

The Effect of Intraperitoneal Ropivacaine for Post-Operative Pain Management in Patients Undergoing Laparoscopic Cholecystectomy: A Prospective Double-Blind Randomized Control Study

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ABSTRACT

Objective: To compare the effect of intraperitoneal ropivacaine with placebo for post-operative pain management in patients undergoing laparoscopic cholecystectomy. **Material and Methods:** All patients were pre-medicated with glycopyrrolate 0.2 mg, ondansetron 4 mg and ranitidine 150 mg intravenously half an hour prior to induction of anesthesia. All patients were given standard general anaesthesia with propofol (2 - 2.5 mg/kg), fentanyl 2 µg/kg, and succinylcholine (2 mg/kg) to facilitate tracheal intubation. Anesthesia was maintained with 60% N₂O in oxygen with 0.5% to 1% Halothane. Group A: Patients received 20 ml of 0.9% normal saline as placebo (n = 25). Group B: Patients received 20 ml of 0.5% ropivacaine (n = 25). **Results:** The age and sex distribution of both the groups was similar. The heart rate, systolic & diastolic blood pressure, mean blood pressure and mean trend of SpO₂ in both groups remained similar over the periods. The mean VAS varied considerably within (between time) and between the groups (treatment) and was especially comparatively higher in Group A at initial hours 15 min to 30 min and at end hours 12 - 24 hrs as compared with Group B. On an average, the frequent dosing of rescue analgesia and mean No. of rescue analgesia doses were higher in Group A followed by Group B. In both groups, the treatment related adverse events were mostly emetic symptoms and shoulder pain with the highest being in Group A. **Conclusion:** We conclude that intraperitoneal instillation of local anaesthetic is an easy, cheap, and non-invasive method which provides good analgesia in the immediate postoperative period after laparoscopic surgery.

Keywords: Intraperitoneal; Bupivacaine; Cholecystectomy; Anaesthetic

1. Introduction

Pain after laparoscopy results from the stretching of the intra-abdominal cavity (Joris *et al.* 1995) [1], peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity. Pain can prolong hospital stay and lead to increased morbidity. Intra-peritoneal injections of local anaesthetic have been proposed to minimize postoperative pain after laparoscopic surgery (Zmora *et al.* 2000) [2]. Several studies have shown that visceral pain is the major component. Local anaesthetics have been administered into the peritoneal cavity during minimally invasive procedures, such as laparoscopic cholecystectomy and gynaecological laparoscopy for sterilization and diagnosis [3] (A. Helvacioğlu *et al.* 1992), in addition to open abdominal pro-

cedures, such as total abdominal hysterectomy. Administration of intra-peritoneal local anaesthetic (LA), either during or after surgery, is used by many as a method of reducing post-operative pain. Although a number of these studies have reported a significant reduction in postoperative pain after the use of intra-peritoneal analgesia, others have reported no benefit. Most of these initial studies have used small doses of bupivacaine or of lidocaine. The main advantage of using local anaesthetics is that they do not have the adverse effects of opioids, which may delay recovery and discharge from hospital. These effects include postoperative nausea, sedation, impairment of return of gastrointestinal mortality, and pruritus. In addition, time to return of bowel function in the postoperative period may be reduced when the use of

opioids is obviated by administering local anaesthetics. Intra-peritoneal ropivacaine nebulization was also used for pain relief after laparoscopic cholecystectomy [4] (M. Bucciero *et al.* 2011). It was found to be effective in reducing shoulder tip pain. Intraperitoneal ropivacaine injected during laparoscopic cholecystectomy significantly decreased post-operative pain when compared with injection of intra-peritoneal placebo [5] (Labaille *et al.* 2002). Local infiltration of 1% ropivacaine combined with preincisional low dose I.V ketamine reduces post-operative pain after laparoscopic cholecystectomy [6] (G. Pappas-Gogos *et al.*, 2008).

In this study, we designed a prospective double-blind randomized control study to compare the effect of intraperitoneal ropivacaine and saline as placebo for post-operative pain management in patients undergoing laparoscopic cholecystectomy.

2. Material and Methods

After getting approval from ethical Committee of King George's Medical University, UP, Lucknow, for research on human subject, written informed consent was taken from each patients selected for this study. Patients aged 20 - 50 years of either sex belonging to ASA physical status I or II planned for laparoscopic cholecystectomy were included in this prospective, randomized, double blind, placebo-controlled study.

All patients were pre-medicated with glycopyrrolate 0.2 mg, ondansetron 4 mg and ranitidine 150 mg intravenously half an hour prior to induction of anesthesia. All patients were given standard general anaesthesia with propofol (2 - 2.5 mg/kg), fentanyl 2 µg/kg, and succinylcholine (2 mg/kg) to facilitate tracheal intubation. Anesthesia was maintained with 60% N₂O in oxygen with 0.5% to 1% Halothane. Muscle relaxation was achieved with intermittent vecuronium bromide. Ventilation (tidal volume 8 - 10 ml/kg) was adjusted to maintain end-tidal carbon dioxide between 34 and 40 mm Hg. Patients were placed in 15° - 20° reverse Trendelenburg's position with left-side down tilting position. During laparoscopy, intra-abdominal pressure was limited to 10 - 12 mmHg. The CO₂ was carefully evacuated at the end of surgery by manual compression of the abdomen with open trocars. At the end of surgery, using a computer generated table of random numbers patients were randomized into one of the three groups.

Group A: Patients received 20 ml of 0.9% normal saline as placebo (n = 25).

Group B: Patients received 20 ml of 0.5% Ropivacaine (n = 25).

Drug solution was prepared by an anaesthesiologist who had not participated in the study, and drug was filled in pre-coded 20 ml syringes. Surgeon and the anaesthesi-

ologist in the post-anaesthesia care unit were unaware of the treatment to which each patient was randomized.

The drug was injected intra-peritoneally before the removal of trocar at the end of the surgery, in Trendelenburg's position to facilitate dispersion of drug solution in sub hepatic region. Local anaesthetic or placebo solutions were given as follows: the surgeon sprayed 10 mL of solution into the hepato-diaphragmatic space, 5 mL in the area of the gallbladder, and 5 mL into the space between liver and kidney. During the operation non-invasive blood pressure, heart rate, EtCO₂ and peripheral oxygen saturation were recorded regularly. Surgical wounds were not infiltrated with local anaesthetic solution.

Before induction of anaesthesia, the patients were instructed how to use a 100 mm visual analogue scale (VAS; with end point to be labelled "no pain" and "worst possible pain"). The degree of postoperative pain was assessed using the VAS at 15 min, 30 min, 1 hr, 2, 4, 8, 12 and 24 hours post-operatively. Those patients had VAS > 40, were administered a bolus of Diclofenac aqueous (75 mg) as rescue analgesia. Ondansetron (4 mg i.v.) was administered on complaint of nausea and vomiting. Time to first analgesic requirement, total analgesic consumption in the first 24 hours postoperatively and occurrence of adverse events was also recorded.

Analysis

Continuous data were summarized as Mean ± SD while discrete (categorical) in %. The primary outcome measures (heart rate, systolic BP, diastolic BP, MBP and SpO₂, EtCO₂, and VAS) of three groups over the periods (time) were compared by repeated measures two factor (Groups and Periods) analysis of variance (ANOVA) using general linear models (GLM) followed by Tukey's post hoc test after ascertaining the normality by Shapiro-Wilk test and the homogeneity of variance by Levene's test. Groups were also compared by unpaired t-test. The discrete (categorical) variables were compared by chi-square (χ^2) test. A two-sided ($\alpha = 2$) $p < 0.05$ was considered statistically significant. All analyses were performed on STATISTICA (Windows Version 6.0).

3. Results

The age of Group A and Group B ranged from 20 - 50 yrs and 20 - 50 yrs, respectively with mean (±SD) 39.80 ± 9.07 yrs and 38.96 ± 9.56 yrs, respectively. In both the groups, the %age of females was higher than males and mostly with ASA grade 1 (**Table 1**).

The heart rate (HR) in both the groups remained similar over the periods with slightly being higher in Group A at intraoperative periods as compared to Group B. For

each time, comparing the mean HR between the groups, Tukey's test revealed significantly higher HR of Group A at intraoperative periods and 30 min of postoperative periods as compared to Group B. SBP and DBP were also remained similar over the periods with slightly being higher in Group B at postoperative periods as compared to Group A. The mean blood pressure (MBP) in both the groups remained similar over the periods in both Group A and Group B. The mean MBP did not differed significantly ($p > 0.05$) between Group A and Group B at all periods *i.e.* found to be statistically the same (**Table 2**).

The mean trend of SpO₂ in both the groups remained

similar over the periods with slightly being higher in Group B at all periods as compared to Group A (**Table 3**). For each time, comparing the mean EtCO₂ between the groups, Tukey's test revealed insignificant ($p > 0.05$) difference in EtCO₂ between the groups at all periods *i.e.* found to be statistically the same (**Figure 1**).

The mean VAS in both the groups varied considerably within (between time) and between the groups (treatment) especially comparatively higher in Group A at initial hours 15 min to 30 min and at end hours 12 - 24 hrs as compared to Group B. Comparing the mean VAS scores of both the groups over the periods, unpaired t-test revealed significant effect of both groups (treatments) ($p < 0.001$) and time (periods) ($p < 0.001$) on pain. The interaction (groups \times time) effect of both on pain was also found to be significant ($p < 0.001$). For each time, comparing the mean VAS between the groups, Tukey's test revealed significantly ($p < 0.001$) higher VAS score in Group A as compared to Group B C at 15 min, 30 min, 12 hrs and 24 hrs (**Figure 2**).

On an average, the frequent dosing of rescue analgesia was higher in Group A than Group B. Further, the requirement in subjects was also higher in Group A (**Table 4**).

Table 1. Basic characteristics of three groups.

Characteristics	Group A (n = 50)	Group C (n = 50)	p-value
Age (yrs):			
Mean \pm SD	39.80 \pm 9.07	38.96 \pm 9.56	0.838
Range (min-max)	(20 - 50)	(20 - 50)	
Sex:			
Males	20 (40%)	20 (40%)	0.73
Females	30 (60%)	30 (60%)	
ASA Physical Status:			
Grade I	36 (72%)	34 (68%)	0.22
Grade II	14 (28%)	16 (32%)	

Table 2. Comparison of heart rate and blood pressure among the three groups.

Time	Heart Rate		Systolic Blood Pressure		Diastolic Blood Pressure		Mean Blood Pressure	
	Group A (n = 50)	Group B (n = 50)	Group A (n = 50)	Group B (n = 50)	Group A (n = 50)	Group B (n = 50)	Group A (n = 50)	Group B (n = 50)
Baseline	83.24 \pm 7.08	77.56 \pm 5.29	121.52 \pm 12.66	119.56 \pm 6.67	77.52 \pm 12.47	76.76 \pm 7.68	90.12 \pm 11.33	87.72 \pm 8.56
Intra-operative								
15 min	83.88 \pm 9.17	79.44 \pm 5.72	124.28 \pm 11.96	119.96 \pm 7.38	79.56 \pm 12.08	78.32 \pm 7.49	88.80 \pm 12.86	88.16 \pm 9.23
30 min	85.40 \pm 8.15	76.72 \pm 6.52	122.96 \pm 11.88	116.96 \pm 6.07	81.00 \pm 10.46	75.92 \pm 7.88	89.68 \pm 12.77	86.56 \pm 9.76
45 min	84.60 \pm 8.87	79.16 \pm 6.12	122.40 \pm 14.32	117.68 \pm 5.54	79.04 \pm 11.92	77.12 \pm 6.25	89.60 \pm 12.80	87.20 \pm 8.73
60 min	85.20 \pm 9.89	78.24 \pm 4.63	123.92 \pm 10.63	117.48 \pm 6.05	81.96 \pm 10.63	75.64 \pm 6.30	90.60 \pm 11.78	87.32 \pm 7.38
75 mi	88.32 \pm 10.78	79.12 \pm 6.31	124.64 \pm 11.71	117.68 \pm 5.44	81.44 \pm 12.52	77.44 \pm 4.87	93.28 \pm 12.20	87.52 \pm 5.90
90 min	84.48 \pm 9.48	80.24 \pm 5.12	121.80 \pm 10.71	121.00 \pm 7.07	80.40 \pm 9.51	79.84 \pm 6.16	89.44 \pm 9.86	90.56 \pm 9.07
Post-operative								
15 min	84.04 \pm 8.35	79.48 \pm 5.99	122.68 \pm 12.10	120.68 \pm 5.76	78.48 \pm 11.15	78.80 \pm 7.62	90.88 \pm 10.84	90.44 \pm 10.94
30 min	86.92 \pm 8.39	79.76 \pm 3.59	124.12 \pm 10.28	118.84 \pm 5.42	79.24 \pm 11.53	78.04 \pm 6.76	91.88 \pm 8.98	87.68 \pm 8.60
1 hr	83.88 \pm 8.95	80.96 \pm 5.07	120.80 \pm 11.76	120.44 \pm 4.71	78.00 \pm 11.59	81.68 \pm 6.12	88.68 \pm 10.18	89.44 \pm 8.09
2 hr	83.32 \pm 8.52	82.12 \pm 5.54	118.92 \pm 9.82	119.88 \pm 5.64	76.08 \pm 11.28	80.52 \pm 4.67	87.20 \pm 9.84	89.88 \pm 7.87
4 hr	83.32 \pm 8.69	83.40 \pm 6.30	121.24 \pm 9.36	122.80 \pm 7.19	80.08 \pm 10.53	82.24 \pm 5.89	90.28 \pm 11.57	93.20 \pm 9.50
8 hr	85.60 \pm 8.99	82.32 \pm 4.31	121.36 \pm 8.72	122.00 \pm 4.25	78.04 \pm 9.62	82.04 \pm 5.98	90.00 \pm 10.12	93.84 \pm 9.37
12 hr	85.80 \pm 7.59	82.76 \pm 5.01	123.24 \pm 9.21	122.60 \pm 5.29	79.84 \pm 9.21	82.68 \pm 4.68	92.36 \pm 10.07	94.48 \pm 9.32
24 hr	85.68 \pm 7.04	86.76 \pm 3.56	124.08 \pm 8.52	122.84 \pm 5.65	80.92 \pm 8.61	82.76 \pm 5.94	92.44 \pm 10.45	94.04 \pm 9.18

Table 3. Comparison of SpO₂ among the three groups.

Time	Group A (n = 50)	Group B (n = 50)
Baseline	99.56 ± 0.65	99.92 ± 0.28
Intra-operative		
15 min	99.52 ± 0.65	99.96 ± 0.20
30 min	99.48 ± 0.77	100.00 ± 0.00
45 min	99.36 ± 0.81	100.00 ± 0.00
60 min	99.56 ± 0.71	100.00 ± 0.00
75 mi	99.28 ± 0.84	99.88 ± 0.33
90 min	99.40 ± 0.87	100.00 ± 0.00
Post-operative		
15 min	99.56 ± 0.51	99.96 ± 0.20
30 min	99.76 ± 0.44	99.96 ± 0.20
1 hr	99.72 ± 0.46	100.00 ± 0.00
2 hr	99.64 ± 0.49	99.96 ± 0.20
4 hr	99.88 ± 0.33	100.00 ± 0.00
8 hr	99.72 ± 0.54	99.96 ± 0.20
12 hr	99.80 ± 0.41	99.96 ± 0.20
24 hr	99.72 ± 0.61	99.92 ± 0.28

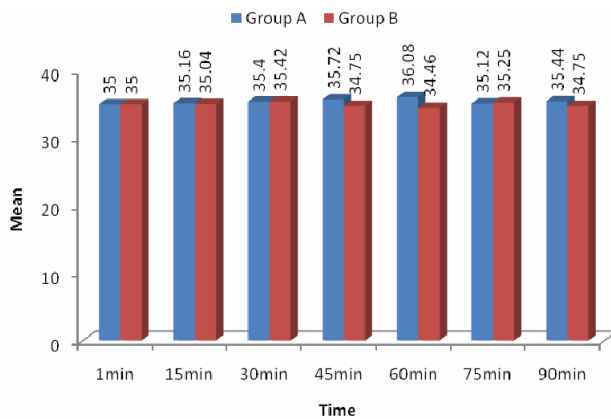


Figure 1. Intra-operative EtCO₂ levels.

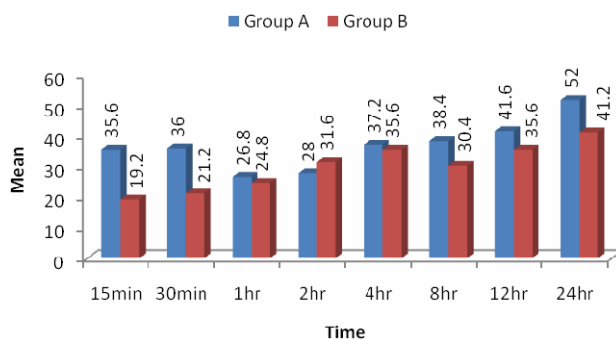


Figure 2. Postoperative pain levels (VAS scores).

The mean no. of rescue analgesia doses of Group A (3.84 ± 0.75) was comparatively higher than Group B (2.72 ± 0.46). Comparing the mean no. of rescue analgesia doses between the groups, unpaired t-test revealed significantly different no. of rescue analgesia doses both the groups (p < 0.001). Further, Tukey test revealed significantly (p < 0.001) higher mean no. of rescue analgesia doses in Group A as compared to Group B (Table not shown).

In both the three groups, the treatment related adverse events were mostly emetic symptoms and shoulder pain with highest being in Group A. However, hypotension, bradycardia and sedation were not seen. The frequency of emetic symptoms ($\chi^2 = 12.32$, p = 0.002) and shoulder pain ($\chi^2 = 29.55$, p < 0.0001) were significantly higher in Group A as compared to Group B (Table 5).

4. Discussion

Postoperative pain is multifactorial in origin, and therefore, multimodal therapy may be needed to optimize pain relief. After laparoscopic cholecystectomy, patients complain of pain from the incision of the skin (somatic pain), of visceral pain, and of shoulder pain from diaphragm stimulation. Incisional pain is defined as superficial pain, wound pain, or pain located in the abdominal wall. Visceral pain is defined as pain inside the abdomen, which may be deep, dull, and more difficult to localize, and may

Table 4. Comparison of Rescue analgesia time among groups.

Rescue analgesia at time (min)	Group A (n = 50)	Group B (n = 50)
1ST DOSE	24.60 ± 10.50 (50)	264.00 ± 120.00 (50)
2ND DOSE	345.60 ± 156.15 (50)	902.40 ± 348.34 (50)
3RD DOSE	912.00 ± 415.69 (50)	1440.00 ± 0.00 (36)
4TH DOSE	1215.00 ± 344.67 (32)	NIL
5TH DOSE	1440.00 ± 0.00 (10)	NIL

Numbers in parenthesis indicates no. of subjects.

Table 5. Adverse events summary of three groups.

Complications	Group A (n = 50)	Group B (n = 50)	p-value
Pruritus	2 (4%)	0 (0.0)	0.36
Emetic symptoms	34 (68%)	18 (36%)	0.002*
Hypotension	0 (0.0%)	0 (0.0)	NA
Bradycardia	0 (0.0%)	0 (0.0)	NA
Shoulder pain	46 (92%)	22 (44%)	p < 0.0001*
Sedation	0 (0.0%)	0 (0.0%)	NA

*Significant, NA: not applicable.

resemble biliary colic. Shoulder pain is defined as a sensation of pain in the shoulder. Rapid distension of the peritoneum by CO₂ insufflation results in tearing of blood vessels, traction of nerves, and release of inflammatory mediators producing visceral pain; inflammation or local irritation around the gallbladder bed, liver, diaphragm or peritoneum, or both, secondary to gallbladder removal and abdominal muscle distension add to tissue injury and produce visceral pain. The exact mechanism of shoulder pain after laparoscopic surgery still remains unclear. Shoulder pain results from peritoneal insufflation especially when an exaggerated Trendelenburg position is used. Most authors believe it is an irritation of the phrenic nerve causing referred pain of C4 projected to the shoulder.

Improved postoperative pain management using opioid-sparing regimens may facilitate a high success rate of out patient laparoscopic cholecystectomy [7] (Bisgaard *et al.*, 1999). Various techniques have been investigated to reduce shoulder pain. Local anaesthetic techniques are part of the multimodal approach to postoperative pain management [8] (Alkhamesi *et al.*, 2007). The main advantage of using local anaesthetics is that they do not have the adverse effects of opioids, which may delay recovery and discharge from hospital. These effects include postoperative nausea, sedation [9] (Papagiannopoulou *et al.*, 2003), impairment of return of gastrointestinal motility, and pruritus. In addition, time to return of bowel function in the postoperative period may be reduced when the use of opioids is obviated by administering local anaesthetics.

The present study showed that visceral pain accounts for most of the discomfort experienced in the early postoperative period after laparoscopic cholecystectomy in Placebo group. Visceral pain developed after laparoscopic cholecystectomy was not affected by mobilization. However, coughing increased its intensity. This can be explained by that, mobilization requires contraction of the abdominal muscles, and does not involve movement of the intra-abdominal viscera. On the other hand, cough produces an abrupt displacement of the liver, and consequently results in stimulation of the inflamed cholecystectomy wound. Also, our results showed that incisional pain is less intense than visceral pain and worsened only by coughing not by mobilization. This can be explained by that cough not mobilization causes intense abdominal muscle contraction. The postoperative pain induced by laparoscopic cholecystectomy has a considerable visceral component (owing to surgical handling and diaphragmatic irritation by dissolved carbondioxide). At times the visceral component is such that it results in shoulder pain, similar in location and type to the pain that occurs with biliary colic. Incisional pain is less intense than visceral

pain, owing to the small abdominal incisions made in the abdominal wall for the trocars and the limited damage to the abdominal wall.

Our study demonstrates the intra-peritoneal instillation of ropivacaine reduces pain after LC significantly. It shows reduced incidence of both shoulder pain and postoperative nausea and vomiting. The total analgesic consumption was reduced significantly as compared to placebo. VAS scores were lower in group B (ropivacaine) than group A (placebo) during the overall estimated time and as well as the interval times of estimation. During the study, none of the patients were excluded from the study because of uncontrolled pain or undesirable surgical outcomes such as delayed bowel movements and patient intolerance.

Pain is a highly personal experience which is whatever the experiencing person expresses and exist whenever the person appeals. The ambiguity of pain lies in that it is a subjective sensation or emotion and thorough objective observation of such is difficult. Because VAS scores are estimated by patients the accurate measurement is limited and objective estimation of pain could be deleterious. In the study of [10] Gupta *et al.* (2002), intermittent injections of 0.5% ropivacaine through a catheter reduced early postoperative pain after laparoscopic cholecystectomy. In our study the same concentration of intraperitoneal ropivacaine reduced pain significantly after LC. In the study of Labaille *et al.* (2002) [5], thirty seven ASA physical status I or II patients received in double-blinded fashion 20 mL of 0.9% saline solution (placebo), ropivacaine 0.25% (Rop 0.25%), or ropivacaine 0.75% (Rop 0.75%) immediately after trocar placement and at the end of surgery. They observed visceral pain at rest, during cough, and on movement and total consumption of morphine were significantly smaller in Groups Rop 0.25% and Rop 0.75% when compared with Placebo. Similar findings were also reported in other studies [11-14] (Goldstein *et al.*, 2000; Jian-Zhu *et al.*, 2009; Ljiljana *et al.*, 2011; Mohamed *et al.*, 2006). Similarly, in our study intraperitoneal ropivacaine reduced the pain after laparoscopic surgery as compared to placebo.

The findings of the present study reveal that intraperitoneal ropivacaine administered after surgery pre-emptly postoperative pain relative to an untreated placebo controlled group. This is similar to the study by Pasqualucci A *et al.* (1996) [15]. Kucuk *et al.* (2007) [16] compared the effect of intraperitoneal ropivacaine (150 mg) in patients undergoing a laparoscopic cholecystectomy. They found that for preventing postoperative pain 150 mg ropivacaine proved to be significantly more effective than placebo group. Almost similar findings were seen in the present study.

5. Conclusion

We conclude that intraperitoneal instillation of local anesthetic is an easy, cheap, and non-invasive method which provides good analgesia in the immediate postoperative period after laparoscopic surgery.

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