 (1–2)	0.193

Data are presented as median (IQR).

Table 4 Numerical Rating Scale (NRS) during shoulder movement in the first 24 hours.

	Group K (n = 44)	Group KM (n = 43)	*p*
0 h	6 (5–7)	6 (5–7)	0.450
4 h	4 (4–5)	4 (3–4.5)	0.071
8 h	4 (3–5)	4 (3–4)	0.351
12 h	3 (3–4)	3 (2–4)	0.254
24 h	3 (2–3)	3 (2–3)	0.255

Data are presented as median (IQR).

In this study, demographic data were comparable in the two groups (Table 1).

Group KM consumed less amount of postoperative morphine (14.12 ± 5.11 mg) than Group K (19.43 ± 6.8 mg; $p < 0.001$). Group KM consumed less amount of intraoperative fentanyl (195.58 ± 42.95 μg) than group K (222.27 ± 56.19 μg; $p = 0.015$) (Table 2).

The current trial revealed no significant difference in postoperative NRS during rest and shoulder movement at all times of measurement (Table 3 and 4).

PONV was increased in Group K (8 patients) than in Group KM (5 patients) but without statistical significance ($p = 0.344$). No other side effects related to the study medications were found in this study.

Incidence of sedation was comparable between both groups; two patients in each group showed a sedation score > 2. Regarding the incidence of chronic postoperative neuropathic pain, it was comparable between both groups; nine patients in Group K had a DN4 score > 4, while seven patients in Group KM with a *p*-value of 0.615 (Table 2).

Discussion

This study showed that adding Mg infusion to ketamine infusion in BC surgeries resulted in reductions of postoperative morphine and intraoperative fentanyl consumptions. The use of fewer doses of postoperative opioids during this combined infusion of ketamine and Mg achieved an adequate pain control similar to that achieved by using a larger amount of postoperative opioids during ketamine infusion alone. However, this combination failed to significantly reduce the incidence of PONV nor the incidence of development of chronic post-mastectomy neuropathic pain.

NMDA antagonists prevent the activation of NMDA receptors which are stimulated by the excitatory amino acids (as glutamate and aspartate) released in response to painful stimuli produced by tissue damage. Inhibition of NMDA receptors prevents the intracellular calcium influx, resulting in attenuation of the cascades of central sensitization and hyperexcitability of the central nervous system, leading to a reduction in the intensity and the duration of the postoperative pain.[6,7,17]

The use of a combination of ketamine and Mg infusion was proved by Liu et al.[6] to act in a superadditive manner on the modulation of NMDA receptors, resulting in a better analgesic action and morphine-sparing effect.

This combination was used by Jabbour et al.[17] in a prospective double-blind study to evaluate its analgesic efficacy in scoliosis surgery. Their results were consistent with

our results in improving analgesic efficacy and sparing postoperative morphine consumption. They also found no effect of this combination in reducing postoperative pain scores. In opposition to our results, they found no decrease in intraoperative opioid requirements with the combination, and this may be attributed to different doses and different populations and types of operation. Also, they found no decrease in intraoperative opioid requirements and a higher incidence of PONV in patients receiving ketamine alone. This difference may be due to the lower needed doses of morphine after mastectomy, unlike scoliosis, and they stopped infusions with extubation.

Ketamine was evaluated in several studies as one of the adjuvant analgesics for acute postoperative pain. In a trial done by Akhavanakbari et al.,[9] the use of the ketamine added to morphine in PCA has shown to be more analgesic than the use of morphine alone in PCA after orthopedic surgery, and it produced a significant opioid-sparing effect with reduced pain scores. Remérand et al.[18] also proved the opioid-sparing effect of ketamine in managing pain after total hip arthroplasty. They found that intraoperative and postoperative ketamine infusion can reduce postoperative opioid consumption in these patients. Zakine et al.[19] used ketamine infusion for 48 postoperative hours to control the postoperative pain in abdominal surgeries, and the infusion produced better analgesia with a less postoperative opioid consumption than the use of intraoperative ketamine alone.

Adding Mg to ketamine infusion may carry the benefit of minimizing the required effective analgesic dose of ketamine, leading to fewer side effects of ketamine. This can explain the absence of adverse effects of ketamine as hallucination and nightmares in our study. We used the recommended dose of ketamine used in Kim et al.[8] study. They found that ketamine 0.5 $mg.kg^{-1}$ bolus followed 2 $\mu g.kg^{-1}.min^{-1}$ infusion could safely produce an opioid-sparing effect in lumbar spinal fusion surgeries without evident ketamine side effects. Ketamine infusion at doses < 2.5 $\mu g.kg^{-1}.min^{-1}$ was not associated with cognitive impairment or psychomimetic effects.[20]

The first trial to use the perioperative Mg in analgesia was done by Tramer et al. in 1996.[21] They used a Mg bolus dose followed by a Mg infusion for 20 hours and found that Mg decreased postoperative analgesic requirements. However, a single dose of Mg (30 $mg.kg^{-1}$) failed to prove an analgesic efficacy in children undergoing tonsillectomy.[22] In another trial on inguinal hernia repair or varicose vein surgeries, Tramèr and Glynn[23] found that a 4 g bolus dose of Mg had no impact on postoperative pain and analgesic consumption. In another trial on total abdominal hysterectomy, Ryu et al.[11] found that intraoperative Mg infusion after a bolus dose improved the postoperative analgesia as it reduced postoperative analgesic consumption and pain scores. Our study followed the single-dose of Mg by a 24 postoperative hours continuous infusion to intensify and prolong its analgesic efficacy.

In line with our results, a meta-analysis[24] demonstrated that systemic Mg had a significant opioid-sparing effect but with no effect on adverse events of opioids (as PONV).

Recently, Jendoubi et al.[10] tried to use postoperative ketamine or lidocaine infusion to control postoperative pain after open nephrectomy. They demonstrated that infusion of ketamine decreased postoperative pain scores and consumption of opioids but failed to decrease the chronic postoperative neuropathic pain incidence after three months.

A recent randomized, crossover trial[25] showed that neuropathic pain intensity wasn't significantly different between the three groups (ketamine [0.5 $mg.kg^{-1}$]/placebo or ketamine [0.5 $mg.kg^{-1}$]/Mg sulfate (3 g) or placebo/placebo) over 35 days. The results of this trial showed that ketamine provided pain relief after 35 days versus placebo and that a combination with Mg had no additional analgesic effect. These results were in line with our results.

Although ketamine has been approved to be an efficient analgesic, as mentioned in many previous trials, the absence of a placebo group to show the opioid-sparing effect of ketamine may be one of our study's limitations. Another limitation was the small sample size. Further studies with a larger sample size may be needed to show if there is a statistical difference in opioid side effects or the incidence of chronic postoperative neuropathic pain. These studies should consider the other factors that may affect the incidence of chronic pain, such as tobacco use and mental health. Also, further studies in different types of operations are needed.

Conclusion

Adding Mg to ketamine infusion can safely improve intraoperative and postoperative analgesia with opioid-sparing effect in BC surgery but failed to significantly reduce the incidence of PONV or chronic post-mastectomy incidence neuropathic pain.

Funding

This trial was recorded at ClinicalTrials.gov (NCT04111848), url: https://clini)caltrials.gov/ct2/show/NCT04111848

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Poleshuck EL, Katz J, Andrus CH, et al. Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain. 2006;7:626–34.
2. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017; 10:2287–98.
3. Viscusi ER. Patient-controlled drug delivery for acute postoperative pain management: a review of current and emerging technologies. Reg Anesth Pain Med. 2008; 33:146–58.
4. Martinez V, Beloeil H, Marret E, et al. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth. 2017;118:22–31.
5. Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg. 2003;97:1108–16.

6. Liu HT, Hollmann MW, Liu WH, et al. Modulation of NMDA receptor function by ketamine and magnesium: Part I. Anesth Analg. 2001;92:1173–81.
7. 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;98:1385–400.
8. Kim SH, Kim SI, Ok SY, et al. Opioid sparing effect of low dose ketamine in patients with intravenous patient-controlled analgesia using fentanyl after lumbar spinal fusion surgery. Korean J Anesthesiol. 2013;64:524–8.
9. Akhavanakbari G, Mohamadian A, Entezariasl M. Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery. Perspect Clin Res. 2014;5:85–7.
10. Jendoubi A, Naceur IB, Bouzouita A, 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;11:177–84.
11. Ryu JH, Kang MH, Park KS, et al. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth. 2008;100:397–403.
12. El Mourad MB, Arafa SK. Effect of intravenous versus intraperitoneal magnesium sulfate on hemodynamic parameters and postoperative analgesia during laparoscopic sleeve gastrectomy-A prospective randomized study. J Anaesthesiol Clin Pharmacol. 2019;35:242–7.
13. Mendonça FT, Pellizzaro D, Grossi BJ, et al. Synergistic effect of the association between lidocaine and magnesium sulfate on perioperative pain after mastectomy: A randomised, double-blind trial. Eur J Anaesthesiol. 2020;37:224–34.
14. Helander EM, Menard BL, Harmon CM, et al. Multimodal Analgesia, Current Concepts, and Acute Pain Considerations. Curr Pain Headache Rep. 2017;21:3.
15. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2:656–9.
16. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114:29–36.
17. Jabbour HJ, Naccache NM, Jawish RJ, et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. Acta Anaesthesiol Scand. 2014;58:572–9.
18. Remérand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg. 2009;109:1963–71.
19. Zakine J, Samarcq D, Lorne E, et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg. 2008;106:1856–61.
20. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82:111–25.
21. Tramer MR, Schneider J, Marti RA, et al. Role of magnesium sulfate in postoperative analgesia. Anesthesiology. 1996;84:340–7.
22. O'Flaherty JE, Lin CX. Does ketamine or magnesium affect posttonsillectomy pain in children? Paediatr Anaesth. 2003;13:413–21.
23. Tramèr MR, Glynn CJ. An evaluation of a single dose of magnesium to supplement analgesia after ambulatory surgery: randomized controlled trial. Anesth Analg. 2007;104:1374–9.
24. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, et al. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2013;119:178–90.
25. Pickering G, Pereira B, Morel V, et al. Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-blind, Crossover Trial. Anesthesiology. 2020;133:154–64.