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Original Research Article

To assess the role of multisite instillation of bupivacaine-xylocaine combination for reducing post-operative pain after elective laparoscopic cholecystectomy

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ABSTRACT

Background: Pain following laparoscopic surgery is multifactorial, arising from trocar sites (somatic pain), operative site (visceral pain) and shoulder pain (referred from diaphragmatic irritation because of pneumo-peritoneum). Currently no standard of care exists to reduce post-operative pain by use of local analgesia in laparoscopic cholecystectomy. Despite many studies, there are contradictory results. Aim of the study was to assess whether instillation of local anaesthetics at trocar sites and intraperitoneally, reduces the amount of pain experienced in the immediate postoperative period after laparoscopic cholecystectomy.
Methods: This prospective study was carried out in the Department of General Surgery in a tertiary medical Centre in Mumbai. 75 subjects were randomized into 2 groups. Group A consisting of 38 patients were subjected to multisite instillation of LA combination (bupivacaine+xylocaine) at trocar site, gall bladder fossa, sub diaphragmatic space. Group B, (control group) consisting of 37 patients was given no such LA. Post operatively, pain was assessed by VAS scale (0-100) at 1,4,24 hours. Both the groups were compared and analysed.
Results: Group A showed significantly reduced pain scores at 1, 4 and 24 hours post operatively as compared to group B.
Conclusions: Our results indicate that multisite infiltration of local anesthetic combination (bupivacaine+xylocaine) after laparoscopic cholecystectomy surgery significantly reduces pain at 1, 4 and 24 hours postoperatively.

Keywords: Bupivacaine, Laparoscopic cholecystectomy, Multisite instillation, Postoperative pain, Xylocaine

INTRODUCTION

Laparoscopic techniques have evolved rapidly over the last two decades. This mode of access offers patients the benefits of quick recovery and early return to normal activities, compared with the traditional laparotomy approach. In spite of advancements, pain is often the main factor that hinders return to normal activities. Pain following laparoscopic surgery is multifactorial, arising from trocar sites (somatic pain), operative site (visceral pain), and shoulder pain (referred from diaphragmatic irritation because of pneumo-peritoneum). Currently no standard of care exists regarding the use of local analgesia in laparoscopic surgeries. Previous clinical trials have shown controversial results with intraperitoneal and trocar site analgesia after cholecystectomy in minimizing postoperative pain.[1,2] The site of local anaesthetic instillation, timing of administration, differences in local anaesthetic dosages, and non-homogeneous delivery of analgesic solutions within the abdominal cavity all may contribute to inconsistent results. Aim of the study was to assess

whether instillation of local anaesthetics at trocar sites and intraperitoneally, reduces the amount of pain experienced in the immediate postoperative period after laparoscopic cholecystectomy.

METHODS

A prospective randomised study of 80 cases of electively operated laparoscopic cholecystectomies from March 2015 to April 2016. This is a single-centre, randomized, study. All patients provided verbal and written informed consent.

Inclusion criteria

- Age 18- 60 years
- ASA status I-III
- Elective laparoscopic cholecystectomy Indication of symptomatic gallstone disease
- Patients with cholecystitis (acute/chronic)
- Patients with biliary pancreatitis
- Patients with choledocholithiasis (after CBD clearance by ERCP and stenting).

Exclusion criteria

- Pregnant females
- Lactating mothers
- Allergic to LA.

Written and oral informed consent regarding the intervention and surgery were duly taken and confirmed by the co-investigator on the day before surgery. Patients were randomly assigned by a co-investigator using simple randomization procedures (computerized random numbers) to 1 of 2 treatment groups. Group A consisted of 40 subjects and they received a test dose of local anaesthetic (bupivacaine and xylocaine) (0.5 cc, anterior aspect of forearm) on the day before surgery to check for allergic reactions.

A standard 4 port laparoscopic cholecystectomy was conducted on both groups with placement of ports as shown (Figure 1) in all patients. Pneumoperitoneum was achieved using non-humidified, non-heated carbon dioxide at a pressure of 12 to 14 mmHg and flow of 7-10 L/min.

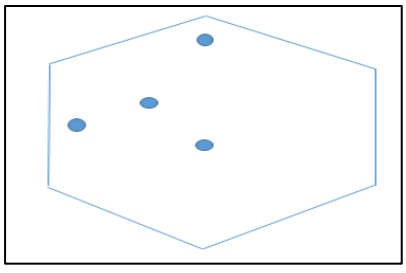

Figure 1: Laparoscopic cholecystectomy port placement.

Operating room temperature was 20°C. Duration of surgery ranged from 45 min to 130 minutes. Closure of the ports was done using absorbable braided coated polyglactin 910 violet (No.0 vicryl port closure, 70 cm, 23 mm, ½ circle heavy reverse cutting, VP2825) suture material. Skin closure was done either by using skin stapplers or by subcuticular stitches using 3-0 polyglecaprone 25 suture (3-0 monocryl, 26 mm, 3/8 circle, 70 cm, MCP3326).

A standardized general anaesthetic technique was used in all patients. Patients received 2 mg of iv fentanyl as premedication. Induction of anaesthesia was performed using 3 to 4 mg/kg propofol administered intravenously, and tracheal intubation was facilitated using (1mg/kg) rocuronium. Anesthesia was maintained using 1.5% to 2.5% sevoflurane, with end-tidal concentration titrated to maintain entropy values between 45 and 60.

Fentanyl, 1 to 2 mg/kg, was administered to maintain mean arterial blood pressure and heart rate within 30% of baseline values. Ventilation was controlled to maintain end-tidal carbon dioxide values between 35 and 40 mmHg. At the end of surgery, residual muscle paralysis was (neostigmine 2.4 mg and glycopyrolate 0.5mg), and tracheal extubation was performed.

Group A patients received infiltration of local anaesthetic combination (7 cc bupivacaine and 8 cc lignocaine) at all 4 port sites before incision by the inside-out technique (thus anesthetising all preperitoneal layers). During the surgery local anesthetic combination (20 cc) was instilled in gall bladder fossa and subphrenic area after removal of gall bladder using laparoscopic needle. Group B patients were not given local anesthetic drug.

Prophylaxis for postoperative nausea and vomiting included 4 mg IV/oral ondansetron for 1-3 days. Prophylaxis of postoperative pain included administration of 15 mg/kg IV paracetamol for 1-3 days.

Postoperative pain was assessed in all patients of group A and B. Pain intensity at 1, 4 and 24 hours after surgery was measured using a visual analogue scale (0-100) at rest, where 0 represented no pain and 100 the worst possible pain. 3 sites of pain were assessed - visceral pain in abdomen, somatic pain at port sites and referred pain to shoulder.

Data collected also included patient's age, sex, weight; diagnosis; duration of surgery, signs of local anaesthetic toxicity (e.g. intraoperative arrhythmias, unexplained hypotension and unexplained delayed awakening).

Statistical analysis

The planned study consisted of VAS data from independent control and experimental subjects, with 1 control per experimental subject. About 33 to 38 experimental and control subjects in each group would be

needed to reject the null hypothesis that pain intensity after surgery in patients receiving local anaesthetic and no intervention are equal, with a power of 0.9 and type I error of 0.05 (2-sided) (PS power and sample size calculations version 3.0, January 2009). 40 patients were enrolled in each group to allow for protocol violations. Continuous variables are given as mean (SD). All data were entered into excel database and converted to a SAS file (SAS/STAT user's guide, version 6: SAS Institute Inc, Cary, NC) for statistical analysis.

Ordinal and categorical data were compared using the chi square test or the chi-square test for trend. The Mantel-Haenzel test was used to compare groups stratifying on quartiles of morning VAS scores, to control for group differences in the morning scores. The Wilcoxan or Kruskal-Wallis test was used to compare continuous variables. Differences were considered significant at $P < 0.05$.

Logistic regression analysis was used to study the connection between use of additional analgesia and VAS scores, the fit being tested by chi-square goodness-of-fit criteria.

Estimates of probability of requesting additional analgesia at specified VAS values were obtained from the fitted logistic regression model as $p = inv (1 + e-(a+bx))$, where a is the value of the fitted intercept, b the slope, and x the VAS measurement. Because the present study evaluated the effect of multi-site instillation of local anaesthetic on pain intensity after laparoscopic cholecystectomy surgery, in case of conversion to open (laparotomy) surgery, 5 patients were excluded from the analysis of the main end point.

For safety analysis, these patients received the same follow-up evaluations in their general ward until their hospital discharge.

RESULTS

Demographic characteristics

Of the total of 91 patients assessed for eligibility in the study, 11 ones were excluded. 7 patients did not meet inclusive criteria and 4 patients declined to participate. Then 80 patients were recruited into the study, with 75 included in the final data analysis. There were no significant differences among the two groups with regard to age, gender, weight, ASA physical status, duration of surgery and temperature of OR (Table 1).

Table 1: Demographic data of 75 patients who underwent laparoscopic cholecystectomy.

Characteristics	Group A (n = 38)	Group B (n = 37)	P-value
Age (year)	42.9 (14.2)	46.4 (10.6)	0.7338
Gender (M/F)	23/25	21/26	0.5679
Weight (kg)	54.3 (15.8)	53.5 (13.1)	0.8312
ASA (I/II)	32/16	34/13	0.9052
Duration of surgery (min)	25.1 (9.6)	21.2 (7.6)	0.7724

Group A- Study group; Group B- Control group; M, male; F, female; ASA, American Society of Anaesthesiologists; Data are expressed as means (SD) or the number of patients.

VAS score

With an increase in time following surgery, the pain in each group gradually declined. At every evaluation 1, 4, 24 hours after the surgery, patients in the group B reported higher pain scores compared with those in the Group A (Table 2). No patients exhibited signs of local anesthetic toxicity during or after surgery.

Table 2: Postoperative pain and analgesic requirement in 75 patients after laparoscopic cholecystectomy with the help of VAS score after laparoscopic cholecystectomy.

	Group I			Group II		
	1 Hour	4 hours	24 hours	1 hour	4 hours	24 hours
Mild pain	30	27	28	5	17	25
Moderate pain	8	11	10	32	20	12
Severe pain	-	-	-	-	-	-
No. of injection diclofenac	8	11	10	32	20	12
No. of injection tramadol	-	1	-	-	15	3

Group I- Study group; Group II- Control group.

At 1 hour, 8 patients from group I and 32 from group II had moderate pain; an intramuscular injection of diclofenac 50 mg was administered to the patients having moderate pain and no injection was administered to those with mild pain. Injection tramadol was not administered to any patient (Table 2). At 4 hours 11 patients from group I and 20 patients from group II had moderate pain. Injection diclofenac was administered to 10 patients in group I and intravenous injection tramadol and diclofenac to 1 patient who had previously received injection diclofenac. Diclofenac injection was administered to 20 patients in group II; among them, 15 patients had persistent pain, who were later administered with tramadol injection. At 24 hours, 10 patients from group I

and 12 from Group II had moderate pain, who received injection diclofenac. Patients in group II had adjuvant analgesia with injection tramadol on persistence of pain (Table 2).

Total number of injection diclofenac administered in first 24 hours after extubation in group I was 29, and that in group II was 64. The mean number of intramuscular diclofenac injection in 24 hours after extubation in group I was 0.84±0.40 and in group II was 2.02±0.42; this difference was statistically significant (p = 0.001). The total number of injection tramadol administered in first 24 hours after extubation was 1 in group I and 18 in group II. The mean number of intramuscular tramadol injection in 24 hours after extubation in group I was 0.04± 0.20 and in group II was 0.92±0.38; the difference between the two groups was highly statistically significant (p = 0.001). Shoulder pain was noticed among four patients in group I and five patients in group II; the difference between the two groups as per the shoulder pain was not significant (p≥ 0.05).

DISCUSSION

In spite of advancements in laparoscopic cholecystectomy, pain is often the main factor that hinders return to normal activities. Pain following laparoscopic surgery is multifactorial, arising from trocar sites (somatic pain - 50 to 70%), operative site (visceral pain - 10 to 20%) and shoulder pain (referred from diaphragmatic irritation because of pneumo-peritoneum-20 to 30%).[3,4] There is a significant degree of abdominal pain in the post-operative period which peaks within the first few hours after the operation but diminishes with time. There are various methods of using local anaesthetic to reduce post-operative pain like infiltration at trocar site to reduce somatic pain, in gall bladder fossa for reducing visceral pain, in sub diaphragmatic areas to reduce referred pain to shoulders.[5,6] These agents reduce pain by reversibly decreasing the rate of depolarisation and repolarisation of excitable membranes.[7] It is important that the local infiltration of long-acting anesthetic be made before giving incision.[8]

In a study of Ke et al preemptive analgesia using 0.5% bupivacaine was found to be superior to postsurgical analgesia at 24 hours postoperatively.[9] A study by Saleh ET al found significant differences in pain levels only at 30 minutes after surgery when comparing preemptive analgesia using 0.5% bupivacaine with placebo.[10] This study did not evaluate use of postsurgical analgesia.

However, Sozbilen M et al found that administration of ropivacaine preoperatively and postoperatively for LC has similar effects on postoperative pain over a 24 h postoperative follow-up.[11] A study by Fong et al found no difference in postoperative pain scores when either preemptive or postsurgical infiltration of 30 ml of 0.25% bupivacaine was used.[12] However, a recent study by Lam et al found that postsurgical infiltration of 1% lidocaine was effective for postoperative pain control and that pre surgical infiltration was not.[13]

In a previous study, combined usage with incisional ropivacaine (2 mg/ml, 20 ml) and its intraperitoneal infusion (2 mg/kg, 100 ml) ahead of the surgical procedure exerted additive effects on decreasing postoperative pain.[14] There is another similar report that local skin infiltration of bupivacaine and intraperitoneal lidocaine (2%, 10 ml) or bupivacaine (0.5%, 10 ml) after LC also were proven to lower the intensity of postoperative pain in a synergistic fashion.[15]

Various studies have tested the efficacy of these modalities, as outlined above. But none of the studies have employed combined usage of LA at all 3 sites. We hypothesized that a combined use of long acting (bupivacaine) and short acting (xylocaine) local anaesthetics, at all 3 sites should efficaciously reduce post-operative pain. We chose our primary endpoint at 24 hours because effect of local anaesthesia is not expected to last beyond 24 hours. Considering the patients' safety, the maximum dosage of combination (bupivacaine+ xylocaine) used in the present trial was 160 mg of xylocaine and 17.5 mg of bupivacaine, which is far below the maximum dose for anesthesia (4.5 mg/kg for lignocaine and 2.5 mg/kg for bupivacaine) in an adult patient. Our results indicate that multisite infiltration of local anesthetic combination (bupivacaine+xylocaine) after laparoscopic cholecystectomy surgery significantly reduces pain at 1, 4 and 24 hours postoperatively.

CONCLUSION

Present study suggested the efficacy of port-site infiltration of local anesthetic in reducing post-operative pain. It achieves peripheral blockade of pain stimuli, which is more advantageous than treating pain after it occurs. It also results in significant reduction in the requirement of NSAIDs and opioids, thus also reducing drug-induced nausea and vomiting.

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