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Effect of intraoperative magnesium sulphate infusion on pain relief after laparoscopic cholecystectomy

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Introduction: The aim of the study is to evaluate the analgesic efficiency of perioperative magnesium sulphate infusion in patients undergoing laparoscopic cholecystectomy (LC).
Methods: In a randomized, double-blind trial study, 83 patients were divided into two groups. Group MT received 50 mg/kg i.v. magnesium sulphate in 100 ml of 0.9% normal saline and Group T received the same volume of isotonic saline during the intraoperative period. The cumulative post-operative tramadol consumption was measured to assess the analgesic effect using a patient-controlled analgesia device. Pain intensities at rest and while coughing were evaluated at 0, 2, 4, 8, 12, and 24 h post-operatively.
Results: The pain scores in Group MT were significantly lower than Group T at 0, 4, and 12 h post-operatively. The average of visual analogue scale at rest and during cough during 24 h post-operatively was found to be statistically significant between groups. The total dose of tramadol the 24-h period in Group MT and Group T was found to be 281.34 ± 90.82 and 317.46 ± 129.59, respectively.
Conclusion: Per-operative 50 mg/kg magnesium sulphate infusion is effective in reducing post-operative pain in patients undergoing LC.

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GALLSTONE disease and its effect on patients have a huge impact on a general surgeon's daily routine. The prevalence rate of gallstone disease ranges between 3% and 12% in populations.[1] Laparoscopy has changed the surgical approach to symptomatic gallstone disease. Mühe and Movret performed the first laparoscopic cholecystectomy (LC) in Europe in 1987 using a pneumoperitoneum.[2,3] Over the last two decades, many studies have shown the preference of LC over open cholecystectomy, and LC has become the standard procedure for gallstone disease and was first called the 'gold standard' in 1989.[4] Compared with open traditional cholecystectomy, LC reduces the inflammatory stress response, morbidity, pain, fatigue, and pulmonary dysfunction.[5–8] However, pain is the most frequent complaint after LC in 17–41% of the patients and it is the main reason for staying overnight in the hospital on the day of the operation.[9] Post-operative pain after LC may remain severe in approximately 13% of the patients throughout the first week.[10] Certain factors may influence the degree of pain after pressure created by the pneumoperitoneum, and the temperature of insufflated gas.[10–13] The *N*-methyl-D-aspartate (NMDA) receptor is an excitatory amino acid receptor that has been implicated in the modulation of prolonged pain states in animal models.[14] NMDA antagonists have been shown to be useful in the reduction of acute post-operative pain, analgesic consumption, or both when they are added to more conventional means of providing analgesia in the perioperative period. Magnesium is the fourth most plentiful cation in the body. It has antinociceptive effects in animal and human models of pain. These effects are primarily based on the regulation of calcium influx into the cell and that is the natural physiological antagonism of the NMDA receptor. These effects have prompted the investigation of magnesium as an adjuvant for post-operative analgesia.[15,16] Our study was designed to investigate the role of magnesium sulphate in the post-operative pain in the patients undergoing elective LC.

Patients and methods

With institutional approval and written informed consent, 83 physical status I and II patients ASA scheduled for elective LC were included in the study and randomly divided into two groups. Patients in the magnesium group (Group MT) received i.v. $MgSO_4$ 50 mg/kg in 100 ml of 0.9% normal saline during surgery and patients in the control group (Group T) received 100 ml of 0.9% normal saline during surgery. The criteria for exclusion were major hepatic renal or cardiovascular dysfunction, especially atrioventricular block; previous treatment with calcium channel blocker; history of neuropathy or myopathy, ASA physical status III, or greater; and having papillotomy by endoscopic retrograde cholangiopancreatography within 1 month before operation. Patients were excluded if they had an operation for acute cholecystitis or if the operation was converted to an open procedure.

Patients were evaluated for pain in the right upper quadrant and port wounds during the first 24 h. We explained how to use the visual analogue scale (VAS) (0 = no pain and 100 = worst pain imaginable) for pain rating and the operational aspect of the patient-controlled analgesia (PCA) pump (Abbott Pain Management Provider, North Chicago, IL) to each patient during a pre-operative visit on the day before the surgery.

Spirometry (Micro Plus Spirometer, Micro Medical Limited, Rochester) was performed the day before the operation and 24 h after the operation. Pulmonary function was evaluated with the patient in the sitting position by measuring forced vital capacity (FVC) and forced expired volume in the first second (FEV_1). In each session, the best of three attempts was recorded. At the same time, spot checks of peripheral oxygen saturation (SpO_2) were recorded with pulse oximetry.

Patients fasted for 6 h before surgery. LC was performed by the standard 'French' technique with two 10 and 5 mm trocars. A single dose of cefazolin 1 g was administered 30 min before the skin incision for prophylaxis. The gallbladder was retracted via the epigastric side-port. During laparoscopy, intra-abdominal pressure was maintained at 12 mmHg. The CO_2 was evacuated at the end of the procedure by manual compression of the abdomen with open trocars.

All patients received the same general anaesthetic technique. No pre-medication was used. General anaesthesia was induced with i.v. fentanyl (0.003 mg/kg) and propofol (2.0–2.5 mg/kg). Orotracheal intubation was facilitated by cisatracurium (0.15 mg/kg) and patients were maintained with 1.5–2% sevoflurane in a mixture of 66% nitrous oxide and 34% oxygen, propofol (10 mg/kg/h) and supplemental doses of alfentanil (0.5–1.0 mg), if required, given at the discretion of the anaesthesiologist. Following the endotracheal extubation, patients were started on a PCA solution. The PCA device (Abott Pain Management Provider) was programmed by the anaesthesiologist.

The mixture of medication was prepared using tramadol (4 mg/ml) and PCA was prepared with 20 mg bolus doses, background infusion (5 mg/h; lock-out time, 30 min). At 24 h after the start of PCA, we assessed the bolus PCA doses and the number of demands made by patients on the PCA pump, and total tramadol (mg) consumption was also recorded 24 h after surgery.

Pain intensities at rest and while coughing were evaluated using VAS at 0, 2, 4, 8, 12, and 24 h post-operatively. Total pain relief (TOTPAR) at 2, 4, and 8 h derived from VAS was calculated as follows:

$$\text{Pain relief}\,(\text{PAR}_t) = \text{PAR}_{\text{baseline}} - \text{PAR}_{\text{time } t}$$

$$\text{TOTPAR h} = \Sigma\text{PAR}_t/n$$

The haemodynamic parameters systolic blood pressures, diastolic blood pressures, heart rate (HR) and SpO_2, and respiratory rate (RR) were recorded before operation 0, 2, 4, 8, 12, and 24 h post-operatively by nurses of the Pain Management Team. Patient satisfaction was assessed using a five-point numerical scale from 0 to 4 (0 = extreme discomfort to 4 = perfect) at 12 and 24 h post-operatively. Sedation was also assessed using a five-point scale, with 0 = alert and 4 = deep sleep, at 0, 2, 4, 8, 12, and 24 h post-operatively. Side effects related to drugs were recorded by self-reporting and were treated as necessary.

Statistical analysis

All data were expressed as mean ± SD. Differences in demographic data between groups were evaluated by the Mann–Whitney *U*- and the χ^2 test. The Mann–Whitney *U*-test was used to compare VAS pain scores at rest, during coughing, and TOTPAR scores between groups at different time points. FVC, FEV_1, tramadol consumption, bolus PCA doses, the number of demands, and haemodynamic parameters were evaluated by the Mann–Whitney *U*- and the Wilcoxon signed rank test.

Patient satisfaction and sedation were evaluated by Fisher's exact test. An *a priori* power analysis was performed as a component of design to estimate the required total sample size as a function of power $1-\beta=0.80$, with the medium effect size 0.55, and $\alpha=0.05$. The power calculation was computed using G power version 2 (Franz Faul and Edgar Erdfelder). Consequently, the adequate inclusion number was determined to be 42 patients in each study group (a total of 84 patients). We included 83 patients (Group MT = 41, Group T = 42) in the study. All statistical analysis was two tailed. A *P*-value <0.05 was considered statistically significant.

Results

For this study, 83 patients were randomized (Fig. 1). All patients' operations were concluded to be uncomplicated LC and all patients completed the study. Demographic data, age, weight, sex, ASA physical status, and duration of surgery were similar in both groups (Table 1). VAS scores for pain at rest at 0, 4, and 12 h were significantly lower in Group MT ($P<0.05$, Fig. 2). VAS scores for pain at 2, 8, and 24 h were statistically similar in both groups but Group MT scores were lower than Group T at these post-operative hours. VAS scores during coughing at 0, 4, and 8 h were also significantly lower in Group MT ($P<0.05$, Fig. 3). The averages of VAS at rest and during coughing after 24 h post-operatively are shown in Fig. 4 ($P<0.05$). TOTPAR scores at 2, 4, and 8 h were similar in both groups (Table 2). Discomfort scores at 12 h were significantly lower in Group MT ($P=0.006$) but were similar in both groups at 24 h ($P=0.494$). There was a significant difference in the average RR between the two groups pre-operatively and at every hour post-operatively but there was a significant difference in the average SpO_2 between the two groups only at 0 and 2 h post-operatively. There was no significant difference in the average HR, and mean arterial pressure (MAP) in any period. The values remained within the normal range throughout the study period. There was no significant difference in average pre- and post-operative FVC and FEV_1 values between the two groups, but there was a significant difference between the average pre- and post-operative FVC and FEV_1 in both groups (Fig. 5). The mean bolus dose and the number of patient demands on the PCA pump for both MT and T groups were found to be statistically significant, whereas consumed mean total tramadol doses were not statistically significant. However, the averages of VAS pain scores of Group MTs were lower than those of Group T (Table 3). Four patients (9.7%) in Group MT and seven patients (16%) in Group T suffered from post-operative nausea and vomiting, which was treated with an injection of ondansetron 0.1 mg/kg i.v. All these patients completed the study.

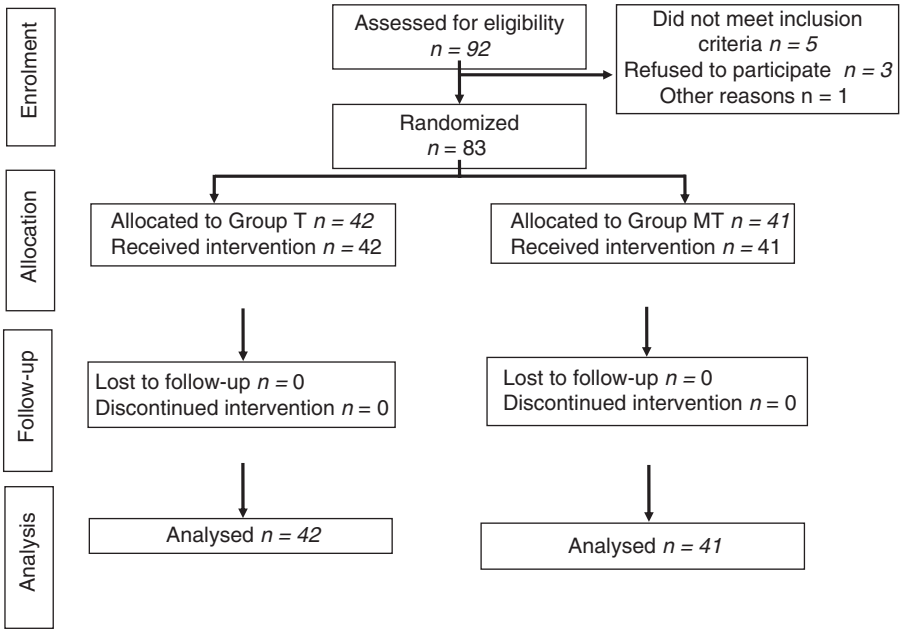

Fig. 1. Flow of the participants through each stage of randomization.

Table 1

Patient characteristics.*

	Group MT ($n = 41$)	Group T ($n = 42$)	*P*
Age	47.68 ± 13.58	46.14 ± 15.40	0.636
Weight (kg)	72.76 ± 10.8	73.69 ± 10.78	0.812
Duration of surgery (min)	72.20 ± 21.18	74.05 ± 22.77	0.475
Gender (M/F)	6/35	12/30	0.123
ASA (I/II)	29/12	33/9	0.411

*Data are expressed as number of patients or mean ± SD.

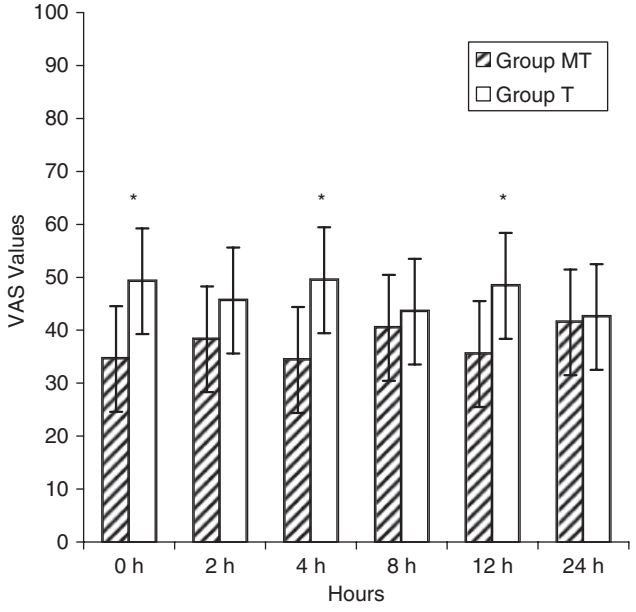

*Fig. 2. Visual analogue scale (VAS) pain scores at rest. Values are mean ± SD. (*P < 0.05 as compared between Group MT and Group T).*

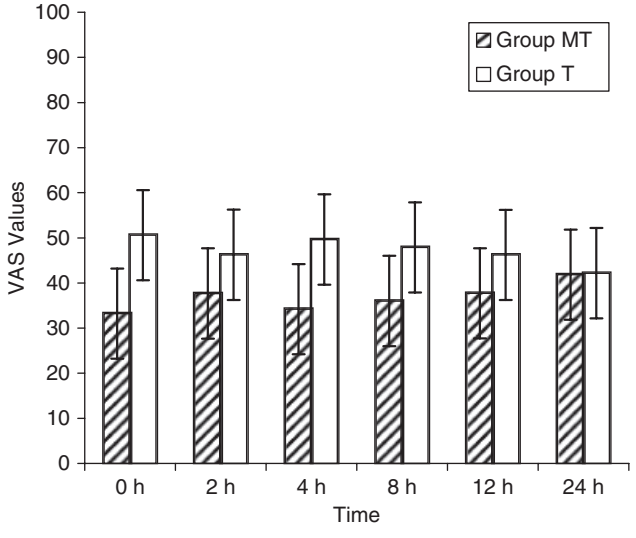

Fig. 3. Visual analog scale (VAS) pain scores during cough. Values are mean ± SD. P < 0.05 as compared between Group MT and Group T.

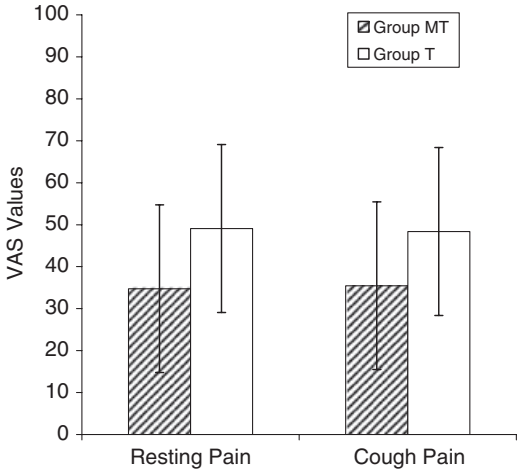

Fig. 4. Average of visual analog scale (VAS) pain scores at rest and during cough. Values are mean ± SD. P = 0.007 at rest and P = 0.015 during cough when compared between Group MT and Group T.

Table 2

Total pain relief (TOTPAR) scores in the two groups at 2, 4, and 8 h post-operatively.*

	Group MT ($n = 41$)	Group T ($n = 42$)	*P*
TOTPAR 2 h	16.1 ± 18.28	21.88 ± 26.27	0.438
TOTPAR 4 h	16.83 ± 17.05	12.05 ± 17.02	0.212
TOTPAR 8 h	9.02 ± 9.3	18.21 ± 21.03	0.079

*Results are expressed as mean ± SD.

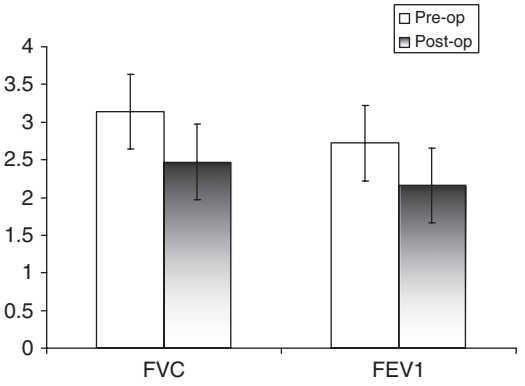

Fig. 5. Average of FVC and FEV_1 pre- and post-operatively. Values are mean ± SD.

Table 3

Tramadol consumption, patient-controlled analgesia (PCA) bolus dose, and PCA patient demand numbers in groups.

	Group MT	Group T	*P*
Tramadol (mg)	281.34 ± 90.82	317.46 ± 129.59	0.320
PCA bolus dose	14.2 ± 6.13	31.16 ± 68.28	0.018
PCA patient demand number	115.76 ± 111.04	159.55 ± 240.48	0.024

Discussion

Despite all the benefits that have emerged with the introduction of LC, post-operative pain remains an issue. Ineffectively treated post-operative pain is still one of the common surgical complications, and this medical problem may result in clinical and psychological changes that may increase morbidity and mortality as well as costs and may decrease the quality of life.[15] Ineffective post-operative pain management may lead to deep vein thrombosis, pulmonary embolism, coronary stress, atelectases, pneumonia, poor wound healing, insomnia, and demoralization.[13] Prevention and effective relief of acute pain may improve clinical outcomes, avoid clinical complications, save health care resources, and improve quality of life.[17,18]

NMDA receptors play a major role in central nociceptive transmission, modulation, and sensitization of acute pain states and can prevent the induction of central sensitization due to peripheral nociceptive stimulation and abolish the hypersensitivity once it is established, and may play a role in post-operative hyperalgesia. Magnesium is a physiologic calcium channel blocker and an antagonist of the NMDA receptor. The magnesium block is removed as part of the molecular sensitization process. Therefore, theoretically, magnesium could modulate post-operative pain by preventing nociception-associated central sensitization via blockade of NMDA receptors.[19]

Serum magnesium concentrations are lower after major surgery. The prevention of hypomagnesaemia may be an important factor for reducing post-operative analgesic requirements. Parenteral magnesium has been used for a long time in obstetric and cardiovascular practice.[20,21] The results regarding intraoperative and post-operative analgesia after magnesium supplementation are contradictory. Some investigators observed a decreased analgesic requirement after pre-operative magnesium administration; others could not confirm this observation.

Bhatia et al. found that administration of magnesium 50 mg/kg in the pre-operative and 15 mg/kg/h in the per-operative periods to patients undergoing open cholecystectomy did not significantly decrease the requirement of morphine during the first 24 h of the post-operative period. Also, they found that the cumulative intra- and post-operative need for morphine was similar in the magnesium and the control groups.[22] In their study, all patients underwent open cholecystectomy involving an upper abdominal incision, which is more painful and that is associated with higher post-operative morbidity compared with laparoscopic, lower abdominal operations. They preferred intermittent bolus doses of morphine rather than PCA pumps due to a lack of technical facility. These factors may have affected the results of magnesium in the treatment of post-operative pain.

Ko et al.[23] reported that administering magnesium in patients undergoing abdominal hysterectomy 50 mg/kg in the pre-operative period and 15 mg/kg/h intraoperatively and 6 h after the operation had no effects on post-operative pain. However, the precise reason for this discrepancy is unknown; epidural analgesia was used in this study. Thus, it is possible that the superior analgesic efficacy of epidural analgesia might have masked the analgesia-potentiating effect of magnesium sulphate.

Tramer and colleagues reported the first clinical study concerning the perioperative application of magnesium. In that study, patients received 20% magnesium sulphate or saline (control) ml intravenously before the start of surgery and 2.5 ml/h for the next 20 h. The result of this study showed that the perioperative application of magnesium is associated with a smaller analgesic requirement, less discomfort, and a better quality of sleep in the post-operative period and was without adverse effects for patients who underwent elective abdominal hysterectomy.[11]

Abdel-Raouf and Amer[24] reported that intraperitoneal administration of either ketamine (1 mg/kg) or magnesium sulphate (30 mg/kg), combined with 0.25% bupivacaine (i.m. 50 ml volume), was closely associated with nearly a similarly improved post-operative analgesia in reduction of both post-operative pain and analgesic requirements in patients undergoing elective LC. Kara et al.[25] found that by administering 30 mg/kg magnesium sulphate before the start of elective hysterectomy and 0.5 mg/h infusion for the next 20 h with continuous magnesium infusion, including the pre-, intra-, and post-operative periods, resulted in reduced analgesic requirements. In a randomized, double-blind study by Koinig et al., in which the patients received either magnesium sulphate 50 mg/kg pre-operatively or 8 mg/kg/h, there were reduced intra- and post-operative analgesic requirements in patients undergoing arthroscopic knee surgery.[26] In their prospective, randomized study, Levaux et al. demonstrated a significant decrease in opioid con-

sumption in patients who received 50 mg/kg magnesium sulphate during the pre-operative periods.[27]

Administration of 50 mg tramadol has been reported as effective in establishing adequate post-operative pain control.[28] Lehmann et al.[29] reported that the average PCA tramadol consumption (after a loading dose of 97.5 ± 42 mg) was 160 ± 99.5 over 20.5 ± 4.8 h in patients. In this study, the total dose of tramadol used during the 24-h period in Group MT and Group T was found to be 281.34 ± 90.82 and 317.46 ± 129.59, respectively.

The incidence of nausea is nearly 30–35% when tramadol is used in post-operative pain medication. In our study, the incidence of nausea in Group MT and Group T was found to be 9.7% and 16%, respectively. All patients were treated with ondansetron i.v. and they completed the study. The incidence of nausea was found to be lower in Group MT but this was not statistically significant.

In conclusion, 50 mg/kg magnesium sulphate given during the per-operative period resulted in a significant reduction in post-operative pain in patients undergoing LC.

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