THE EFFECT OF PREEMPTIVE INTRAVENOUS LOW-DOSE MAGNESIUM SULFATE ON EARLY POSTOPERATIVE PAIN AFTER LAPAROSCOPIC CHOLECYSTECTOMY

Iva Bačak Kocman[1], Renata Krobot[2], Jadranka Premužić[2], Ivica Kocman[3], Ranko Stare[4], Lea Katalinić[5] and Nikolina Bašić-Jukić[5]

[1]Department of Anesthesiology, Resuscitation and Intensive Care, Zagreb University Hospital Center, Zagreb; [2]Department of Anesthesiology, Resuscitation and Intensive care, Varaždin General Hospital, Varaždin; [3]Clinical Department of Surgery, Merkur University Hospital, Zagreb; [4]Department of Surgery, Varaždin General Hospital, Varaždin; [5]Clinical Department of Internal Medicine, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – As an N-methyl-D-aspartate antagonist, magnesium sulfate has analgesic properties and reduces noxious input during surgery. The aim of the study was to determine the effect of preemptive intravenous low-dose magnesium sulfate on early postoperative pain after laparoscopic cholecystectomy. In this prospective, randomized study, 60 ASA I-II patients undergoing elective laparoscopic cholecystectomy were assigned to three groups (n=20 each). After anesthesia induction, prior to surgical incision, patients received magnesium sulfate 5.0 mg/kg (group A), magnesium sulfate 7.5 mg/kg (group B) or saline intravenously (group C). General anesthesia was performed with the same drugs in all three groups. Postoperative pain intensities at rest, according to the visual analog scale (VAS 0-10), were evaluated at 1, 3, 6, 9 and 24 hours after surgery. According to the VAS scores, patients intravenously received metamizol 2.5 g (VAS 3-4), diclofenac 75 mg (VAS 5-7) or tramadol 1 mg/kg (VAS 8-10). VAS scores at 1 hour postoperatively were significantly lower in groups A (4.7±1.7; $p<0.05$) and B (3.2±1.8; $p<0.01$) than in group C (5.2±2.0). At 3 hours postoperatively, VAS score was significantly lower in group B (2.4±1.5) than in group A (3.7±1.8) or group C (3.8± 2.3) ($p<0.05$). After 6, 9 and 24 hours postoperatively, there were no differences in VAS scores among the groups. In conclusion, preemptive intravenous administration of both 5.0 mg/kg and 7.5 mg/kg of magnesium sulfate significantly reduced early postoperative pain after laparoscopic cholecystectomy, but 7.5 mg/kg was found to be more effective. There was no effect on pain reduction at 6, 9 and 24 hours after surgery and no adverse effects were recorded.

Key words: *Magnesium sulfate; Cholecystectomy, laparoscopic; Pain, postoperative*

Introduction

Laparoscopic cholecystectomy is the gold standard in the treatment of symptomatic cholelithiasis. One of the major advantages over open cholecystectomy is reduced postoperative pain[1,2], although it still remains the most prevalent complaint in the early postoperative hours after laparoscopy.

Postoperative pain after laparoscopic cholecystectomy can be divided into three major groups according to localization: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain) and shoulder pain[3]. Incisional pain predominates and is the most intense on the day of surgery and the following day[4,5]. Interventions before the noxious stimulus causing central sensitization may attenuate or block sensitization and reduce acute pain and analgesic consumption[6].

Correspondence to: *Iva Bačak Kocman, MD*, Department of Anesthesiology, Resuscitation and Intensive Care, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: bacakkocman.iva@gmail.com

Received November 16, 2012, accepted July 5, 2013

Magnesium, the fourth most common cation in human body, is a calcium channel blocker and regulates calcium influx in the cell[7]. The N-methyl-D-aspartate (NMDA) receptor is an ionotropic receptor for glutamate and aspartate situated throughout the brain and spinal cord and is modulated by a number of endogenous and exogenous compounds. NMDA receptor blockade prevents induction of central sensitization due to peripheral nociceptive stimulation and abolishes hypersensitivity once it is established[8,9]. Magnesium is a noncompetitive antagonist of the NMDA receptors and its associated ion channels, and therefore a very effective drug in the treatment of postoperative pain.

The aim of this prospective randomized study was to determine the effect of two preemptive intravenous low-doses of magnesium sulfate (7.5 mg/kg and 5.0 mg/kg) on early postoperative pain (during the first three hours after surgery) in patients with symptomatic cholelithiasis undergoing laparoscopic cholecystectomy.

Patients and Methods

With the approval of the Hospital Ethics Committee and after a written informed consent had been obtained, 60 ASA I or II physical status patients of both sexes, aged 18-75 years, with symptomatic cholelithiasis scheduled for elective laparoscopic cholecystectomy were enrolled and randomly assigned to one of the three groups (n=20 each). Exclusion criteria were contraindications to any of the drugs used in the study, preexisting neurologic or psychiatric illness, and a history of drug or alcohol abuse. Patients were randomized to receive intravenously magnesium sulfate before surgical incision in a dose of 5.0 mg/kg (group A), magnesium sulfate 7.5 mg/kg (group B) or saline (group C).

The anesthetic management of patients was standardized. All patients were premedicated with oral midazolam (7.5 mg) 45 minutes before surgery. Anesthesia was induced with midazolam 0.2 mg/kg and propofol 1.5 mg/kg, followed by vecuronium 0.1 mg/kg to facilitate tracheal intubation. Fentanyl in a dose of 3 μg/kg was given before surgical incision and nasogastric tube was inserted during the procedure. The lungs were mechanically ventilated with oxygen/N_2O, keeping the end-tidal CO_2 at 35-40 mm Hg. Throughout the procedure, intravenous infusion of 500-1000 mL of Ringer solution was administered and in case of inadequate muscle relaxation, intermittent bolus of vecuronium 0.04 mg/kg was added. During the laparoscopy, intra-abdominal pressure was maintained at 12 mm Hg. Trocar insertion sites were not infiltrated with local anesthetic nor was intraperitoneal local anesthetic administered. Postoperative pain was assessed at rest using the visual analog scale (VAS) starting from 0 (no pain at all) to 10 (worst pain imaginable). The intensity of postoperative pain was assessed by the investigator blinded to patient group allocation. Assessment was made at 1, 3, 6, 9 and 24 hours postoperatively. According to VAS scale score, a bolus dose of intravenous analgesic was administered. Metamizol 2.5 g was given for VAS scores 3-4, diclofenac 75 mg for VAS scores 5-7, and tramadol 1 mg/kg for VAS scores 8-10. During the postoperative period, any adverse events or side effects, especially nausea, vomiting, bradycardia and hypotension, were recorded. Data were statistically analyzed and expressed as mean ± standard deviation (SD). Parametric data were compared using analysis of variance (ANOVA) and postoperative analgesic data using χ^2-test. Mann Whitney U test was used to evaluate differences between the groups in VAS scores according to postoperative hours, and Fisher's exact test to compare differences between the groups in the number of patients requiring analgesic at first postoperative hour and during 24 hours after surgery. *P* value <0.05 was considered statistically significant.

Results

Groups were comparable with respect to age, weight, sex, preoperative pain level, duration of pneumoperitoneum and duration of operation (Table 1). No complications related to anesthesia, operative procedure or conversion were recorded.

There was no statistically significant difference in the incidence of postoperative nausea and vomiting among the three groups. There were no cases of hemodynamic instability in the first 24 postoperative hours in all three groups of patients. The mean VAS scores for each group according to postoperative hour are shown in Table 2 and Figure 1. At 1 hour postop-

Table 1. Patient data

	Group A (n=20)	Group B (n=20)	Group C (n=20)
Age (yrs)	53.3±13.4	52.2±15.1	56.7±17.9
Weight (kg)	73.4±13.6	76.6±11.2	75.2±12.3
Sex (M/F)	3/17	5/15	4/16
Preoperative pain level	1.7±1.5	1.6±1.6	1.7±1.5
Duration of pneumoperitoneum (min)	28±12.4	29±13.6	26.7±8.8
Operation duration (min)	51.4±14.9	52.4±14.6	52.9±13.6
PONV	6/20	3/20	5/20

Values are given as mean ± SD; PONV = postoperative nausea and vomiting

eratively, VAS scores at rest in group B were significantly lower compared to group C ($p<0.01$) and group A ($p<0.05$). At 3 hours postoperatively, VAS scores in group B were also significantly lower compared to both group C and group A ($p<0.05$). There were no significant differences in VAS scores between groups C and A at 1 and 3 hours postoperatively. At 6, 9 and 24 hours postoperatively, no statistically significant differences in VAS scores were recorded among the three groups.

In the first postoperative hour, all (100%) group C patients, 19 (95%) group A patients and 12 (60%) group B patients required analgesic. This difference was statistically significant ($p<0.01$ group B *vs.* group C and $p<0.05$ group B *vs.* group A).

During the 24-hour period, all group C and group A patients required analgesic, while in group B there were 4 patients who did not require any analgesic, however, the difference was not statistically significant. Within the first 24 hours, metamizol consumption was significantly lower in group B than in groups

Table 2. Mean visual analog scale scores for each group according to postoperative hour

Postoperative hour	Group A	Group B	Group C
1	4.7±1.7	3.2±1.8*†	5.2±2.0
3	3.7±1.8	2.4±1.5*	3.8±2.3
6	2.5±1.2	2.2±1.4	1.9±1.7
9	2.0±1.6	1.8±1.5	2.0±1.6
24	1.6±1.5	1.1±1.3	1.3±1.6

Values given as mean ± SD; *$p<0.05$ compared to group A; †$p<0.01$ compared to group C

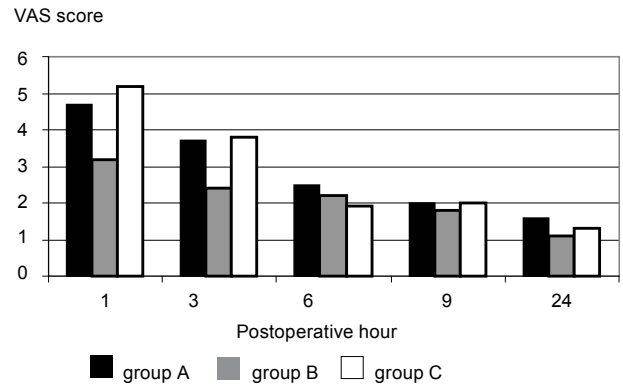

Fig. 1. Mean visual analog scale (VAS) scores according to postoperative hours.

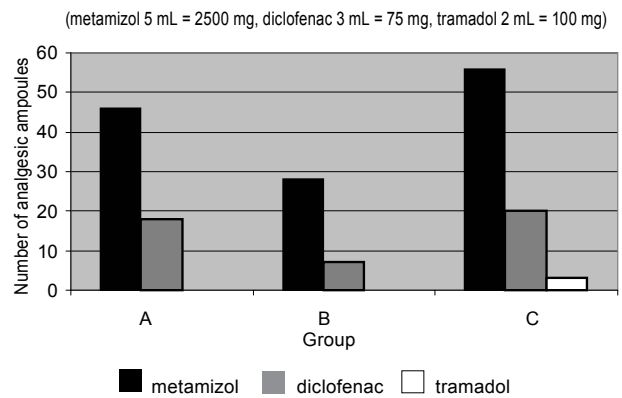

Fig. 2. Analgesic consumption during 24-hour period.

C and A ($p<0.001$ *vs.* group C and $p<0.05$ *vs.* group A). Diclofenac consumption was also lower in group B ($p<0.05$ *vs.* groups C and A).

Tramadol was administered to three patients in group C. No patient needed tramadol in groups A and B (Fig. 2).

Discussion

Although laparoscopic cholecystectomy is a procedure with many advantages over open cholecystectomy, early postoperative pain still remains the main problem for some patients.

There is evidence that preoperative pain and inflammation cause worse postoperative pain level, probably through sensitization of the central nervous system.

In the first 24 hours, the site of most severe pain is the upper abdominal quadrant and port wounds[2]. In 30%-40% of patients, second peak of pain occurs after 24 hours and is referred to shoulder tip[1]. The nature and mechanisms of pain after laparoscopic cholecystectomy are multifactorial because pain originates from three sources: port wounds, pneumoperitoneum (type of gas, pressure, temperature and volume of residual gas[1]) and cholecystectomy (visceral pain)[1,10]. In some studies, incisional pain predominated over visceral and shoulder tip pain[3]. Pneumoperitoneum causes neuropathic pain by chemical irritation, ischemia and compression[1,11,12].

Pain is a subjective sensation, which makes measurement of pain very difficult. Multimodal analgesic approach is recommended for the treatment of postoperative pain after laparoscopic cholecystectomy because of enhanced recovery and reduced risk of side effects[13]. According to consensus recommendations, paracetamol and NSAIDs are efficacious combination for postoperative analgesia following laparoscopic cholecystectomy and strong opioids should be avoided postoperatively[13].

In this study, a weak opioid was used as a rescue analgesic for the worst pain levels, otherwise postoperative pain was treated with NSAIDs or metamizol. In our country, metamizol was one of the most used analgesics until parenteral paracetamol has become available.

NMDA receptor is an amino acid receptor in the brain and spinal cord responsible for excitatory synaptic transmission[14]. NMDA antagonists may reduce pain and opioid consumption by two mechanisms: reduction in central hypersensitivity and wind-up-like states and by reducing opioid tolerance[15]. Magnesium as a NMDA receptor antagonist can prevent the induction of central sensitization after peripheral nociceptive stimulation[7]. Analgesic efficacy of magnesium depends on the dose and regimen (bolus *vs*. continuous infusion), surgical procedure (minor *vs*. major) and homeostasis[16-19].

With intraoperative continuous iv. administration of magnesium sulfate, it is possible to raise serum magnesium levels and problems like prolonged action of nondepolarizing muscle relaxants, vasodilatation due to direct interaction with calcium ions at vascular membranes and cardiac conductivity disorders may occur[14]. This fact was used as a limitation in our study, so we used minimal dose (bolus dose of magnesium sulfate given for control of adrenergic response during intubation[6]) to detect if it can be effective in treating early postoperative pain. Using this regimen, we had no major adverse effects of magnesium sulfate.

An increased pain relief was observed in patients who received 7.5 mg/kg magnesium sulfate iv. before surgical incision and it was evident in the first three postoperative hours. Pharmacological duration of a single intravenous injection of magnesium is significantly shorter than of continuous administration and it could be the reason of a relatively short period of postoperative analgesic effect[17,20]. The most convincing result of magnesium efficacy in a dose of 7.5 mg/kg in preventing postoperative pain was the lowest analgesic consumption when compared with magnesium sulfate dose of 5 mg/kg or saline.

In conclusion, preemptive intravenous administration of both 5.0 and 7.5 mg/kg of magnesium sulfate significantly reduced early postoperative pain after laparoscopic cholecystectomy, but 7.5 mg/kg was found to be more effective. No effect on pain reduction was recorded at 6, 9 and 24 hours after surgery and no adverse effects were noticed.

The results of our study suggest that magnesium has a significant specific antinociceptive effect through NMDA blockade. Further prospective, randomized studies should investigate the role of magnesium as a useful adjuvant to postoperative analgesia after laparoscopic surgery, especially differences in magnesium doses and regimens in postoperative pain control.

References

1. WILLS VL, HUNT DR. Pain after laparoscopic cholecystectomy. Br J Surg 2000;87:273-84.
2. URE BM, TROIDL H, SPANGENBERGER W, DIETRICH A, LEFERING R, NEUGEBAUER E. Pain after laparoscopic cholecystectomy: intensity and localization

of pain and analysis of predictors in preoperative symptoms and intraoperative events. Surg Endosc 1994;208:90-6.

3. BISGAARD T, KLARSKOV B, ROSENBERG J, KEHLET H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 2001;90:261-9.
4. BISGAARD T, KEHLET H, ROSENBERG J. Pain and convalescence after laparoscopic cholecystectomy. Eur J Surg 2001;167:84-96.
5. BISGAARD T. Analgesic treatment after laparoscopic cholecystectomy. Anesthesiology 2006;104:835-46.
6. KATZ J, McCARTNEY CJL. Current status of pre-emptive analgesia. Curr Opin Anaesthesiol 2002;15:435-41.
7. DUBÉ L, GRANRY JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. Can J Anaesth 2003;50:732-46.
8. TRAMER MR, SCHNEIDER J, MARTI RA, RIFAT K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996;84:340-7.
9. ALBRECHT E, KIRKHAM KR, LIU SS, BRULL R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia 2013;68:79-90.
10. BARCZYNSKI M, HERMAN RM. Low pressure pneumoperitoneum combined with intraperitoneal saline washout for reduction of pain after laparoscopic cholecystectomy. Surg Endosc 2004;18:1368-73.
11. WOOLF CJ, MANNION RJ. Neuropathic pain: aetiology, symptoms, mechanisms and management. Lancet 1999;353:1959-64.
12. BAŠIĆ-KES V, ZAVOREO I, BOSNAR-PURETIĆ M, IVANKOVIĆ M, BITUNJAC M, GOVORI V, DEMARIN V. Neuropathic pain. Acta Clin Croat 2009;48:359-65.
13. KEHLET H, GRAY AW, BONNET F *et al*. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy. Surg Endosc 2005;19:1396-415.
14. KOINIG H, WALLNER T, MARHOFER P, ANDEL H, HORAUF K, MAYER N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg 1998;87:206-10.
15. McCARTNEY CJL, 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.
16. TRAMER MR, GLYNN CJ. An evaluation of single dose of magnesium to supplement analgesia following ambulatory surgery: randomized controlled trial. Anesth Analg 2007;104:1374-9.
17. MENTES O, HARLAK A, YIGIT T, BALKAN A, BALKAN M, COSAR A, SAVASER A, KOZAK O, TUFAN T. Effect of intraoperative magnesium sulphate infusion on pain relief after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2008;52:1353-9.
18. SAADAWY IM, KAKI AM, ABD El LATIF AA, ABDELMAKSOUD AM, TOLBA OM. Lidocaine *vs*. magnesium: effect on analgesia after a laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2010;54:549-56.
19. KOGLER J. The analgesic effect of magnesium sulfate in patients undergoing thoracotomy. Acta Clin Croat 2009;48:19-26.
20. LYSAKOWSKI C, DUMONT L, CZARNETZKI C, TRAMER M, PHIL D. Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials. Anesth Analg 2007;104:1532-9.

Sažetak

UČINAK NISKE DOZE PREEMPTIVNOG INTRAVENSKOG MAGNEZIJ SULFATA NA RANU POSLIJEOPERACIJSKU BOL NAKON LAPAROSKOPSKE KOLECISTEKTOMIJE

I. Bačak Kocman, R. Krobot, J. Premužić, I. Kocman, R. Stare, L. Katalinić i *N. Bašić-Jukić*

Magnezij sulfat kao antagonist N-metil-D-aspartata ima analgetski učinak i smanjuje osjet boli tijekom operacijskog zahvata. Cilj ove studije bio je odrediti učinak preemptivne intravenske primjene male doze magnezij sulfata na bol u ranom poslijeoperacijskom tijeku nakon laparoskopske kolecistektomije. U ovom prospektivnom randomiziranom istraživanju 60 bolesnika ASA I-II koji su podvrgnuti laparoskopskoj kolecistektomiji podijeljeno je u tri skupine po 20 bolesnika. Nakon uvoda u anesteziju, a prije kirurškog reza, bolesnici su intravenski dobili 5 mg/kg magnezij sulfata (skupina A), 7.5 mg magnezij sulfata (skupina B) ili fiziološku otopinu (skupina C). Intenzitet poslijeoperacijske boli je ocijenjen vizualnom analognom skalom (VAS 0-10) 1, 3, 6, 9 i 24 sata nakon operacijskog zahvata. Na osnovi zbroja VAS bolesnici bi intravenski primili metamizol 2,5 mg (VAS 3-4), diklofenak 75 mg (VAS 5-7) ili tramadol 1 mg/kg (VAS 8-10). Zbrojevi VAS su prvog poslijeoperacijskog sata bili značajno niži u skupini A (4,7±1.7; $P<0,05$) i skupini B (3,2±1,8; $P<0,01$) nego u skupini C (5,2±2,0). Tri sata nakon operacijskog zahvata zbroj VAS u skupini B (2,4±1,5) je bio značajno niži nego u skupini A (3,7±1,8) ili skupini C (3,8±2,3) ($P<0,05$). Nakon 6, 9 i 24 sata nije bilo razlike među skupinama. U zaključku, preemptivna intravenska primjena 5,0 i 7,5 mg/kg magnezij sulfata značajno smanjuje poslijeoperacijsku bol nakon laparoskopske kolecistektomije, ali je 7,5 mg/kg bilo učinkovitije.

Ključne riječi: *Magnezij sulfat; Kolecistektomija, laparoskopska; Bol, poslijeoperacijska*