Acta Clin Croat 2025; 64:137-141

Original Scientific Paper

doi: 10.20471/acc.2025.64.02.7

IMPACT OF EARLY-STAGE IV MINERAL SUPPLEMENTATION ON DISCOMFORT FOLLOWING MINIMALLY INVASIVE GALLBLADDER SURGERY

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SUMMARY – Magnesium sulfate, an N-methyl-D-aspartate (NMDA) receptor antagonist, is known for its potential analgesic effects in perioperative settings. This study aimed to assess whether administering low-dose intravenous magnesium sulfate before surgical incision could influence the intensity of early postoperative discomfort in patients undergoing minimally invasive gallbladder removal. In a prospective, randomized design, 60 patients classified as ASA I–II scheduled for elective laparoscopic procedures were divided into three equal groups (n=20 each). After the induction of anesthesia and prior to surgical incision, participants received either 5.0 mg/kg magnesium sulfate (group A), 7.5 mg/kg magnesium sulfate (group B), or normal saline as a control (group C).

All groups underwent standardized general anesthesia protocols. Post-surgical pain was assessed at rest using a 0–10 visual analog scale (VAS) at 1, 3, 6, 9, and 24 hours postoperatively. Pain management was administered based on VAS intensity: metamizole for mild pain (VAS 3–4), diclofenac for moderate pain (VAS 5–7), and tramadol for severe pain (VAS 8–10). Results at 1 hour post-surgery showed a significant reduction in pain in both magnesium groups compared to control (Group A: 4.7±1.7; Group B: 3.2±1.8; Group C: 5.2±2.0; $p<0.05$). At 3 hours, Group B showed notably lower pain scores than Groups A and C (2.4 ±1.5 vs. 3.7±1.8 and 3.8±2.3 respectively; $p<0.05$). However, from 6 hours onward, no significant differences in VAS scores were observed among the groups.

In summary, administering magnesium sulfate intravenously at 5.0 or 7.5 mg/kg prior to surgery provided meaningful early postoperative pain relief, with the higher dose yielding superior results during the initial hours. Pain levels after 6 hours were unaffected, and no adverse reactions were recorded during the study period.

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].

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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

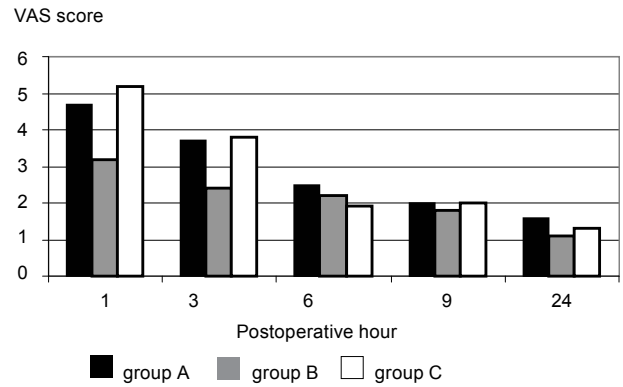

Fig. 1. Mean visual analog scale (VAS) scores according to postoperative hours.

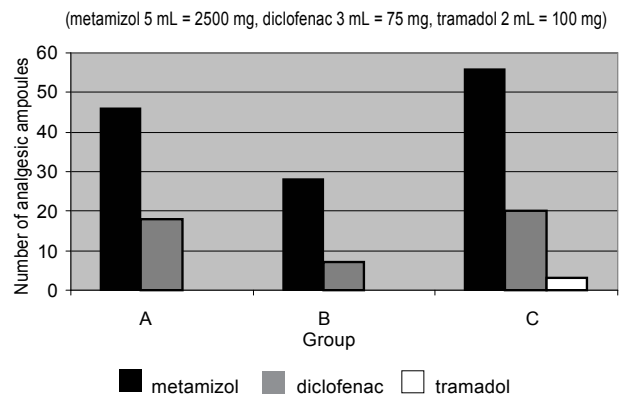

Fig. 2. Analgesic consumption during 24-hour period.

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.

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