Original Article

Opioid-free anesthesia for breast cancer surgery: A comparison of ultrasound guided paravertebral and pectoral nerve blocks. A randomized controlled trial

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Abstract

Background and Aims: Pectoral block (PECS)-based anesthesia without opioids decreases analgesic requirement, pain scores and post-operative nausea vomiting (PONV) compared to conventional opioid-based general anesthesia in patients undergoing modified radical mastectomy and axillary dissection (MRM-AD). We compared PECS versus Paravertebral Block (PVB) in providing an opioid free, nerve block-based regimen. Outcomes of interest were post-operative analgesic requirement, duration of analgesia, PONV and patient and surgeon satisfaction.

Material and Methods: This randomised controlled study involved 58 adult ASA I-III patients posted for MRM-AD. After randomization patients were induced with propofol and maintained on spontaneous ventilation with isoflurane (0.8-1.0 MAC) through i-gel. Ultrasound-guided PECS or PV blocks (30 ml of 0.1% lignocaine + 0.25% bupivacaine + 1 μg/kg dexmedetomidine) were administered. Post-operative pain scores, non-opioid analgesic requirement over 24 hours, PONV, satisfaction of surgeon and patient were measured.

Results: Between the two groups, there was no difference in demographics, ASA status, location and volume of breast tumour excised or the duration of surgery. The time from block to incision was significantly longer in the PV group ($P = 0.01$). There was no difference between the two groups in terms of intra and post-operative parameters, and the median VAS scores for pain at rest or during shoulder abduction were similarly low in both the groups.

Conclusion: Both blocks result in equally prolonged analgesia and preclude requirement of opioid analgesics intra and post-operatively. PECS block is associated with lesser time to allow incision. Complications are low in both the groups. Routine use of these blocks to avoid opioids may be studied further.

Clinical trial number – Registered in Clinical Trials Registry of India (CTRI/2017/02/007897). http://ctri.nic.in.

Keywords: Modified radical mastectomy, nerve block, opioid free anesthesia, paravertebral block, PECS block

Introduction

Breast cancer surgery (modified radical mastectomy with axillary dissection) under general anesthesia is associated with >30%-40% incidence of post-operative nausea vomiting (PONV) and acute post-operative or chronic debilitating pain.[1] Opioids increase the incidence of nausea, respiratory depression, ileus, increased post-operative pain (hyperalgesia), tolerance and possible metastasis. Previously, we have demonstrated that this surgery done under opioid-free anesthesia with pectoral (PECS) block resulted in decreased analgesic requirements, pain scores and PONV

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than in patients who were operated under opioid-based anesthesia and analgesia.[2] With conflicting reports of the superiority of pectoral (PE) block over paravertebral (PV) block in opioid-based anesthesia for breast surgery,[3-6] we wished to compare these two blocks when administered under ultrasound guidance for breast surgery, in an opioid-free environment. We hypothesized that in a background of opioid-free anesthetic regimen, PECS 1 and 2 block with dexmedetomidine will provide better analgesia and less non-opioid analgesic requirement perioperatively than the PV block. Primary outcome of interest was the post-operative analgesic requirement and secondary outcomes were the duration of analgesia, PONV and patient and surgeon satisfaction.[3-6]

Material and Methods

Study Design: In a 500-bedded tertiary care teaching hospital, we randomised all adult ASA I-III patients posted for modified radical mastectomy with axillary resection (MRM) to receive ultrasound-guided PE block or PV block, under anesthesia without any opioids. The study was approved by the Institutional Ethics Committee (T/IM-NF/TEM/15/32) and registered in Clinical Trials Registry of India (CTRI/2017/02/007897).

Study Population: We assessed the eligibility of all ASA I-III patients admitted for MRM between September 2016 and June 2017. Lack of patient consent, coagulopathy, allergy to local anesthetics (LAs) and chronic therapy with opioids were criteria to exclude patients. In the evening before surgery, an anesthesia resident discussed the study (risks vs. benefits, voluntary participation, procedures) with the patients. The concept of VAS scoring for pain and the reason for avoiding opioids was explained. A written informed consent was signed by the patient in the presence of the surgeon and the anesthetist the next day morning prior to surgery. Fifty-eight patients were recruited in this trial planned as a double-blind randomised controlled trial. The flow of patients in the study is shown in Figure 1.

Study Interventions: The patients were randomly assigned to receive either PECS (PE) or PV blocks under ultrasound guidance. In the PE group, an I-gel was inserted after administering injection midazolam 1-2 mg and induction with intravenous propofol (2-3 mg/kg). Patient was maintained on spontaneous ventilation (assisted if needed with pressure support to keep $ETCO_2$ between 30 and 40 mmHg). Isoflurane was delivered to achieve 0.8-1.0 MAC. After local anesthetic (LA) infiltration, under ultrasound guidance PECS block was administered at the level of the fourth rib in

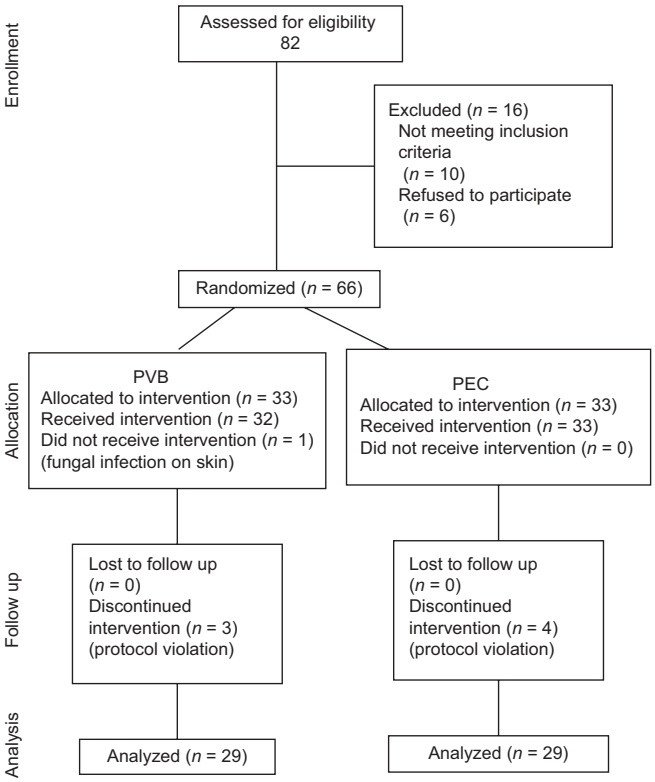

Figure 1: Consort diagram showing patient flow

the mid axillary line. A single prick technique (modified from the original description of Blanco *et al.*) was used.[5] Keeping the needle tip in view, 20 and 10 ml of the solution (0.3 ml/kg 0.5% bupivacaine, 0.3 ml/kg 2% lignocaine with adrenaline and 1 μg/kg dexmedetomidine not exceeding toxic dosage of either LA agent) was administered: first at the level of fourth rib, at the serratus anterior and then by withdrawing the needle to lie in between the pectoralis minor and major muscles respectively (PECS II and PECS I blocks, respectively). Drug spread in the correct plane was documented and incision allowed in 10-15 minutes after testing for absence of response to skin pinch stimulus with forceps.

In the PV group, after I gel insertion similar to the PE group, the patient was turned lateral. After LA infiltration, under ultrasound guidance, a PV block was administered at the level of fourth vertebra. The needle tip was visualised and 30 ml of drug (0.3 ml/kg 0.5% bupivacaine, 0.3 ml/kg 2% lignocaine with adrenaline and 1 μg/kg dexmedetomidine not exceeding toxic dosage of either LA agent) was injected with the depression of the parietal pleura being the end point to identify a successful block. Drug spread in the correct plane was documented and incision allowed in 10-15 minutes after testing for absence of response to skin pinch stimulus with forceps. The procedural details were similar to our previous study.[2]

In either group, if one or more of three predefined signs (20% rise in the baseline heart rate or blood pressure, purposeful movement of limbs or facial grimacing) was noted on incision, add on analgesia was administered (Inj. paracetamol 1 gm, local infiltration with 5-10 ml 1% Lignocaine and deepening of the plane of anesthesia up to 1.2 MAC. Incision was attempted again in 5 minutes. Block inadequacy was defined as recurrence of any of the three predefined signs after the rescue. In case of block inadequacy, the anesthetist could administer opioids as required if previous methods failed.

In the post-operative period, VAS scores were documented and the patient was administered 1 gm paracetamol (maximum dose of 4 gm in 24 hours) if the VAS score was >4, or if patient demanded. If VAS was >6, or beyond full dose (4 gm in 24 hours) of paracetamol, patient was administered 75 mg diclofenac intravenously. No oral analgesics were prescribed in the first 24 hours after surgery.

Randomization: Random assignment was ensured by using a sequence generated by 'Research Randomizer' which is a free resource for researchers and students (www.randomizer.org). Allocation concealment was ensured as the numbers were put into sealed opaque envelopes and drawn up by the anesthetist scheduled to administer the block. The surgeon, nurse, patient, relative and data collector were blinded to the type of block administered; the block was administered after induction of anesthesia and before the surgeon or nurse were present, with a sham application of betadine on the front of chest in all cases.

Study outcomes

Analgesic (paracetamol) consumption between the two groups in the first 24 hours was selected as the primary outcome as it helped to formalize an opioid-free post-operative regimen. Also, it maintained uniformity with previous studies.

Pain: Visual analogue scale (VAS) pain scores were recorded in the post-operative period on a 10-cm scale half hourly for the first hour, hourly for next two hours and second hourly thereafter for 24 hours. Data were entered as the VAS scores and the total number of times that analgesic was administered.

Duration of Analgesia: The time to first request for or administration of non-opioid analgesic after the surgery or a VAS score ≥4, whichever was earlier, was defined as the duration of block.

PONV: PONV was defined as any nausea, retching, or vomiting occurring during the first 24 hours after surgery. In the post anesthesia care unit and the ward, patients were asked to report nausea "which makes you uncomfortable" or an event of retching or vomiting in a yes/no format at 4-hour intervals. Data was entered as PONV present/absent per patient.

Satisfaction Scores: Surgeon and patient satisfaction scores were obtained at the end of surgery and at 24 hours, respectively, on a Likert scale of 1-5 with 1 being most dissatisfied and 5 being very satisfied. Overt recall of intraoperative events was also enquired of the patient.

Others: Observers who were blinded to the study groups recorded the intraoperative hemodynamic parameters (noted from the anesthesia charts), volume of breast tissue excised, location of the tumour and length of stay in post anesthesia care unit. Complications such as pneumothorax, severe hypotension or epidural anesthesia were noted.

Sample size and statistical analysis: The sample size was calculated based on a pilot study. Taking the mean paracetamol consumption as 1.560 mg with SD 520 mg, for 25% difference in 24 hour post-operative paracetamol consumption at a significance level of 0.05 and power of 0.8, we required a minimum of 28 patients in each group. Adjusting for possible protocol violations like inadvertent or routine analgesic administration (instead of administration based on VAS scores or patient demand) in the post-operative period or missed VAS score assessments, it was decided to recruit 65 patients.

SPSS 21 was used for analysis. Normality of data was checked by Kolmogorov–Smirnov test and expressed as Mean (Standard Deviation) or Median (Inter quartile Range). Continuous variables were compared by using Student's unpaired *t* test, and categoric variables by χ^2 test if variables were normally distributed, else the alternate tests for non-parametric variables were used. The pain scores were considered continuous variable. Confidence intervals were calculated for statistically significant differences

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on request.

Results

We recruited patients from July 2016 to June 2017. The participant flow diagram is presented in Figure 1. Of the 82 patients screened for eligibility, 16 were excluded (6 did not give consent, 6 were on therapy for chronic pain, and 4 had deranged coagulation profile or petechial patches on skin). One patient in PV group was excluded after randomization as the skin on her back appeared to

have a fungal infection. Of the 65 patients who received the intervention, 7 patients were excluded from the final analysis due to protocol violation. Among the two groups, there was no difference in age, body mass index, education, ASA status, location and volume of breast tumour excised or the duration of surgery. It was observed that the time from block to incision was significantly more in the PV group ($P = 0.01$) [Table 1].

Table 1: Baseline characteristics of patients enrolled in the study

Variable	PE (*n*=29)	PV (*n*=29)	*P*
Age (years)	52.4, 12.3	51.8, 10.5	0.8
BMI (kg/m^2)	23.6, 4.2	23.0, 4.2	0.6
Volume of Tumour (cc)	698.1, 445.0	653.4, 504.7	0.7
Duration from Block to Incision (min)	24, 16	42, 31	0.01
Duration of Surgery (min)	97, 42	105, 39	0.5
ASA Category (*n*, %)			0.9
I	16, 55	16, 55	
II	19, 35	11, 38	
III	3, 10	2, 7	
Education Level (*n*, %)			0.9
No formal education	7, 24	8, 28	
Up to 6th Grade	9, 31	8, 31	
Up to 12th Grade	6, 21	4, 14	
Graduate	5, 17	7, 24	
Post Graduate	2, 7	1, 3	
Breast Quadrant (*n*, %)			0.7
Upper Medial	1, 3	3, 10	
Lower Medial	1, 3	3,10	
Upper Lateral	10, 35	11, 38	
Lower Lateral	1, 3	1, 3	
Central	7, 24	5, 17	
More than one quadrant	9, 31	6, 21	
Block Failure - need for intraoperative opioids	0	0	

The values are in mean±SD and number (%). PE=Group getting PECS block; PV=Group getting paravertebral block; BMI=Body mass index; ASA=American Society of Anesthesiologists

There was no significant difference between the two groups in terms of requirement of add on analgesia intraoperatively (no cases of inadequate block requiring opioid administration intraoperatively- two patients in PV and three in PE group needed deepening of plane of anesthesia to 1.2 MAC and local site infiltration of 5-10 ml of 1% lignocaine at incision as per protocol), time in the recovery room, time to administration of first analgesia, requirement of post-operative analgesic or PONV [Table 2]. The median VAS scores for pain at rest or during shoulder abduction was also similar in both the groups [Table 3].

There was neither difference in intra or post-operative hemodynamic parameters nor in block-related complications such as pneumothorax or vessel puncture. One patient in each group had PONV grade 2 and received ondansetron.

Discussion

In this study, we demonstrated that modified radical mastectomy with axillary dissection for breast cancer can be performed without using any opioids intra or post-operatively. Either PECS or PV block using local anesthetic and dexmedetomidine along with isoflurane inhalation anesthesia may be used. The requirement for intraoperative opioid rescue and post-operative pain, nausea, analgesic requirements and block-related complications were similar in both the groups.

In spite of adequate evidence for reduced opioid requirement when the truncal nerve blocks are used, there is limited evidence of avoiding opioids altogether in breast surgery. In a previous study, we compared opioid-based general anesthesia to opioid-free anesthesia under PECS block and found improved patient outcomes in terms of less PONV, analgesic requirement and pain scores.[2] Various reasons have been put forth to how a PV block directly blocks the spinal

Table 2: Comparison of block characteristics in the two groups

Variable	PE (*n*=29)	PV (*n*=29)	Mean Difference (95% CI)	*P*
Post-operative paracetamol consumption (mg)	1.21 (1.2)	1.07 (1.1)	0.14 (-0.5 to 0.7)	0.7
Duration of Analgesia (min)	798 (598)	799 (606)	1.6 (-318.5 to 315.4)	0.9
Surgeons satisfaction score (*n*)				0.6
4	8	6		
4.5	2	1		
5	19	22		
Patients' satisfaction score (*n*)				0.3
3	1	0		
4	2	5		
4.5	1	0		
5	25	24		
Post-operative nausea or vomiting (*n*)	2	1		0.5
Time in post-operative recovery room (min)	61.5 (15.6)	66.8 (18.4)		0.7

Values are in mean (SD)

Table 3: Comparison of pain scores 24 h after surgery

Time after Surgery (h)	Vas Score PE (Median, IQR)	VAS score PVB (Median, IQR)	*P*
0 r	0,0	0,0	0.9
0 m	0,0	0,0	0.6
0.5 r	0,2	0,2	0.9
0.5 m	0,2	0,2	0.8
1 r	0,2	0,2	0.7
1 m	2,3	1,2	0.2
2 r	2,2	1,2	0.6
2 m	2,3	2,3	0.3
4 r	2,3	1,3	0.7
4 m	2,4	2,3	0.7
6 r	2,3	1,2	0.2
6 m	2,4	2,3	0.2
8 r	2,2	2,2	0.9
8 m	2,3	2,1	0.7
10 r	2,2	2,3	0.8
10 m	2,4	2,3	0.9
12 r	2,3	1,2	0.5
12 m	3,4	2,2	0.4
14 r	2,3	0,2	0.1
14 m	2,4	2,3	0.2
16 r	2,2	0,2	0.4
16 m	2,2	2,3	0.8
18 r	1,2	1,2	1
18 m	2,2	2,3	0.8
20 r	0,2	1,2	1
20 m	2,2	2,1	0.6
22 r	2,2	1,2	0.6
22 m	2,2	2,2	0.5
24 r	2,3	1,2	0.4
24 m	2,3	2,3	0.6

r - at rest; m - with movement (above shoulder abduction)

nerves, extends laterally to block the intercostal nerves, extends medially into the epidural space through the intervertebral foramina and affects the sympathetic chain, leading to profound analgesia for MRM with axillary dissection.[7,8] Similar reasons have also been forwarded in favour of the PECS block. With the controversy between PECS and PVB being better for MRM gaining momentum,[4-6] we compared the efficacy of these two blocks in an opioid-free technique. Unlike the studies of Kulhari *et al.*, Wahba and Kamal, and Syal and Chandel, we did not find any significant difference between the two groups of patients except the time from block to incision being greater in the PVB group, which is intuitive with the required patient positioning involved. We speculate that this difference may have arisen due the effects of dexmedetomidine in our drug mixture and avoiding of opioids perioperatively.

Among studies which have used opioids perioperatively, Bashandy *et al.* have compared GA alone with PECS blocks and reported better results with the latter.[9] Others have then reported better outcomes in GA with PECS block than GA with single-level PV block in this patient population.[4,5] Authors have suggested that no single nerve block technique effectively covers the entire breast tissue.[10] There have, however, been reports of breast surgeries performed under nerve block with sedation, without muscle paralysis, as in our study.[11-13] Multiple nerve blocks may not be socially or practically acceptable and may lead to toxic volumes of LA being used.

Opioid-free anesthesia has been advocated for various procedures such as surgeries for the morbidly obese, for chronic opioid addicts, patients with sleep apnea and cancer surgeries.[14,15] Various methods have been used to provide opioid-free anesthesia – adjuvants used range from intravenous infusions of lignocaine, ketamine, dexmedetomidine, clonidine or β blockers.[16-18] Dexmedetomidine has anxiolytic, sympatholytic, and analgesic properties and has been shown to lower post-operative pain scores, opioid consumption, and the risk of opioid-related adverse events similar to lignocaine. The combination of intravenous lignocaine and dexmedetomidine has been used previously in opioid-free anesthesia for spine surgery and cholecystectomy.[16,18] We postulate that slow absorption of large volume of LA and dexmedetomidine deposited in the block may be contributing in a similar manner.

Using inhalational sedation with the nerve block in place of an intravenous agent may be seen as a limitation in our study. BIS monitoring not being routine in breast surgery at the time of this study, we preferred to use isoflurane with air as the agent for sedation with close monitoring of MAC values. We avoided nitrous oxide to decrease the risk of PONV. Although previous studies have suggested that propofol inhibits cancer recurrence and metastasis, the association between anesthetic agents and the recurrence of breast cancer has not been clearly investigated.[19] The team of doctors and nurses caring for these patients in the perioperative period were similar for both groups- the team of surgeons and anesthetists was always a mix of one senior doctor with a minimum of 8 years experience with two or more trainees. All assessors were trained in VAS scoring. Seven patients needed to be removed from final assessment due to the post-operative analgesic protocol violation (analgesia was given in a time bound manner and not according to VAS score or patient request).

We feel the results of our study will have a wide generalisability, as the patients included and the protocol followed is a fairly standard one. Paracetamol and diclofenac which are used for post-operative analgesia and have sufficed in our population may need titration based on population-based pain thresholds.

Conclusion

We conclude that either PEC or PV block with dexmedetomidine and isoflurane sedation may be used safely as opioid-free anesthetic technique for patients undergoing MRM with axillary dissection in the perioperative period. Immediate benefits of avoiding opioids are apparent; long-term benefits in terms of improved long-term quality of life, decreased incidence of chronic pain after surgery and possible increased cancer-free survival will need further studies.

List of abbreviations

PEC/PE - Pectoral block; PVB - Paravertebral block; PONV - Post-operative nausea vomiting; ASA - American Society of Anesthesiologists; VAS - Visual analogue scale.

Declarations

Ethics approval and consent to participate: Details in methods section.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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