Original Article

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Anaesthesia Section

Intraperitoneal Instillation of Magnesium Sulphate and Dexmedetomidine for Postoperative Analgesia after Laparoscopic Cholecystectomy- A Randomised Clinical Study

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ABSTRACT

Introduction: Magnesium sulphate and dexmedetomidine can decrease the duration and intensity of postoperative pain due to their antinociceptive effects. Magnesium sulphate blocks N-methyl-D-aspartate receptor (NMDA) channel in a voltage dependant way, while dexmedetomidine acts on dorsal root neurons.

Aim: To compare the analgesic efficacy and duration of postoperative analgesia after intraperitoneal instillation of magnesium sulphate and dexmedetomidine in laparoscopic cholecystectomy.

Materials and Methods: The present study was a randomised clinical study, in which 90 patients of age 18-60 years, belonging to American Society of Anaesthesiologists (ASA) grade I or II were randomly selected and divided in three groups. Group M received magnesium sulphate 50 mg/kg with 0.25% bupivacaine 30 mL, group D received dexmedetomidine 1 µg/kg with 0.25% bupivacaine 30 mL, and group B received 0.25% of plain bupivacaine 30 mL. Pain was assessed using Visual Analog Scale (VAS) score as primary outcome, recorded at 0, 2, 4, 6, 8, 10, 12 and 24 hours after surgery. Time to rescue analgesia (VAS ≥4 or on demand) and patients satisfaction score were the secondary outcomes. All recorded data were analysed by statistical test (Analysis of Variance (ANOVA), post-hoc Tukey's HSD (Honest Significant Difference) test and Chi-square test).

Results: The mean VAS score was 2.40±0.84, 2.57±0.78 and 2.88±0.92 in group M, group D and group B, respectively ($p<0.05$). The total analgesic requirement (Paracetamol) in first 24 hours postoperatively was lower in group M (1.73±0.58 gm), and group D (2.17±0.53 gm), than group B (2.70±0.47 gm). Highly satisfied patients in group M were 10, group D were 03, and none in group C. There were 14 highly dissatisfied patients in group B. The difference in the patient satisfaction score between groups was statistically significant ($p=0.0002$). Time to first rescue analgesia was highest in group M then group D.

Conclusion: Intraperitoneal instillation of magnesium sulphate 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: Bupivacaine, Patient satisfaction, Visual analogue scale score

INTRODUCTION

Laparoscopic cholecystectomy is a common day care procedure. The pain after open cholecystectomy is mostly parietal whereas it is more of visceral following laparoscopic cholecystectomy [1]. The pain occurs due to stretching of the abdominal wall during the pneumoperitoneum and release of inflammatory mediators, local dissection and irritation of the peritoneum, or CO_2 used for pneumoperitoneum [2]. The pain can be prevented or reduced by blocking the nociceptor before their stimulation via use of local anaesthetics [3]. Many studies have demonstrated the effectiveness of local anaesthetics instilled intraperitoneal, alone or mixed with other drugs for postoperative analgesia in laparoscopic cholecystectomy but, there is no consensus regarding the dose, concentration, site and manner of administration [4-6].

The antinociceptive effect of magnesium sulphate relieves chronic pain and it can also decrease the duration and intensity of postoperative pain [7]. The postoperative pain free period is longer after intraperitoneal instillation of bupivacaine additive with magnesium sulphate [7].

Dexmedetomidine, used in combination with local anaesthetic, is associated with prolonged analgesic effects. Studies on the role of intraperitoneal instillation of dexmedetomidine for postoperative analgesia, suggest its role in prolonging the duration of analgesia in Transversus Abdominis Plane (TAP) block in various surgeries [8,9].

There is need for multimodal postoperative analgesia for laparoscopic procedure. Comparative studies have not been done between magnesium sulphate and dexmedetomidine for postoperative analgesia in laparoscopic cholecystectomy. This study was designed to compare, duration of analgesia after intraperitoneal instillation of magnesium sulphate with bupivacaine to dexmedetomidine with bupivacaine. Primary outcome was VAS score, and secondary outcomes were time to first resque analgesia, patient's satisfaction score and side effect (if any).

MATERIALS AND METHODS

This randomised clinical study was carried out in the Department of Anaesthesia, Government Medical College, Rewa, Madhya Pradesh, India, from April 2018 to March 2019. After getting clearance from Institutional Ethics Committee (IEC) (91/19) and informed consent from every patient, this study was carried out on 90 patients.

Inclusion criteria: Patients between 18-60 years of age, ASA grade I and II, of either sex, posted for laparoscopic cholecystectomy under general anaesthesia.

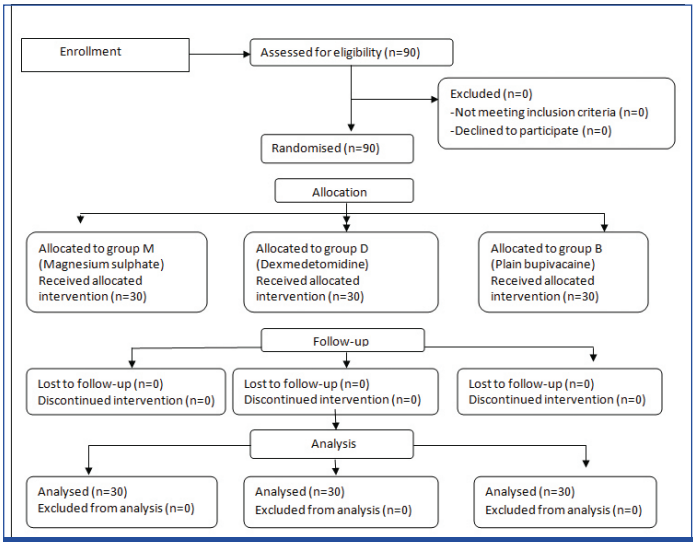
Exclusion criteria: Patients with allergy to study drugs, chronic alcoholism, systemic diseases like severe heart disease, lung disease, diabetes mellitus etc., renal dysfunction, and patients who refused to consent.

Sample size calculation: After considering power of study by 90% and level of significance with 5%, calculated sample size came out 28 patients in each group, so decided to select total 90 patients after randomisation (n=30) using computer based randomisation software, "Random Allocation Software 1.0" (Copyright © 2017 Informer Technologies, INC) as under [Table/Fig-1].

Group M- Received intraperitoneal instillation of 30 mL, inj. bupivacaine 0.25% and inj. magnesium sulphate 50 mg/kg b.w.

Group D- Received intraperitoneal instillation of 30 mL, inj. bupivacaine 0.25% and inj. dexmedetomidine 1 µg/kg b.w.

Group B- Received intraperitoneal instillation of 30 mL of inj. bupivacaine 0.25%.



[Table/Fig-1]: CONSORT flow diagram.

Procedure

All patients were kept nil by mouth for at least six hours prior to surgery. After shifting them to the operation theatre, monitors were attached and baseline parameters (heart rate, non invasive blood pressure, and Oxygen Saturation (SpO_2) and End Tidal Carbon Dioxide ($ETCO_2$) values) were recorded. Intravenous access secured with 18 G i.v. (intravenous) cannula. All the patients were premedicated with Inj. glycopyrrolate 0.01 mg/kg, Inj. midazolam 0.03 mg/kg and Inj. fentanyl 2 µg/kg. After preoxygenation for 3 minutes, patients were induced with Inj. propofol 2.5 mg/kg and Inj. succinylcholine 1.5 mg/kg, laryngoscopy was performed and orotracheal intubation was done. The correct placement of endotracheal tube was confirmed by five point auscultation and $ETCO_2$. Anaesthesia was maintained with O_2 40%, N_2O 60%, isoflurane and intermittent Inj. atracurium i.v.

After cholecystectomy and achievement of haemostasis, abdomen was thoroughly washed to remove the blood clots and debris. The surgeon instilled 10 mL of study solution in the subdiaphragmatic space and 10 mL at suprahepatic surface of liver and remaining drug in the gallbladder fossa under vision, which was prepared by investigator. Patients who required intraperitoneal drain after surgery were excluded from this study. All the patients received inj. diclofenac 75 mg IV at the end of surgery and same dose was repeated after 12 hours, as per institutional protocol.

All the patients were reversed with Inj. neostimine 0.05 mg/kg and Inj. glycopyrrolate 0.01 mg/kg. Patients were extubated after absence of residual neuromuscular deficit.

After surgery, patients were transferred to the postanaesthesia care unit. Pain severity was assessed using a VAS at 0, 2, 4, 6, 8, 10, 12 and 24 hours after surgery. When patients complained of pain or VAS ≥4 for first time in postoperative period, paracetamol 1 gm i.v. infusion (max 4 gm in 24 hours) was given as rescue analgesic. The duration of analgesia and total paracetamol consumption in first 24 hours were duly noted.

Patient's satisfaction score was assessed and noted at 24 hours after surgery, using a 5-point patient's satisfaction score to evaluate the level of postoperative analgesic satisfaction.

STATISTICAL ANALYSIS

All recorded data were tabulated and statistically analysed by appropriate statistical test (ANOVA, post-hoc tukey's HSD test and Chi-square test). Mean values were compared for normally distributed parameters by using ANOVA. Post-hoc (tukey's HSD) test was used if statistically significant difference was found with ANOVA to assess pair wise comparisons. Categorical outcomes were compared using Chi-square test between study groups. The p-value <0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) software version 22.0.

RESULTS

All the three groups were comparable with respect to demographic profiles and there was no statistically significant difference found in between the groups [Table/Fig-2].

Parameters	Group M	Group D	Group B	p-value (Post-hoctukey's test)		
				M vs. D	M vs. B	D vs. B
Age (years) (Mean±SD)	40.1±12.3	38.53±10.29	37.6±11.8	0.8574	0.6779	0.9474
Height (centimeter) (Mean±SD)	164±7.54	161.6±7.92	162.5±7.41	0.4453	0.7273	0.8914
Weight (kg) (Mean±SD)	59.2±9.63	62.3±9.43	60.0±9.23	0.4142	0.9423	0.6138
Sex ratio (F:M)[¥]	24 F 6 M	25 F 5 M	23 F 7 M	0.7386	0.7540	0.5186

[Table/Fig-2]: Demographic characteristics between the three groups.
[¥]Chi-square test used for sex ratio

The duration of analgesia was longest in patients of group M, and shortest in patients of group B (4.93±1.14 hrs). Duration of analgesia was significantly different between all the three groups. Paracetamol requirement was lower in group M (1.73±0.58 gm) [Table/Fig-3].

Parameters	Group M	Group D	Group B	p-values (post-hoc tukey's test)		
	Mean±SD	Mean±SD	Mean±SD	M vs. D	M vs. B	D vs. B
Duration of analgesia (hrs)	9.30±1.64	7.60±1.22	4.93±1.14	<0.0001	<0.0001	<0.0001
Total paracetamol requirement (gm)	1.73±0.58	2.17±0.53	2.70±0.47	0.0050	<0.0001	0.0006

[Table/Fig-3]: Duration of analgesia and total paracetamol requirement.
The p-value <0.05 was considered statistically significant

Immediately after surgery, VAS was zero in all patients. After 2 hours and 4 hours of surgery, no statistical difference was noted between group M and group D. After 6 hours of surgery, VAS was significantly lower (p-value <0.0001) in patients of group M (2.53±0.86) and (p-value=0.0338) in patients of group D (3.00±0.95) as compared to patients of group B (3.53±0.90). However, no statistical difference noted between group M and group D. After 8 hours of surgery, VAS was significantly lower in patients of group M as compared to patients of group D (3.57±0.86) and patients of group B (3.00±0.79). However, no statistical difference (p-value=0.0805) was noted between groups D and group B. The patients of group D have received rescue analgesia at mean time 7.60±1.22 hours which led to lower VAS at subsequent points of time. After 10 hours of surgery, VAS was not statistically comparable (p-value >0.05) between patients of all the three groups. The patients of group M received rescue analgesia at mean time 9.30±1.64 hours which led to decreased VAS at subsequent point of times [Table/Fig-4].

VAS score	Group M Mean±SD	Group D Mean±SD	Group B Mean±SD	p-values (Post-hoc test) M vs.D	M vs. B	D vs. B
Immediately after the surgery	0	0	0	-	-	-
2 hrs postoperatively	1.57±0.63	1.57±0.82	1.97±1.07	0.9875	0.2258	0.1714
4 hrs postoperatively	1.73±0.74	1.93±0.58	3.07±1.11	0.5285	<0.0001	<0.0001
6 hrs postoperatively	2.53±0.86	3.00±0.95	3.53±0.90	0.1238	<0.0001	0.0338
8 hrs postoperatively	2.47±1.01	3.57±0.86	3.00±0.79	<0.0001	0.0281	0.0805
10 hrs postoperatively	3.37±1.10	2.93±0.87	2.93±0.87	0.2352	0.1841	0.9898
12 hrs postoperatively	2.57±0.82	2.50±0.78	2.97±0.96	0.9512	0.1728	0.0937
24 hrs postoperatively	2.53±0.73	2.47±0.63	2.70±0.75	0.9288	0.6319	0.4091

[Table/Fig-4]: VAS score at different time intervals.

According to patients' satisfaction score, group M patients were highly satisfied (33.33%) by pain relief procedure than patients of group D and group B at any point of time. Group B patients were highly dissatisfied patients (46.67%). The difference in the patient satisfaction score between groups was statistically significant [Table/Fig-5].

Patient satisfaction score	Group M N (%)	Group D N (%)	Group B N (%)	p-value (ANOVA)
Highly satisfied	10 (33.33)	03 (10.00)	0	0.00001
Satisfied	11 (36.67)	14 (46.67)	06 (20.00)	0.00004
Neither satisfied nor dissatisfied	05 (16.67)	06 (20.00)	06 (20.00)	0.0111
Dissatisfied	04 (13.33)	07 (23.33)	14 (46.67)	0.0194
Highly dissatisfied	0	0	04 (13.33)	0.0004
Total	30 (100)	30 (100)	30 (100)	

[Table/Fig-5]: Patients' satisfaction score.

Bradycardia (Heart rate <60/Min.) was seen in six patients of group D. The incidence of nausea was seen in six patients of group M, four patients of group D and six patients of group B. Vomiting was not seen in any of the patients of all the three groups. No incidence of sedation, hypotension or hypertension was seen in any of the group in first 24 hours postoperatively [Table/Fig-6].

Adverse events	Group M	Group D	Group B
None	24 (80%)	20 (66.66%)	24 (80%)
Bradycardia (Heart rate <60/min)	0	06 (20%)	0
Nausea	06 (20%)	04 (13.34%)	06 (20%)
Vomiting	0	0	0
Total	30 (100)	30 (100)	30 (100)

[Table/Fig-6]: Adverse events across the study group.

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 randomised and controlled study shows that intraperitoneal instillation of magnesium sulphate and dexmedetomidine both provide postoperative analgesia after laparoscopic cholecystectomy however, magnesium sulphate prolongs the duration of analgesia more than the dexmedetomidine.

The dose of magnesium sulphate used in this study was based on previous studies [10]. Maharjan S and Shrestha S, in their randomised study on 60 patients found that magnesium sulphate adjuvant with bupivacaine prolonged the duration of postoperative analgesia after laparoscopic cholecystectomy in comparison to bupivacaine alone but they did not compared it with any other additive [11]. Similar results were also found in a study done by Yadava A et al., when they compared bupivacaine-magnesium sulphate (MB) with tramadol [7]. In the present study, duration of analgesia was also high with magnesium sulphate as in previous studies [11,12].

Magnesium reduces calcium influx to the cell, and also antagonises NMDA receptors blocking pain processing in the central nervous system [13]. Due to blockade of this receptor, magnesium sulphate decreases postoperative pain.

Rapolu S et al., evaluated the intraperitoneal instillation of dexmedetomidine adjuvant with bupivacaine for postoperative analgesia in 100 patients in two groups following laparoscopic cholecystectomy [14]. Similarly, they found the mean duration of analgesia was more in dexmedetomidine group as compared to control group. Ali U et al., compared the intraperitoneal instillation of bupivacaine alone with dexmedetomidine or tramadol for postoperative analgesia following laparoscopic cholecystectomy [8]. They concluded that intraperitoneal instillation of dexmedetomidine 1 mcg/kg in combination with bupivacaine after laparoscopic cholecystectomy significantly increases the duration of postoperative analgesia and significantly reduces the analgesic requirement in postoperative period, as compared to bupivacaine alone and may be better than bupivacaine combined with tramadol. Present study also found long duration of analgesia as previous studies but, it was lower than magnesium sulphate [14,15].

Several studies has been done using intraperitoneal instillation of magnesium sulphate [12,13,16] and dexmedetomidine [17-19] but not compared their analgesic efficacy which was compared in this study.

The total analgesic requirements (paracetamol) in first 24 hours postoperatively were lower in group M and group D than group B which was statistically significant, and the results were in concordance with a study done by Yadava A et al., where they have compared magnesium sulphate with tramadol [7]. Pati BK, observed the total analgesic consumption was lower in group BD (Bupivacaine with Dexmedetomidine) compared to group B (Bupivacaine), which was statistically significant [15].

Mean VAS score increased till 8 hours in group M in present study. Similarly, Yadava A et al., was also found lower mean VAS score in MB (magnesium sulphate+bupivacaine) group then TB (tramadol+bupivacaine) group, which was statistically significant ($p<0.05$) [7]. In some previous studies [19,20], lower mean VAS score was also evaluated with dexmedetomidine in comparisons to control group but this VAS score was more than the VAS with magnesium sulphate as with present study.

This study assessed patient's satisfaction score at 24 hours after surgery, and revealed number of highly satisfied patients in group M, group D and group B were 10, 3 and nil respectively. Fourteen patients in group B were dissatisfied. The difference in the patient satisfaction score between the groups was statistically significant ($p=0.0002$).

In this study, postoperative bradycardia (Heart rate <60/min) was 20% among group D and it was easily manageable, while patients of group M have no such episode. The mechanism of dexmedetomidine induced bradycardia is activation of the alpha-2 adrenergic receptors, results in a decrease in the discharge of the sympathetic signals and a rise in the parasympathetic activity. Similarly, Elnabtity AM and Ibrahim M reported bradycardia among patients of group BD (bupivacaine with dexmedetomidine), with an incidence of 11.5 [9].

Shukla U et al., found 3 cases having nausea in postoperative period with dexmedetomidine [17] and Ali U et al., found the incidence of nausea in 80% patients with magnesium sulphate group [8]. This may be due to opioids used for rescue analgesia. In present study, nausea was seen in six cases in group M and four cases in group D. No episode of vomiting was observed in any patients of all the three groups.

In present study, authors did not found other side-effects like sedation or hypotension in any of the study group in first 24 hours postoperatively; similar results were concluded in study conducted by Rapolu S et al., and Oza VP et al., [14,20]. This was due to intraperitoneal instillation of drugs not by intravenous route.

Present study showed the superiority of intraperitoneal instillation of magnesium sulphate over dexmedetomidine in providing analgesia in first 24 postoperative hours, as evident by longer duration of analgesia along with lesser consumption of paracetamol and lower VAS score.

Limitation(s)

Postoperative pain is a subjective experience and can be difficult to quantify and compares objectively. As it was a single centre study, there is a need for multicentric studies for more conclusive results.

CONCLUSION(S)

It can be concluded that intraperitoneal instillation of magnesium sulphate 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 along with lesser consumption of paracetamol. 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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