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Effect of Intraoperative Magnesium Infusion on Perioperative Analgesia in Open Cholecystectomy

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Study Objective: *To study the role of magnesium sulphate ($MgSO_4$) on analgesic requirement, pain, discomfort, and sleep during perioperative period.*
Design: *prospective, double-blinded, randomized study.*
Settings: *Operating room and recovery ward at a university teaching hospital.*
Patients: *50 ASA physical status I and II patients scheduled for elective open cholecystectomy with general anesthesia.*
Interventions: *patients were randomly allocated to receive $MgSO_4$ or saline intravenously (IV). Patients in the magnesium group received 50% $MgSO_4$ (50 mg kg^{-1}) in 100 mL saline and those in the control group received an equal volume of saline IV during the preoperative period followed by 50 mL hr^{-1} infusion of either $MgSO_4$ (15 mg kg^{-1} hr^{-1}) or saline until the end of surgery.*
Measurements and Main Results: *Morphine requirement, pain during rest and on coughing, discomfort, and insomnia were assessed during the postoperative period for 24 hours. Intravenous morphine 40 μg kg^{-1} increments were given to all patients in the postoperative period for analgesia. Patients in the magnesium and control groups had similar morphine requirement during the first 24 hours postoperatively ($p = 0.07$). Patients in the magnesium group experienced less discomfort during the first hour after the operation. They also had better sleep quality during the first postoperative night than did the control group patients ($p < 0.05$). The frequency of side effects was similar in the two groups.*
Conclusion: *Administration of intraoperative $MgSO_4$ as an adjuvant analgesic in patients undergoing open cholecystectomy resulted in better pain relief and comfort in the first postoperative hour, but it did not significantly decrease the postoperative morphine requirement. Magnesium sulphate resulted in better sleep quality during the postoperative period, without any significant adverse effects. The role of $MgSO_4$ as an adjuvant analgesic in open cholecystectomy needs to be studied further.*

Keywords: Analgesics; postoperative: magnesium sulphate; postoperative outcomes: comfort; insomnia; pain; receptors: N-methyl-D-aspartate.

Introduction

Calcium-channel blockers have antinociceptive effects in animals[1] and they potentiate morphine analgesia in patients with cancer pain.[2] Magnesium sulfate

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($MgSO_4$) is a physiologic calcium-channel blocker[3] and an antagonist of the N-methyl-D-aspartate (NMDA) receptor.[4] NMDA receptor antagonists can prevent the induction of central sensitization caused by peripheral nociceptive stimulation and abolish the hypersensitivity once it is established.[5] Thus, it has been suggested that substances with calcium-channel blocker effects and NMDA antagonism can play a role in prevention of pain. Use of $MgSO_4$ as an adjuvant has been associated with significantly less analgesic requirement in the postoperative period in patients undergoing abdominal hysterectomy and lower limb operations.[6–9] Previous clinical trials on the analgesic role of $MgSO_4$ have concentrated mainly on postoperative pain in lower abdominal and limb surgeries. To date, there are no studies on the use of $MgSO_4$ as a supplement to opioids in patients undergoing upper abdominal surgery. We conducted this study to evaluate the analgesic efficacy of $MgSO_4$ administered intravenously (IV) on the perioperative analgesic requirements, pain at rest and on coughing, discomfort, and quality of sleep in patients undergoing open cholecystectomy.

Materials and Methods

After obtaining approval from the Institutional Ethics Committee of the All India Institute of Medical Sciences and informed consent, we studied 50 ASA physical status I and II patients in a double-blinded, prospective, randomized manner. Patients with prior abdominal surgery, major systemic illness, those receiving calcium-channel blockers, those with renal dysfunction, or history of neuropathy or myopathy were excluded from the study.

Patients were randomly allocated, via computer-generated random numbers table, to one of two groups of 25 each: a magnesium group and a control group. Patients in the magnesium group received an IV bolus of $MgSO_4$ 50 mg kg^{-1} in 100 mL of 0.9% normal saline (50% $MgSO_4$ USP inj., Hindustan Pharmaceuticals, New Delhi, India), and those in control group received 100 mL of 0.9% normal saline 15 minutes before induction of anesthesia. The bolus dose was followed by a continuous infusion of $MgSO_4$15 mg $kg^{-1}hr^{-1}$ or 0.9% normal saline 50 mL every hour in both groups. The bolus dose of the $MgSO_4$ regimen corresponded to 75% of a usual bolus dose in the treatment of preeclamptic women and a maintenance dose corresponded to 25% of the normal amount given in these patients.[10]

A standard horizontal 100-mm linear visual analog scale (VAS) was used to assess pain at rest and on coughing (0 = no pain at all to 100 = worst pain imaginable). Discomfort was assessed by asking the patient, "How much discomfort do you feel right now?" and was rated by patients on a VAS (0 = no discomfort at all to 100 = extreme discomfort). Insomnia was assessed by asking, "How well did you sleep last night?" and quality of sleep was rated by patients on the VAS (0 = no insomnia, excellent quality of sleep to 100 = absolute insomnia). During the preoperative visit, patients were instructed in the use of the VAS, after which baseline values of pain at rest, discomfort, and insomnia were obtained.[6]

Patients were fasted orally for 6 hours before surgery, and no premedication was given. General anesthesia was induced with thiopental sodium and tracheal intubation was facilitated with 0.1 mg kg^{-1} vecuronium. Anesthesia was maintained with 66% nitrous oxide in oxygen, vecuronium, and 0.5% to 1% halothane. The top-up doses of vecuronium were given following visual and tactile monitoring of train-of-four, because $MgSO_4$ has been implicated in prolonging neuromuscular blockade. Morphine 0.1 mg kg^{-1} was administered IV at induction of anesthesia, and subsequent incremental doses of 0.04 mg kg^{-1} were given if a patient had sweating, lacrimation, or a 20% increase above baseline in heart rate (HR) or blood pressure. The total amount of vecuronium and morphine administered and time of last dose of intraoperative morphine during surgery were recorded. Intraoperative monitoring included electrocardiography, HR, pulse oximetry, noninvasive blood pressure (NIBP), end-tidal carbon dioxide concentration, and neuromuscular junction monitoring. At the end of surgery, neuromuscular blockade was reversed with neostigmine 0.05 mg kg^{-1} and atropine 0.02 mg kg^{-1}.

All patients were monitored in the postanesthesia recovery room for the first 24 hours. Postoperative monitoring included HR, NIBP, and pulse oximetry. A trained anesthetist who was not involved in the study assessed pain, and analgesia was administered to achieve a VAS $\leq$ 40. Pain relief in the postoperative period was given with IV increments of morphine 40 μg kg^{-1} to patients in both groups. Morphine requirement during the first 24 hours after surgery was recorded. Pain and discomfort were recorded for comparison between the two groups at 0, 1, 6, and 24 hours postoperatively, and insomnia was assessed after the first postoperative night. Sedation was assessed at 0, 1, 6, and 24 postoperative hours using a 4-point rating scale,[7] in which 1 = patient fully awake; 2 = somnolent, responds to call; 3 = somnolent, no response to call but responds to tactile stimulation; and 4 = asleep, responds to painful stimulation. No other sedatives or analgesics were used during the perioperative period. Any side effects or any significant events were noted.

Statistical Analysis

Prestudy power analysis indicated that 25 patients per group would be necessary to have a 80% chance ($\beta = 0.2$) at a 5% level of significance of detecting a difference of at least 25% in morphine consumption between the two groups [version 6.0 of Epi Info (Centers for Disease Control, Atlanta, GA, and World Health Organization, Geneva, Switzerland)]. Continuous variables such as demographic data and the intraoperative and postoperative morphine consumption were analyzed using Student's *t*-test. and ordinal data (VAS scores, sedation score, pain rating score) were analyzed using the Mann-Whitney U test. Chi-square testing was used to analyze categorical data. Probability values <0.05 were considered statistically significant.

Table 1. Patient Characteristics (mean ± SD) and Analgesic Requirement

Group (n = 25)	Control	Magnesium
Gender (M: F)	5: 20	7: 18
Age (ys)	36.70 (10.7)	38.90 (9.5)
Weight (kg)	54.20 (10.8)	59.40 (10.8)
Duration of surgery (min)	76.24 (15.16)	77.33 (17.61)
Intraoperative morphine requirement (mg)	6.78 (1.59)	7.16 (1.89)
Total vecuronium consumption(mg)	7.74 (1.43)	6.52 (1.10)
Postoperative morphine consumption (mg/kg)	0.28 (0.05)	0.23 (0.05)

Note: No significant differences between groups were noted.

Results

Fifty patients who underwent open cholecystectomy were studied in two groups of 25 patients each. The two groups were comparable with respect to age, weight, gender distribution, and duration of surgery (*Table 1*). Morphine requirement during the intraoperative period was statistically similar in both groups. The cumulative morphine consumption during the first 24 hours of the postoperative period was 0.28 ± 0.05 mg/kg in the control group and 0.23 ± 0.05 mg/kg in the $MgSO_4$ group ($p = 0.07$).

VAS scores for pain in the preoperative period were similar in the two groups. After the operation, pain scores on coughing at 0 hour and 1 hour were significantly lower in the magnesium group ($p < 0.05$, *Figure 1*). VAS scores for pain at 6 and 24 hours postoperatively were similar in both groups. Preoperative discomfort and insomnia levels were also similar in both groups. Discomfort scores at 0 hour and 1 hour were significantly lower in the $MgSO_4$ group than in the control group ($p < 0.05$, *Table 2*). At 6 hours postoperatively, discomfort was significantly increased in both groups compared with preoperative values. However, discomfort was comparable in both groups at 6 and 24 hours postoperatively. There was no difference in sedation scores between the two groups at 0, 1, 6, and 24 hours postoperatively. Patients who were administered $MgSO_4$ had significantly less insomnia during the first postoperative night compared with patients from the control group ($p < 0.05$, *Table 3*).

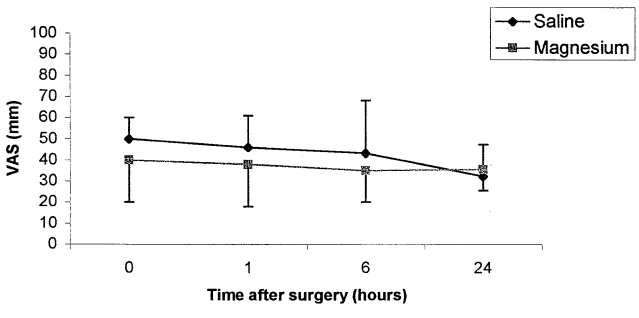

Figure 1. Visual Analog Scale (VAS) scores for pain on coughing during the first 24 hours after surgery (data are medians and 25% to 75%). Scores at 0 and 1 hour were significantly lower in the magnesium group ($p < 0.05$).

The time of onset and duration of neuromuscular blockade of vecuronium were similar in both groups. None of the patients in the $MgSO_4$ group had any sign or symptoms of prolonged neuromuscular blockade. Four patients in the control group and three patients in $MgSO_4$ group did suffer postoperative nausea and vomiting, which was treated with an injection of ondansetron 0.1 mg/kg IV. Postoperative shivering was observed in four patients from the control group. No patient in the MgO_4 group had any postoperative shivering.

Discussion

We found that administration of $MgSO_4$ intraoperatively to patients undergoing open cholecystectomy did not significantly decrease the requirement of morphine during the first 24 hours of the postoperative period. The cumulative intraoperative and postoperative need for morphine was similar in the magnesium and control groups ($p = 0.07$). Patients in the $MgSO_4$ group experienced significantly less discomfort during the first hour in the postoperative period compared with the control group. The quality of sleep during the first postoperative night in the $MgSO_4$-treated patients was better than that of the control group.

Parenteral $MgSO_4$ has been used for a long time in obstetric and cardiovascular practice but its role as an analgesic during the perioperative period is controversial.[6–9,11] In current medical practice, opioids are commonly used as perioperative analgesic drugs but high doses may produce adverse effects such as respiratory

Table 2. Visual Analog Scale Scores (median and range) for Discomfort

Period	Control (n = 25)	Magnesium (n = 25)
Preoperative	5.60 (0–25)	3.0 (0–25)
Postoperative		
0 hour	62.60 (25–85)	46.40 (25–80)*
1 hour	57.40 (25–80)	47.00 (25–80)**
6 hours	43.20 (25–75)	40.00 (25–60)
24 hours	33.20 (10–60)	35.60 (20–60)

Note: No significant differences between groups except at the 0 and 1 hour timepoints: *$P < 0.05$; **$P < 0.01$.

Table 3. Visual Analog Scale Scores (median and range) for Insomnia

Period	Control	Magnesium
Preoperative	5.3 (0–25)	4.6 (0–10)
Postoperative	51.0 (26–75)*	42.8 (10–70)

Note: No significant differences between groups except $*P < 0.05$.

depression and nausea and vomiting. Use of $MgSO_4$ as an adjuvant analgesic may reduce the requirement for opioids, thus reducing or avoiding such side effects.

There is limited literature on the role of $MgSO_4$ as an analgesic drug. Magnesium has been used as a sole or adjuvant analgesic during the intraoperative period in patients undergoing hysterectomy or lower limb operations.[6–9] Wilder-Smith and colleagues[11] used a perioperative infusion of magnesium levulinate in patients undergoing elective abdominal hysterectomy and concluded that perioperative magnesium infusion does not improve postoperative analgesia. A small study group size and inadequate dose of $MgSO_4$ might have been possible causes for this finding.

Tramer and colleagues[6] reported that postoperative administration of $MgSO_4$ for 20 hours is associated with significantly less morphine requirement during the first 48 hours after the operation. Magnesium has a short duration of action and its administration during the postoperative period for 48 hours has been found to cause less discomfort and a better quality of sleep. We could not use $MgSO_4$ in the postoperative period, because facilities for the measurement of serum $MgSO_4$ concentration are not available at our institution.

The analgesic requirement with $MgSO_4$ during the intraoperative period has been investigated in patients undergoing knee arthroscopy.[8] The requirement of fentanyl in patients who were administered $MgSO_4$ was significantly less than patients of the control group during the intraoperative and first 4 postoperative hours. We have used $MgSO_4$ infusion along with morphine in patients undergoing open cholecystectomy. This procedure involves an upper abdominal incision, which is more painful and which is associated with higher postoperative morbidity compared with lower abdominal or limb operations.

In our study, VAS scores for pain during cough and discomfort were significantly lower in the $MgSO_4$ group compared with the control group at 0 hour and 1 hour postoperatively (< 0.05). This finding may be because of better analgesia achieved by administration of a combination of morphine and $MgSO_4$ to patients in the $MgSO_4$ group. However, this decrease in VAS score for pain and discomfort did not affect the requirement of morphine postoperatively. Later, at 6 and 24 hours postoperatively, these VAS scores were statistically similar in the two groups.

Intermittent bolus doses of morphine were used for postoperative analgesia in this study rather than patient-controlled analgesia (PCA) pumps due to a lack of technical facility with PCA. Patient-controlled analgesia for postoperative analgesia administration could have been a better option to study, but patient mood and anxiety level may significantly have affected use of the PCA pump. Titration of the analgesic doses by intermittent assessment and administration of analgesia by an independent investigator are not influenced by patient factors and therefore unlikely to reflect the postoperative analgesic requirement more accurately.

A relatively low requirement of morphine was found in both the groups in our study. This finding may be a result of the low mean weight of our patients as compared with other studies.[6,8] An ethnic variation in pain perception and pain tolerance may have affected the analgesic requirement. Finally, a higher level of pain may be acceptable to some patients as this varies in different cultures.[12]

In conclusion, $MgSO_4$ administration in patients undergoing open cholecystectomy does not significantly decrease the requirement of morphine during the first 24 postoperative hours as compared with that of control patients. Magnesium administration resulted in better pain relief and comfort in the initial postoperative period. The quality of sleep was also better during the first postoperative night in the $MgSO_4$-treated patients. Further studies with varying dose regimens of $MgSO_4$ infusion in the perioperative period in patients undergoing upper abdominal operations may be required to evaluate its analgesic efficacy.

References

1. Wong CH, Dey P, Yarmush J, Wu WH, Zbuzek VK: Nifedipine-induced analgesia after epidural injection in rats. *Anesth Analg* 1994;79:303–6.
2. Santillan R, Maestre JM, Hurle MA, Florez J: Enhancement of opiate analgesia by nimodipine in cancer patients chronically treated with morphine: a preliminary report. *Pain* 1994;58:129–32.
3. Iseri LT, French JH: Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984;108:188–93.
4. Mayer ML, Westbrook GL, Guthrie PB: Voltage dependent block by Mg2+ of NMDA responses in spinal cord neurons. *Nature* 1984;309:261–3.
5. Dickenson AH: A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol Sci* 1990;11:307–9.
6. Tramer MR, Schneider J, Marti RA, Rifat K: Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996;84:340–7.
7. Wilder-Smith OH, Arendt-Nielsen L, Gaumann D, Tassonyi E, Rifat KR: Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine. *Anesth Analg* 1998;86:95–101.
8. 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.
9. Lo B, Honemann CW, Durieux ME: Preemptive analgesia: ketamine and magnesium reduce postoperative morphine requirements after abdominal hysterectomy. *Anesthesiology* 1998;89:A1163.
10. Sibai BM, Graham JM, McCubbin JH: A comparison of intravenous and intramuscular magnesium sulfate regimens in preeclampsia. *Am J Obstet Gynecol* 1984;150:728–33.
11. Wilder-Smith CH, Knopfli R, Wilder-Smith OH: Perioperative magnesium infusion and postoperative pain. *Acta Anaesthesiol Scand* 1997;41:1023–7.
12. Wilder-Smith CH, Schuler L: Postoperative analgesia: pain by choice? The influence of patient attitudes and patient education. *Pain* 1992;50:257–62.