Original Article

Intraperitoneal Instillation of Magnesium Sulphate vs Bupivacaine for Post-Operative Analgesia following Laparoscopic Cholecystectomy

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Abstract

Background: Postoperative pain following laparoscopic cholecystectomy, though less severe than open procedures, remains clinically significant due to its multifactorial origin involving somatic, visceral, and referred components. Intraperitoneal instillation of analgesic agents has emerged as an effective strategy to target visceral nociception while minimizing systemic opioid-related adverse effects. Magnesium sulphate, an N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promise as an adjuvant analgesic due to its anti-nociceptive and opioid-sparing properties. The aim and objective is to evaluate and compare the analgesic efficacy of intraperitoneal instillation of magnesium sulphate versus bupivacaine in patients undergoing elective laparoscopic cholecystectomy. **Material and Methods:** The present study was a randomized clinical study, in which 105 patients of age 18-60 years, belonging to American Society of Anaesthesiologists (ASA) grade I or II, for laparoscopic cholecystectomy were randomly selected and divided into three groups of 35 patients each: Group B received 30 ml of 0.25% Bupivacaine, Group M received 30 mL of mixture of 50mg/kg MgSO4 and (0.9%) NS, Group C received 30 ml of (0.9%) NS Intraperitoneally. Visual Analog Scale (VAS) score as primary outcome, recorded for 24 hours after surgery. Secondary outcomes included time to first rescue analgesia, total dose requirements of rescue analgesia, and adverse events. **Results:** The VAS Score was significantly lower in group B as compared to group M and group C. The average Time to 1st dose of post-operative analgesia demand was also the longest in Group B compared to Group M and Group C (7.38±1.01 hours compared to 5.23±0.92 hours and 2.5±1.12 hours respectively) which was also highly significant. Total rescue analgesic requests in group B was significantly lower than that in the group M and group C (P-value <0.05), with no significant difference observed between the group M and group C. Neither drug caused a significant difference in the incidence of postoperative nausea and vomiting (P-value > 0.05). **Conclusion:** Intraperitoneal instillation of both magnesium sulphate and bupivacaine are effective for postoperative pain management following laparoscopic cholecystectomy. But intraperitoneal instillation of bupivacaine was found to be superior for postoperative analgesia in first 24 hours after laparoscopic cholecystectomy as reflected by a lower VAS score and longer duration of analgesia.

Keywords: Laparoscopic cholecystectomy, intraperitoneal analgesia, magnesium sulphate, bupivacaine, postoperative pain, multimodal analgesia.

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Introduction

Postoperative pain after laparoscopic cholecystectomy (LC), despite its less invasive benefits, remains a serious worldwide health problem, significantly influencing patient recovery and placing large expenses on healthcare systems. Poorly managed pain after surgery may lead to more illness, longer hospital stays, slower recovery, and a higher chance of developing chronic pain.[1] This inadequate management adversely affects patient quality of life and increases healthcare costs, highlighting the urgent necessity for advanced analgesic strategies that promote swift, comfortable recovery pathways, in alignment with the requirements of modern surgical practice and improved postoperative recovery protocols.

The fundamental pathogenesis of postoperative pain after laparoscopic cholecystectomy is complex and diverse, including unique somatic, visceral, and referred elements. Somatic discomfort originates from surgical incisions at port locations, leading to direct tissue damage to the abdominal wall musculature and fascia.[2] Visceral pain, often characterized as profound and broad, arises from the manipulation of intra-abdominal organs, peritoneal distension, and the inflammatory response elicited by surgical stimuli. Shoulder-tip discomfort is a common and frequently painful symptom that occurs when leftover carbon dioxide and acidic peritoneal fluid irritate the

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diaphragm. Nociceptive signals are sent by the phrenic nerve which causes shoulder pain and discomfort.[3] This complex interaction requires specific approaches for successful pain relief.

The current standard for postoperative pain relief after laparoscopic cholecystectomy mostly uses multimodal analgesia, which mixes non-opioid drugs, localized methods, and systemic opioids. There has been various research in using localized analgesic strategies to target the particular pain mechanisms associated with laparoscopic cholecystectomy.[4]

Intraperitoneal administration of local anaesthetics one such approach which has been effective in diminishing postoperative pain intensity and lowering opioid use.[5] According to a previous meta-analysis, intraperitoneally instilled agents can potentially block the visceral afferent signal and inhibit the release and action of prostaglandins. Moreover, after systemic absorption from through the large peritoneal surface, they may further modulate peritoneal and visceral signal to the brain, thereby attenuating the metabolic impact of visceral manipulations.[6] Bupivacaine, a long-acting amide local anesthetic, has been widely used for this purpose due to its prolonged duration of action and excellent safety profile.

In this scenario, magnesium sulphate has surfaced as a potential supplementary drug, with multiple meta-analyses demonstrating its ability to markedly diminish postoperative pain ratings and total opioid consumption when injected intraperitoneally. There is a strong translational reason and a plausible mechanism for using magnesium sulphate intraperitoneally.[7] Magnesium serves mostly as a non-competitive antagonist of the N-methyl-D-aspartate receptor, which is a crucial component in central sensitization and the 'wind-up' phenomena of pain processing. Magnesium efficiently reduces neuronal hyperexcitability by restricting the flow of calcium ions into neurons, which changes how pain is transmitted. This technique works with the sodium channel blocking mechanism that local anaesthetics use. By giving magnesium directly into the peritoneal cavity, you may acquire high local concentrations at the region of visceral nociception, which targets pain pathways with less systemic exposure and a lower risk of dose-dependent systemic adverse effects.[8,9]

Hence this study was undertaken with an aim of evaluating the analgesic efficacy of Intraperitoneal instillation of magnesium sulphate as compared to bupivacaine in postoperative period following elective laparoscopic cholecystectomy, along with to compare the time of first rescue analgesic in both groups and to compare 24hr analgesic consumption and to assess adverse effect if any. Use.[6]

Materials and Methods

This is a prospective, double-blind, randomized clinical study conducted at VIMSAR, Burla, a tertiary medical center in Odisha, India, from October 2025 to May 2026. Ethical approval was obtained from the institute's Ethics Committee (VIREC No-010-2025/I/S/T/012/Dt.25.09.2025).

Study design and sample size

The study followed a prospective, randomized design. The sample size was calculated based on a previous study by Maharjan SK et al,[10] considering the time to1st rescue analgesia for pain as the primary outcome variable. To detect a clinically significant difference in analgesic requirement with a projected effect size of an alpha error of 0.05, and a power of 80%, a sample size of 35 patients per group was determined. This resulted in a total sample size of 105 patients to account for potential dropouts and ensure statistical robustness.

Randomization and allocation method: One hundred five patients who underwent elective laparoscopic cholecystectomy were randomly recruited and divided into three groups. Computer-generated random sequence was concealed in a sealed opaque envelope.

GROUP B: Received 30 ml of 0.25% Bupivacaine Intraperitoneally.

GROUP M: Received 30 mL of 50mg/kg MgSO4 in (0.9%) NS Intraperitoneally.

GROUP C: Received 30 ml of (0.9%) NS Intraperitoneally.

The drugs were prepared by an anaesthesiologist not involved in the study. Anaesthesiologists who observed the patient and surgeon were also made unaware of the study group until the end of the study.

Inclusion and exclusion criteria

Patients with symptomatic gallstone disease planned for elective LC, aged 18–64 years of any gender, and the American Society of Anaesthesiologists (ASA) class I and II were included in the study. Patients with a known allergy to bupivacaine or magnesium sulphate, BMI >30Kg/m2, long-term use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or other pain medications due to chronic pain, known hepatic or renal dysfunction, history of prior abdominal surgery, chronic abdominal or pelvic pain syndrome, diagnosed hypo- or hypermagnesemia, pregnancy or lactation, on beta blockers, calcium channel blockers, sedatives or antipsychotics, surgical procedure converted to open cholecystectomy were excluded from the study.

Preoperative preparation: A pre-anaesthetic check was performed including thorough history taking, investigations and complete physical examination. A 10-cm Visual Analog Scale (VAS) was explained for postoperative pain assessment (0 = no pain,10 = worst pain imaginable). After pre anaesthetic evaluation and explanation of procedure and risks involved; written informed consent was taken from each patient. On the night before surgery, all patients were medicated with tab. Alprazolam 0.5mg and Ranitidine 150mg orally. Patients were kept NPO for 8 hours for solid food and up to 2 hours for clear fluids before initiation of anaesthesia.

Intraoperative management: The anaesthesia protocol was standard for all patients. In the operative room, IV access was obtained with 18G cannula and Standard monitors ECG, Pulse oximeter, NIBP, end tidal carbon dioxide (EtCO2) were connected to the patients and baseline vital parameters were recorded. Patients were premedicated with inj. glycopyrrolate 4mcg/kg IV, inj. midazolam 0.04mg/kg IV, inj. ondansetron 0.1

mg/kg IV and inj. Nalbuphine 0.2mg/kg IV. After a 3-min preoxygenation with 100% oxygen, patients were induced with propofol 2 mg/kg, followed by vecuronium 0.1 mg/kg. Anaesthesia was then maintained with 0.5%–1% isoflurane, N2O:O2 mixture at 2:1, and top-up doses of vecuronium (0.02 mg/kg) at regular intervals.

Patients were mechanically ventilated while keeping ETCO2 between 35–40 mm Hg. The intra-abdominal pressure was kept at 10–12 mmHg, and an identical surgical technique was used in all patients by the same experienced surgeon who also carried out the IP instillation of the study solutions.

Intraperitoneal instillation of study drug solution was done after the removal of gallbladder before removal of trocar in Trendelenburg's position, into the hepato-diaphragmatic space, on the gall bladder bed and near and above hepatoduodenal ligament at through laparoscopic ports under vision of laparoscope. The CO2 was evacuated at the end of surgery by active suctioning. The patient was placed in a right Trendelenburg position for 5 minutes to facilitate drug dispersion. All patients received injection paracetamol (15mg/kg) after removal of gall bladder. Neuromuscular blockade was reversed with Neostigmine 0.05mg/kg IV and Glycopyrrolate 0.01mg/kg IV. Extubation was performed only when extubation criteria were met. Patients were transferred to post-anaesthesia care unit (PACU) for further monitoring.

Postoperative assessment: All patients in PACU were observed till full recovery (modified Aldrete score ≥9), then they were transferred to the ward. The intensity of post-operative pain both for abdominal and shoulder tip was recorded for all the patients using VAS score at 0.5, 1, 2, 4, 6, 12, 16, 20 and 24 hours after surgery and over all VAS score (mean of all VAS scores). Patients who reported VAS≥3 were given IV tramadol at 1 mg/kg (max dose 100 mg) intravenously as rescue analgesia. If pain persisted after 30 min of the first rescue analgesia, the second rescue analgesia was given with IV diclofenac 75 mg. Patients were also be observed for post-operative nausea and vomiting. Patients who suffered nausea or vomiting were given ondansetron 4 mg IV. Time to the first request of analgesia (considering the extubation as time 0), VAS score, total dose of analgesia, nausea/vomiting, adverse effects and hemodynamic changes over 24 h postoperatively were noted.

Outcome measures: The primary outcome in the present study was the severity of post-operative pain by VAS score. The secondary outcomes included time of first post-operative analgesic requirement, and total post-operative analgesic consumption during the first 24 post-operative hours. The Mean Arterial Pressure (MAP) and Heart Rate (HR) after instillation of the study drugs and through the first 24 post-operative hours; and the incidence of adverse events including local anaesthetic systemic toxicities (numbness in tongue or lips, irritability, dysrhythmias, and convulsions), any adverse events related to MgSO4 (sedation, shivering, respiratory depression), and PONV.

Statistical analysis: Data were analysed using Statistical Package for Social Sciences (SPSS) Statistics version 23. Normally distributed numerical data were presented as mean and standard deviation, and skewed data as median and interquartile range. Qualitative data were number and percentage. Comparison of normally distributed numerical data were done using the unpaired t-test. Skewed data were compared using the Mann-Whitney test. Categorical data were compared using the Pearson chi-squared test or fisher's exact test, if appropriate. A two-sided p-value <0.05 were considered statistically significant.

Results

A total of 105 patients were recruited for the study and all were completed the study without any dropout. The groups were comparable in terms of patient characteristics and duration of surgery [Table 1].

Table 1: Demographic and other baseline parameters of the Study Groups

Parameters	Group B (Bupivacaine)	Group M (Magnesium sulphate)	Group C (Normal Saline)	p-value
Age(yrs) (Mean±SD)	42.05±3.60	38.74±2.98	40.45±3.46	0.494
BMI(kg/m2) (Mean±SD)	22.79±3.04	23.46±2.57	22.32±3.17	0.471
Gender M/F	11/24	10/25	13/22	0.738
ASA I/II	8/27	11/24	9/26	0.694
Duration of surgery	84.65±13.70	91.20±13.33	89.40±9.65	0.253
Duration of Anaesthesia	93.20±10.56	103.00±15.67	94.50±13.45	0.673

When we analyzed the VAS score the cumulative mean pain score was less in Bupivacaine group compared to Magnesium group and Control group and the difference was statistically significant (p<0.05). Immediately after surgery, VAS was zero in all patients. Till1 hours of surgery, no statistical difference was noted between group B and group M. After 2 hours of surgery, VAS was significantly lower (p-value <0.05) in patients of group Bas compared to patients of group M.VAS was significantly lower (p-value <0.05), in group Mas compared to group C, till 4 hours of surgery, after that no statistical difference noted between group M and group C. In between group B and group C, VAS was significantly lower (p-value <0.05) in group B in all the time intervals till 20hrs of surgery [Table 2].

Table 2: Comparison of the VAS Scores of Patients at different time intervals in the Study Groups

VAS score Postoperative period	Group B (Bupivacaine)	Group M (Magnesium sulphate)	Group C (Normal Saline)	p-values (Post-hoc test)		
				B vs. M	B vs. C	M vs. C
30mins	0.49±0.50	0.66±0.36	1.26±0.41	0.179	0.002	0.001
1hr	0.89±0.58	1.04±0.52	1.76±0.82	0.584	0.003	0.013

2hr	1.07±0.63	1.53±0.82	2.56±0.64	0.008	0.001	0.001
4hr	1.93±0.82	3,12±1.02	3.32±1.1	0.006	0.001	0.046
6hr	3.23±1.01	2.48±0.92	2.90±1.03	0.031	0.86	0.661
8hr	2.84±1.1	2.91±1.3	2.76±0.84	0.023	0.012	0.861
10hr	2.13±0.96	2.73±0.46	2.81±0.76	0.018	0.003	0.746
12hr	1.77±1.02	2.30±0.92	2.61±1.02	0.014	0.010	0.652
16hr	1.67±0.82	1.91±0.76	2.13±0.91	0.066	0.026	0.671
20hr	1.57±0.63	1.76±0.44	1.87±1.03	0.162	0.042	0.823
24hr	1.43±0.30	1.56±0.66	1.62±0.50	0.764	0.682	0.781

The average time to 1st dose of post-operative analgesia demand was also the longest in Bupivacaine group compared to Magnesium group and Control group (7.38±1.01 hours compared to 5.23±0.92 hours and 2.5±1.12 hours respectively) which was also highly significant. After 20 hours of surgery, VAS was comparable (p-value >0.05) between patients of all the three groups [Figure 1 and Table 2]. When total analgesia consumption in 24 hours was analyzed, group B had 82.50±30.19 mg, group M had 112.33±34.94 mg and group C had 120.56±48 mg of Tramadol consumption which was highly significant.

Regarding total rescue analgesic requests, 5 patients in the bupivacaine group, required no rescue analgesia within the first 24 h postoperatively (Table-3) and 5 patients in the bupivacainegroup,12 in the magnesium sulfate group, and 13 in the normal saline group required second rescue analgesia within the first 24 h postoperatively. The results showed a significant difference in total rescue analgesic requests of group B as compared to group M and group C. (P-value<0.05), while no significant differences were observed between the group M and group C. The incidence of PONV was 5, 3, and 6 patients in the bupivacaine, magnesium sulfate, and normal saline groups, respectively, with no statistically significant intergroup differences (P-value >0.05).

Table 3: Comparison of the time to 1st rescue analgesia, no. of rescue analgesia demand and incidence of PONV in the Study Groups

Variables	Group B (Bupivacaine)	Group M (Magnesium sulphate)	Group C (Normal Saline)	p-values (Post-hoc test)		
				B vs. M	B vs. C	M vs. C
Time to 1st Rescue Analgesia (hours)	7.38±1.01	5.23±0.92	2.5±1.12	<0.001	<0.001	<0.001
Total dose of rescue analgesia- Tramadol (mg)	82.50±30.19	112.33±34.94	120.56±48	0.003	<0.001	0.063
Demand of Rescue Analgesia(no.%) 0 1 2 3	 5 25 5 0	 0 21 12 2	 0 16 13 6	0.017	0.010	0.086
PONV Yes No	 5(14.3%) 30(85.7%)	 3(8.6%) 32(91.4%)	 6(17.1%) 29(82.96%)	0.452	0.743	0.284

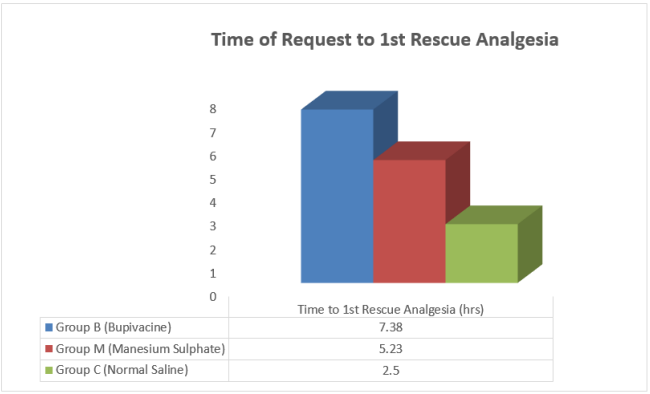

Figure 1: Time of request to 1st rescue analgesia

Discussion

Intraperitoneal instillation of analgesics drugs is a single-shot technique and provides a substantial period of postoperative analgesia with negligible side-effects. The present randomized and controlled study shows that intraperitoneal instillation of Bupivacaine and Magnesium sulphate both provide postoperative analgesia after laparoscopic cholecystectomy however, bupivacaine prolongs the duration of analgesia more than the magnesium sulphate.

Bupivacaine is the most common local anesthetic used intraperitoneally for postoperative pain relief because of its high potency and longer duration of action. In our study, the VAS score was lower in Group B as compare to Group M and Group C. Our results revealed that bupivacaine significantly reduced total rescue analgesic requests within the first24 h postoperatively. Aligning with these findings, Symons et al., Devalkar et al., Suma et al., and Chundigaret al., demonstrated that intraperitoneal bupivacaine instillation at the end of surgery reduced analgesic consumption in patients.[11-14] Similarly, Boulianne et al., in their systematic review, reported that intraperitoneal bupivacaine use decreased analgesic and opioid requirements without increasing side effects.[15] There are a few studies in which the administration of a local anesthetic didn't

show any efficacy. These failures could be due to the use of lower drug dose, lower concentration. Raetzell et al. compared lower concentrations of bupivacaine (0.125%) with normal saline and found no difference in the pain scores between the groups, this could be attributed to the lower concentration of bupivacaine that was used.[16] In meta-analysis by Choi et al., who studied 39 random control trial reviews, the authors concluded that intra-peritoneal local anesthetics significantly reduce parietal pain and exhibited a favorable analgesic effect towards visceral pain and shoulder pain.[17]

Our findings revealed that intraperitoneal magnesium sulfate injection significantly reduced postoperative pain at 4 hours compared to the control group. However, this drug did not demonstrate a significant effect on total rescue analgesic requests compared to the control group. Consistent with these results, El Mourad and Arafa demonstrated that intraperitoneal magnesium sulfate administration reduced postoperative pain following sleeve gastrectomy for up to 4 h without increasing adverse events.[18] SK Maharjan et al used a similar dose of magnesium sulphate intraperitoneally i.e. 50mg/kg and demonstrated better the post-operative pain control in laparoscopic cholecystectomy.[10] Furthermore, studies by Elfiky et al., Kansal et al., Ali et al., and Obaid et al., involving patients undergoing laparoscopic cholecystectomy found that intraperitoneal magnesium sulfate injection was a safer and more effective method for managing acute postoperative pain compared to intravenous injection.[9,19-21] The intraperitoneal delivery of magnesium sulfate allows for targeted drug concentration at the site of action while minimizing systemic exposure to excessive doses. This localized approach may be particularly advantageous in clinical scenarios where systemic drug exposure raises safety concerns.[22] The dissociation between reduced pain scores at 2–6 h and unchanged total rescue analgesic requests in the magnesium sulfate group may stem from its pharmacodynamic profile. As an NMDA receptor antagonist, magnesium sulfate transiently modulates central sensitization and pain perception,[23] but does not fully inhibit peripheral nociceptive signaling from surgical trauma.[24] Consequently, despite lower early pain scores, persistent nociceptive input likely maintained demand for supplemental analgesics. However, our results indicate a shorter duration compared to bupivacaine (7.38 ± 1.01 hours, $p < 0.001$), suggesting local anaesthetics mechanism provides a more sustained effect.

Haemodynamic parameters of both the groups were within normal limits. Oxygen saturation ranged from 99% to 100% and there was no respiratory compromise. In the present study, though within normal limits, there was a significant reduction in mean arterial pressure in MgSO4 group compared to bupivacaine group at 5,15 and 20-minutes post drug instillation ($P < 0.05$). This could be attributed to the effect ofMgSO4 in attenuating haemodynamic stress response at extubation as the above time roughly corresponded to reversal and extubation.[17,18]

There was no significant difference in Ramsay sedation scores between the two groups at all time points ($P > 0.05$). Scores remained around 2 which means that patients were co-operative and oriented, withoutany residual sedation. None of our patients had any signs of systemic toxicity of Bupivacaine or MgSO4.The lower dose used for both the local anaesthetic agent and MgSO4 reduced the risk of systemic toxicity.

In our study, nausea/vomiting was found in 5 patients among group B patients, in3 patients among groups M and in 6 patients among group C. The anesthetic and analgesic sparing effects of magnesium might have contributed to the decreased incidence of PONV in magnesium groups; another explanation is the antagonist effect of MgSO4 on NMDA receptors located in the common pathway of nausea and vomiting. However, no clear data regarding this effect is available.

Limitations: This work has several limitations that need to be taken into account. Postoperative pain is a subjective experience and can be difficult to quantify and compares objectively. As it was a single center study, there is a need for multicentric studies for more conclusive results. The limited sample size and single-center design constrain the applicability of the results to larger and more heterogeneous patient groups. Additionally, the set dosage technique for both magnesium sulphate and bupivacaine, without investigation of dose-response relationships, may not reflect ideal treatment regimens.

Conclusion

Intraperitoneal instillation of both magnesium sulphate and bupivacaine are effective for postoperative pain management following laparoscopic cholecystectomy. But intraperitoneal instillation of bupivacaine was found to be superior for postoperative analgesia in first 24 hours after laparoscopic cholecystectomy as reflected by a lower VAS score and longer duration of analgesia. Intraperitoneal instillation can be considered as a part of multimodal analgesia technique for laparoscopic surgeries in future. An optimal dose finding study is also the need of hour with using large number of patients.

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Conflicts of interest

There are no conflicts of interest.

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