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ORIGINAL ARTICLE

Comparison between Levobupivacaine and Levobupivacaine with Clonidine in Erector Spinae Plane Block in Patients undergoing open Cholecystectomy: A Prospective Randomized Double Blinded Study

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Abstract

Background: Erector spinae plane (ESP) block is effective for post-operative analgesia in thoracic and abdominal surgeries. There is minimal experience with clonidine (alpha2 agonist) as an adjuvant to levobupivacaine in ESP block. The objective of the present study is to compare the duration of postoperative analgesia between levobupivacaine and levobupivacaine with clonidine in open cholecystectomy following ESP block. **Methods:** One hundred patients, randomly divided into two groups, undergoing open cholecystectomy under general anaesthesia (GA), were given ESP block 20 min before administration of GA. Group L received 19 ml of 0.25% levobupivacaine with 1 ml of normal saline and group LC received clonidine (1.5 mcg/ kg) prepared in 1 ml of normal saline as adjuvant with 19 ml of 0.25% levobupivacaine for ESP block. In the postoperative period, the duration and requirement of analgesia were recorded.

Results: Duration of post-operative analgesia in group LC was 595.78± 71.5 min compared to 357.2± 18.14 min in group L. (P<0.0001). The requirement of analgesic in the first 24 hours was also significantly less in group LC (P<0.0001).**Conclusion:** Clonidine as adjuvant with levobupivacaine in erector spinae plane block provides longer duration of analgesia and reduces analgesic requirement postoperatively without any significant adverse effects.

Key Words

Adjuvant, Analgesia, Levobupivacaine, Clonidine, Erector Spinae Plane Block

Introduction

The efficacy of erector spine plane (ESP) block in the reduction of post-operative pain and analgesic consumption without any major side effects in different types of abdominal and thoracic surgeries is well established.[1] However, as ultrasound machines are not always available in the operation theatre of all institutes even in developed countries, landmark guided ESP block has been described.[2]

Pain following open cholecystectomy has a significant adverse effect on post-operative pulmonary function due to ineffective ventilation and lower lobe atelectasis.[3] Recent meta-analysis reports that for upper abdominal surgery, ESP block provides better analgesia than other

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commonly used truncal blocks and placebo.[4]

Alpha-2 adrenergic agonists like dexmedetomidine and clonidine are effective in increasing the duration of anaesthesia and postoperative analgesia when used with local anaesthetic (LA) for different types of peripheral nerve blocks.[5] Dexmedetomidine has been used as an adjuvant with LA in ESP block whereas there is a paucity of randomized controlled trials (RCT) using clonidine as an adjuvant to LA in ESP block.[6] To enlighten this grey area in the field of anaesthesiology present study was designed. As there was no RCT available using clonidine as an adjuvant in ESP block using levobupivacaine, we accepted the null hypothesis for the present study.

The primary objective of the study was to compare the duration of postoperative analgesia in open cholecystectomy following ESP block using 0.25% levobupivacaine and 0.25% levobupivacaine with clonidine. Comparison of analgesic requirement in 1st 24 hrs postoperatively was secondary objective.

Material and Methods

After getting approval from the institutional ethical committee (MMC/ICE-2021/435/12 dated 18.02.21) and registration in the clinical trial registry-India (CTRI/2021/07/035222 dated 28.07.2021) patient enrolment was started. This prospective, randomized, double-blinded study was conducted over 12 months (August 2021 to July 2022) in the surgery operation theatre of this tertiary care institution according to the principles of the Declaration of Helsinki, 2013.

Initially, 130 patients were assessed for eligibility. Nine patients refused to participate in the study and 21 patients did not meet inclusion criteria . After obtaining written informed consent from all the patients to participate in the study and use the patient data for research and educational purposes, 100 consenting patients of ASA grade I & II between the age groups of 18-60 years undergoing elective open cholecystectomy were enrolled for the study and randomly divided into two groups.

Patients with severe systemic disease (Cardio-respiratory, hepatic, renal, neurological, or endocrine), psychiatric problems, pregnancy, or allergies to study drugs were excluded. Patients with inadequate sensory block, demonstrated by cold perception, were also dropped out of the study and excluded from data analysis.

We performed a pilot study with 12 patients with the same inclusion and exclusion criteria; undergoing open cholecystectomy. The duration of postoperative analgesia observed was 325.67 ± 55.43 min. A 10% increase in the duration of post-operative analgesia was considered to be adequate to reject the null hypothesis. Assuming an alpha error of 0.05 and power of study 80%, the sample size was calculated to be 45 in each group. To compensate for dropouts, we have included 10% more patients, allocating 50 patients in each group. Sample size calculation was done using PS Power and Sample Size Calculator version 3.1.2 released in August 2014.

Randomization was done using a computer-generated random number table; patients were allocated randomly into two groups using a sealed envelope technique. Each group was allocated 50 patients. Group L received 19 ml of 0.25% levobupivacaine with 1 ml of normal saline for ESP block whereas patients of group LC received clonidine (1.5 mcg/kg) prepared in 1 ml of normal saline as adjuvant with 19 ml of 0.25% levobupivacaine. All patients received 20 ml of the study drug.

All study drugs were prepared by an anaesthesiologist outside the operation theatre, who according to the random number, prepared the drug for ESP block. Anaesthesiologist who prepared the drug for the ESP block did not participate in the procedure and data collection.

In the operation theatre10 point visual analogue scale [VAS] for assessment of postoperative pain was explained to the patient before the procedure. No premedication was given. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), and peripheral arterial oxygen saturation (SpO_2) were recorded.

ESP block was performed under strict aseptic conditions in the sitting position at the level of the 6th thoracic vertebra (T6), 3 cm right lateral to spinous process after infiltrating the skin with 2 ml of 2% lignocaine. Immediately following the block, the patients were made supine, and vital parameters were recorded at 2-minute intervals for the first 20 minutes. All patients were given moist O_2 @ 4-6 L/min during this period. The onset of sensory block was tested by bilateral cold perception with an alcohol-soaked sponge over T4, T6, and T10 dermatome every 2 min for 20 min after the drug was administered. If the sensory block was not achieved at all the three dermatomes, the patient was excluded from the study. The time of onset of the block was recorded as the time of first detection of decreased sensation to cold.

General anaesthesia was administered 20 min after the block was administered. Premedication was done with glycopyrrolate 0.2 mg and fentanyl 2 mcg/kg intravenously.

Anaesthesia was induced with propofol 2 mg/kg intravenously. Three min after administration of atracurium (0.5 mg/kg) and mask ventilation, tracheal intubation was done. Anaesthesia was maintained using a nitrous oxide to oxygen ratio of 60:40 along with 0.6 % isoflurane. Muscle relaxation was maintained by atracurium 0.1 mg/kg as assessed by the neuromuscular monitor intra-operatively. Intravenous fentanyl was repeated at the dose of 1 mcg/kg every 30 min till the completion of surgery. Reversal was done using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg after surgery.

The quality of postoperative analgesia was assessed by using VAS immediately after reversal and then at every 15 min till the patient complained of VAS ≥ 4. The time from the onset of the block to the time of complaining VAS ≥ 4 was recorded as the duration of post-operative analgesia. Injection paracetamol 15 mg/kg was administered intravenously when the patient complained of VAS ≥ 4. If VAS was $\geq$ 4 even after 30 min of giving paracetamol, pentazocine 30 mg (2^{nd} analgesic) was administered intramuscularly. VAS was compared between the groups every hour for the first 6 hrs then at 8, 10, 12, and 24 hrs post-operatively. The total dose of analgesic drugs (paracetamol) required was calculated for the first 24 hrs after surgery. The number of patients requiring 2^{nd} analgesic was also recorded.

Postoperatively Ramsay sedation score of the patients were compared between the two groups at the time just after recovery and then at 10 min and 30 min after recovery.[7] The sedation score was also recorded at the time of recording the VAS score.

Side effects such as hypotension, bradycardia, nausea, vomiting, sedation, pruritus, shivering, and respiratory depression were recorded in the first 24 hour postoperative period. Intra-operative vital parameters and SpO_2 were recorded throughout the procedure and at the end of the procedure for 6 hours.

Data were analysed by Statistica version 8 [Tulsa, Oklahoma: Stat Soft Inc., 2007]. Mann-Whitney U-test for nonparametric data and unpaired Student's t-test for parametric data were employed to assess the significance of the difference in means between the independent samples. Chi-square test and Fisher's exact test were used for categorical data. Analysis was two-tailed and $p \leq 0.05$ was considered statistically significant.

Results

One patient in group L failed to achieve sensory block after the ESP block was administered. No patient of either group had any hemodynamic instability or respiratory discomfort after the ESP block. Finally, data analysis was done with 49 patients of group L and 50 patients of group LC.

The two groups were comparable regarding age, sex, weight, height, and ASA physical status (Table 1).

Table 1: Demographic Profile

	Group L (n=49)	Group LC (n=50)	*P* value
Age (year)	42.67± 9.14	42.04± 8.435	0.723
Male	13 (26%)	15(30%)	0.705
Female	37 (74%)	35(70%)	0.813
ASA I	42 (84%)	37 (78%)	0.573
ASA II	8 (16%)	13 (26%)	0.275
Weight (kg)	63.16 ± 6.27	65.04 ± 8.23	0.209
Height (cm)	159.22 ± 5.41	159.52 ± 5.92	0.798
Duration of Surgery (min)	97.49 ± 11.33	95.74 ± 13.06	0.482

ASA-American Society of Anesthesiologists; Group L-0.25% levobupivacaine, Group LC-0.25% levobupivacaine with clonidine

VAS score was significantly higher in group L throughout the post-operative period than in group LC except in the 1st hour when it was comparable to group LC (Table 2).

The requirement of analgesia was significantly delayed in group LC compared to group L. The total dose of the analgesic requirement was also less in group LC. The second analgesic requirement was significantly less in

Table 2: Distribution of Visual Analogue Scale Score

VAS Score	Group L (n=49)	Group LC (n=50)	*P* value
0 hour	0.29± 0.45	0.22± 0.41	0.457
1 hour	0.80± 0.53	0.62± 0.66	0.151
2 hours	1.57± 0.6	1.34± 0.51	0.045*
3 hours	2.14± 0.35	1.6± 0.63	<0.0001*
4 hours	2.24± 0.52	1.66± 0.59	<0.0001*
5 hours	3.10± 0.3	1.84± 0.76	<0.0001*
6 hours	4.20± 0.78	2.04± 0.82	<0.0001*
8 hours	4.20± 0.67	3.34± 0.92	<0.0001*
10 hours	3.90± 0.73	3.34± 0.97	0.002*
12 hours	4.92± 4.24	3.36± 0.66	0.015*
24 hours	3.63± 0.66	2.36± 0.89	<0.0001*

VAS-Visual Analogue Scale;Group L-0.25% levobupivacaine; Group LC-0.25% levobupivacaine with clonidine
**Statistically significant*

group LC compared to group L (Table 3). Ramsay sedation score was significantly high in the first eight hours post-operatively in group LC. (Table 4)

Table 3: Post-operative Analgesia

	Group L (n=49)	Group LC (n=50)	*P* value
Time for rescue analgesia (min)	357.20 ± 18.14	595.78 ± 71.50	<0.0001*
Dose of PCM required in 1st 24 hrs (gm)	2.83 ± 0.37	1.88 ± 0.43	<0.0001*
Requirement of 2nd Analgesic (no of patient)	14 (28%)	3 (6%)	<0.0001*

PCM-Paracetamol; Group L-0.25% levobupivacaine; Group LC-0.25% levobupivacaine with clonidine; hrs-hours; gm-gram
**Statistically significant*

Table 4: Ramsay Sedation Score

Ramsay sedation score	Group L (N=49)	Group LC (N=50)	*P* value
Baseline	1.55 ± 0.5	1.5 ± 0.5	0.615
10 min	1.63 ± 0.52	2.98 ± 0.95	<0.0001*
30 min	1.51 ± 0.5	2.92 ± 0.87	<0.0001*
1 hour	1.48 ± 0.5	2.96 ± 0.87	<0.0001*
2 hours	1.48 ± 0.5	2.78 ± 0.73	<0.0001*
4 hours	1.55 ± 0.54	2.34 ± 0.62	<0.0001*
8 hours	1.61 ± 0.49	1.44 ± 0.5	0.03*
10 hours	1.58 ±0.51	1.61 ± 0.46	0.09
12 hours	1.59 ± 0.49	1.56 ± 0.5	0.715
24 hours	1.57 ± 0.49	1.56 ± 0.5	0.909

Group L-0.25% levobupivacaine; Group LC-0.25% levobupivacaine with clonidine
**Statistically significant*

MAP was also comparable among the groups in the perioperative period. Heart rate was also similar in both the groups except at 10 min intraoperatively when group LC (78.14± 4.7) had lower HR than group L (80.83± 4.78)(*P* 0.006).

No incidence of hypotension, bradycardia, respiratory depression, shivering, or pruritus was noted in any patients of either group in the postoperative period. Incidence of nausea and vomiting were comparable in both groups in the first 24 hours.

Discussion

In the present study, addition of clonidine with levobupivacaine in ESP block significantly increased the duration of postoperative analgesia. In the ESP block LA is deposited between the erector spinae muscle and the tip of the transverse process. LA diffuses into the paravertebral space from there and acts on both the rami (ventral and dorsal) of the spinal nerves developing sensory block over multiple dermatomes of the thoracic and abdominal wall.[8]

Clonidine potentiates the action of LA by opening the potassium channels which results in hyperpolarization, producing a refractory state in the nerve fibres.[9] Studies have shown that clonidine prolongs the duration of action of LA in paravertebral block and brachial plexus block.[9-14] But there is only one case report of using 10 mcg clonidine along with 8 ml of 0.375% ropivacaine in ESP block for excision of chest wall tumour under general anaesthesia in a 14 kg patient, where the duration of post-operative analgesia was near 24 hours.[15]

Previous studies of paravertebral block have used either 1 mcg/kg[10-12] or 75 mcg[13] of clonidine with LA. A study with supraclavicular block suggests that 1.5 mcg/kg clonidine is more effective than 1 mcg/kg for prolongation of the duration of the block and postoperative analgesia without any adverse effect.[14]As there was no previous reference on the dose of clonidine for ESP block, 1.5 mcg/kg of clonidine was used in the present study.

Meta-analysis on ESP block has observed that most of the studies have used ropivacaine and bupivacaine with or without adjuvants but study using levobupivacaine in ESP block is hard to find.[4] Levobupivacaine being more potent than ropivacaine and less cardiotoxic than bupivacaine has an edge over both. [16,17]

Average volume of drug required in ESP block varies from 2.2 ml to 3.4 ml per dermatome.[18] For open cholecystectomy usually 4-5 dermatomes (T6-T10) are to be blocked for analgesia, so 20 ml of study drug was used in the present study.[19]

In the present study, the reduction in the requirement of paracetamol in the first 24 hours of the postoperative period in the clonidine group was statistically significant, similar to the observation made by Gupta *et al* using clonidine in ESP block.[15]

The increase in the sedation score in the clonidine group in the post-operative period was statistically significant compared to the control group in the present study. A similar incidence was reported by previous study that used clonidine in the dose range of 30-150 mcg as an

adjuvant to LA in brachial plexus block.[9]

No significant hemodynamic difference was recorded between the two groups in our study, which is similar to the observation made by Kelika *et al* when 1.5 mcg/kg of clonidine was used as an adjuvant with LA for brachial plexus block.[14]

The present study is not beyond limitations. Using an ultrasound-guided technique for the administration of block may have a better outcome. Future studies with different volumes of anaesthetic drugs and different doses of clonidine may produce different results.

Based on the present study it can be concluded that clonidine when used as an adjuvant with 0.25% levobupivacaine in ESP block, provides a longer duration of post-operative analgesia and decreases the requirement of analgesics post-operatively without any significant adverse effects.

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Conflict of Interest : Nil

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