



Intraperitoneal Magnesium Sulphate with Bupivacaine for Pain Relief after Laparoscopic Cholecystectomy. A Randomized Double-Blind Comparison Study

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Abstract:

Introduction: laparoscopic cholecystectomy is the gold standard form of treating patients with cholelithiasis, pain after laparoscopic cholecystectomy is less intense than after open cholecystectomy. A number of methods have been proposed to control postoperative pain such as injection of local anesthetics at the incision, intraperitoneal injection of local anaesthetics and intravenous non-steroidal anti-inflammatory drugs.

Methods: After obtaining our institutional ethics committee approval and written informed consent from each patient, study was conducted on 60 patients scheduled for laparoscopic cholecystectomy. Patients were randomly allocated into two groups 30 patients each. Group A (bupivacaine group): 30 patients received 30 ml of 0.25% bupivacaine not exceeding the dose 2.0 mg/kg intraperitoneal. Group B (bupivacaine + magnesium sulphate group): 30 patients received 0.25% bupivacaine along with 50 mg/kg of magnesium sulphate to total volume of 30 ml intraperitoneal. Patients were followed by a blind investigator postoperatively for abdominal pain using Visual analog scale. for postoperative analgesic requirements we used intramuscular tramadol 50 mg as a rescue analgesic on demand as well for Visual analog scale 4-7 and 8-10 respectively. Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. The level statistical significance was set at 5% ($P < 0.05$) Highly significant.

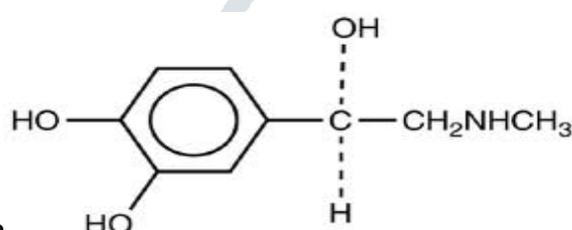
Result: There is statistically significant difference between the studied groups regarding Visual analog scale pain score at any point of time in the first 24 hours postoperative. In each group, there is significant fluctuation in visual analog scale score over time. Visual analog scale pain peaked 4 hours postoperatively in only bupivacaine group. No obvious peak was noticed within the other group.

Conclusion: Intraperitoneal instillation of 0.25% bupivacaine not exceeding 2.0 mg /kg along with 50.0 mg/kg of magnesium sulphate renders patients less pain in first 24 hours after surgery, more pain free period and less consumption of analgesics in post-operative period as compared to intraperitoneal instillation of bupivacaine alone.

Key words: Magnesium sulphate, Bupivacaine, laparoscopy ,cholecystectomy, postoperative pain

Introduction

laparoscopic cholecystectomy (LC) is the gold standard form of treating patients with cholelithiasis. LC is associated with reduced surgical trauma, more cosmetic incision, less blood loss, fewer postoperative complications and short hospital stay.⁽¹⁾ pain after LC is less intense than after open cholecystectomy (OC), but some patients still have considerable discomfort and pain during the first and second postoperative days.⁽²⁾ A number of methods have been proposed to control postoperative pain such as injection of local anesthetics at the incision, intraperitoneal injection of local anesthetics, intravenous non-steroidal anti-inflammatory drugs, intramuscular narcotics and decreasing the number of operative ports.⁽³⁾⁽⁴⁾ magnesium sulphate is N-methyl D-aspartate (NMDA) receptor antagonist and inhibits these receptors induced inflammation and hyper responsiveness.⁽⁵⁾ As these receptors regulate neuronal signalling and are involved in pain processing, magnesium sulphate by blocking this receptor, decreases postoperative pain as well.⁽⁶⁾⁽⁷⁾



Bupivacaine

figure (1): Pharmacologic structure of bupivacaine.⁽⁸⁾

Bupivacaine is an amino-amide local anaesthetic introduced to clinical practice in 1963.⁽⁹⁾ it acts by blocking the voltage-gated sodium channels.⁽¹⁰⁾

Sodium currents are reduced by local anesthetics because the drug-bound channels fail to open. Pain impulses fail to traverse the drugged axon. Impulse activity entering the anesthetized region thus maintains its own failure.⁽¹¹⁾ Systemic and localized toxic reactions of bupivacaine can occur due to accidental intravascular injection or to the administration of excessive dose.⁽¹²⁾ The symptoms of toxicity involve dizziness, visual and auditory disturbances, muscular twitching, drowsiness, disorientation, tremors, seizure & up to respiratory depression and respiratory arrest.⁽¹³⁾ on the cardiovascular system it causes an increase in the PR, QRS and QT intervals thus potentiating tachycardia with aberrant conduction.⁽¹⁴⁾ Magnesium (Mg⁺²) has been used as a therapeutic agent in acute pain. This may be due to magnesium's role as an NMDA receptor blocker.⁽¹⁵⁾ Usual dose of magnesium sulphate administration is a loading dose of 30-50 mg/kg followed by a maintenance dose of 6-20 mg/kg/h (continuous infusion) until the end of surgery. However, a single bolus of magnesium without maintenance infusion was also effective for postoperative analgesia in some previous reports.⁽¹⁶⁾

Review of Literature

Maharjan SK, Shrestha S et al 2012,⁽¹⁷⁾ Studied the analgesic effect of intraperitoneal instillation of magnesium sulphate with bupivacaine in patients undergoing laparoscopic cholecystectomy, concluded that the combined intraperitoneal instillation of bupivacaine and magnesium sulphate at the end of laparoscopic surgery renders patients less pain and less consumption of analgesics in first postoperative day compared to bupivacaine used alone.

Hemant Gupta et al 2015,⁽¹⁸⁾ Studied the postoperative pain relief in patients undergoing laparoscopic cholecystectomy with intraperitoneal administration of bupivacaine, magnesium sulphate and their combination concluded that the intraperitoneal administration of bupivacaine, magnesium sulphate and their combination in reduced doses provides effective postoperative pain control in laparoscopic cholecystectomy patients though their combination when the doses of both the drugs were reduced to half was less effective than bupivacaine alone.

Aim of the study:

The purpose of this study is to compare the analgesic effect of intraperitoneal instillation of bupivacaine with magnesium sulphate (MgSO₄) versus bupivacaine alone to provide effective postoperative pain relief in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

Patients and method:

After obtaining our institutional ethics committee approval and written informed consent from each patient a prospective, double-blinded randomized control study was conducted on 60 patients scheduled for laparoscopic cholecystectomy at Al Jala hospital, university of Benghazi. Patients were randomly allocated into two groups 30 patients each

Group A (bupivacaine group): 30 patients received 30 ml of 0.25% bupivacaine not exceeding the dose 2.0 mg/kg intraperitoneal, Group B (bupivacaine + magnesium sulphate group): 30 patients received 0.25% bupivacaine along with 50 mg/kg of magnesium sulphate to total volume of 30 ml intraperitoneal. Patients between 18 to 65 years both males and females with American Society of Anesthesiologists (ASA) physical status I-II were included in the study, while patients with ASA physical status III or IV, Patients with diabetes, Chronic respiratory disease, advanced renal or hepatic diseases, patients using opioids, tranquilizers or steroids, psychiatric patients, patients with peritoneal drain after surgery, patients allergic to local anaesthetics and the drugs to be used in this study, patients treated with calcium channel blockers are excluded from the study. All patients were premedicated with IV metoclopramide 10 mg, ranitidine 50 mg and 0.02 mg/kg of midazolam before induction of general anaesthesia. After preoxygenation with 100% O₂ for 3 minutes, anaesthesia was induced with IV propofol 2 mg/kg, 2 µg/kg of fentanyl followed by 0.5 mg/kg of rocuronium to facilitate endotracheal intubation. Anaesthesia was maintained with isoflurane 1-1.5% in 100% O₂ and a state of muscle relaxation was maintained by IV rocuronium 0.1 mg/kg every 30 minutes. All patients were continuously monitored by ECG, non-invasive arterial blood pressure, continuous end-tidal CO₂ and SpO₂ by pulse oximetry. Recovery was performed by discontinuation of general anaesthetics and reversal of neuromuscular blockers, and extubation was performed after ensuring adequate respiratory efforts & motor power and no other analgesics were given to patients before recovery. At the end of the operation and before closure of the laparoscopic entering sites the patients received either instillation of 30 ml of 0.25% bupivacaine into the peritoneum or received 0.25% bupivacaine along with 50 mg/kg of magnesium sulphate to total volume of 30 ml intraperitoneal by the surgeon through the epigastric port. Patients were followed by

a blind investigator postoperatively for abdominal pain using VAS based on a zero to ten scale to assess the pain score (with zero meaning no pain; score of one, two and three for mild pain; four, five, six and seven for moderate pain; and eight, nine and ten for severe pain), for postoperative analgesic requirements we used intramuscular tramadol 50 mg as a rescue analgesic on demand as well for VAS 4-7 and 8-10 respectively. Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Fisher exact test. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare means of two groups, independent sample t test (for normally distributed data) were used to compare means of two groups. To compare change in one group over time, repeated measure analysis of variance (ANOVA). The level statistical significance was set at 5% ($P < 0.05$) Highly significant

Results:

Table (1) Comparison between the studied groups regarding demographic characteristics and body weight:

Demographic characteristic and body weight	Groups		Test	
	Bupivacaine group	Bupivacaine + Magnesium sulphate group	χ^2/t	P Value
	N=30 (%)	N=30 (%)		
Gender:				
Female	27 (90)	26 (86.7)	Fisher	>0.999
Male	3 (10)	4 (13.3)		
Age (years):				
Mean \pm SD	36.3 \pm 9.15	37.5 \pm 11.64	-	0.659
Range	20 – 54	23 – 58	0.444	
Weight (kg):				
Mean \pm SD	66.5 \pm 1.18	69.7 \pm 7.29	-	0.078
Range	55 – 80	58 – 80	1.796	

Table (2) Comparison between the studied groups regarding duration of surgery and anaesthesia:

Duration	Groups		Test	
	Bupivacaine group	Bupivacaine + Magnesium sulphate group	t	P Value
	N=30 (%)	N=30 (%)		

Duration of surgery (minutes) Mean ± SD Range	57.17 ± 6.91 50 – 70	53.8 ± 6.07 45 – 63	2.006	0.05
Duration of anesthesia (min) Mean ± SD Range	68.6 ± 8.36 56 – 85	65.5 ± 7.11 55 – 75	1.547	0.127

Table (3) Comparison between the studied groups regarding time and dose of analgesia:

Parameters	Groups		Test	
	Bupivacaine group	Bupivacaine+ Magnesium sulphate group	t	P Value
	N=30 (%)	N=30 (%)		
Time of 1st analgesia (hour): Mean ± SD Range	3 ± 1.2 1 – 4	5.2 ± 0.89 4 – 7	- 8.061	<0.001**
Total of Tramadol in 24 hour (mg): Mean ± SD Range	140 ± 38.06 100 – 200	80 ± 24.91 50 – 100	7.225	<0.001**

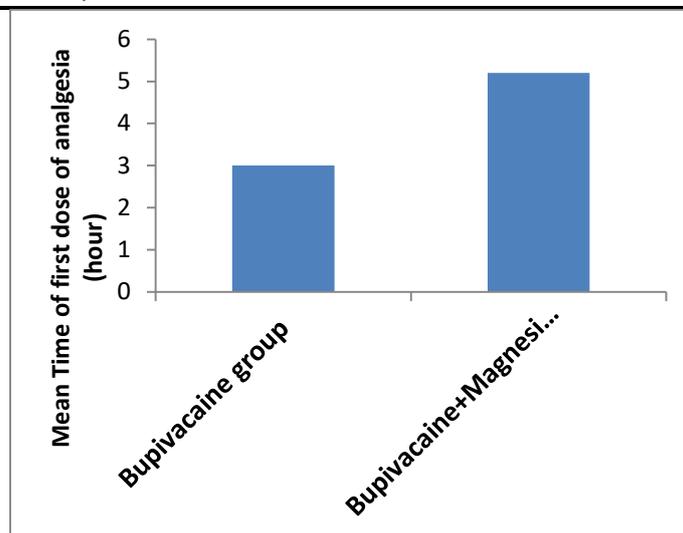


Figure (2) Simple bar chart showing comparison between the studied groups regarding time of first dose of analgesia

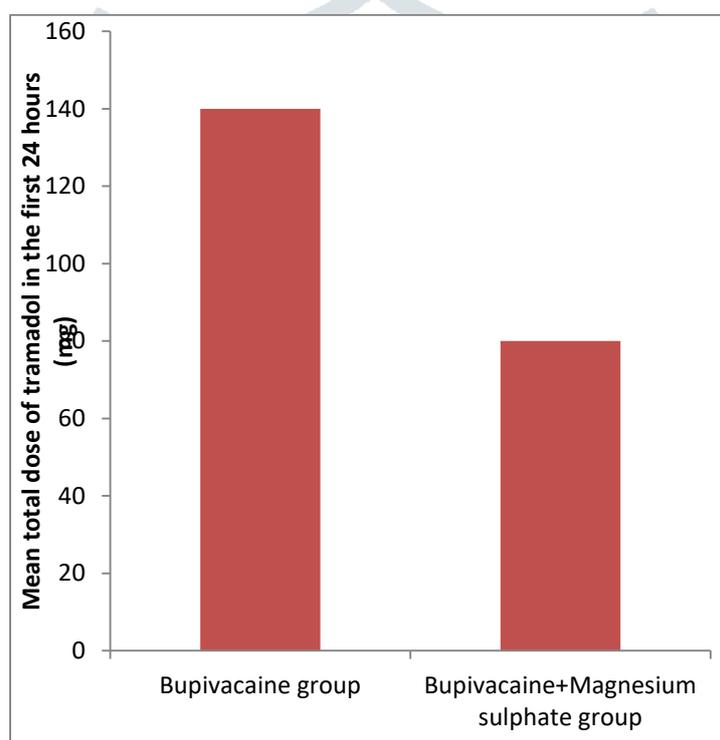
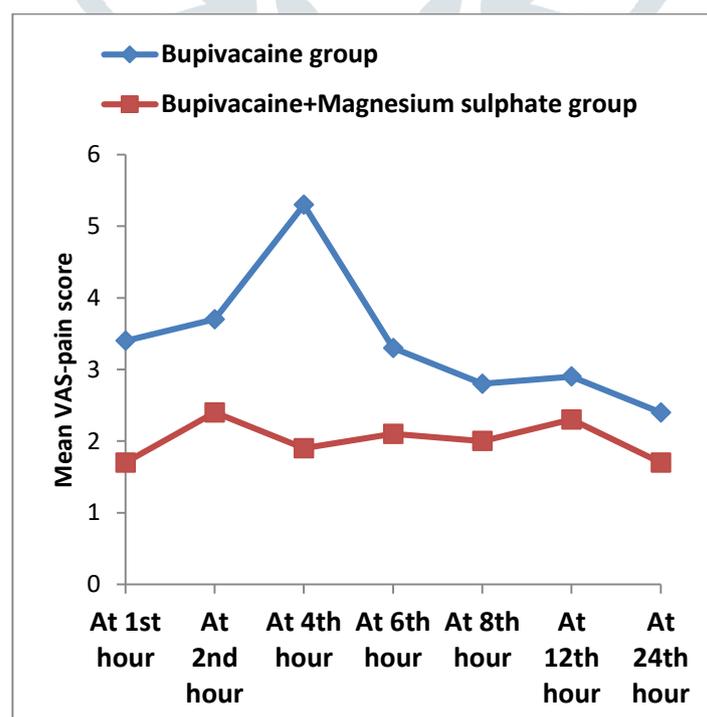


Figure (3) Simple bar chart showing comparison between the studied groups regarding total amount of Tramadol needed in the first 24 hours

Table (4) Comparison between the studied groups regarding VAS score over 24 hours:

VAS	Groups				Test	
	Bupivacaine group		Bupivacaine+ Magnesium sulphate group		t	P Value
	Mean \pm SD	Range	Mean \pm SD	Range		
At 1 st hour	3.4 \pm 1.65	1 - 6	1.7 \pm 0.66	1 - 3	5.242	<0.001**
At 2 nd hour	3.7 \pm 1.58	2 - 7	2.4 \pm 0.93	1 - 4	3.883	<0.001**
At 4 th hour	5.3 \pm 1.64	2 - 7	1.9 \pm 0.71	1 - 3	10.931	<0.001**
At 6 th hour	3.3 \pm 2.14	1 - 7	2.1 \pm 0.55	1 - 3	2.981	0.005*
At 8 th hour	2.8 \pm 1.42	1 - 5	2 \pm 0.79	1 - 3	2.693	0.01*
At 12 th hour	2.9 \pm 0.96	1 - 4	2.3 \pm 0.79	1 - 4	2.638	0.011*
At 24 th hour	2.4 \pm 0.93	1 - 4	1.7 \pm 0.47	1 - 2	3.679	<0.001**
P (F)	<0.001**		<0.001**			

**Figure (4)** Multiple line graph showing comparison between VAS-pain score among the studied groups in the first 24 hours postoperatively

Discussion

Intra peritoneal administration of local anaesthetics, around the operative site, can obstruct conduction from visceral sites and will minimize intensity of referred pain to the shoulder.⁽¹⁹⁾ The current study showed that addition of magnesium sulphate to bupivacaine decreases postoperative pain and analgesic consumption in first 24 hours after surgery along with longer pain free period compared to patients who were given sole bupivacaine after laparoscopic cholecystectomy. There is statistically non-significant difference between the studied groups regarding gender, age or body weight. 10% versus 13.3% of patients within Bupivacaine and Bupivacaine+Magnesium sulphate groups respectively were females. Patients' age and weight were non-significantly higher in Bupivacaine + Magnesium sulphate group (Table 1). There is statistically significant difference between the studied groups regarding VAS-pain score at any point of time in the first 24 hours postoperative. (VAS-pain score was significantly higher in Bupivacaine group at 1, 2, 4, 6, 8, 12 and 24 hours). In each group, there is significant fluctuation in VAS score over time (Table 4, figure 4). VAS-pain peaked 4 hours postoperatively in only bupivacaine group. No obvious peak was noticed within the other group. Abdel Rouf and Amer (2004) studied the postoperative analgesic effects of intraperitoneal NMDA receptor antagonist, magnesium sulphate and ketamine in patients undergoing laparoscopic cholecystectomy. They used 30 mg/kg of magnesium sulphate in patients receiving intraperitoneal 0.25% bupivacaine and 1 mg/kg of ketamine along with 0.25% bupivacaine. They conveyed that demand for first analgesia in NMDA receptor antagonist was around 130 minutes after surgery compared to control and bupivacaine group (15.30 minutes and 35.30 minutes respectively).⁽²⁰⁾

A previous study compared intra peritoneal instillation of bupivacaine, solely and in addition to MgSO₄ in a dose of 50 mg/kg. They concluded that patients receiving intra peritoneal bupivacaine with MgSO₄ at the end of the surgery had better pain relief for a period of 2–5 h compared with patients who were given only intra peritoneal bupivacaine.⁽¹⁷⁾

Edmunds S et al (2002) reported that when magnesium sulphate was used as an adjunct for anaesthesia, it reduced the doses of analgesics required and their action was strengthened but there was no prolongation of analgesic effects.⁽⁷⁾

The current result shows that time of introducing first dose of analgesia was significantly late in Bupivacaine + magnesium sulphate group (5.2 hour \pm 0.89) versus (3 hours \pm 1.2) in Bupivacaine group. Time range before 1st analgesia used was from 4 to 7 hours in combined group (Table 3). This comes in agreement with that stated by Yadava et al., (2016). This was slightly less than time reported in different studies; 9 hours in (Anand et al., 2014) and 8 hours in (Bhardwaj et al., 2002) and (Malhotra et al., 2007).^(21,22,23,24)

Total dose of tramadol needed in the first 24 hours postoperatively was significantly lower in Bupivacaine+magnesium sulphate group (80 mg \pm 24.91) versus (140 mg \pm 38.06) in Bupivacaine group.

Total dose of tramadol needed in the first 24 hours postoperatively was significantly lower in Bupivacaine+ magnesium sulphate group (80 mg± 24.91) versus (140 mg± 38.06) in Bupivacaine group (Table 3). A previous study reported that the mean number of doses of intramuscular tramadol in 24 hr were significantly lower in Bupivacaine+ magnesium sulphate group in approximate to our findings (Anand et al., 2014).⁽²³⁾ Further Studies have shown a significant reduction in analgesic consumption between the groups up to 24 hr upon intraperitoneal administration of local anesthetics (Yadava et al., 2016)⁽²¹⁾ (Bhardwaj et al., 2002)⁽²³⁾, The study can be explained in context of some strength points. The study included control group 'Bupivacaine group' to determine additive value of magnesium sulphate. Due to good randomization, there was non-significant difference between the studied groups, which remove any possible confounders.

Conclusion

Intraperitoneal instillation of 0.25% bupivacaine not exceeding 2.0 mg /kg along with 50.0 mg/kg of magnesium sulphate after completion of laparoscopic surgery renders patients less pain in first 24 hours after surgery, more pain free period and less consumption of analgesics in post-operative period as compared to intraperitoneal instillation of bupivacaine alone in patients undergoing laparoscopic surgery without any significant side effects.

Recommendation:

Based on the results of this study, it is recommended to consider the intraperitoneal instillation of 0.25% bupivacaine 2.0 mg /kg along with 50.0 mg/kg of magnesium sulphate after completion of laparoscopic Cholecystectomy in order to control pain and less consumption of analgesics in post-operative period.

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