Original Article

A prospective randomised controlled study for evaluation of high-volume low-concentration intraperitoneal bupivacaine for post-laparoscopic cholecystectomy analgesia

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ABSTRACT

Background and Aims: Low-volume high-concentration bupivacaine irrigation of the peritoneal cavity has been reported to be ineffective for short-term analgesia after laparoscopic cholecystectomy (LC). This study was conducted to evaluate the effectiveness of intraperitoneal instillation of high-volume low-concentration bupivacaine for post-operative analgesia in LC. **Methods:** Sixty patients undergoing LC were included in this prospective, double-blind, randomised study. Patients were divided into two ($n = 30$) groups. In Group S, intraperitoneal irrigation was done with 500 ml of normal saline. In Group B, 20 ml of 0.5% (100 mg) bupivacaine was added to 480 ml of normal saline for intraperitoneal irrigation during and after surgery. Post-operative pain was assessed by numeric pain rating scale (NRS) at fixed time intervals. Duration of analgesia (DOA), total rescue analgesic requirement (intravenous tramadol), presence of shoulder pain, nausea and vomiting were recorded for the initial 24 h post-operatively. **Results:** Mean DOA in Group S was 0.06 ± 0.172 h (3.6 ± 10.32 min) and that in Group B was 19.35 ± 8.64 h ($P = 0.000$). Cumulative requirement of rescue analgesic in 24 h in Group S was 123.33 ± 43.01 mg and that in Group B was 23.33 ± 43.01 mg ($P = 0.000$). There was no significant difference in incidence of shoulder pain, nausea and vomiting between the groups. **Conclusion:** High-volume low-concentration of intraperitoneal bupivacaine significantly increases post-operative DOA and reduces opioid requirement after LC.

Key words: Analgesia, bupivacaine, laparoscopic cholecystectomy

INTRODUCTION

Patients undergoing laparoscopic cholecystectomy (LC) experience less post-operative pain than conventional cholecystectomy.[1] Still pain remains the predominant complaint after LC in the initial 24 h postoperatively.[2,3] Effective post-operative analgesia after LC remains a clinical challenge. Recently, intraperitoneal instillation of different local anaesthetics (LAs) has been gaining popularity for post-operative analgesia in LC. Most of the studies have used bupivacaine irrigation of peritoneal cavity in low volume (20 ml to 100 ml) and high concentration (0.5%–0.125%). However, their analgesic action is effective for only a few hours in the post-operative period.[4-7]

We hypothesised that a higher volume of LA would cover a larger sub-hepatic area and the surrounding peritoneum, producing more effective analgesia. Therefore, we conducted this study to evaluate the results of high-volume (500 ml) low-concentration (0.02%) bupivacaine for post-operative analgesia in LC.

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METHODS

This prospective, randomised, double-blind study was approved by the Hospital Ethics Committee. ASA grade I and II patients of either sex, between 20 and 60 years of age, undergoing elective LC under general anaesthesia, were enrolled for the study. Written informed consent was obtained after due counselling. Patients were familiarised with numeric pain rating scale (NRS), where 0 represented no pain and 10 represented maximum possible pain. Exclusion criterion included pregnancy, allergy to LAs, acute pancreatitis, choledocholithiasis, chronic pain, current opioid use, inability to comprehend NRS and conversion of LC to open cholecystectomy.

All the patients fasted for 8 h before surgery and were given uniform premedication with intravenous (IV) injection midazolam 0.025 mg/kg, fentanyl 2 μg/kg and ondansetron 0.1 mg/kg. General anaesthesia was induced with IV 2 mg/kg of propofol, muscle relaxation was obtained with IV 0.1 mg/kg of vecuronium bromide and trachea was intubated. Anaesthesia was maintained with 0.8%–1% isoflurane in a mixture of oxygen and nitrous oxide. Intra-abdominal pressure was restricted to ≤12 cm H_2O during surgery. Haemodynamic parameters (mean arterial pressure [MAP] and heart rate [HR]) were recorded every 5 min. All patients also received IV 1.5 mg/kg of diclofenac sodium for analgesia during surgery. No further analgesic was given during surgery. Subsequently, post-operative attending nurse gave 1.5 mg/kg of diclofenac sodium at 8 and 16 h post-operatively.

Randomisation was done by computer-generated random number technique and patients were divided into two groups of 30 patients each, i.e., Group S and Group B. Random group assigned was enclosed in a sealed envelope to ensure concealment of allocation sequence. After transferring the patient to the operation theatre, sealed envelope was opened by the anaesthesiologist, not involved in the study, who then prepared the drug solution according to randomisation. The study was double blinded; the attending anaesthesiologist as well as the nurse who recorded the post-operative data was unaware of patient's group.

In Group S, 500 ml of normal saline was used as the irrigation fluid. In Group B, 20 ml 0.5% (100 mg) bupivacaine (sensorcaine 0.5%, Astra Zeneca, Bengaluru, India) was added to 480 ml of normal saline for intraperitoneal irrigation. Bottles of normal saline were identical for both the groups.

The surgeon used this irrigation fluid during dissection of gall bladder and aspirated the fluid after complete dissection. After gall bladder extraction, the surgeon was asked to irrigate the surgical bed as well as the peritoneal cavity with rest of the irrigating fluid. Patient was placed in Trendelenburg's position with right lateral tilt to facilitate dispersion of drug solution in the sub-hepatic region for 5 min. It was done through subcostal trocar under direct laparoscopic control.

Irrigating fluid was then aspirated, drain was placed and surgical ports were closed. Isoflurane and nitrous oxide were stopped. Reversal of residual neuromuscular blockade was done with a mixture of neostigmine (0.04 mg/kg) and glycopyrrolate (0.01 mg/kg) and the patient was extubated. Patients were subsequently transferred to the recovery area.

The post-operative nursing staff, unaware of the patient's group, recorded NRS at fixed intervals, i.e., immediately after extubation, at 30 min, 1, 2, 4, 6, 8, 12 and 24 h post-operatively and whenever the patient complained of pain. IV injection tramadol 2 mg/kg was given as rescue analgesic whenever the patient experienced pain equal to or more than 4 in the NRS. The length of time between extubation and the first request for rescue analgesic was recorded, which was called as duration of analgesia (DOA).

The primary aim of the study was to compare DOA between two groups at different time intervals. Secondary objective was to record the NRS score, cumulative requirement of rescue analgesic used in 24 h post-operative period, presence of shoulder pain, nausea and vomiting.

We conducted a pilot study on 12 patients and presuming the difference in DOA and effect size (0.8 h) with standard deviation of 0.5, obtained to be true, calculated that 26 patients would be required in each group for the study, with power of 0.8 and alpha error of 0.05. A total of 30 patients were taken in each group to compensate for the dropouts.

Data analysis was performed using SPSS version 16.0 for Windows. Data were presented as mean ± standard deviation or number of patients. Demographic data, duration of surgery, NRS scores at different time intervals, DOA and cumulative requirement

of rescue analgesic were compared between the groups by analysis of variance and Tukey honest significant difference was used for *post hoc* multiple comparisons. Pearson Chi-square test was applied to analyse differences in categorical values. The value of $P < 0.05$ was considered statistically significant.

RESULTS

The study began in February 2016, and there were 64 patients who underwent LC during the study period; out of which 4 were excluded as per exclusion criterion and 60 patients were randomly divided into two groups of 30 patients each. After recruitment, none of the patients were excluded from the study due to conversion from LC to open cholecystectomy [Figure 1].

Demographic profile in terms of age, weight and sex distribution, as well as duration of surgery, was comparable between both the groups [Table 1]. Intra-operative hemodynamic parameters (MAP and HR) were also comparable between the groups [Figures 2 and 3]. Propofol at induction and minimum alveolar concentration of isoflurane during surgery was comparable in both the groups [Table 1]. All the patients in both the groups received similar intra-operative analgesics (fentanyl 2 μg/kg and diclofenac sodium 1.5 mg/kg).

DOA in Group S were 0.06 ± 0.172 h (3.6 ± 10.32 min) and that in Group B was 19.35 ± 8.64 h ($P = 0.00$).

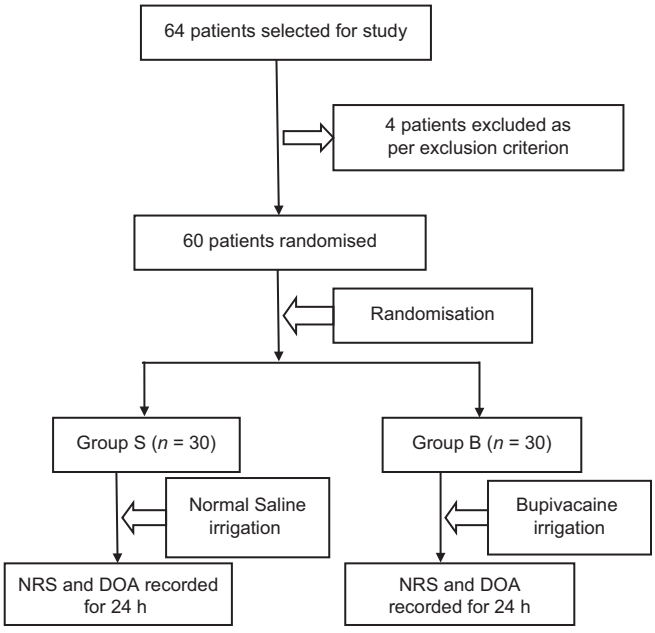

Figure 1: Consort diagram. (NRS: Numerical pain rating score; DOA:duration of analgesia)

Cumulative requirement of tramadol in 24 h in Group S was 123.33 ± 43.01 mg which was significantly higher ($P = 0.00$) than Group B (23.33 ± 43.01 mg) [Table 2].

At extubation, patients of Group S reported significantly higher NRS score as compared to Group B ($P = 0.0$) [Table 2]. In Group S, out of 30 patients, 26 required rescue analgesic immediately after extubation, and the rest four patients required rescue analgesic within half an hour post-operatively. Three patients required one additional dosage of

Table 1: Demographic and operative characteristics of the patients

Variable	Mean±SD		*P*
	Group S	Group B	
Age (years)	41.97±12.0	37.03±10.52	0.303
Sex			
Male	7	4	
Female	23	26	
Weight (kg)	53.87±8.32	54.57±7.27	0.798
Duration of surgery (min)	57.90±8.47	58.77±8.97	0.878
Propofol requirement (mg)	108.73±14.52	107.73±16.65	0.76
MAC of isoflurane	0.90±0.07	0.93±0.07	0.70

MAC – Minimum alveolar concentration; SD – Standard deviation

Table 2: Duration of analgesia, tramadol requirement and numeric pain rating scale at different time intervals of patients

Parameters	Group S	Group B	*P*
Duration of analgesia (h)	0.06±0.172 (3.6±10.32 min)	19.35±8.64	0.000*
Cumulative requirement of tramadol in 24 h (mg)	123.33±43.01	23.33±43.01	0.000*
NRS at extubation	4.67±1.2	0.47±0.77	0.000*
30 min	1.44±1.88	0.80±1.06	0.148
1 h	0.83±0.88	1.17±0.95	0.301
2 h	1.17±0.74	1.53±0.97	0.189
4 h	1.47±0.50	1.70±0.95	0.504
6 h	1.70±0.59	2.23±1.27	0.663
8 h	1.57±0.62	1.37±0.61	0.599
12 h	1.47±0.73	1.77±0.67	0.234
24 h	1.27±0.45	1.17±0.46	0.631

*Significant *P*<0.05. NRS – Numeric pain rating scale

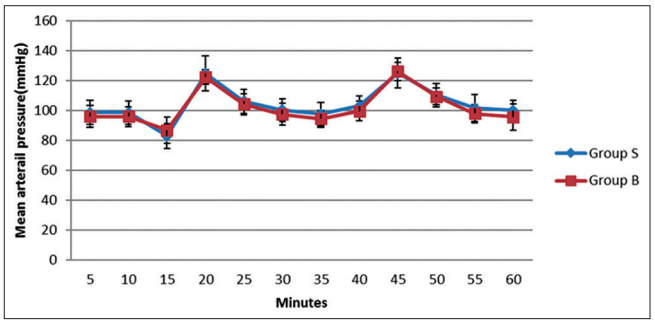

Figure 2: Changes in mean arterial pressure during surgery in both the groups

rescue analgesic over 24 h. In Group B, only one patient required rescue analgesic within half an hour post-operatively. Overall, only seven patients out of 30 required rescue analgesic in 24 h and none required any additional dosage. Reported pain was restricted to the right hypochondrium only.

Incidence of shoulder pain was 20%, while that of nausea and vomiting was 16.66% in both the groups [Table 3] ($P > 0.05$). There were no complications or unintended effects of bupivacaine in the study group.

DISCUSSION

In this study, we found that intraperitoneal instillation of high-volume low-concentration bupivacaine significantly increased DOA and reduced opioid requirement after LC.

Early pain after LC is multifactorial.[2,3] It is a combination of different pain mechanisms: parietal pain is caused by abdominal wall penetration by trocar; visceral pain is due to dissection of gall bladder and tearing of blood vessels, traction on nerves and peritoneal inflammation are caused by raised intra-peritoneal pressure secondary to CO_2 insufflations. While referred pain in the shoulder tip is due to diaphragmatic irritation by residual CO_2.[2,8] Visceral pain is the main contributory factor for abdominal pain after LC.[6] Pain following LC is maximum on the first post-operative day and declines over next 3 to 4 days.[8]

This complex pain can be managed with multimodal and opioid sparing regimen to accelerate post-operative recovery.[9,10] In this study, both the groups received pre-operative fentanyl and diclofenac sodium during surgery as well as post-operatively. In addition, irrigation of peritoneal cavity was done with bupivacaine, during as well as at the end of surgery, in patients of Group B. We believed that diclofenac sodium would treat parietal pain, while bupivacaine would provide visceral analgesia post-operatively. Bupivacaine was selected for irrigating peritoneal cavity as it is an amide type of LA that provides prolonged analgesia.[11]

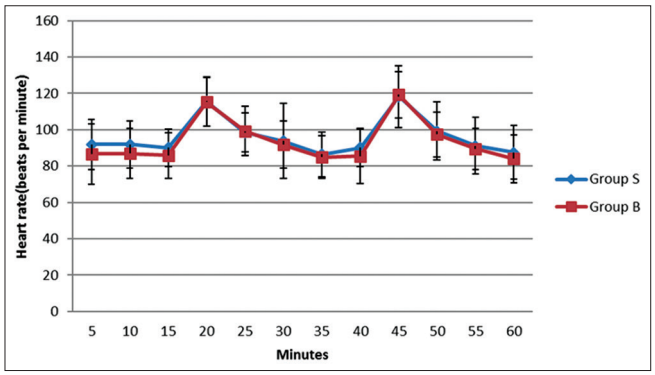

Figure 3: Changes in heart rate during surgery in both the groups

Table 3: Incidence of shoulder pain and nausea/vomiting

Parameters	Group S	Group B	*P*
Shoulder pain	6	6	0.738
Nausea/vomiting	5	5	0.905

Previous studies had used low-volume (20 ml to 100 ml) high-concentration (0.5% to 0.125%) instillation of bupivacaine in gall bladder bed and has been reported to be ineffective[12-14] to short-acting analgesia only.[4-7] The Cochrane review on intraperitoneal instillation of LA concluded that there is very low-quality evidence that this method reduces pain in LC.[15] We believe that was due to the fact that a low volume of LA was not sufficient to cover the entire gall bladder bed nor address all factors causing visceral pain.

High-volume low-concentration bupivacaine (500 ml, 0.02%) used in this study has not previously reported. We believed that the high volume used in this study was able to effectively cover a larger surface area of sub-hepatic space and the surrounding peritoneum, while its continuous use in irrigating fluid during surgery increased the contact period producing longer DOA. Supporting rationale for our choice of high-volume low-concentration bupivacaine solution was a study by Gupta and Hopkins[16] who reported that ED_{50} of bupivacaine is not dependent upon its concentration. While, Nunez *et al*.[17] reported more efficacious sensory block with high-volume low-concentration as compared to low volume high concentration of levobupivacaine in brachial plexus block.

We used 100 mg of bupivacaine in this study, as the range of mean plasma concentration after intraperitoneal administration of 100–150 mg of plain bupivacaine has been reported to be below the toxic concentration of 3 μg/ml.[18]

In this study, NRS score of Group S was significantly higher than Group B immediately after extubation, but the difference was not significant at other time intervals. This occurred because in Group S, all the patients required rescue analgesic within half hour post-operatively. This immediate post-operative administration of rescue analgesic brought down the NRS scores in Group S at subsequent time intervals.

Overall requirement of tramadol on the day of surgery was 100% in Group S and 23% for Group B. Boddy *et al*.[19] and Gupta[20] in a systemic review reported no reduction in analgesic requirement with intraperitoneal instillation of bupivacaine. In both the systemic reviews, the volume of LAs used in different studies varied from 10 ml to 200 ml with concentrations ranging from 0.1% to 0.5%. Since in our study high-volume low-concentration (500 ml, 0.02%) bupivacaine gave long post-operative analgesia, the requirement of tramadol was significantly less in Group B.

There was no significant difference in the incidence of shoulder pain between the groups. Some studies had shown that bupivacaine instillation in peritoneal cavity effectively reduces the shoulder pain,[21] but others have refuted this claim.[22] We had restricted the intraperitoneal pressure to <12 mm Hg, and this has been reported to decrease shoulder pain after LC.[23] Moreover, intensity of shoulder pain has been reported to be highest on the second post-operative day, while our study was limited to initial 24 h post-operatively only.[18]

No significant difference was found in the incidence of nausea and vomiting between the groups. This may be attributed to the use of ondansetron in all the patients.[24] Previous studies have also demonstrated that bupivacaine instillation did not decrease the incidence of nausea and vomiting.[25]

There are certain limitations of our study. We did not study the analgesic effect for dynamic pain and also we did not add low-volume high-concentration group as it would had prevented proper blinding of study.

CONCLUSION

Intraperitoneal irrigation with high-volume low-concentration bupivacaine significantly increases DOA and reduces opioid requirement after LC.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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