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Analgesic efficacy, immunomodulation and complications of Erector spinae plane block in breast cancer surgeries: A randomized controlled trial

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ABSTRACT

Background: To investigate the effect and drawbacks of different LA volumes and concentrations of ESPB on postoperative need for opioids and rescue analgesics, post-mastectomy acute neuropathic pain, and NK cells cytotoxicity.

Methods: 60 breast cancer patients, ranging in age from 18 to 70 and with an ASA I–II, were randomly assigned to receive ESPB with 20 ml 0.25% bupivacaine (Standard volume ESPB), 40 ml 0.125% bupivacaine (High volume ESPB), or no ESPB (GA only group) after being scheduled for surgery. The primary outcome was total morphine administered over the first 24 postoperative hours. The secondary endpoints were amount of rescue analgesia needed, acute neuropathic pain assessed by DN4 questionnaire, NKC cytotoxicity and complications.

Results: Total amount of morphine consumed was less in both ESPB groups compared with the control (1.13 ± 1.77 vs. 1.35 ± 3.15 vs. 9.58 ± 5.76, $p < 0.001$).

Ketorolac was less needed, as postoperative rescue analgesic, in both ESPB groups compared with the GA group Similar incidence of acute postoperative neuropathic pain was observed . NKC cytotoxicity did not differ among the three studied groups; however, the high volume of LA enhanced the postoperative cytotoxicity relative to the preoperative one. No complications of the block had been recorded and the incidence of PONV is less in ESPB groups than the control .

Conclusions: ESPB is an effective and safe analgesic modality as it attenuates the postoperative need for opioids and rescue analgesics, when bupivacaine is used in a dose of 50 mg with variable volumes and concentrations. It does not alter the incidence of acute post-mastectomy neuropathic pain; nevertheless, it delays its onset and mitigates its severity. Its role in enhancing the NK cells cytotoxicity needs further evaluation.

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Erector spinae plane block; Ultrasound guided; analgesia; NK cells; immunomodulation and Breast cancer surgery

1. Background

Breast cancer is the most frequent malignancy in Egyptian women (38.8%), and the most common surgical procedure is modified radical mastectomy (MRM) [1]. The chest wall, axilla, and ipsilateral arm experience severe acute nociceptive and neuropathic pain after breast cancer surgery [2]. Postoperative pain, nausea and vomiting, and anxiety are the most prevalent causes for an overnight stay following breast cancer surgery [3]. The ESP (Erector Spinae Plane) block is a revolutionary interfascial plane block widely used nowadays with variable volumes, and concentrations, injected in many surgeries involving different anatomical locations as the fascia of Erector spinae muscle starts cranially from the nuchal fascia and continues caudally to the sacrum and the block can cover many dermatomes [4]. volumes utilised ranged from 10 to 40 mL [5]; however, the effect of different volumes and concentrations has not yet been fully elucidated, either for the analgesic efficacy or for the drawbacks [6].

Acute postoperative pain following breast cancer surgeries encompasses both nociceptive and neuropathic components but in general the post-surgical acute neuropathic pain is under-diagnosed and when not optimally treated leads to chronic post-mastectomy pain [7].

NK cells play a pivotal role in the perioperative period in surveillance and protection against cancer metastases. Studies on the effect of many anaesthetics on NKC cytotoxicity have paved the way to other new regional anaesthesia techniques to be involved in this area [8–10].

Anti-tumor cell mediated immunity is negatively affected in the perioperative period by surgical stress, inhalational anaesthetics, and opioids. The anaesthetic

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approach can ameliorate this immunosuppression and evaluate if the innate immunity is competent of eliminating the ectopic malignant cells [11,12].

As a result, our primary aim is to investigate how different volumes and concentrations of ESPB are effective as an analgesic in breast cancer surgeries. Our hypothesis is that high-volume pre-emptive ESPB can enhance analgesia while also increasing or at least preserving NK cell cytotoxicity.

2. Methods

2.1. Study design

- On 19 November 2020, the ethics committee approved this study (IRB NO: 00012098), in conformity with the notions of the Helsinki Declaration (1964) and its later revisions. All participants signed a written informed consent form.
- The NCSS 2004 and PASS 2000 programs were used to compute the sample size.
- Between March 2021 and January 2022, a single-center, prospective, randomised controlled, experiment was conducted. It was triple-blinded as the intervention was unknown to patients, researchers and statisticians. The trial was prospectively registered at ClinicalTrials.gov (NCT04796363; date of registration: 03/2021).

2.2. Patients

Patients who were between the ages of 18 and 70 who had been scheduled for mastectomy and had ASA I–II were eligible for this study. A known allergy or contraindication to any medication used, cognitive dysfunction, history of previous breast surgery, morbid obesity (BMI of 40 kg/m2 or more), scoliosis, kyphosis or previous spinal surgeries, pregnancy, chronic opioid dependence, infection at the injection site, surgery lasting more than 90 minutes, and renal impairment were all considered exclusion criteria.

2.3. Randomization and blinding

A random table created by a computer (Graphpad Software, Inc, La Jolla, CA) and a 1:1:1 allocation ratio were used to assign patients to receive either ESPB with 20 ml 0.25% bupivacaine (**Standard volume ESPB**), or with 40 ml 0.125% bupivacaine (**High volume ESPB**), or no ESPB (**GA only** group). The study team was kept completely blind during the entire observation period.

2.4. Intervention

All patients received intravenous midazolam (0.05 mg per kg) and fentanyl (0.5 mg per kg) 3 minutes before ESPB in the block room. Ultrasound high-frequency linear probe (5–10 MHz) of SonoSite, S nerve, 2 D machine, USA was prepared and wrapped with clear covering (Tegaderm®) and applied in sagittal orientation while the patients were in the prone position. After skin preparation and sono-anatomical identification of T4 transverse process, 2 cc of 2% lidocaine was used to numb the skin and an 18-gauge Tuohy needle was advanced in-plane towards the tip of T4 transverse process. (Figure 1).

Hydrodissection by 2 ml of saline into ESP confirmed the proper needle tip location. Thereafter, we injected 20 ml bupivacaine 0.25% in the standard volume ESPB group and 40 ml bupivacaine 0.125% in the high volume ESPB group (Figure 2).

Both ESPB groups then had an epidural catheter inserted 2–3 cm over the tip of Tuohy needle under ultrasound guidance in T4-T5 interspace.

A piece of cotton soaked in icy water was used to test the adequacy of ESPB from T1 to T6 every 3 minutes throughout 15 minutes.

In the control group, for the purpose of blinding, the skin was infiltrated by the local anaesthetic and the catheter was leaved on the skin and similar to the intervention groups it was covered by opaque adhesive tape.

All patients were equal in terms of the same general anaesthesia provided. The trachea has been intubated after induction with 2.5 mg/kg Propofol, 1 µg/kg Fentanyl, and 0.15 mg/kg Cisatracurium. Maintenance was achieved by Isoflurane (1.2%) in O_2-air mixture

Figure 1. Ultrasound probe in parasagittal plane at level of 4th thoracic vertebra.

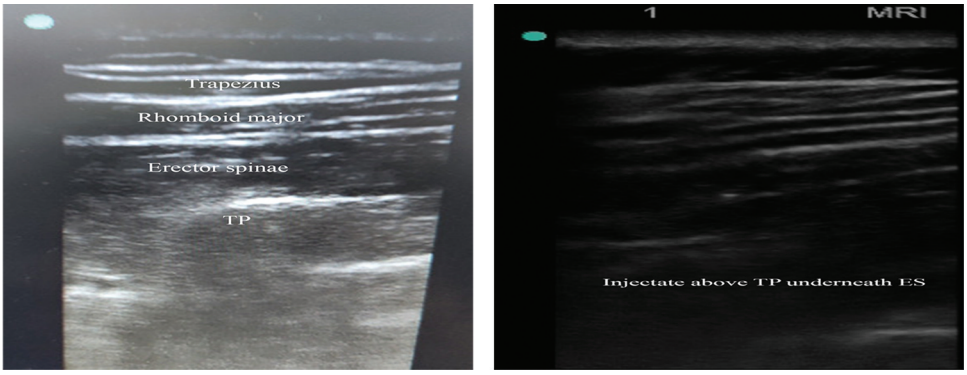

Figure 2. Left image: US scan of TP of 4th thoracic vertebra and the three muscles overlying it. Right image: Injectate in the fascial plane between TP of 4th thoracic vertebra and Erector Spinae muscle.

(1:1) and incremental doses of the muscle relaxant 0.03 mg/kg, led by train of four (TOF) count applying the nerve stimulator module of (TOF watch – Organon-Ireland).

Using the ventilator (Fabius GS- Drager-Germany), ventilation maintained for a target $ETCO_2$ from 35 to 40 mmHg.

Anaesthesia was halted after completing the procedure, residual neuromuscular block was treated with atropine 0.015 mg per kg and neostigmine 0.04 mg per kg, and the patients were transported to the post-operative anaesthesia care unit (PACU) for the following 24 hours.

2.5. Postoperative analgesia

The specialized regional anaesthesia team administered a bolus of bupivacaine in the epidural catheter at arrival to the PACU in the standard volume and high volume ESPB groups, with the same concentration and volume allotted to each group.

All variables were measured in by a physician who was not engaged in the research.

To establish intravenous morphine patient-controlled analgesia (PCA),{Mizuno, 2011 #217} 50 mg morphine was diluted with 45 ml of normal saline at a concentration of 1 mg morphine/1 ml.

(1) 0.05 mg/kg bolus dosage,
(2) 10 minute lockout interval,
(3) The limiting dose was 10 mg every four hours.{Mizuno, 2011 #217}

Patients were administered Ketorolac 30 mg IV as rescue analgesia if the VAS remained at 4 or above.

2.6. Assessment of NKC cytotoxicity [11,12]

Blood samples were withdrawn and collected on EDTA immediately before ESPB and 24 h after surgery. Flow cytometry was utilized to quantify both cytotoxic lymphocyte populations (NKC and cytotoxic T cells). CD 56 was employed as an NK cell marker, whereas CD 8 was used as a cytotoxic T lymphocytes marker.

The cytotoxicity assay was carried out according to the manufacturer's instructions, which involved measuring the release of lactate dehydrogenase (LDH) from non-viable cells (LDH cytotoxicity colorimetric assay kit E-BC-K771-M, Elabscience, USA).

The result of LDH was correlated with the percentage of NKCs, obtained from flow-cytometry. Mitogen is added and the LDH released was calculated. LDH index was obtained by dividing the result of LDH with mitogen over the result of LDH without mitogen.

2.7. Study endpoints

- The total morphine quantity administered during the first 24 postoperative hours was the 1ry outcome of this trial.

Secondary endpoints included:

- Doses of ketorolac needed as rescue analgesia at the end of 24 postoperative hours.
- Acute neuropathic pain after surgery by 10 days, assessed by the Arabic validated version of Douleur Neuropathique 4 (DN4) questionnaire (cut-off value is 4 from 10 items) [13]. (Figure 3).
- LDH cytotoxicity assay of NK cells before ESPB and 24 hours thereafter.
- Postoperative nausea and or vomiting (PONV) and any complications observed.
  - PONV score:
    1. Was not present.
    2. Was Present, and responded to therapy.
    3. PONV was present, however therapy did not alleviate the problem.
  - First and second modalities of therapy for PONV were metoclopramide, 10 mg IV, then ondansetron, 4 mg IV, accordingly.

DN4 Questionnaire for neuropathic pain	استبيان عن الآلام ذات المنشأ العصبي ، من فضلك ضع علامة (✓) في المكان المناسب لك:	
مقابلة المريض		
(أ) هل تشعر بأن الألم الحالي يحمل خاصية أو أكثر من الخواص التالية:	نعم	لا
1. حارق		
2. بارد مؤلم		
3. يشبة الصدمات الكهربائية		
(ب) هل يترافق الألم مع واحدة أو أكثر من الأعراض التالية في نفس المنطقة:	نعم	لا
4. خدر (خدران)		
5. وخز دبابيس او مسامير		
6. تنميل		
7. حكة		
فحص المريض		
(ج) عند فحص منطقة الألم، هل وُجدت أي من الأعراض التالية ؟	نعم	لا
8. نقص في الإحساس عند اللمس		
9. نقص في الإحساس عند الوخز		
(د) في منطقة الألم، هل يصدرالألم أو يزيد ب:	نعم	لا
10. التفريش (تدليك المنطقة بالفرشاة)		
From: Bouhassira et al, Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 114 (2005) 29-36.		

Figure 3. The Arabic validated version of DN4 questionnaire.

2.8. Statistical analysis

The data were analyzed using the IBM SPSS software tool, version 20.0. To describe qualitative data, we utilized numbers and percent. The Shapiro-Wilk test was done to verify if the distribution was normal. Range (minimum and maximum), median, mean and standard deviation were used to characterize numerical data. The results' significance was assessed at a 5% level.

2.9. The used tests were

(1) Chi-square test: for comparison of qualitative variables among groups. When more than 20% of the cells have an anticipated count of less than 5, Fisher's Exact or Monte–Carlo correction was implemented.
(2) F "one way ANOVA": For quantitative data with normal distribution. The ANOVA test was implemented to compare between the three groups, whereas the post-hoc test (Tukey) was used for pairwise comparisons.
(3) The Mann–Whitney test was used to compare among the two intervention groups with numerical data and abnormal distribution.
(4) For quantitative data and abnormal distribution, the Kruskal Wallis test was implemented to compare among the three groups, whereas the post hoc (Dunn's multiple comparisons test) was imolemented for pairwise comparisons.

3. Results

Between March 2021 and January 2022, 60 of the 80 patients who were screened (20 patients in each group) were recruited. Attrition ratio was 0% (Figure 4).

Patients' characteristics are demonstrated in Table 1. Changes in HR and MABP in the intraoperative and postoperative periods are demonstrated in Figures 5 and 6.

Regarding the primary outcome, the amount of morphine needed was markedly less in both ESPB groups compared to the GA only group (1.13 ± 1.77 vs. 1.35 ± 3.15 vs. 9.58 ± 5.76, $p < 0.001$). The high volume of LA in ESPB made no difference. (Figure 7)

The total amount of ketorolac needed, as rescue analgesia, was less in both ESPB groups than the GA only group (0 vs. 3.0 ± 9.23 vs. 36.0 ± 30.16, $p < 0.001$) (Table 2).

There was no difference across the groups in the incidence of postoperative acute neuropathic pain, defined as ≥4 on DN4 questionnaire (30% vs. 50% vs. 60%, $p = 0.153$). However, this type of pain had been started later in both ESPB groups relative to the control (7.29 ± 0.76 vs. 7.20 ± 0.79 vs. 3.58 ± 0.90 days, $p < 0.001$). From all the cases diagnosed with acute postoperative neuropathic pain, interference with work sleep or mood was less in both ESPB groups than the GA group (0 vs. 20% vs. 100%, $p < 0.001$) (Table 3).

Regarding LDH index, unlike the standard volume ESPB group and the GA only group, the postoperative LDH index was greater than the preoperative one in

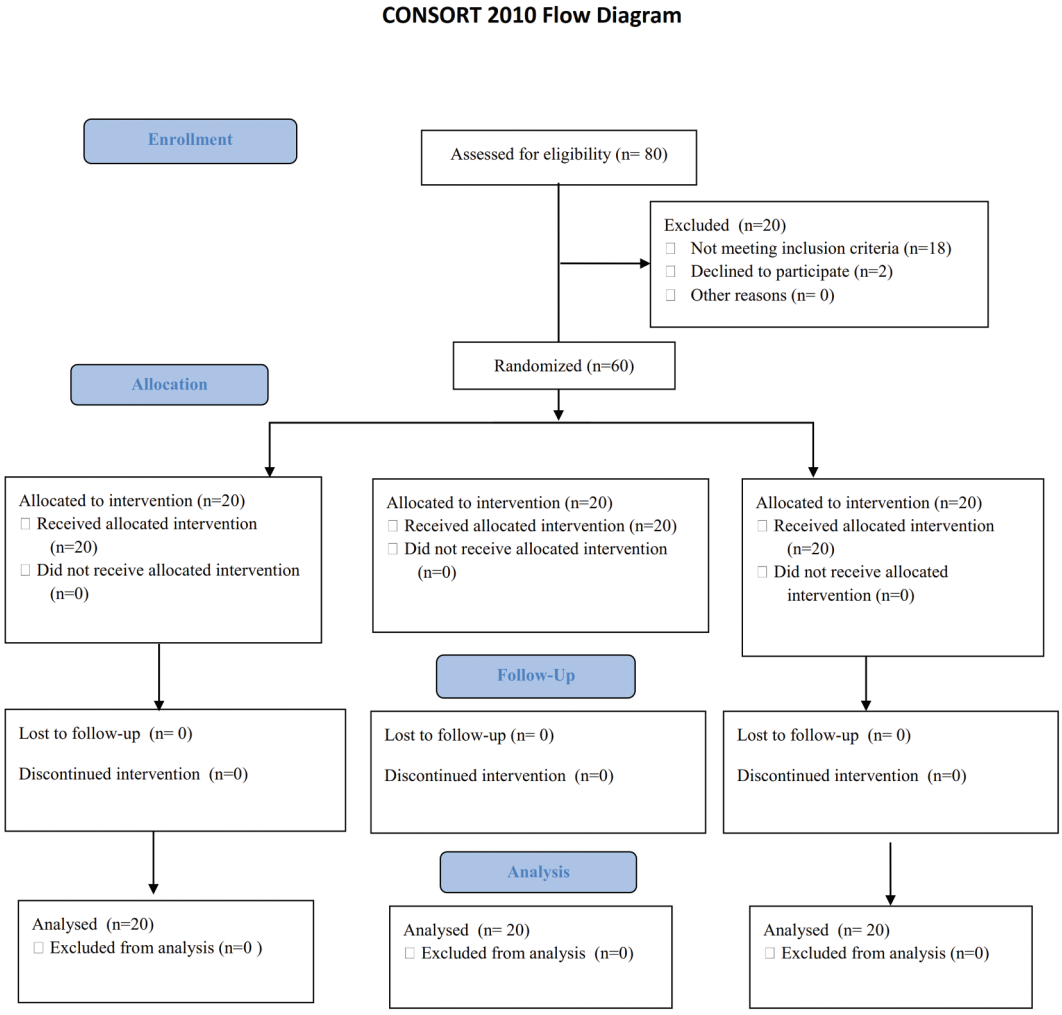

Figure 4. Demonstrating CONSORT flow diagram of the study participants.

the high volume ESPB group (1.47 ± 0.71 vs. 1.04 ± 0.47,p = 0.03). Furthermore, there was no difference among the three groups in the preoperative or postoperative periods (p = 0137 and 0.652, respectively) (Table 4).

No complications had been recorded in any of the studied groups as regard to local anaesthetic toxicity, arrhythmias, haematoma at the injection site or respiratory depression.

PONV incidence was less in both ESPB groups than the GA group (0 vs. 10% vs. 50%, p < 0.001) (Figure 8).

4. Discussion

This prospective, randomised, triple-blind clinical trial evaluated the different volumes and concentrations of local anaesthetic in breast cancer surgeries and clarified that high volume of LA in ESPB does not improve the analgesic effect, in terms of decreasing opioid consumption, decreasing the need for rescue analgesia, incidence or effect of acute postoperative neuropathic pain. Moreover, high-volume LA, compared to standard volume, failed to ameliorate NKC cytotoxicity or decrease the incidence of PONV. However, all these parameters had been markedly improved relative to no ESPB.

In the current study, bupivacaine 50 mg was used in both the intervention groups with 20 ml volume and 0.25% concentration in the standard volume ESPB group and 40 ml volume with 0.125% concentration in the high volume ESPB group. Altiparmak [1415] and his colleagues used the same volume of 20 ml with different concentrations (0.375 & 0.25%) in the two intervention groups resulting in a different dose of bupivacaine in each group (75 mg & 50 mg). The current study showed no difference in opioid consumption between the two intervention groups while Altiparmak [14] and his colleagues showed less NRS and opioid consumption in the high concentration group. So, the analgesic efficacy of ESPB seems to be determined by the total local anaesthetic dose which is the multiplication of volume and concentration.

In concordance with the current study, a meta-analysis of 11 RCTs involving 679 patients by Zhang et al [16], showed that USG ESPB is an effective analgesic technique after breast cancer surgeries with regard

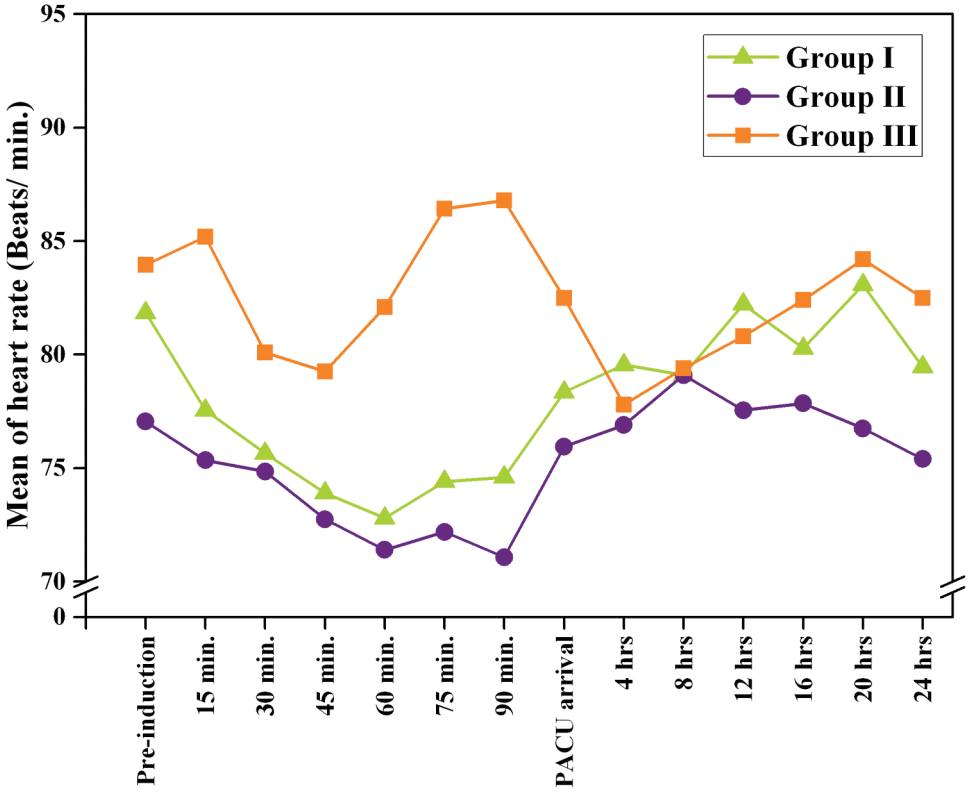

Figure 5. Comparison between the three studied groups according to HR (beats/min).

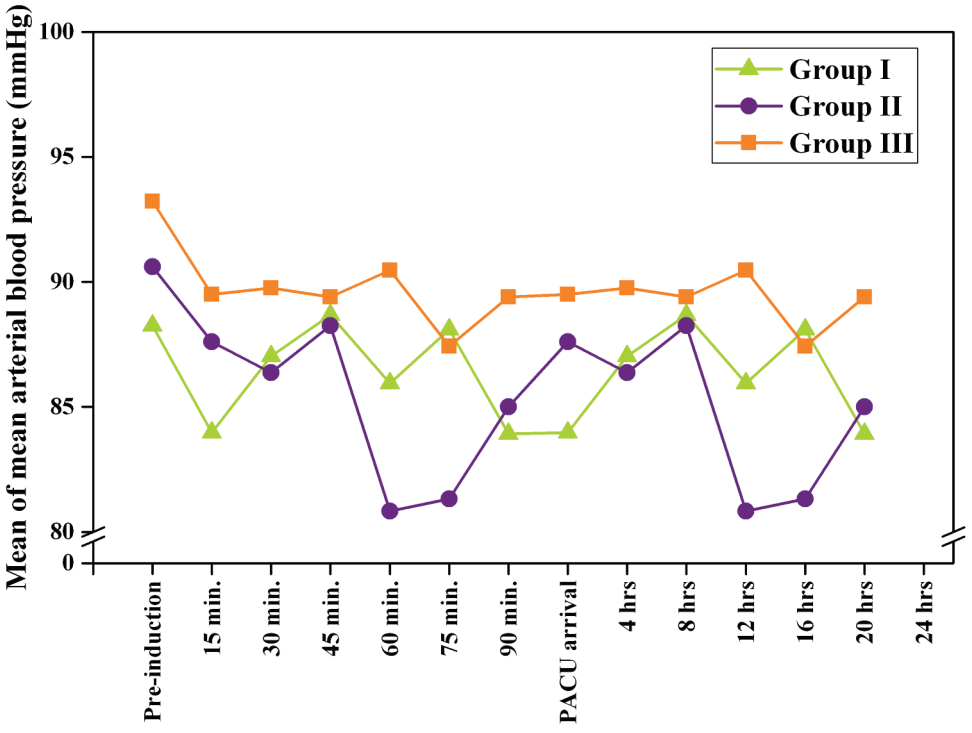

Figure 6. Comparison between the three studied groups according to mean arterial blood pressure (mmHg).

to the pain intensity and total amount of morphine consumed within the first 24 postoperative hours, compared with GA alone.

A systematic review and meta-analysis of 13 RCTs and 861 patients by Leong and his coworkers [17], revealed that ESPB is more successful in reducing opioid use and pain scores for up to 24 hours after breast surgeries when compared to general anaesthesia alone and its effectiveness was comparable to paravertebral block.

A more recent and larger meta-analysis of 52 RCTs, by Cui et al [18], involving 3000 patients of different surgeries showed that ESPB lowered the cumulative amount of opioids consumed in the first 24 hours

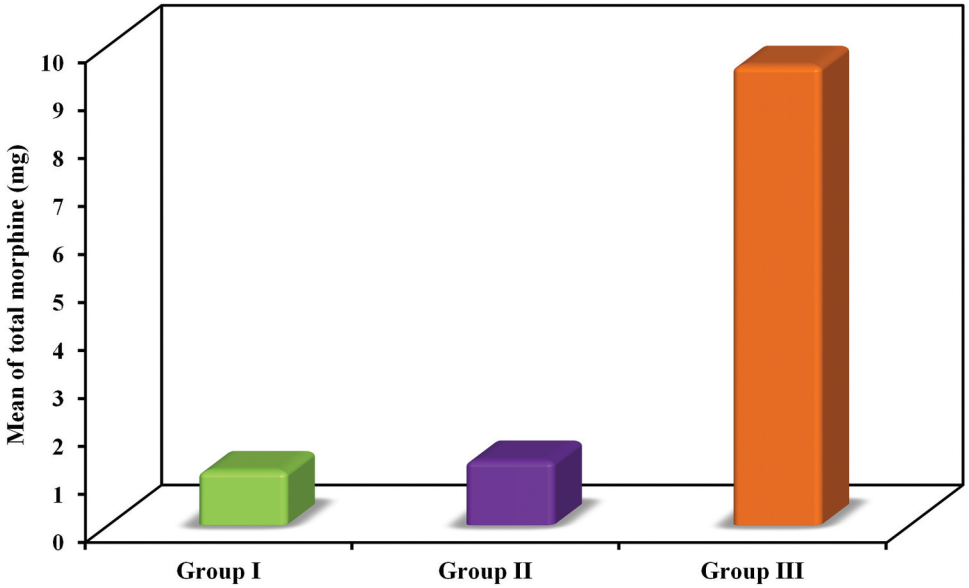

Figure 7. Comparison among the three groups according to total amount of IV morphine.

Table 1. Comparison among the three groups according to patients' characteristics.

Demographic data	Standard volume ESPB Group (n = 20)	High volume ESPB Group (n = 20)	GA only Group (n = 20)	F	p
Age (years)					
Mean ± SD.	42.95 ± 7.48	41.05 ± 9.20	43.20 ± 7.15	0.433	0.651
Median (Min. – Max.)	44.50(24.0–50.0)	44.0 (26.0–50.0)	45.0 (28.0–50.0)		
Weight (kg)					
Mean ± SD.	80.50 ± 10.69	79.25 ± 12.02	83.60 ± 9.45	0.865	0.427
Median (Min. – Max.)	81.0(65.0–105.0)	77.50(60.0–100.0)	82.50(68.0–105.0)		

Table 2. Comparison among the three groups on the basis of the amount of ketorolac (mg) and the time of its first need (hours).

Rescue analgesia	Standard volume ESPB group	High volume ESPB group	GA only Group	Test of Sig.	P
Total amount (mg)	**(n = 20)**	**(n = 20)**	**(n = 20)**		
Mean ± SD.	0.0 ± 0.0	3.0 ± 9.23	36.0 ± 30.16	H = 29.687	<0.001*
Median (Min. – Max.)	0.0 (0.0–0.0)	0.0 (0.0–30.0)	30.0 (0.0–90.0)		
Significance between groups		$p_1 = 0.544, p_2 < 0.001^*, p_3 < 0.001^*$			
Number of patients needed rescue analgesia					
None	20 (100.0%)	18 (90.0%)	6 (30.0%)	$\chi^2 = 29.318^*$	<0.001*
Needed	**0 (0.0%)**	**2 (10.0%)**	**14 (70.0%)**		
Time of first need (hours)					
Mean ± SD.	–	1.0 ± 0.0	6.86 ± 5.61	U = 4.0	0.150
Median (Min. – Max.)	–	1.0 (1.0–1.0)	4.0 (1.0–16.0)		

The Post Hoc Test (Dunn's for multiple comparisons test) was implemented to compare each two groups pairwise.
p: p value for comparing among the three groups.
p_1: p value for comparing among **Standard volume** and **High volume ESPB groups.**
p_2: p value for comparing among **Standard volume ESPB group** and **GA only group.**
p_3: p value for comparing among **High volume ESPB group** and **GA only group.**
*: Statistically significant at p ≤ 5%.

following surgery and shortened the period between surgery and the first rescue analgesia. Furthermore, the patients who required rescue analgesia after surgery were fewer than in the control group.

According to AAAPT (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), American Pain Society (APS), and the American Academy of Pain Medicine (AAPM)), Acute neuropathic pain is difficult to diagnose and can be caused by surgery such as mastectomy. The DN4 questionnaire was the tool used to detect acute postoperative neuropathic pain 10 days after surgery in the current study. There was no difference in its incidence between either of the ESPB groups and the GA group. However; when this type of pain occurred it had been delayed in both ESPB groups as compared to the GA group. And the early onset acute neuropathic pain in the GA group had interfered with work, sleep or mood. So, ESPB had not affected the incidence of acute postoperative neuropathic pain but it had affected the onset and interference with work, sleep, and mood.

In line with our findings, Xin et al [19], found that preoperative USG ESPB did not alter the incidence of neuropathic pain after surgeries for breast cancer.

The current study showed that postoperative NK cells activity is enhanced in the high-volume group, as compared to the preoperative values; however,

Table 3. Comparison of the three groups in terms of acute postoperative neuropathic pain.

Acute postoperative neuropathic pain	Standard volume ESPB group (n = 20)	High volume ESPB group (n = 20)	GA only Group (n = 20)	Test of Sig.	P
DN4 Breast, Axilla, Arm					
<4	14 (70.0%)	10 (50.0%)	8 (40.0%)	$\chi^2 = 3.750$	0.153
≥4	**6 (30.0%)**	**10 (50.0%)**	**12 (60.0%)**		
Mean ± SD.	3.0 ± 0.86	3.40 ± 2.26	4.30 ± 2.34	H = 4.874	0.087
Median (Min. – Max.)	3.0 (1.0–4.0)	3.50 (0.0–7.0)	5.50 (0.0–7.0)		
Onset (days)					
Mean ± SD.	7.33 ± 0.82	7.20 ± 0.79	3.58 ± 0.90	F = 64.606*	<0.001*
Median (Min. – Max.)	7.50 (6.0–8.0)	7.0 (6.0–8.0)	4.0 (2.0–5.0)		
Significance between groups		$p_1 = 0.950, p_2 < 0.001^*, p_3 < 0.001^*$			
Interference with work, sleep, mood	0 (0.0%)	2 (20.0%)	12 (100.0%)	$\chi^2 = 23.251^*$	$^{MC}p < 0.001^*$

The Post Hoc Test was used to do a pairwise comparison between each of the two groups (Tukey)
p: p value for comparing among the three groups.
p_1: p value for comparing among **Standard volume** and **High volume ESPB groups.**
p_2: p value for comparing among **Standard volume ESPB group** and **GA only group.**
p_3: p value for comparing among **High volume ESPB group** and **GA only group.**
*: Statistically significant at p ≤ 5%

Table 4. Comparison among groups in terms of LDH index.

LDH index	Standard volume ESPB group (n = 20)	High volume ESPB group (n = 20)	GA only group (n = 20)	H	p
Before Surgery					
Mean ± SD.	1.19 ± 0.53	1.04 ± 0.47	1.27 ± 0.45	3.975	0.137
Median (Min. – Max.)	1.16(0.37–2.60)	0.97(0.46–2.79)	1.28(0.58–2.24)		
After Surgery					
Mean ± SD.	1.32 ± 0.61	1.47 ± 0.71	1.32 ± 0.40	0.855	0.652
Median (Min. – Max.)	1.12(0.56–2.76)	1.38(0.46–3.22)	1.27(0.54–2.16)		
p_0	0.737	0.030*	0.433		

p: p value for comparing among the three groups.
p0: **Wilcoxon signed ranks** test p value for each group comparing before and after surgery.
*: Statistically significant at p ≤ 5%.

when compared to the standard volume of LA or to GA alone there is no difference. The cause of this observation is related to the concentration of LA rather than the volume as there is low concentration of the LA in the high volume ESPB group. Ramirez et al [10], in concordance with the current study findings, proved that therapeutically relevant concentrations of lidocaine improve NK cell cytotoxicity by releasing the lytic NKC granules. On the contrary Krog et al [9], proved that the high concentrations of lidocaine inhibit NK cell cytotoxicity.

Studies investigating the optimum volume of LA in regional anaesthetic techniques and its relation to the cytotoxicity of NK cells are scanty but generally regional anaesthetic techniques seem to boost the NK cells activity. Buckley et al [11], proved that NK cells cytotoxicity was greater when PVB and propofol were used as the anaesthetic technique in breast cancer surgery as opposed to the general anaesthesia technique (Sevoflurane and opioids).

Also, Dong et al [12] showed that in females having radical resection for ovarian cancers, combined general/epidural anaesthesia increases NK cells cytotoxicity and cytokine responsiveness.

Furthermore, Kim [20] proved that Local anesthetics and regional anaesthesia, as compared to volatile anaesthetics and opioids, attenuate the neuroendocrine surgical stress response, promote NK cells activity and mitigate the immunosuppression and recurrence of certain types of neoplasms, including breast cancer.

Zhu et al [21], proved that combining epidural with general anesthesia may enhance overall cellular immunity after surgery, however the NKC survival rates showed no difference between combined epidural-general anaesthesia technique versus general anaesthesia alone.

On the other hand, most of the clinical data is particularly weak, being mostly retrospective, with smaller sample size and sometimes conflicting, resulting in a plethora of questions and few answers. There was no difference in cancer recurrence following potentially curative surgery between regional and general anaesthesia according to recent randomised controlled clinical trials, including the largest (NCT0041845[7]) [22].

This study support that ESPB is a safe analgesic option in the perioperative period. No cases of local anaesthetic systemic toxicity (LAST) were reported in either the standard volume or high volume groups with the dose used of 50 mg bupivacaine. On this behalf, Maximos et al [23] measured Peak plasma concentration (C_{max}) of total and free bupivacaine after ESPB and they concluded that C_{max} of both the total

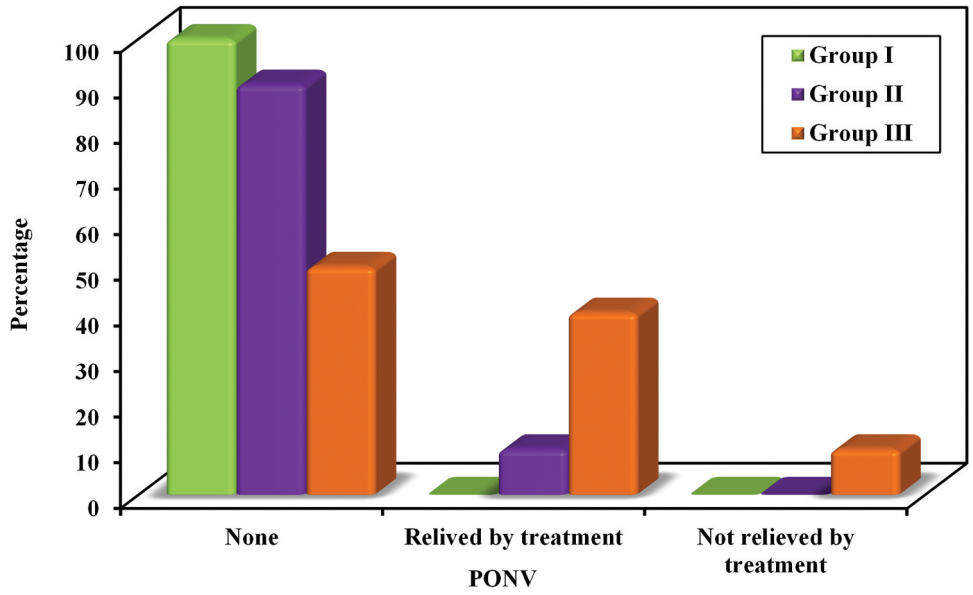

Figure 8. Comparison among the three groups according to PONV incidence.

and free serum levels were 5 to 20 times lower than values deemed hazardous in the literature after using 2 mg per kg bupivacaine and 5 µg per mL epinephrine.

Also, Shigeta et al [242526272829] did not report LAST in evaluating the LA pharmacokinetics after ESPB for breast cancer surgeries.

A study of patients' preferences for postoperative anaesthetic outcomes indicated that preventing PONV was preferred above postoperative pain [30]. In the current study, the incidence of PONV was lowered after ESPB compared to GA only and the cause of this may be due to higher doses of opioids used in GA group. Similarly, Gurkan et al [31], and Wang et al [32], delineated that ESPB is associated with decreased incidence of PONV in as opposed to the control. Furthermore, a meta-analysis by Zhang et al [16], confirmed this result.

On the other hand, Li et al. [33] conducted a meta-analysis and discovered that ESPB didn't alter the incidence of PONV after breast surgery. The included studies in this meta-analysis showed a significant risk of bias, small sample size, most studies were not blinded, and subgroup analysis hadn't been conducted.

No haematoma had been recorded in this study. Koo et al [34], reported in their systematic review and meta-analysis a lower incidence of haematoma after ESPB when compared to thoracic paravertebral block or serratus anterior plane block.

5. Conclusion

Preoperative ESPB is an effective analgesic modality that should be considered in breast cancer surgeries, yet the volume injected, with the same dose, has no effect on the quality of analgesia as regard opioids consumed or the need for rescue analgesia. It can mitigate the deleterious effect of the neuropathic component of post-mastectomy pain and attenuate its severity. Furthermore, it is safe and has minimal complications. Its role in enhancing the NK cells cytotoxicity needs further evaluation as it failed to demonstrate a favorable immune-modulatory outcome; however, when low concentration of LA in the ESPB is favorable.

List of abbreviations

AAAPT: (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), American Pain Society (APS), and the American Academy of Pain Medicine (AAPM)),
AAPM: American Academy of Pain Medicine
ACTTION: Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks,
ANOVA: Analysis of variance,
APS: American Pain Society,
ASA: American Society of Anesthesiologists,
BMI: Body mass index,
C_{max}: Peak plasma concentration,
CONSORT: Consolidated Standards of Reporting Trials,
CT: Computed tomography,
DICOM: Digital Imaging and Communications in Medicine,
DN4: Douleur Neuropathique 4,
ES: Erector Spinae,
ESPB: Erector Spinae Plane Block,
F: One way ANOVA test,
GA: General anaesthesia,
H: Kruskal Wallis test,
HR: Heart rate,

IRB: Institutional review board,
LA: Local anaesthetic,
LAST: Local anaesthetic systemic toxicity,
LDH: Lactate Dehydrogenase enzyme,
LDH-NKC: Lactate Dehydrogenase enzyme released from Natural Killer Cells,
MABP: Mean arterial blood pressure,
MC: Monte Carlo,
NK: Natural killer,
NKC: Natural killer cells,
O_2: Oxygen,
PACU: Post-anaesthetic care unit,
PCA: Patient controlled analgesia,
PONV: Post-operative nausea or vomiting,
PV: Paravertebral,
PVB: Paravertebral block,
RASS: Richmond agitation sedation scale,
SD: Standard deviation,
TOF: Train of four,
TPVB: Thoracic paravertebral block,
U: Mann Whitney test,
USG: Ultrasound guided,
VAS: Visual analogue scale,
χ^2: Chi square test.

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Disclosure statement

The authors report no conflict of interest

Data availability statement

The data that support the findings of this study are openly available in [Clinical trial] at https://clinicaltrials.gov/ct2/show/NCT04796363, reference number [NCT04796363].

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