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A Randomized Double Blinded Study to Determine the Effectiveness of Local Bupivacaine to Decrease Post Operative Pain Following Laparoscopic Cholecystectomy

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Abstract: To determine if instillation of local Bupivacaine into the umbilical port site before closure of laparoscopic port site wound, would decrease postoperative pain after laparoscopic cholecystectomy. And to determine if the patients would consequently require less rescue analgesia postoperatively. In this randomized double-blind placebo-controlled study with the parallel trial design which was carried out over a period of one year. Data was collected prospectively from consecutive patients of 18 to 65 years of age, of American Society of Anesthesiologists (ASA) physical status I and II, who are scheduled to undergo elective laparoscopic cholecystectomy, with a diagnosis of Chronic calculus Cholecystitis or Cholelithiasis between 1 January 2015 and 31 December 2015. Ethical approval was obtained from the Institutional Review Board of the Hospital Authority of Nazareth hospital, Shillong. Findings of the present study show that the multimodal approach to pain management following laparoscopic cholecystectomy is best achieved with local infiltration of 10 ml of Bupivacaine 0.25% at the umbilical port site at the end of the operation. This method is easy and effective, it has shown to significantly reduce the postoperative pain in the early postoperative period and improve the post-operative recovery. This effect also helps in the early mobilization of the patients postoperatively. The use of local infiltration of injection Bupivacaine 0.25% at the umbilical port site has shown to significantly reduce the need for postoperative analgesia. This could reduce the cost and eliminate the need for additional analgesia in early postoperative period.

Keywords: Bupivacaine, Cholecystitis, VAS, Laparoscopic Cholecystectomy

INTRODUCTION

Conventional laparoscopic cholecystectomy (CLC) with three or more ports remains the 'gold standard' for cholecystectomy. Although the postoperative pain is generally less intense and lasts for a shorter time than that following open cholecystectomy, postoperative pain, and effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge [1]. Inadequate postoperative pain control can delay patient's recovery, lengthen the hospital stay and increase morbidity and costs [2-4].

Improving postoperative analgesia in laparoscopic surgery is an area of continued interest. Studies have been done in all parts of the world on various methods available to reduce the postoperative pain after laparoscopic cholecystectomy.

Numerous clinical studies have investigated the use of regional local anesthetics, in combination with other modalities for pain relief following laparoscopic cholecystectomy to avoid the adverse effects of opioids, which may delay recovery and hospital discharge [5]. Thirteen controlled studies have investigated the analgesic effects of Bupivacaine administered in the right subdiaphragmatic or gallbladder region; only 7 of the 13 trials found that the overall pain scores were significantly reduced as compared with those of the control patients [6]. There are various methods of pain relief used, but none have been assessed or compared. The purpose of this prospective randomized double-blind study is to study and evaluate the analgesic efficacy of local Bupivacaine injection into the umbilical port to decrease pain following elective laparoscopic cholecystectomy.

METHODS

The present study, which is a randomized double-blind placebo-controlled study with the parallel trial design was carried out in surgical ward, operation theatre and post operative ward of department of

surgery, Nazareth hospital, Shillong, Meghalaya (a tertiary level hospital). The study was conducted between 1st January 2015 and 31st December 2015.

Informed written consent was taken after explaining the need and importance of the study prior to filling of the patient's proforma. Patients of 18 to 65 years of age, of American Society of Anesthesiologists (ASA) physical status I and II, who are scheduled to undergo elective laparoscopic cholecystectomy, with a diagnosis of Chronic calculus Cholecystitis or Cholelithiasis were included in the study. A detail clinical history including general and systemic examination and various relevant investigations has been done.

Patients with known sensitivity to the study drugs, Inability to understand the pain score, patients on chronic pain medication, anticonvulsant or antidepressant, patients who refused to participate in the study, pregnant and lactating mothers, patients with acute cholecystitis and patients who were converted to open cholecystectomy were excluded from the present study.

Based on previous studies on port site infiltration with local anesthetics [7] the mean outcome in group Control and mean outcome in group Bupivacaine was obtained, the standard deviation of the outcome was also obtained. A sample size of 170 is taken with 85 in each group.

Randomization was done for 170 patients (the sample size) using computer-generated randomizing table (Urbaniak, G. C., & Plous, S. (2013). Research Randomizer (Version 4.0) [Computer software]. Retrieved on June 22, 2013, from http://www.randomizer.org) A doctor who was not participating in the trial randomly assigned 170 patients to either Group Bupivacaine or Group control. The patients after being randomly assigned into two groups were allotted a sealed opaque envelope containing information regarding the group allocation to maintain blinding.

One nurse, who was not part of the study, would open the opaque envelope containing information regarding the group allocation. She would then prepare the medication and give to the operating surgeon for infiltration.

Group Bupivacaine: Skin, subcutaneous tissue, fascia, muscle, and pre-peritoneal space was infiltrated with 10 ml of Bupivacaine 0.25% at umbilical port site at the end of the operation.

Group Control: Skin, subcutaneous tissue, fascia, muscle, and pre-peritoneal space were infiltrated with 10 ml of normal saline at umbilical port site at the end of the operation. The patient, investigator and outcome assessor were not aware of the type of medications.

The data was recorded according to a standard questionnaire. Acute postoperative pain was assessed using VAS at rest and during deep breathing/coughing/movement on which 0 indicates “no pain” and 10 indicates “worst imaginable pain”. Pain score was recorded at 0, 1, 2, 4, 6, and 24 hours postoperatively, where 0 indicates arrival at POCU. Injection Diclofenac aqueous form 75 mg IV at eight hours after surgery was given as post-operative analgesia. For any patient who asks for more analgesic or VAS more than 2, injection Tramadol 100 mg was given as a rescue analgesic. The need for rescue analgesia in the form of injection Tramadol was recorded.

Data analysis was performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Frequency means and standard deviation (SD) were generated using descriptive statistics. The mean VAS at rest and movement in Group Bupivacaine and Group Control were compared using Z-test. Statistical significance was fixed at $P < 0.05$. The difference between the use of rescue analgesia in the form of injection Tramadol was compared between the Group Bupivacaine and Group Control using Z-test for the test of significance for the difference of proportions. Statistical significance was fixed at $P < 0.05$. Ethical approval for the study was obtained from the Institutional Ethical Committee of Nazareth Hospital, Shillong.

RESULTS

Figure 1 A flow chart of the present study (parallel study design). Total sample size of the present study was 170. Out of 170, in 9 patients laparoscopic cholecystectomy was converted to open cholecystectomy and they were excluded from the present study. Table 1 Depicts the baseline characteristics in group Bupivacaine (N=81) and group Control (N=80).

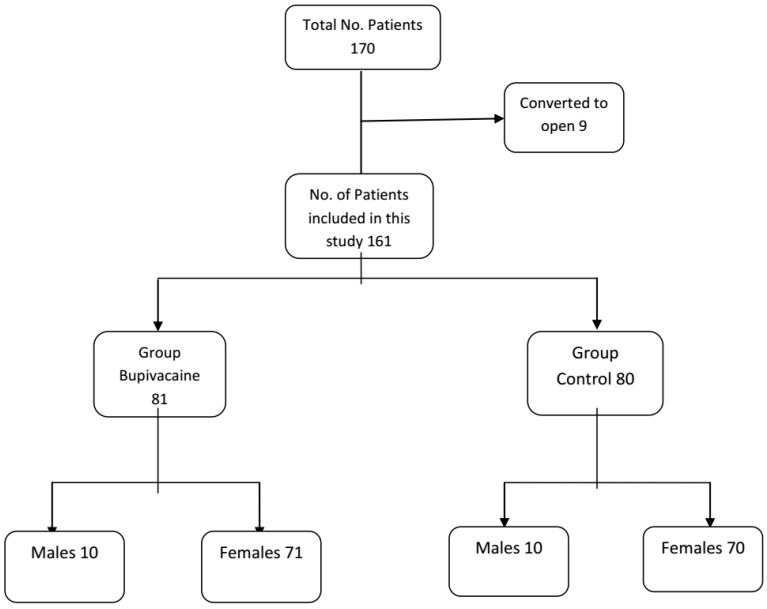

Fig-I: Consort diagram of patients enrolled into the present study

Table-1: Baseline characteristics

Characteristics	Total(n=161)	Group Bupivacaine n=81	Group Control n=80	*p*-value
Gender	20(12.43)	10(12.34)	10(12.50)	0.976
Male (%)				
Female (%)	141(87.57)	71(87.66)	70(87.50)	
Age: mean and (SD)years	39.12(12.59)	38.17(12.52)	40.08(12.66)	0.33

Table-2: Duration of surgery in minutes

Duration of surgery	Total	Group Bupivacaine	Group Control	Calculated $\|Z\|$	*p*-value
N	161	81	80	0.15	0.88
Minimum	50	50	50		
Maximum	80	80	80		
Mean(SD)	61.37(8.1)	61.56(8.5)	61.39(7.8)		
Median	60.00	60.00	60.00		
Mode	60	60	60		
Variance	66.871	73.161	60.857		

Table 2 Depicts the mean duration of laparoscopic cholecystectomy in the present study, which is 61.3(8.1) minutes. There is no significant difference between the duration of surgery in group Bupivacaine and group Control (*p*-value 0.88).

Table 3: Comparison of mean VAS at rest between group Bupivacaine and group Control

Post op assessment time in hours.	Mean VAS at rest in Group Bupivacaine	Mean VAS at rest in Group Control	Calculated $\|Z\|$at 5% level of significance	95%Confidence limits		*p*-value
				Lower limit	Upper limit	
0	1.42	2.73	11.80	1.09	1.51	<0.00001
1	1.42	1.95	9.00	0.44	0.62	<0.00001
2	1.72	1.99	5.30	0.18	0.36	<0.00001
4	1.91	2.00	2.86	0.04	0.14	0.004236
6	1.75	2.11	5.62	0.25	0.47	< 0.00001
24	2.35	2.45	1.22	0	0.25	0.222465.

Table 3 Depicts comparison of mean VAS at rest between Group Bupivacaine and Group Control (using the Z test for difference of means). Mean VAS is less in group Bupivacaine compared to group Control at 0,1,2,4,6 which is statistically significant. But the mean VAS is not statistically significant at 24 hours.

Table-4: Comparison of mean VAS at movement between group Bupivacaine and group Control

Post op assessment time in hours.	Mean VAS at movement in Group Bupivacaine	Mean VAS at movement in Group Control	Calculated $\|Z\|$at 5% level of significance	95%Confidence limits		*p*-value
				Lower limit	Upper limit	
0	1.54	3.15	11.37	1.34	1.88	< 0.00001.
1	1.54	1.98	7.61	0.35	0.53	< 0.00001.
2	1.83	1.99	3.71	0.09	0.23	0.000207.
4	1.94	2.00	2.41	0.03	0.09	0.015953.
6	1.79	2.24	6.30	0.32	0.58	< 0.00001.
24	2.49	2.51	0.21	0.15	0.19	0.833668.

Table 4 Depicts comparison of mean VAS at movement between Group Bupivacaine and Group Control. Mean VAS is less in group Bupivacaine compared to group Control at 0,1,2,4,6 which is statistically significant. But the mean VAS is not statistically significant at 24 hours.

Table-5: Use of rescue analgesia (injection Tramadol) within 24 hours of laparoscopic cholecystectomy.

Rescue Analgesia	Group Bupivacaine	Group Control	Calculated $\|Z\|$ at 5% level of significance	95%Confidence limits		*p*-value
				Lower limit	Upper limit	
Number (and %) of people who did not receive any dose	46(56.70%)	11(13.75%)	5.72	0.32	0.54	< 0.00001.
Number (and %) of people who received one dose	29(35.80%)	34(42.50%)	0.87	0.06	0.20	0.3843.
Number (and %) of people who got ≥ 2 doses.	6(7.40%)	35(43.75%)	5.32	0.25	0.47	< 0.00001.

Table 5 Depicts the use of rescue analgesia (injection Tramadol) within 24 hours of laparoscopic cholecystectomy. People who did not receive any dose of Tramadol are more in group Bupivacaine(46) and people who received two or more doses of injection Tramadol are more in group Control (35).

DISCUSSIONS

In the present study patients belonging to Group Bupivacaine had significantly lower pain scores in term of VAS at 0,1,2,4,6 hours postoperatively as compared to the Group Control. However, in the present study, the pain scores are not significantly different at 24 hours postoperatively. This lack of statistically significant difference in pain at 24 hours could be explained as the duration of action of local anesthetic i.e injection Bupivacaine is 10 hours [8]. Results are in concordance with a study conducted by S. Loizides *et al*. [9] the author mentioned that the pain scores as measured by the visual analogue scale (0 to 10 cm) were lower in the local anaesthetic infiltration group than the control group at 4 to 8 hours.

A. AlKafrawy *et al*. [10] found that the intraperitoneal and port site use of LA showed significant effect in the first, second, fourth, sixth, and eighth hours on reducing postoperative pain, whereas it showed no significant effect in the 10th and 12th hours postoperatively.

K. Gurusamy *et al*. [11] noted that the pain at 4 to 8 hours was generally reduced by about 1 to 2 cm on the visual analogue scale of 1 to 10 cm in the comparisons involving the different pharmacological agents and inactive controls.

M. Alam *et al*. [12] found a significantly lower pain scores in term of VAS in patients belonging to Group Bupivacaine at 6 and 12 hours postoperatively as compared to Group Control. In their study, there was no significant difference in pain scores at 24 hours postoperatively.

P. Papagiannopoulou *et al*. [13] reported that patients receiving levobupivacaine 0.5% administration prior to trocar placement experienced significantly less

pain than the Placebo and Ropivacaine groups at 4 h and 24 h postoperatively.

D. Dath *et al.* [7] found a significantly lower pain scores in term of VAS in patients belonging to Group Bupivacaine at 2 and 6 hours postoperatively as compared to Group Control. In their study there was no significant difference in pain scores at 10 hours postoperatively and next morning after the surgery.

In the present study, in Group Bupivacaine the number of patients who did not receive any dose of injection tramadol were 46(56.70%), which is more when compared to Group Control where number of patients who did not receive any dose of injection tramadol were 11(13.75%). This is statistically significant (p-value is < 0.00001). Similarly in Group Bupivacaine the number of patients who received two or more doses of injection tramadol was 6(7.40%), which is less when compared Group Control where the number of patients who received two or more doses of injection tramadol was 35(43.75%). This is statistically significant (p-value is < 0.00001).

Thus, in the present study it is observed that need of rescue analgesia is less in group Bupivacaine as compared to group Control.

This finding is in accordance with the findings of the study done by C. Yeh *et al.* [14] in this study the author noted that patients who received local wound anesthetic after Laparoscopic cholecystectomy had the lowest VAS scores and therefore required the least amount of meperidine (rescue analgesic) used in their study.

However, D. Dath *et al*. [7] reported that there were no significant differences between the groups in the total dosages of narcotics given in either the PACU or the short-stay unit.

In the present study the duration of surgery in Group Bupivacaine and Group Control are not significantly different (p-value 0.88). Thus in this study, the duration of surgery is not a confounding factor in the final outcome that is postoperative pain.

CONCLUSION

Findings of the present study show that the multimodal approach to pain management following laparoscopic cholecystectomy is best achieved with local infiltration of 10 ml of Bupivacaine 0.25% at the umbilical port site at the end of the operation. This method is easy and effective, it has shown to significantly reduce the postoperative pain in the early postoperative period and improve the post-operative recovery. This effect also helps in the early mobilization of the patients postoperatively. The use of local infiltration of injection Bupivacaine 0.25% at the umbilical port site has shown to significantly reduce the need for postoperative analgesia. This could reduce the cost and eliminate the need for additional analgesia in early postoperative period.

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Conflict of Interest– Nil

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