Original Article

Intraoperative thoracic interfascial plane block with levobupivacaine versus levobupivacaine with dexmedetomidine for postoperative analgesia after modified radical mastectomy: A randomised controlled double-blinded trial

Address for correspondence:
Dr. Annu Choudhary, Department of Anaesthesiology, IGIMS, Patna, Bihar, India.
E-mail: anucdry@gmail.com

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Nidhi Arun, Raja Avinash[1], Annu Choudhary
Department of Anaesthesiology and Critical Care Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, [1]Cardiac Anaesthesia, Dr RML Hospital, ABVIMS, New Delhi, India

ABSTRACT

Background and Aims: Nearly half of the patients following breast cancer surgery experience postoperative pain. The interfascial plane for the pectoral nerve (PECS) block, along with dexmedetomidine, can alleviate this pain. **Methods:** After institutional ethics committee clearance and written informed consent, this randomised, double-blind study was conducted on 60, 18–60 years female patients, who were scheduled for modified radical mastectomy (MRM) under general anaesthesia. Patients were randomised into Group L (20 ml of 0.25% levobupivacaine) and Group DL (20 ml of 0.25% levobupivacaine with 0.5 μg/kg of dexmedetomidine). After resection of the tumour and securing haemostasis, under strict aseptic precaution, 10 ml of the study drug was injected under direct vision between the pectoralis major and pectoralis minor and 10 ml between pectoralis minor and serratus anterior muscles by the operating surgeon (direct PECS block). The primary outcome was to compare the duration of analgesia. Normally distributed variables were compared using Student's t-test, and non-normally distributed variables were compared using the Mann–Whitney U-test. Qualitative data were analysed using Chi-square/Fisher's exact test. Statistical significance was kept at $P < 0.05$. **Results:** The median time of the first analgesic requirement was 8 [inter-quartile range (IQR): 6–8] h in Group L and 18 (IQR: 16–20) h in Group DL (W = 17.000, $P < 0.001$). The mean total opioid consumption of Group L was 12.53 [standard deviation (SD): 2.29] mg in the first 24 h and 6.93 (SD: 1.89) mg in Group DL. **Conclusion:** Adding 0.5 μg/kg dexmedetomidine to 20 ml of levobupivacaine enhances the duration of analgesia of direct PECS block in patients undergoing MRM.

Keywords: Analgesia, bupivacaine, dexmedetomidine, levobupivacaine, modified radical mastectomy, PECS, pectoral nerve block, thoracic interfascial plane block

INTRODUCTION

The considerable pain associated with breast surgery requires a significant amount of analgesics for postoperative analgesia.[1] Various medications and interventions are being investigated for postoperative analgesia following breast surgery. Peripheral blocks provide a reasonable degree of analgesia without causing significant side effects. R. Blanco introduced ultrasound (USG)-guided pectoral nerve (PECS) block

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as an alternative to the thoracic epidural and thoracic paravertebral block for daycare breast surgery.[2] The procedure-specific pain management (PROSPECT) guideline for oncological breast surgery recommends employing USG-guided PECS block as an alternative to thoracic paravertebral block in conjunction with systemic analgesics.[3]

Anaesthesiologists could offer a potentially more accurate plane targeting and less time-consuming strategy by instilling drugs in the desired interfascial planes (direct PECS block) or placing interfascial catheters intraoperatively for continuous administration of local anaesthetic (LA) agents for prolonged postoperative analgesia.[4] In this trial, we assessed single-shot direct intraoperative instillation of medication to extend analgesia rather than placing interfascial catheters because of the significant risks of catheter blockage from blood collection, dislodgement, or infection and the operating surgeon's unwillingness. We hypothesised that the addition of dexmedetomidine as an adjuvant with levobupivacaine would prolong the duration of postoperative analgesia. The primary objective was to compare the duration of analgesia, defined as the time in hours, to the first request for postoperative analgesics [numerical rating scale (NRS) ≥4] in patients undergoing modified radical mastectomy (MRM) under general anaesthesia (GA) and direct PECS block using levobupivacaine with or without dexmedetomidine. The secondary objectives were to compare the pain scores at rest and movement at different time points, the total amount of morphine consumption in the first 24 h, and the incidence of any intervention-related adverse events.

METHODS

This randomised, double-blind controlled trial was conducted from January 2021 to June 2022 at a tertiary care hospital on the patients undergoing MRM under GA after obtaining Institutional Ethics Committee approval (vide letter no. 847/IEC/IGIMS/2019, dated 23/12/2020) and registration of trial with the Clinical Trials Registry-India (vide registration number CTRI/2020/12/030004, accessible at www.ctri.nic.in/). Written informed consent was obtained from all the participants to use their data for research and educational purposes (the study protocol was explained in their native language). The study procedures follow the guidelines of the World Medical Association and are conducted in accordance with the Declaration of Helsinki, 2013 and good clinical practice.

Female patients diagnosed with breast cancer, aged 18 to 60 years, belonging to the American Society of Anesthesiologists physical status (ASA-PS) I or II, and posted for MRM under GA were included in the study. Patients with a history of allergy to LA, bleeding diathesis, deranged liver function, or locally advanced breast malignancy with infiltration of the chest wall were excluded from the trial.

After enrolment in the study, patients were assessed preoperatively and educated to rate pain using NRS scores 0–10; 0 = no pain, 1–3 = mild pain, 4–6 = moderate pain, and 7–10 = severe pain. Standard fasting guidelines were followed, and all patients were premedicated with diazepam 5 mg and ranitidine 150 mg orally in the night and morning before surgery.

Patients were randomly assigned to Group L and Group DL using a computer-generated random number table (http://www.random.org). Sealed, opaque envelopes concealed study group allocation until the study drugs were prepared. An independent anaesthesiologist prepared the study drug. The patient, attending anaesthesiologist, and surgeon were unaware of the group allocation. Group L received 20 ml of 0.25% levobupivacaine, and Group DL received 20 ml of 0.25% levobupivacaine with 0.5 μg/kg of dexmedetomidine.

In the operation theatre, an 18G intravenous (IV) line and standard ASA monitoring [non-invasive blood pressure, electrocardiogram, and pulse oximeter] were established. Baseline haemodynamic parameters like heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were recorded. All patients received GA using the uniform standard technique. Induction was done with IV propofol (2 μg/kg) and fentanyl citrate (2μgm/kg). Intermittent positive pressure ventilation with oxygen – medical air – isoflurane with IV vecuronium (0.8 mg/kg) for neuromuscular blockade was used for maintenance. The trachea was intubated with the cuffed endotracheal tube of appropriate size to secure the airway. IV ondansetron (4 mg) and dexamethasone (4 mg) were given 30 minutes before the end of the surgery for antiemetic prophylaxis. IV paracetamol (15 mg/kg) was used intraoperatively for analgesia.

After resection of the tumour and securing haemostasis, under strict aseptic precaution, 10 ml of the study drug was injected under direct vision between the pectoralis major and pectoralis minor and 10 ml between

pectoralis minor and serratus anterior muscles by the operating surgeon (direct PECS block). IV bolus of atropine (0.04 mg/kg) was used to treat any significant bradycardia (defined as HR < 60/min and MAP < 65 mm of Hg) following the administration of the study drug. All patients were shifted to the anaesthesia care unit (PACU) postoperatively. IV paracetamol (15 mg/kg) was administered 8th hourly daily for postoperative analgesia. IV morphine (0.1 mg/kg, a minimum dosing interval of 4 h, and a maximum allowable dose of 0.6 mg/kg in 24 h) was used as rescue analgesia on the NRS rating of >3. The time of request for the first rescue analgesia from the immediate postoperative period was recorded. Haemodynamic parameters and pain scores at rest and movement by requesting patients to turn laterally towards the operative side just after shifting the patient in PACU and then at 2 h, 4 h, 8 h, 12 h, and 24 h, were assessed and recorded using the NRS scores by the attending anaesthesiologist. The total amount of morphine given in the first 24 h after surgery was calculated and documented. Incidence of bradycardia and use of IV atropine to treat significant bradycardia were recorded.

The sample size for the trial was based on the study conducted by Shaiqa Manzoor *et al*.,[5] who reported the mean time in minutes to rescue analgesia in the group receiving PECS block with bupivacaine was 726.4 (standard deviation [SD]: 155.3) and that with bupivacaine plus dexmedetomidine was 1024.0 (SD: 124.9). The sample size required in each arm of the study was calculated according to the formula given by Snedecor and Cochran (1989). Thus, assuming 90% power and 95% confidence interval, the minimum calculated sample size for each arm was 30 (total = 60).

Data were coded and recorded in the Microsoft Excel spreadsheet program. Statistical Package for Social Sciences (SPSS) program (version 23.0 NY: International Business Machines Corp, USA) was used for data analysis. Descriptive statistics were elaborated as means (SD), medians [interquartile range (IQR)] for continuous variables, and frequencies for categorical variables. Data were presented graphically wherever appropriate for data visualisation. Most data (time to first rescue analgesia, change in NRS score at rest and movement over time, total opioid consumption, and haemodynamic parameters over time) were found to be non-normally distributed. Hence, the non-parametric Wilcoxon–Mann–Whitney U-test was used for group comparisons. The incidence of bradycardia and atropine use was compared between the two groups using the Chi-square and Fisher exact tests, respectively. Statistical significance was kept at $P < 0.05$.

RESULTS

Of 70 patients, 60 (30 in each group) received the intervention and finished the final analysis [Figure 1]. Demographic information was comparable for both groups [Table 1].

The mean time of the first analgesic requirement in Group L was 7.70 (SD: 2.67) [95% confidence interval (CI): 6.75, 8.65] h, and that in Group DL was 18.53 (SD: 2.52) (95% CI: 17.63,19.44) h. The median time of the first analgesic requirement, which was considered as the duration of analgesia, was 8 (IQR: 6–8) h in Group L and 18 (IQR: 16–20) h in Group DL (W = 17.000, $P < 0.001$). The range of the first analgesic requirement time in Group L was 4–19 h, whereas in Group DL, it ranged from 12 to 22 h. Thus,

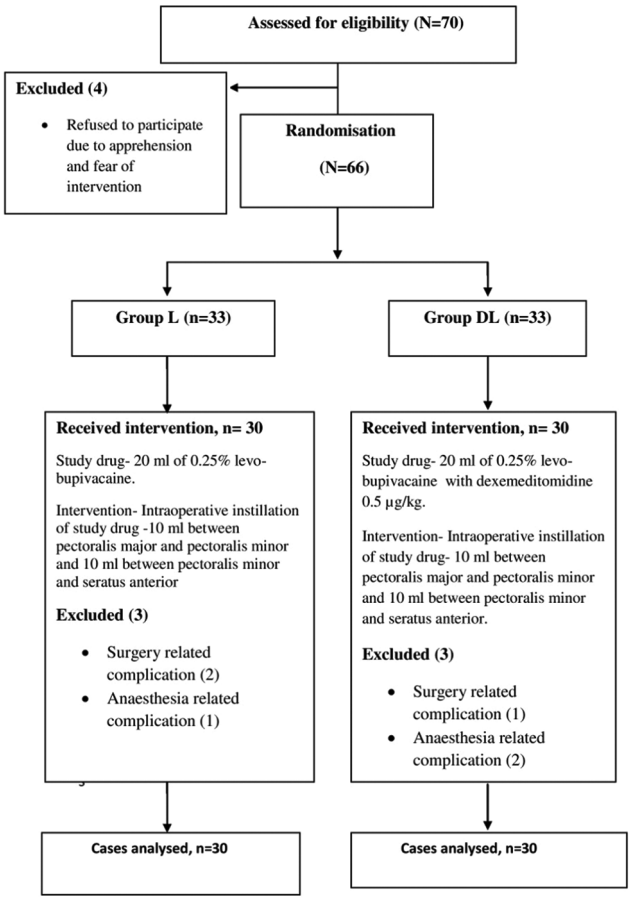

Figure 1: Consolidated Standards of Reporting Trial (CONSORT) diagram showing the flow of patients through various stages of the randomised trial. Group L=levobupivacaine, Group DL=Levobupivacaine with dexmedetomidine

we noticed that the median and mean were roughly comparable, but the data distribution differed in both groups, as depicted in the violin plot [Figure 2].

The generalised Estimating Equations method was used to explore the difference in change in NRS at rest and movement at different time points between the two groups. In Group L, the mean NRS score at rest was substantially higher at 4 h (P = 0.003) and 8 h (P < 0.001) postoperatively. In Group L, resting NRS >4 was recorded at 8 h, whereas in Group DL, it was recorded at 12 h. Additionally, we observed a significant difference in the trend of NRS at movement over time between the two groups. In Group L, the NRS at movement differed significantly from the immediate post-operative (0 h) to 4 h, 8 h, 12 h, and 24 h. In Group DL, the NRS at movement differed significantly from the 0 h time point at 8 h, 12 h, and 24 h. The maximum change from the 0 h time point in Group L was observed at 24 h, whereas in Group DL, it was observed at 12 h. Compared to Group DL, the mean NRS in Group L on movement was considerably higher at 2 h (P < 0.001), 4 h (P < 0.001), and 24 h (P = 0.020) postoperatively [Figure 3].

Group L had a mean total opioid consumption of 12.53 (SD: 2.29) (95% CI: 11.71, 13.35) mg in the first 24 h. In comparison, Group DL had a consumption of 6.93 (SD: 1.89) (95% CI: 6.25, 7.60) mg of opioids, which was statistically significant [Figure 4]. The total opioid use in 24 h in Group L and Group DL was in the range of 7–16 mg and 0–12 mg, respectively. The single peak on the density distribution graph of Group DL indicates the uniform distribution of data with roughly equal mean and median values. In contrast, Group L had several peaks and a right skew, showing a non-uniform distribution with a mean greater than the median [Figure 4].

The mean baseline haemodynamic parameters (HR, MAP) and SpO_2 were similar in both groups. The MAP, SpO_2, and HR did not significantly differ at any time points monitored, except the HR following the instillation of the study drug. HR was significantly lower in group DL [63.17 (SD: 5.03) (95% CI: 61.37, 64.97)] than in Group L 82.73 (SD: 6.92) (95%CI: 80.25, 85.20] after the instillation study drug. A significant difference (P = 0.010) in the incidence of bradycardia was noted between Group L (n = 2) and Group DL (n = 11). However, just six patients in Group DL and none in Group L required atropine for the management of symptomatic bradycardia, which was also substantially high (P = 0.020) [Table 2]. No other adverse event was noted due to study intervention.

Table 1: Demographic and operative data

Variables	Group L (*n*=30)	Group DL (*n*=30)
Age (years)	48.33 (14.80)	49.60 (13.05)
ASA physical status: I/II	8/22	7/23
Weight (kg)	62.13 (8.76)	60.87 (8.12)
Duration of surgery (min)	89.63 (10.46)	90.12 (9.72)
Diagnosis: Carcinoma Breast: Right/Left	13/17	18/12

Data expressed as mean (standard deviation) or numbers. ASA=American Society of Anesthesiologists, *n*=number of patients, L=levobupivacaine, DL=dexmedetomidine with levobupivacaine

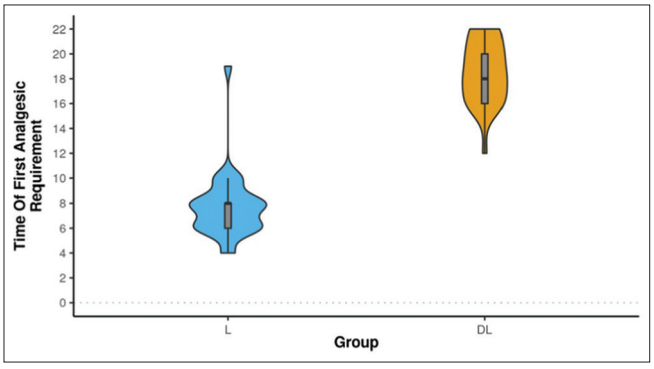

Figure 2: Violin plot showing median time with 75th and 25th centiles of the first analgesic requirement of the two groups. L = levobupivacaine, DL = dexmedetomidine with levobupivacaine

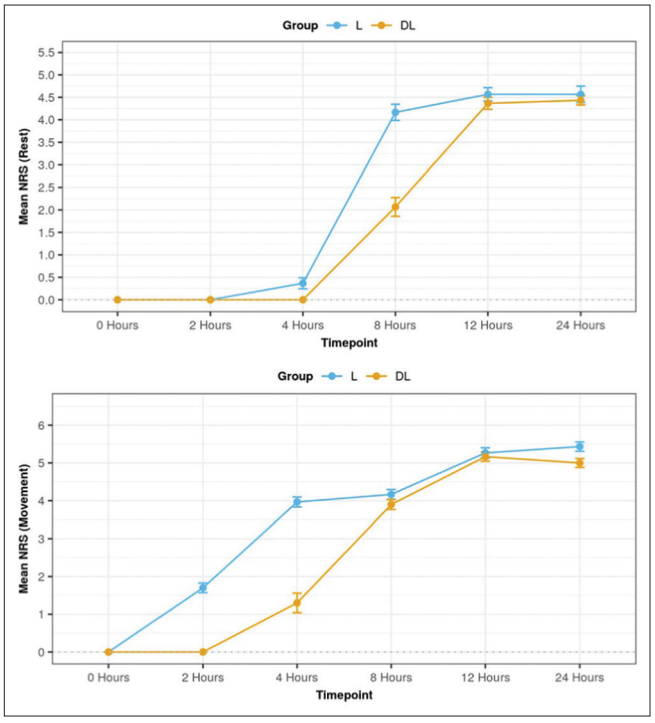

Figure 3: Pain scores as measured using NRS score. NRS = Numerical rating score; L = levobupivacaine and DL = dexmedetomidine with levobupivacaine

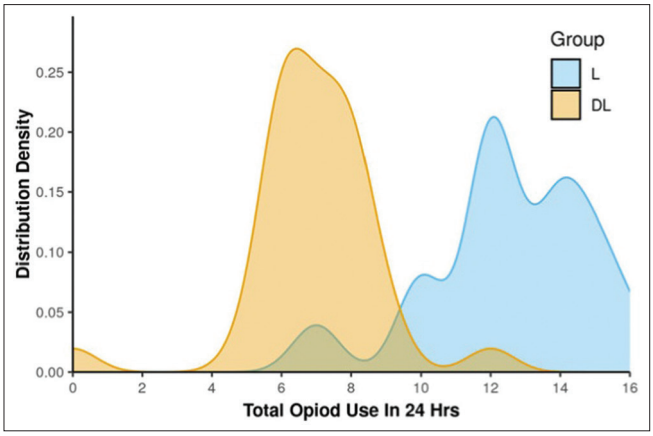

Figure 4: Density plot depicting the total opioid consumption in the first 24 h. L = levobupivacaine, DL = dexmedetomidine with levobupivacaine

Table 2: Incidence of bradycardia and requirement of atropine

Variable	Group L (*n*=30)	Group DL (*n*=30)	χ^2	*P*
Bradycardia: Yes/No	2/28	11/19	7.954	0.005
Atropine requirement: Yes/No	0/30	6/24	6.667	0.024

Data expressed as numbers. *n*=number of patients, L=levobupivacaine, DL=dexmedetomidine with levobupivacaine

DISCUSSION

We found that the duration of postoperative analgesia was extended by a factor of 2.4 when dexmedetomidine was used as an adjuvant with levobupivacaine for direct PECS block. While recording the postoperative pain scores, it was observed that dexmedetomidine improved the quality of postoperative analgesia by decreasing pain scores both at rest and in movement. Total opioid consumption in the first 24 hours after surgery was also substantially reduced by 45% after the addition of dexmedetomidine.

Among Group L, we observed an intriguing fact that the distribution of the time of first analgesic requirement and total opioid usage in the first 24-hour period was not uniform, unlike what was observed in Group DL. This suggests that the analgesic effect was more consistent and predictable when dexmedetomidine was added. This indirectly confirms our hypothesis that the quality and duration of postoperative analgesia were enhanced by the addition of dexmedetomidine to levobupivacaine.

PECS block lessens discomfort following MRM surgery.[6,7] Compared with erector spinae plane (ESP), the PECS block is more effective in terms of postoperative analgesia and opioid consumption.[8] It has also demonstrated benefits over the thoracic epidural and thoracic paravertebral block, such as stable haemodynamic parameters and fewer block-related side effects.[9] PECS block is typically given before surgery under USG guidance. However, it has several limitations, such as unavailability or lack of familiarity with USG, distorted sonoanatomy due to cancer infiltration in the chest wall, and large/fungating cancer mass that makes it difficult to position the USG probe. To circumvent the limitations of USG, we administered an intra-operative direct PECS block that allowed us to see the inter-fascial plane with naked eyes following surgical dissection.

When used as an adjuvant to LA, dexmedetomidine has an antihyperalgesic action and improves analgesia, which reduces the need for rescue analgesics without causing any adverse side effects.[10] It also reduces the uptake of LA by causing vasoconstriction, thus prolonging the total duration of LA action.[10]

Installation of the drug in between the fascial planes of the pectoralis major and minor muscles (PEC1) blocks lateral and medial pectoral nerves. It gravitates into the thoracic cavity's lateral wall of the thoracic cavity in between the fascial planes of pectoralis minor and serratus anterior muscles (PEC2). It moves upwards to the axilla to block intercostobrachial, third to sixth intercostals, and long thoracic and thoracodorsal nerves.[11] As a result, it offers total blockage of the nerves supplying the anterior chest wall and is a suitable option for breast surgery with axillary dissection. These interfascial compartments are readily visible following surgical excision; as a result, a smaller dosage produces an effective analgesic. That is why we instilled 10 ml of the study drug in each fascial plane despite the recommended volume of 20 ml in the PEC2 plane. Other studies that used preoperative PECS block under USG guidance used higher doses of dexmedetomidine (1 μg/kg) and a greater volume of the drug (30 ml). PECS block administered intraoperatively improved plane targeting, improving outcomes with reduced LA volume and dexmedetomidine dosage. This could be the cause of our superior results (140% increase in analgesic duration) at smaller volume (20 ml) and low adjuvant dose (0.5 μg/kg of dexmedetomidine), in comparison to around 50% increase observed in other studies.[5,12]

Compared to previous research, our observation showed a greater prevalence of bradycardia (37%) immediately following the instillation of the study drug in Group DL. The administration of a study drug

containing dexmedetomidine on the raw operated area might have accelerated drug absorption, leading to a brief episode of bradycardia because of central sympathetic suppression due to α-adrenoceptor agonist properties of dexmedetomidine.[13] We did not experience any other block-related adverse event.

Previous studies have also concluded that intraoperative lateral PECS block under direct vision is a novel technique for postoperative analgesia for breast reconstruction with sub-pectoral implant placement.[14,15] Hinchcliff *et al*.,[16] pointed out that intra-operative placement can be more accurate regarding plane targeting, save time, and extend the technique's usefulness to practitioners not trained in the USG-guided technique.

The major strength of this study is the assessment of pain scores at rest and movement along with study of distribution of duration of analgesia and total opioid consumption. The postoperative analgesic effect was assessed for the first 24 h using the NRS score, which is considered less accurate than the minimal clinically significant difference (MCID) in evaluating change in postoperative pain.[17] Any level of sedation in the postoperative period can affect the patient's cognitive function, thereby affecting the reported pain score. Another limitation of our trial was the absence of a passive control group.

Future clinical trials are suggested to evaluate the benefits and drawbacks of continuous, direct PECS block after putting an epidural catheter in the fascial plane. Further studies can be designed to find whether the lesser volume can produce effective analgesia in direct PEC block. The multi-faceted benefits of direct PECS block can be further evaluated by assessing the quality of recovery (QoR) score.

CONCLUSION

Direct PECS block is an effective method that provides satisfactory postoperative analgesia after modified radical mastectomy. Adding dexmedetomidine (0.5 μg/kg) to 20 ml of 0.25% levobupivacaine further prolongs the duration and enhances the quality of analgesia.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding authors) and shall be shared upon request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

ORCID

Nidhi Arun: https://orcid.org/0000-0003-4466-7424
Raja Avinash: https://orcid.org/0000-0002-7921-5770
Annu Choudhary: https://orcid.org/0000-0003-2893-2267

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