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Original Research Article

Intraperitoneal Hydrocortisone plus Bupivacaine versus Bupivacaine alone for Pain Relief after Laparoscopic Cholecystectomy: A Randomized Controlled Trial

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ABSTRACT:

Introduction: Laparoscopic cholecystectomy has been the gold standard in the treatment of gallstones since last decades. Beside several benefits of laparoscopic cholecystectomy compared with open surgery, postoperative pain is still a frequent melancholy. Hence, pain management is utmost regarding patients' comfort. The main objective of the study was to compare the effect of intraperitoneal hydrocortisone plus bupivacaine with bupivacaine alone on pain relief following laparoscopic cholecystectomy. **Methods**: A randomized study was conducted from December 2015 to August 2015 that included 100 patients aged 20 to 60 years of both genders who were found to have symptomatic gallstones and were scheduled for elective laparoscopic cholecystectomy at Lumbini Medical College. Patients randomly received 100 mg hydrocortisone plus 100 mg bupivacaine in 200 ml normal saline (group A) or 100 mg bupivacaine in 200 ml normal saline (group B) into the peritoneum. Post-operative abdominal and shoulder pain were evaluated using Visual Analog Score (VAS). The patients were also followed up for postoperative analgesic requirements, and recovery variables. Data were collected, tabulated and analyzed statistically using SPSS version 19. **Results**: Total number of patients in this study were 100. Age and gender among both groups were comparable. VAS scores for pain was significantly lower for group A as compared to group B at 0, 2, 4, 6, 12, and 24 hours. Time of oral intake in hrs for liquids and solids was statistically significant in Group A compared to Group B. Rescue analgesic requirement was also significantly low in Group A compared to Group B. Hospital stay in both group were comparable. **Conclusion**: Combination of hydrocortisone plus bupivacaine can relieve pain after laparoscopic cholecystectomy better compared to bupivacaine alone when administered intraperitoneally.

Keywords: bupivacaine • cholecystectomy • hydrocortisone • intraperitoneal • pain

INTRODUCTION:

Laparoscopic cholecystectomy (LC) is the most common, minimally invasive and gold standard methods in treatment for symptomatic cholelithiasis.[1] Less post-operative pain, early oral intake after surgery, shorter hospital stay, early resumption of normal activities and improved cosmesis have been well recognized advantages of LC.[2,3] Although pain is less intense than following open cholecystectomy, some patients still experience considerable discomfort during the first 24 to 72 postoperative hours, which can delay discharge.[4] Various modalities have been proposed to relieve pain after laparoscopic cholecystectomy like usage of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, intraperitoneal local anesthetics, port site infiltration of local anesthetic etc.[5] Therefore, pre-operative decision for pain relief after laparoscopy is an important aspect of planning laparoscopic cholecystectomy. Since there is a paucity of data on comparison of intraperitoneal efficacy of

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steroids and local anesthesia combination with local anesthetics alone for pain relief after laparoscopic cholecystectomy, the present study was conducted to compare the pain relief with intraperitoneal hydrocortisone with bupivacaine and bupivacaine alone following laparoscopic cholecystectomy Additional objectives of our analysis included features like, requirement of rescue analgesia, duration of hospital stay and oral intake time after laparoscopic cholecystectomy under general anesthesia.

METHODS:

The present study was a hospital-based experimental study conducted in the Department of Anesthesia and Critical Care, Lumbini Medical College Teaching Hospital, Lumbini, Nepal from 1st December 2015 to 30th August 2015. The study was approved by the Institutional Review Committed of Lumbini Medical College. A total of 100 patients with American Society of Anesthesiologists (ASA) physical status I and II, aged 20-60 years, both genders, having symptomatic gallstones, and scheduled for laparoscopic cholecystectomy were included in the study. A detailed history was taken and thorough clinical examinations of all the patients were performed. Information about age, sex, weight and height of the patients was noted. The selected patients were then explained about the procedure and written informed consent was taken. Patients with the following criteria were excluded from this study: (i) associated chronic diseases like diabetes mellitus, significant cardiac, renal or pulmonary diseases; (ii) hepato-biliary malignancies; (iii) positive history of pregnancy or previous abdominal surgery; (iv) allergy to hydrocortisone and bupivacaine; (v) converted to open cholecystectomy, and (vi) presence of acute cholecystitis, choledocholithiasis or portal hypertension.

All the patients were pre-medicated with diazepam 10 mg night before surgery and on the morning of the surgery. The randomization of patients was done on patient's arrival at the operation theatre according to a list of computer generated random numbers.

Operative procedure: On operating table, patient was preloaded with 10 ml/kg Ringer Lactate solution, pre-oxygenated with 100% oxygen for five minutes. Two milligram per kilogram of fentanyl and two mg/kg of propofol was given followed by 0.1 mg/kg of vecuronium to aid endotracheal intubation. After conforming the endotracheal tube, ventilation was adjusted to maintain ECO_2 at 35 to 40 mm Hg. Anesthesia was maintained with oxygen, isoflurane and intermittent dose of vecuronium 0.01 mg/kg and fentanyl 1 mg/kg. After receiving anesthesia and before insufflations of CO2, instillation of 100 mg hydrocortisone plus 100 mg bupivacaine in 200 ml normal saline (Group A) or 100 mg bupivacaine in 200 ml normal saline (Group B) was done into the peritoneum by a surgical scrub nurse who was blind to the study. Following this, the patients were rotated into Trendelenburg, anti-Trendelenburg, left and right lateral positions (each for 2 minutes), and finally brought to supine position. All surgical procedures were performed by the same surgical team. During procedure, intra-abdominal pressure was maintained at 14 mm Hg. Manual compression of abdomen by open trocars was done to evacuate CO_2 at the end of procedure. Ten milliliters of 0.25% bupivacaine were injected in laparoscopic port entering site. Muscle relaxant was reversed at the end of surgery using 0.05 mg/kg of neostigmine and 0.005 mg/kg of glycopyrrolate.

Post-operatively, patients were assessed for pain using Visual Analogue Scale (VAS) in the recovery room (0 hr), and at 2, 4, 6, 12, and 24 hours based on a 0-10 scale (with zero meaning no pain and 10 meaning the most intense pain ever felt). Parameters like rescue analgesic requirements, time of oral intake after the surgery and total hospital stay after operation were also recorded. Fentanyl 1 mg/kg and 2 mg/kg was given as rescue analgesia for VAS 4 - 7 and 8 - 10 respectively.

Collected data was analyzed using the Statistical Package for the Social Sciences, version 19. Arithmetic mean and standard deviation values for different variables were calculated. T-test was used to compare mean, Chi-square test to compare proportions, and Mann–Whitney U test for comparing the ordinal values. A value of $p < 0.05$ was considered statistically significant.

RESULTS:

Females outnumbered males in both the group with F:M ratio of 7.0 and 5.50 for group A and group B respectively. Demographic characteristics of patients in two groups is shown in Table 1. There was no significant difference in age or gender in two groups (Table 1).

Table 1: Demoghaphic characteristics of patients in two groups

Variable	Group A (*N*=48)	Group B (*N*=52)	Statistics
Age Mean (*SD*)	38.92 (10.78)	42.47(12.52)	*t*= -1.51, *df*=97, *p*=0.13
Gender *n (%)*			
Male	6 (12.5)	8 (15.38)	X^2=0.03, *df*=1, *p*=0.86
Female	42 (87.5)	44 (84.61)	

All the patients had post-operative pain due to varied reasons like adhesions, diseases of liver, abnormal anatomy of gallbladder and biliary tract, complication during dissection like bleeding, bile duct injury, gallbladder perforation, stone loss visceral injury, and insertion of drain. The abdominal and shoulder pain scores were significantly lower in group A at 0, 2, 4, 6, 12 and 24 hours (Table 2).

Table 2: Visual analogue scale (VAS) scores for post-operative abdominal pain in two groups

Time from recovery (hours)	Group A (Mean rank)	Group B (Mean rank)	U= Mann Whitney's U value
0	41	58.47	*U*=1656, *p*=0.001
2	44.15	55.51	*U*=1505, *p*=0.004
4	42.59	56.95	*U*=1580, *p*=0.009
6	39.84	59.56	*U*=1712, *p*=0.0001
12	41.57	57.93	*U*=1629, *p*=0.003
24	41.36	58.13	*U*=1639, *p*=0.003

Rescue analgesia requirement: Chi-square test of independence was applied to see relation between rescue analgesia requirement in two groups. Those in control group (not receiving hydrocortisone) were statistically more likely to receive rescue analgesia (X^2=18.14, *df*=1, *p*<0.001).

Time of oral intake: Time for oral intake for liquid and semi-solid post-surgery was significant less for group A compared to group B. However, for normal diet, this was significantly different (Table 3).

Table 3: Time of oral intake after recovery.

Diet	Group	Mean time (hr)	Statistics
Liquid	A	6.01	*t*= -3.33, *df*=89.6 *p*=0.001
	B	6.20	
Semi solid	A	7.68	*t*= -3.61, *df*=56.86 *p*=0.001
	B	8.07	
Normal	A	11.80	*t*= -1.65, *df*=57.2 *p*=0.1
	B	12.05	

Hospital stay: Hospital stay in group A was significantly shorter (*t*=1.73, *df*=91, *p*<0.001). Mean hospital stay in group A was 2.15 days (*SD*=0.36) and in group B was 2.29 days (*SD*=0.49).

DISCUSSION:

Evident benefits of laparoscopic cholecystectomy such as reduction in post-operative disability, cosmesis and early return to work have rendered it the procedure of choice for symptomatic cholelithiasis.[6] Pain after laparoscopic cholecystectomy is inevitable. Pain involves several component (parietal, visceral, and shoulder pain) with different intensities and their own time course.[7] There are various mechanism for visceral pain after laparoscopic cholecystectomy like rapid distension of peritoneum which may be associated with traumatic traction of nerves, tearing of blood vessels, and release of inflammatory mediators. Other mechanism for pain includes local irritation and inflammation around gall bladder bed, liver, diaphragm or peritoneum, gall bladder removal, and abdominal muscle distension.[8-10] Shoulder pain may be due to inflammation of peritoneum reflection supplied by phrenic nerves.[9]

Post-operative pain is multi-factorial in origin, and therefore multi-modal therapy may be needed to optimize pain relief. Intra-peritoneal administration of various drugs are given along with local anesthetic for pain relief after laparoscopic cholecystectomy like bupivacaine with morphine, bupivacaine with meperidine, bupivacaine with tramadol, bupivacaine with magnesium sulphate, ropivacaine, ropivacaine and gas drain, levobupivacaine with epinephrine, lidocaine with tanoxicam.[11]

Hydrocortisone along with bupivacaine have an additional advantage than bupivacaine alone because steroid decreases the pain through various mechanism like suppression of bradykinin, release of neuropeptides, peripheral suppression of phospholipase enzymes thereby decreasing cyclooxygenase and lipooxygenase pathway of inflammatory pathway, and inhibition of other mediators of inflammation eg, TNF, interleukin 6 and 12.[12-15] Hydrocortisone was given before surgery and CO_2 insufflation as the onset of action of hydrocortisone is 1-2 hrs thus allowing time to diffuse across cell membrane and alter gene transcription.[16] Amene S. et al. assessed the analgesic effect of intra peritoneal injection of hydrocortisone alone before

gas insufflation in laparoscopic cholecystectomy and concluded that intraperitoneal hydrocortisone can reduce postoperative pain with no significant postoperative adverse effect. On the contrary, we found bupivacaine with hydrocortisone has significantly low VAS score at 0, 6, 12, 24 hrs and rescue analgesia requirement was low.[11]

The study conducted by Sabzi Sarvestani et al. concluded that the intraperitoneal administration of bupivacaine with hydrocortisone before gas insufflation can reduce post-operative pain similar to intraperitoneal bupivacaine with no significant post-operative adverse effects in laparoscopic cholecystectomy. This finding was in consistent with our study and this might be because the concentration of bupivacaine in which hydrocortisone used was different in our study than that of the previous study.[17] Zahra Asgari et al. studied the effect of hydrocortisone added to intra-peritoneal bupivacaine on post-operative pain after gynecological surgery and concluded that combination to be more effective then bupivacaine alone which is similar to our study.[18]

LIMITATIONS:

1. Studies with larger sample size are recommended.
2. Further studies with a control group and different dose and concentration of the drugs must be carried out to provide maximal benefit in terms of post-operative pain relief with minimal adverse effects after laparoscopic surgery.
3. Combined usage of steroid and local anesthetic solution may not be indicated for all patients. For example, diabetic patients may experience hyperglycemia and patients with a long-term infectious process may be destructively affected by the anti-inflammatory effects of steroids.

CONCLUSION:

Intra-peritoneal instillation of hydrocortisone 100 mg with bupivacaine 100 mg in 200 ml normal saline during laparoscopic cholecystectomy significantly reduces post-operative pain and requirement of rescue analgesia then that of bupivacaine 100 mg in 200 ml normal saline alone.

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