Comparative Study of Preclosure Periportal Instillation of Three Different Concentrations of Ropivacaine (0.125%, 0.25%, 0.5%) for Postoperative Analgesia in Laparoscopic Cholecystectomy

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ABSTRACT

Introduction: Multimodal analgesia is currently recommended for postoperative pain control in laparoscopic surgeries. Our study aimed at comparing the postoperative analgesic efficacy of three different concentrations of Ropivacaine when instilled periportally just before closure in laparoscopic cholecystectomy.

Material and methods: 200 patients posted for laparoscopic cholecystectomy were randomly allocated into four groups of 50 patients each. Three groups received preclosure periportal instillation of 20 ml Ropivacaine 0.125%, 0.25% and 0.5% respectively whereas the fourth group received 20 ml normal saline. Pain was recorded on visual analog scale at frequent intervals for 24 hours postoperatively and categorised as either mild, moderate or severe. Tramadol 1mg/Kg was administered as rescue analgesic in patients with moderate to severe pain.

Results: A statistically significant difference was found among the four groups with the number of patients experiencing mild and moderate pain with *P* values of 0.009 and 0.02 respectively. The number of patients experiencing mild and moderate pain was significantly less with Ropivacaine 0.5% when compared with Ropivacaine 0.125% (P=0.01 and 0.03), Ropivacaine 0.25% (P=0.002 and 0.03) and normal saline (P=0.02 and 0.0007). The number of patients requiring rescue analgesia at various time intervals was also significantly less with Ropivacaine 0.5% when compared to the other groups (P<0.05).

Conclusion: Ropivacaine 0.5% when administered as preclosure periportal instillation in laparoscopic cholecystectomy, provided better postoperative analgesia and significantly less requirement of rescue analgesia, as compared to equivalent volumes of Ropivacaine in lower concentrations of 0.25% and 0.125% which were no better than normal saline.

Keywords: Ropivacaine; Periportal instillation, Laparoscopic Cholecystectomy

INTRODUCTION

Postoperative pain is not completely abolished after laparoscopy as patients frequently describe subdiaphragmatic and shoulder tip pain in addition to the discomfort of port site incisions.[1,2] Some clinicians maintain that the placement of trocars through the abdominal wall is the primary source, whereas others believe that most pain arises from intraperitoneal dissection.[3] Variable analgesic effects of periportal infiltration of local anesthetics, intraperitoneal spraying above the gall bladder, and instillation into the subdiaphragmatic space and into the subhepatic space covering the area of the hepatoduodenal ligament have been reported.[4] Multimodal analgesia is currently recommended for effective postoperative pain control. A multimodal combination of regional anesthetic techniques and systemic administration of anesthetic agents results in better pain control.

Local anesthetics have been injected subcutaneously into the incisional site, into the periportal fascia, and into the muscle and parietal peritoneum to provide pain relief in laparoscopic surgery. The injection of local anesthetic at the incision site blocks Aδ and C fibers and prevents the transmission of pain impulses from the surgical site to the brain.[7] Local anesthetic can be injected into the peritoneum through the ports created either before the start of surgery or prior to closure. It may be injected over the visceral peritoneum through the trocar site or into the surgical bed after the excision of the organ or under the diaphragm. The reason for the injection of sub-diaphragmatic local anesthetic is to decrease the incidence of shoulder pain. Most of the studies have used longer acting local anesthetics like bupivacaine[5], ropivacaine[6] and levobupivacaine[7,8] to provide pain relief. The doses and concentrations used were also variable.

Ropivacaine is a long acting regional anesthetic that is structurally related to bupivacaine. As well as having less cardiotoxicity, there is evidence that any such effect occurring after inadvertent intravascular injection of Ropivacaine may be more easily reversed than is the case with Bupivacaine.[10,11,12] Ropivacaine may be used for infiltration or instillation. Onset of action is almost immediate after intradermal or subcutaneous administration; however, the duration of anesthesia varies. Hence present study was conducted to assess the analgesic efficacy of Ropivacaine when instilled periportally in different concentrations after

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How to cite this article: Prashant Sharma, Amit Gupta. Comparative study of preclosure periportal instillation of three different concentrations of ropivacaine (0.125%, 0.25%, 0.5%) for postoperative analgesia in laparoscopic cholecystectomy. International Journal of Contemporary Medical Research 2020;7(2):B16-B21.

DOI: http://dx.doi.org/10.21276/ijcmr.2020.7.2.46

laparoscopic cholecystectomy.

MATERIAL AND METHODS

The study was a prospective, double blinded, randomized, placebo controlled study conducted in the Department of Anesthesia and Critical Care, Tata Main Hospital, Jamshedpur. Approval by the ethics committee of Tata Main Hospital and written informed consent of all patients was obtained to conduct the study. 200 patients of either sex aged between 18 and 60 years belonging to ASA grades I and II physical status scheduled for elective laparoscopic cholecystectomy were included in the study. Patients with difficulty in communication, patients allergic to study drug, hemodynamically unstable patients, pregnant patients, patients with chronic pain syndrome, patients in whom conversion to open cholecystectomy was done for any reason, were excluded from the study.

The patients were explained in detail about the visual analog scale for pain on the day before surgery. Premedication with tablet metoclopramide 10 mg and tablet ranitidine 150 mg was given on the evening before and on the morning of surgery. The patients were given fasting orders with no solid food from 8 hours prior to surgery and no clear fluids from 2 hours prior to surgery. In the operating room, the WHO surgical safety checklist drill as per the existing hospital protocol was carried out. Monitors for standard monitoring were attached (NIBP, ECG, Respiration, SpO2). Baseline vital parameters such as heart rate, blood pressure, saturation were noted. Intravenous access was established with an 18/20-G intravenous canula on the dorsum of the non dominant hand. The patients were prooxygenated with 100% oxygen in the supine position for three minutes and then Fentanyl 2 µg/Kg was given intravenously. Propofol 2 mg/kg at room temperature was administered through the intravenous cannula and titrated to effect. Vecuronium 0.1 mg/kg intravenous injection was used for muscle relaxation to facilitate tracheal intubation. Under direct laryngoscopic vision, intubation was performed, endotracheal tube was secured and its position confirmed with $ETCO_2$ monitoring and fixed.

Proper positioning for laparoscopic surgery was given. During laparoscopy, intraabdominal pressure was monitored and maintained below 15 mmHg. The mechanical ventilation was set to maintain the $ETCO_2$ between 32 and 40 mmHg depending on the different stages of laparoscopy. Anesthesia was maintained with isoflurane 1% and 66% nitrous oxide with oxygen on controlled ventilation with intermittent bolus of vecuronium in a dose of 0.01 mg/Kg. Repeat dose of fentanyl was given in the dose of 1 µg/Kg after 40 minutes of the start of surgery. All patients received ondansetron 0.1 mg per kg intravenously intraoperatively. Before the start of port closure, the insufflated gas used for pneumoperitoneum was expelled through the port site.

At the time of start of closure of the laparoscopic ports, the surgeon instilled the allocated drug to the patient at all the four ports. The drug allocated to the patient was according to a randomization list generated by random number function using the Microsoft Excel 2003 spreadsheet, resulting in a list of 200 assigned to participants receiving the drugs. They were randomly allocated to four groups of 50 patients each as follows:

Group (A): 50 patients received instillation of 20 ml 0.125% ropivacaine at periportal site before port closure.

Group (B): 50 patients received instillation of 20 ml 0.25% ropivacaine at periportal site before port closure.

Group(C): 50 patients received instillation of 20 ml 0.5% ropivacaine at periportal site before port closure.

Group(D): 50 patients received instillation of 20 ml normal saline at periportal site before port closure.

At the end of surgery, inhalational agents were discontinued and neuromuscular blockade was reversed with injection neostigmine 40 µg/kg and injection atropine 20 µg/kg intravenously. Extubation was done when the patient met the extubation criteria. Immediately after tracheal extubation, 100% oxygen was given via face mask for 5 minutes. After extubation all patients received analgesics to a standard post-operative protocol with diclofenac 75 mg intramuscularly after which they were shifted to the recovery area.

The parameters observed in our study were pulse, blood pressure, respiratory rate, Spo2, pain at the surgical site on visual analog scale (ranging from 0 to 10), sedation score on Ramsay sedation scale, PONV score on PONV impact scale, and the need for rescue analgesic. These parameters were noted at 1st and 2nd hours after extubation in the recovery area by an anesthesiologist not involved in the study. Thereafter they were noted at 3rd, 4th, 8th, 12th, 18th and 24th hour post extubation by the doctor on duty in the high dependency unit (HDU) where the patients had been shifted from the recovery area. Depending on the VAS score the pain experienced by the patient at the surgical site was categorized as either mild (0-3), moderate (4-6) or severe (7-10). Rescue analgesia in the form of Tramadol 1 mg per kg was administered if the pain was moderate to severe (VAS score ≥ 4) at the above mentioned time intervals.

STATISTICAL ANALYSIS

All data were calculated as mean, standard deviation and proportions and percentages. Chi-square test was used to test significance of proportions of age, sex, ASA classification, BMI and VAS. Analysis of variance (ANOVA) was used for comparing weight, height, heart rate, systolic blood pressure, diastolic blood pressure and SpO2. "P" value was calculated by obtaining the "$\chi 2$" value and "df" from the standard statistical table. A '*P*
value < 0.05 was taken as significant.

RESULTS

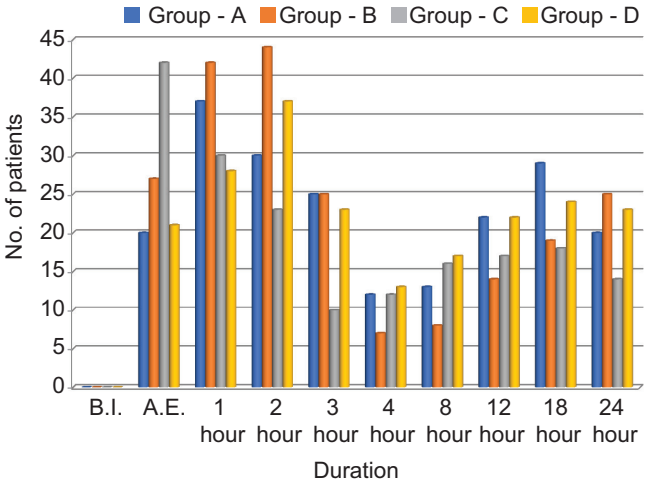
The patients in our study were comparable on the based on their age, sex, weight, height, BMI, ASA physical status classification and duration of surgery with no statistically significant difference among the four groups ($P > 0.05$ }. Changes in heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, Spo2, sedation and PONV scores at various time intervals were also statistically not

VAS	Mild (0-3)				Moderate (4-6)				Severe (7-10)			
Group	A	B	C	D	A	B	C	D	A	B	C	D
B.I.	0	0	0	0	0	0	0	0	0	0	0	0
A.E.	20	27	42	21	29	22	2	22	1	1	0	1
1 hour	37	42	30	28	13	8	2	22	0	0	0	0
2 hour	30	44	23	37	5	2	0	7	0	0	0	0
3 hour	25	25	10	23	4	2	3	6	0	0	0	0
4 hour	12	7	12	13	8	3	0	3	0	0	0	0
8 hour	13	8	16	17	8	6	5	2	0	0	0	0
12 hour	22	14	17	22	10	6	5	10	0	0	0	0
18 hour	29	19	18	24	4	4	0	9	0	0	0	0
24 hour	20	25	14	23	1	0	0	0	0	0	0	0

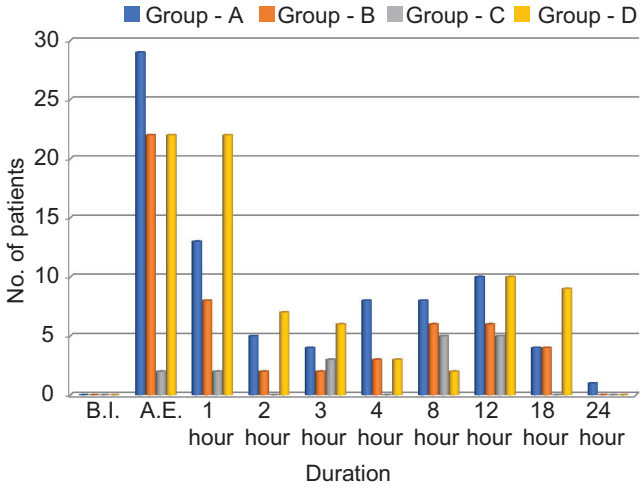
Table-1: No. of patients with mild, moderate and severe pain among all groups

Time	Group - A	Group - B	Group – C	Group – D
B.I.	0	0	0	0
A.E.	30	23	2	23
1 hour	13	8	2	22
2 hour	5	2	0	7
3 hour	4	2	3	6
4 hour	8	3	0	3
8 hour	8	6	5	2
12 hour	10	6	5	10
18 hour	4	4	0	9
24 hour	1	0	0	0

Table-2 : Requirement of Rescue Analgesia at various time intervals



Graph-1: Comparison of number of patients with mild pain among all groups



Graph-2: Comparison of number of patients with moderate pain among all groups

significant (P> 0.05). The number of patients experiencing mild, moderate and severe pain at various time intervals is mentioned in Table-1, graph-1. There was a statistically significant difference among the four groups with respect to the number of patients experiencing mild and moderate pain with P values of 0.009 and 0.02 respectively. The number of patients experiencing mild pain was significantly less in Group C when compared with Group A (P=0.01), Group B (P=0.002) and Group D (P=0.02). The number of patients experiencing moderate pain was significantly less in Group C when compared with Group A (P = 0.03), Group B (P = 0.03) and Group D (P=0.0007). None of the patients in Group C experienced severe pain any time interval. One patient each in Group A, Group B and Group D complained of severe pain immediately after extubation. No statistically significant difference (P > 0.05) was found with the incidence of severe pain between Group A and Group B (P=0.47), between Group B and Group D (P=0.47) and between Group A and Group D (P=0.47). No statistical test was applicable to compare the incidence of severe pain between Group C and

other groups as none of the patients in Group C complained of severe pain. The number of patients requiring rescue analgesia at various time intervals is mentioned in Table-2, graph-2. On comparison of Group C with Groups A, B and D, there were significantly less number of patients requiring rescue analgesia with *P* values of 0.03, 0.02 and 0.0006 respectively.

DISCUSSION

Postoperative pain management aims not only to decrease pain intensity but also to increase patient comfort and to improve postoperative outcome. Other advantages include earlier mobilization, fewer pulmonary and cardiac complications and reduced risk of deep vein thrombosis.[13,14] Multimodal analgesia is currently recommended for effective postoperative pain control. It is achieved by combining different analgesics that act by different mechanisms (e.g. opioids, nonsteroidal anti-inflammatory drugs, local anesthetics etc.), resulting in additive pain relief, lowering the total dose of analgesics, and fewer side effects.[13,14] Ropivacaine is a new aminoamide local anesthetic and is unique amongst this group in that it is prepared for clinical use as a pure s-enantiomer rather than a racemic mixture.[15] When ropivacaine was first developed, bupivacaine was chosen to be marketed as a long acting local anesthetic, its advantages compared to lignocaine being longer duration of block and differential sensory-motor block. However, with time, a number of deaths from cardiac arrest were reported in association with regional anesthesia using bupivacaine.[15] DB Scott et al[16] conducted a randomized double blind study to compare the acute toxicity of ropivacaine compared with that of bupivacaine. The study concluded that ropivacaine is a less toxic drug than bupivacaine with regard to the production of CNS and CVS toxicity by intravenous infusion.[19] Ropivacaine is a less hazardous drug if overdose or accidental intravenous injection occurs.[17] It has a lower cardiotoxic potential and a more rapid clearance[17] and is commercial available in India. So ropivacaine was chosen for our study.

Local anesthetic administration techniques available to prevent pain after laparoscopic surgery include incisional[5-9], intraperitoneal[18-27], and a combination of incisional and intraperitoneal local anesthetic.[28-32] Both 0.5% and 0.75% ropivacaine provide adequate analgesia for wound infiltration[33] and studies have been done to test the efficacy of lower doses of ropivacaine. Liang et al.[34] compared the effect of flubiprofen combined with different concentrations of ropivacaine (0.25% and 0.5%) infiltration on postoperative analgesia after laparoscopic cholecystectomy where they concluded that compared with 0.25% ropivacaine, 0.5% ropivacaine infiltration combined with intravenous flubiprofen has better and longer analgesic effects. The study by Thue Bisgaard et al.[35] has shown that the incisional site pain dominates over other pain components in laparoscopic surgeries. Ropivacaine has been effective in controlling postoperative pain in laparoscopic surgeries when instilled intraperitoneally or infiltrated locally at the incisional sites.[36] However no study had been done to establish the effectiveness of periportal instillation of ropivacaine for postoperative pain relief after laparoscopic surgeries.

The degree of nerve blockade depends on the local anesthetic concentration and volume. A minimal concentration of a local anesthetic is necessary to effect complete nerve blockade. It reflects the potency of the local anesthetic and the intrinsic conduction properties of nerve fibers, which in turn likely depend on the drug's binding affinity to the ion channels and degree of drug saturation necessary to halt the transmission of action potentials.[37] Reducing the total dose of a local anesthetic without reducing the analgesic efficacy is beneficial to reduce the risk of toxicity. Dose can be reduced by either lowering the concentration or volume of the local anesthetic.[37] The present study compared patients with similar demographic profile, type and duration of surgery and revealed that when equal volumes of different concentrations of Ropivacaine was used in the form of preclosure periportal instillation in laparoscopic cholecystectomy, only a concentration of Ropivacaine 0.5% was able to achieve satisfactory postoperative analgesia and reduced the need for rescue analgesics. Lower concentrations of Ropivacaine (0.25% and 0.125%) were not effective in providing adequate postoperative analgesia and were no more effective than normal saline.

CONCLUSION

The present study concludes that preclosure periportal instillation with Ropivacaine 0.5% resulted in a significant decrease in postoperative pain following laparoscopic cholecystectomy. Periportal instillation with ropivacaine 0.25% or ropivacaine 0.125% did not result in any significant reduction in postoperative pain compared with Ropivacaine 0.5% and were no better than normal saline for alleviation of pain after laparoscopic cholecystectomy. No adverse effects were observed in any patient in any of our groups. Therefore it may be concluded from this study that preclosure periportal instillation with Ropivacaine 0.5%, as a part of multimodal analgesia, is safe and effective in alleviating pain following laparoscopic cholecystectomy.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 20-01-2020; **Accepted:** 01-02-2020; **Published:** 29-02-2020