EGYPTIAN JOURNAL OF ANAESTHESIA
2023, VOL. 39, NO. 1, 446–452
https://doi.org/10.1080/11101849.2023.2217593

Analgesic effect of adding calcitonin to bupivacaine in erector spine plane block for breast surgery, a double blind randomised study

Mona Gad Mostafa Elebieby[a], Mohammed Nashaat Mohammd[a], Khaled Abdelwahab[b], Emadeldeen Hamed[b] and Zenat Eldadamony Mohamed Eldadamony[a]

[a]Pain Medicine, and Surgical ICU, Mansoura University, Mansoura, Egypt; [b]Mansoura Oncology Center, Mansoura University, Mansoura, Egypt

ABSTRACT

Background: Surgery for breast malignancy is linked to severe perioperative discomfort. Pain management reduces the need for opioids and general anesthesia. The "erector spinae plane block" (ESPB) recently became an effective choice in this concern. Our trial assessed the effectiveness of calcitonin as an LA adjuvant in ESPB for pain control in patients underwent cancer breast surgery.

Patients and Methods: One hundred and thirty patients were randomly allocated into two groups, BC and B. BC group received ESPB with 20 mL of bupivacaine 0.25% in addition to 50 IU of calcitonin in 2 mL of saline, while the other group received the same bupivacaine dose in addition to saline (2 ml). Main outcome was time for first rescue analgesia. Secondary outcomes included 24-h total morphine consumption postoperatively, postoperative VAS scores, levels of inflammatory cytokines, total intraoperative fentanyl consumption, and side effects.

Results: The period before the first-time analgesia was required was extended (12.18 ± 4.969 h vs 6.60 ± 3.116 h, $P < 0.001$), with less postoperative opioid consumption in the BC group (6.40 ± 1.876 mg vs 7.74 ± 2.117 mg, $P < 0.001$). Pain scores and the number of patients who asked for painkillers after surgery were less in the BC group. Patients in the BC group had a significant decline in serum inflammatory cytokines (TNF-α, IL-6), while IL-10 showed a significant increase in the BC group ($P < 0.001$). Intraoperative fentanyl and postoperative adverse effects recorded were statistically comparable in the two studied groups.

Conclusion: The addition of calcitonin to bupivacaine in the ESPB block can give an extended analgesic effect with lower inflammatory cytokine indicators.

ARTICLE HISTORY
Received 25 March 2023
Revised 5 April 2023
Accepted 21 May 2023

KEYWORDS
Erector spinae plane block; calcitonin; inflammatory cytokines; cancer of the breast

1. Introduction

According to the statistics on breast cancer in women, one in every eight women will develop the disease at some point in their lifetime [1]. About 60% of women who have breast surgery say they are in a lot of severe pain after the procedure. The axilla is likely to be responsible for most of this pain [2]. When acute pain is effectively controlled, stress response is reduced and fewer opioids and general anaesthetics are required [3]. Additionally, in the recent few years, interesting findings were found about the association between regional anaesthesia and inflammatory indicators, since the nerve block prevents the rise in levels of the inflammatory cytokines through blockade of nociception stimulation [4,5]. Multiple techniques can alter postoperative pain, such as, for example, thoracic epidural anaesthesia, paravertebral, pectoral plane block, intercostal, and erector spine plane block (ESPB) [6,7].

ESPB was first used to treat chronic neuropathic pain by deep muscle local anaesthetic (LA) injection at T5 [7]. ESPB has been applied in abdominal [8] and thoracic surgeries [7], with a good success rate in providing both somatic and visceral analgesia [7,8]. Because the duration of action of LA medications is limited, adding adjuvants as opioids, α2 agonists is useful [9].

Contrarily, the thyroid gland's para-follicular C cells produce the 32-amino acid polypeptide hormone calcitonin (CT) that has a crucial role in bone metabolism and calcium homeostasis [10]. It is conceivable that the calcitonin hormone controls the release of CGRP from nerve terminals. Additionally, it might be crucial for mast cell stability [11]. The analgesic effect of calcitonin has been explained in different pain models, such as its role in thromboxane and prostaglandin synthesis, calcium influx, alters in Na+ channel transcription in dorsal root ganglion, B-endorphin release, and its effect on central nervous system (C.N.S.) receptors [12,13].

The purpose of this research was to evaluate calcitonin as a promising adjuvant to bupivacaine in ultrasound-guided ESPB on the analgesic outcome and suppression of the inflammatory process in female patients subjected to cancer breast surgery.

CONTACT Mohammed Nashaat Mohammd moh_nashaat@mans.edu.eg Anesthesia and surgical icu Department, Faculty of Medicine, Mansoura university hospitals, Mansoura, Egypt

2. Patients and methods

The Mansoura University Oncology Center hosted this controlled, prospective, random trial after receiving approval from the Institutional Research Board (R. 21. 12. 1558). Every patient who took part in the study provided informed permission. The research was registered before patients were enrolled (IRCT20220212054002N1). Patients undergoing unilateral cancer breast surgeries (modified radical mastectomy, breast conservation surgery, and simple mastectomy with axillary clearance) between March 2022 and September 2022, aged 18–65 years, and with ASA grade I and II, **were included** in the study. Any patient who refused to participate in the study or had hypersensitivity to the study medications, bleeding disorders, obesity, cognitive disorders, an infection at the site of injection, or narcotic abuse was **excluded** from the study.

Patients were allocated into two equal groups in a parallel manner: **Group bupivacaine calcitonin (BC)**: ($n = 65$) patients underwent US-guided ESPB on the operated side with 20 mL of bupivacaine 0.25% plus 50 IU calcitonin in 2 mL saline. **Group bupivacaine alone (B)**: ($n = 65$) patients received US-guided ESPB on the operated side with 20 mL of bupivacaine 0.25% plus 2 mL of saline. Computer-generated random numbers and opaque envelopes that were sealed shut were used to carry out the randomization process. In order to enrol patients, envelopes containing patient information were opened by an additional anesthesiologist unrelated to the research. A pharmacist was responsible for drug preparation, and patients and anesthesiologist assessing their outcomes were unaware of which group they belonged to.

3. General anaesthesia

An EKG, pulse oximeter, noninvasive arterial blood pressure, capnography, and bispectral index monitoring were all used for monitoring in the operating room (BIS, Philips Healthcare, Andover, MA). After inserting a 22-gauge intravenous line, each patient in both groups had 5 mL of venous blood taken, which was used as time point 1 (T0) for calculating the baseline plasma inflammatory cytokines (IL-6, IL-10, and TNF). Blood samples were collected in EDTA-Vacutainer tubes, centrifuged, separated, and stored at –80°C until measurement. Their levels in plasma were determined using a standard enzyme-linked immunosorbent assay (ELISA) method and commercial ELISA kits **(Fcmacs, Hangzhou, China)**, guided by instructions. Following that, an intravenous infusion of isotonic saline (15 mL/kg/h) was commenced. After 100% oxygen preoxygenation, anaesthesia induction was done with fentanyl (2 µg/kg) and propofol (2–3 mg/kg); endotracheal tube intubation was aided with atracurium (0.5 mg/kg). Isoflurane in a 50/50 mix of O2 and air, with a MAC that kept the BIS between 40 and 60, and breathing settings that kept the Et CO2 between 35 and 45 mmHg. When a patient's blood pressure or heart rate (HR) increased by 20% over baseline or more, 0.5 µg/kg intravenous fentanyl was delivered, and the total dose was recorded. When the procedure was over, isoflurane was stopped, and neuromuscular reversal was completed using an intravenous combination of neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). Following extubation, patients were moved to the post-anesthetic care unit (PACU).

4. Technique of block

ESPB was conducted under perfect aseptic circumstances after induction of anaesthesia and 15 min before skin incision using a 100-mm 21 G needle guided by a US probe (linear) with a frequency of 6–13 MHz in either group (Siemens, CA, 94043, USA). **Chin et al**. demonstrated that ESPB was carried out unilaterally, on the same side of surgery, with the patients in a lateral decubitus position [14]. The block was performed using a sagittal approach, and the probe was positioned 2–3 cm laterally to the spine at the T5 level of the spine. As the transverse processes and the muscle (erector spinae) were located, the needle was advanced deeply into the muscle. Group B served as the control group, receiving 20 mL of 0.25% bupivacaine +2 mL of saline whereas group BC received the study solution (20 mL of bupivacaine 0.25% plus 50 IU of calcitonin in 2 mL of saline). The block performance between the transverse process and the erector spinae muscle were given to both groups, and LA was distributed both cranially and caudally.

5. Postoperative assessments

At rest, VAS was used to assess the patients' level of pain (by an anesthesiologist not related to the study) at 0 h, which was immediately after they arrived in the PACU. On the ward, every patient was assessed for the level of pain they were experiencing using a VAS score at 2, 4, 6, 12, 18, and 24 h postoperatively. When the VAS score was more than three, the patient received intravenous ketorolac (30 mg/12 h). If the VAS was still above three, morphine (0.05 mg/kg) was administered until it fell below three. Dosing was stopped when the SpO_2 fell below 95% or when the respiratory rate reached less than 12 breaths per minute.

The number of patients who requested analgesics, time to the first rescue analgesia (determined by a blind anesthesiologist unrelated to the research), and 24-h-morphine consumption in 24 h were recorded. Side effects such as nausea and vomiting, respiratory inhibition, pruritus, and hypotension were

also recorded. Metoclopramide 10 mg intravenously was used to relieve nausea or vomiting, and ondansetron 4 mg was administered if it did not work. An intravenous 200-ml fluid bolus was used to treat hypotension, but if it did not work, 5 mg of intravenous ephedrine was administered. Three venous blood samples (5 mL for each) were withdrawn at time points T1, T2, and T3, representing 2 h, 12 h, and 24 h after surgery, respectively, to assess the **plasma level of inflammatory cytokines.**

6. Outcome measures

The **main outcome** measure of this study was the time to first rescue analgesia, which was defined as the time from the end of surgery till the first time at which the patient demanded analgesia in hours, whereas the **secondary outcome** measures were the 24-h total postoperative morphine consumption, plasma levels of inflammatory cytokines, the VAS score at time points 0, 2, 4, 6, 12, 18, and 24 h postoperatively, the number of patients who requested analgesia, intraoperative fentanyl, and postoperative complications.

7. Sample size calculation

Power Analysis and Sample Size software programme (PASS) version 2021 for Windows (2021) was used to calculate sample size, with the time to first analgesia needed (hours) as a primary outcome. A sample size of 60 patients in each group is needed to achieve study power of 90% and an effect size of 0.6 (104.3 and 8.01.8, retrieved from a pilot study carried out before the full-scale study) using a two-tailed t-test with a standard error of 5%. Ten percent drop-out patients are expected, so a total of 66 patients will be enrolled in each group at least.

8. Statistical analysis

SPSS software, version 25, was used for the data analysis (SPSS Inc., PASW Statistics for Windows, version 25). Chicago, IL: SPSS, Inc. Quantitative data were described in terms of percentages and numbers. When describing quantitative data, the mean was used for regularly distributed data and the median (range) for non-normally distributed data. Standard deviation for normally distributed data after the Kolmogorov–Smirnov test has confirmed that the data are normal. The 0.05 level was used to determine the significance of the results. The proper tests were utilised to compare qualitative data between groups, including Chi-Square, Fischer's exact test, and Monte Carlo testing. The Mann Whitney Non-normally distributed data from the two groups under study were compared using a U test. Two independent groups with non-normally distributed data were compared using a student t test.

9. Results

One hundred and forty-one patients were screened for the present study. Two patients had declined the study; there were three patients with BMI >35 kg/m2; one patient had injection site infection; one patient belonged to ASA III; one patient had a coagulation disorder; and another patient had opioid abuse, all of them were discarded from the enrollment. The remaining 132 patients were allocated to the groups in this study. Two patients were lost during follow-up as one patient in the A group had hematoma formation that was operated on again and one patient in the B group failed to assess her pain using the VAS. So, the results of 65 patients were analysed in each group [Figure 1]. Demographic data, type, and duration of surgery were statistically comparable among the two studied groups [Table 1]. VAS scores at time points 4, 6, and 12 h postoperatively in group BC decreased significantly more than those in group B. The 24-h total postoperative morphine consumption (6.40 ± 1.876 mg vs. 7.74 ± 2.117 mg, P 0.001) was significantly lower in group BC than in group B. The intraoperative fentanyl consumption was comparable in both study groups [Table 2].

There was a longer period of postoperative analgesia with the BC group as the time to first rescue analgesia was delayed significantly when compared with the B group (12.18 ± 4.969 h vs. 6.60 ± 3.116 h, P 0.001). Also, patients who required postoperative analgesics in group BC were less than in group B [45 (69.2%) vs. 57 (87.7%), P 0.01, Table 2]. At time point T0 (baseline), the levels of inflammatory markers (IL-6, TNF-α, and IL-10) in the plasma were statistically equivalent across the two studied groups, but at time points T1, T2, and T3 (2 h, 12 h, and 24 h) After surgery, it was found that Group BC had much lower levels of IL-6 and TNF-α than Group B. (P 0.001). Comparing groups BC and B, IL-10 was statistically greater in group BC [Figures 2, 3 , and 4]. However, there were fewer side effects (Nausea, vomiting, respiratory depression, pruritus and hypotension) with group BC compared with group B, but the difference was statistically not significant ($P > 0.05$) [Table 3].

10. Discussion

In this randomized, controlled study, we found that adding calcitonin to bupivacaine in an erector spinae myofascial plane block for cancer breast surgery was linked to better postoperative pain relief and a lessening of inflammatory mediators. ESPB can provide postoperative analgesia for either abdominal or

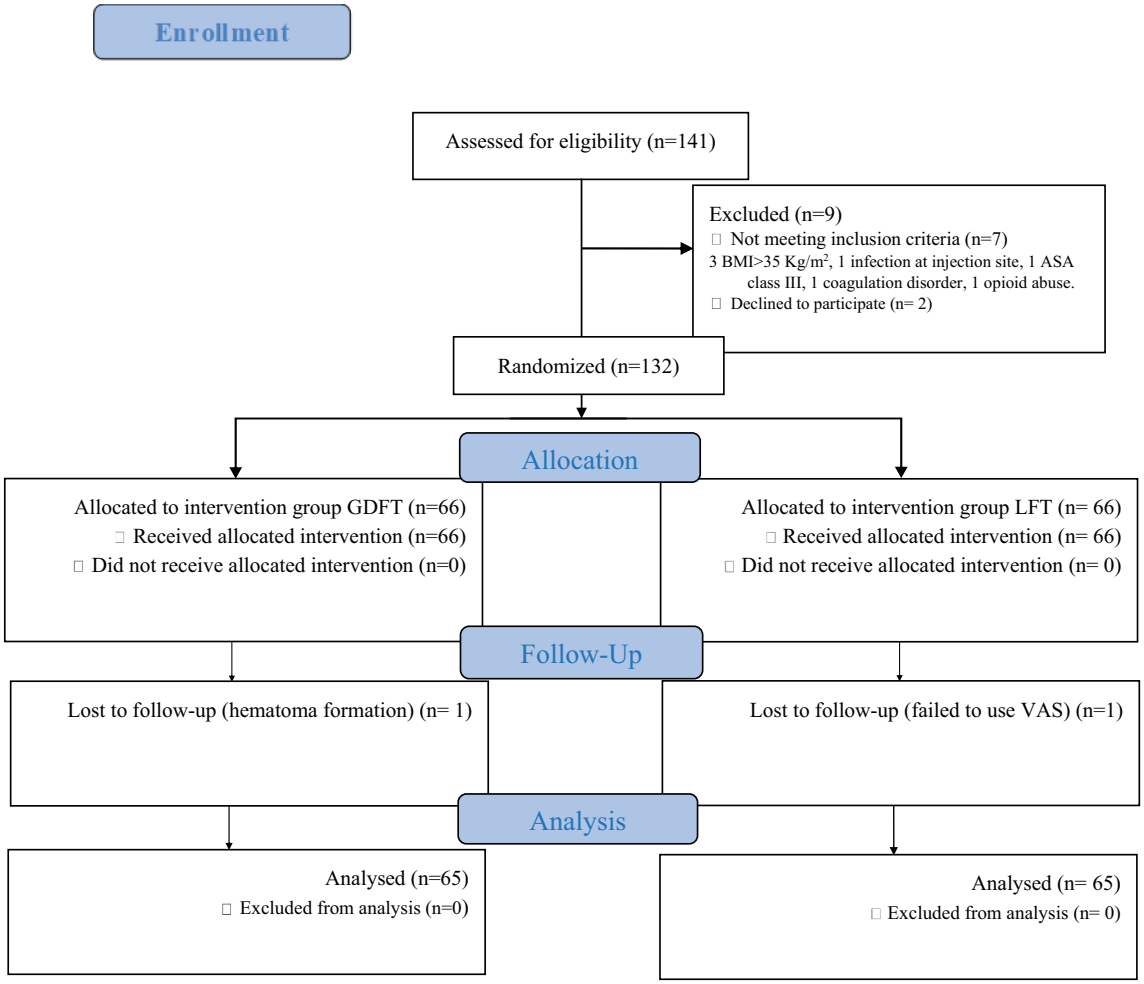

Figure 1. The flow diagram of patient progress through the randomized trial.

Table 1. Demographic characteristics, type, and duration of surgery for the studied groups.

		Group B (n= 65)	Group BC (n= 65)	95% CI	P
Age (years)		46.71 ± 9.730	49.20 ± 9.316	-5.80, 0.81	0.138
Weight (kg)		77.63 ± 9.429	79.27 ± 9.774	-4.97, 1.69	0.333
Height (m)		1.69 ± 0.061	1.69 ± 0.060	-0.02, 0.02	1
BMI (kg/m^2)		27.16 ± 3.033	27.72 ± 2.991	-1.60, 0.49	0.292
ASA	1	39 (60.0%)	41 (63.1%)	-	0.718
	2	26 (40.0%)	24 (36.9%)		
Surgery	Modified radical mastectomy	22 (33.8%)	24 (36.9%)	-	0.911
	Breast conservational surgery	22 (33.8%)	22 (33.8%)		
	Simple mastectomy and axillary clearance	21 (32.3%)	19 (29.2%)		
Duration of surgery (minutes)		104.77 ± 14.319	104.92 ± 14.045	- 5.08, 4.77	0.951

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when ˂ 0.05. n=Number of patients, BMI=Body mass index, ASA= American Society of Anesthesiologists, B=Bupivacaine group, BC=Bupivacaine Calcitonin group.

thoracic surgery, depending on the location level. We targeted the transverse process of T5 as a site to inject the local anesthetics. A significant number of studies analysed the block and considered it safe, effective, and comparable for paravertebral and epidural postoperative analgesia, and it inhibited inflammatory reactions [7,8]. In a study by **Gabopoulou et al.**, it was determined that patients who received calcitonin in epidural space experienced little to no postoperative discomfort (VAS less than 4) after having total hip arthroplasty under epidural anaesthesia [15]. In their investigation on the use of subarachnoid and epidural injections of calcitonin in patients with metastatic cancer pain, **Maytorena et al**. reported that considerable pain alleviation was experienced following calcitonin injection in the epidural space of patients who had failed to respond to conventional therapy [16].

When standard analgesics are ineffective at reducing pain, calcitonin should be utilised, according to previously published studies. In many painful situations, especially those involving acute pain and neuropathies, patients can, according to the authors' review, achieve almost total symptom alleviation. Second, the medication has no substantial negative

Table 2. Postoperative VAS score follow-up and analgesic requirements of the studied groups.

		Group B (n= 65)	Group BC (n= 65)	95% CI	P
VAS	0 hour	1(0-1)	1(0-1)	-0.24, 0.11	0.483
	2 hours	1(0-2)	1(0-1)	-0.42, -0.08	0.112
	4 hours	2(1-4)	1(0-3)	0.53, 1.29	˂ 0.001
	6 hours	4(2-7)	2(0-5)	2.13, 3.01	˂ 0.001
	12 hours	4(1-8)	4(1-6)	0.10, 1.13	0.031
	18 hours	4(1-8)	4(1-7)	-0.05, 1.03	0.091
	24 hours	4(0-8)	4(0-8)	-0.07, 1.18	0.07
Postoperative morphine (mg) (24-h)		7.74 ± 2.117	6.40 ± 1.876	0.54, 2.13	0.001
Intraoperative fentanyl (µg)		116.1±8.74	113.4±14.29	-1.45, 6.77	0.203
Time to first rescue analgesia (hours)		6.60 ± 3.116	12.18 ± 4.969	-7.18, -3.98	˂ 0.001
Patients needed rescue analgesia		57 (87.7%)	45 (69.2%)	-	0.01

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when ˂ 0.05. n=Number of patients, BMI=Body mass index, ASA= American Society of Anesthesiologists, B=Bupivacaine group, BC=Bupivacaine Calcitonin group.

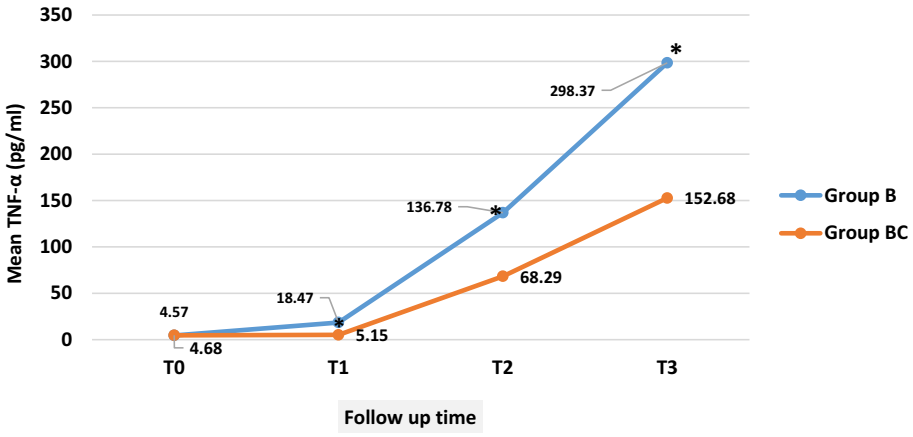

Figure 2. Plasma levels of tumor necrosis factor. **T_0**=1 h before surgery, **T_1**=2 h postoperative, **T_2**=12 h postoperative, **T_3**=24 h postoperative, **TNF-α**=tumor necrosis factor, **B**=Bupivacaine group, **BC**=Bupivacaine Calcitonin group.*=**P** is significant when <0.05

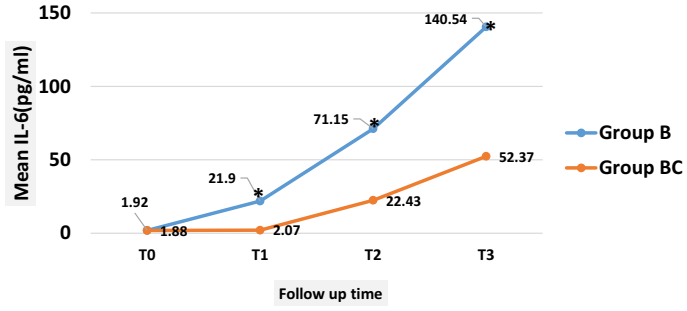

Figure 3. Plasma levels of interleukin −6. **T_0**=1 h before surgery, **T_1**=2 h postoperative, **T_2**=12 h postoperative, **T_3**=24 h postoperative, **IL-6**=Interleukin −6, **B**=Bupivacaine group, **BC**=Bupivacaine Calcitonin group.*=**P** is significant when <0.05

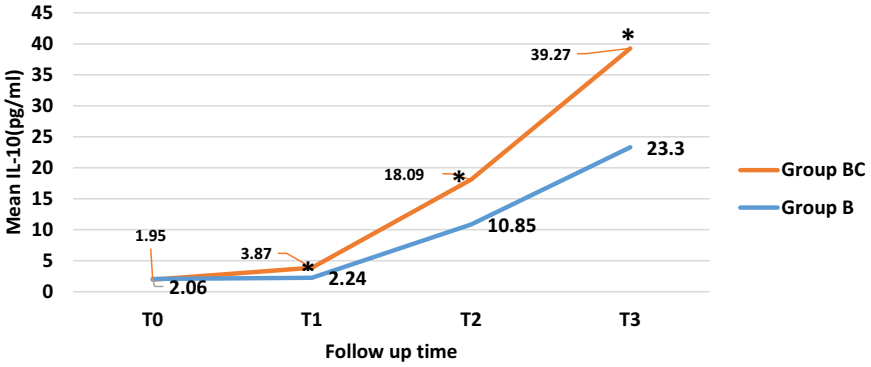

Figure 4. Plasma levels of interleukin −10. T_0=1 h before surgery, T_1=2 h postoperative, T_2= 12 h postoperative, T_3=24 h postoperative, IL-10=Interleukin -6, B = Bupivacaine group, BC = Bupivacaine Calcitonin group.* = P is significant when <0.05

Table 3. Side effect distribution among studied groups.

	Group B (n= 65)	Group BC (n= 65)	P value
Nausea & vomiting	4(6.2%)	2(3.1%)	0.680
Respiratory depression	2(3.1%)	1(1.5%)	1.0
Pruritus	5(7.7%)	2(3.1%)	0.440
Hypotension	3(4.6%)	1(1.5%)	0.619

Data is expressed as percentage and frequency. P is significant when ˂ 0.05. n=Number of patients, B=Bupivacaine group, BC=Bupivacaine Calcitonin group..

effects on several metabolic pathways, is easy to use, and is safe [10,11].

In our study, postoperatively, the proportion of patients who needed rescue analgesia in the present study during the first day (24 h) was significantly less ($p = 0.010$) in patients who received calcitonin with bupivacaine (87.7%) than in patients who received only bupivacaine (69.2%).

The acute-phase reaction brought on by surgical trauma and the TNF expression level are tightly connected. After surgical trauma, the cytokines IL-6 and IL-10, which are inflammatory and anti-inflammatory, respectively, are detected in plasma. IL-6 can be utilised as a measure of tissue damage, but IL-10 is a crucial anti-inflammatory cytokine [17]. In this study, IL-6, and TNF-α levels were lower in the calcitonin group than in the bupivacaine group, meanwhile IL-10 levels were significantly higher in calcitonin group. The ESPB may have prevented the afferent nociceptive stimulation of the damaged area and enhanced the efficacy of IV analgesia, which could be the cause. Local anaesthetics have been shown to directly affect nerve roots [18], [19], effectively blocking the transmission of nociceptive impulses. Consequently, the nociceptive stimulation brought on by the trauma [20] inhibited pituitary-adrenal axis stimulation, and the stress response was diminished [19], which was ultimately manifested as a decreased level of cytokines [21,22].

In patients who had undergone a mastectomy for breast cancer, **Matsumoto and his associates** discovered that the use of regional anesthesia reduced levels of IL-6; however, alterations of perioperative IL-10 were not statistically significant [5].

According to **Gabopoulou Z et al**., local anaesthesia and epidural calcitonin together produced analgesic effects with consistent hemodynamic outcomes that were comparable to fentanyl. The first hour following surgery had no increase in plasma cortisol levels, but the following hour saw a noticeable increase. This study determined that calcitonin is a suitable substitute for managing immediate postoperative pain [15].

As far as we can tell, this could be the first controlled trial to evaluate perioperative analgesia and postoperative effect on inflammatory mediators between calcitonin as an additive to bupivacaine and bupivacaine alone in a myofascial plane block. In addition, more randomised controlled studies are needed for more validation of the results. Our study does have certain limitations. The validity of our study may have been compromised by the fact that all of the participants came from a single centre, necessitating further multicenter research. Second, ESPB was administered as a one-time procedure rather than a continual analgesic procedure. The latter could lengthen analgesia even more. Third, 3 months after surgery, we did not continue to monitor the prevalence of chronic pain.

11. Conclusion

The addition of calcitonin to bupivacaine as an adjuvant in ESPB during cancer breast surgery prolongs the postoperative analgesia, reduces postoperative opioid needs, and reduces the plasma levels of postoperative inflammatory cytokines.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Mohammed Nashaat Mohammd http://orcid.org/0000-0002-0194-2556

References

[1] DeSantis C, Ma J, Bryan L, et al. Breast cancer statistics, 2013. Ca A Cancer J Clinicians. 2014;64(1):52–62.
[2] Fecho K, Miller NR, Merritt SA, et al. Acute and persistent postoperative pain after breast surgery. Pain Med. 2009;10(4):708–715.
[3] Gärtner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA. 2009;302(18):1985–1992.
[4] Wang Y, Cheng J, Yang L, et al. Ropivacaine for Intercostal Nerve Block Improves Early Postoperative Cognitive Dysfunction in Patients Following Thoracotomy for Esophageal Cancer. Med Sci Monit. 2019;25:460–465.
[5] Matsumoto M, Flores EM, Kimachi PP, et al. Benefits in radical mastectomy protocol: a randomized trial evaluating the use of regional anesthesia. Sci Rep. 2018;8(1):7815. DOI:10.1038/s41598-018-26273-z

[6] Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40(1):68–74.
[7] Forero M, Rajarathinam M, Adhikary S, et al. Continuous erector spinae plane block for rescue analgesia in thoracotomy after epidural failure: a case report. A A Case Reports. 2017;8(10):254–256.
[8] Chin KJ, Malhas L, Perlas A. The erector spinae plane block provides visceral abdominal analgesia in bariatric surgery: a report of 3 cases. Reg Anesth Pain Med. 2017;42(3):372–376.
[9] Swain A, Nag DS, Sahu S, et al. Adjuvants to local anesthetics: current understanding and future trends. World J Clin Cases. 2017;5(8):307–323.
[10] Kilinc E, Dagistan Y, Kukner A, et al. Salmon calcitonin ameliorates migraine pain through modulation of CGRP release and dural mast cell degranulation in rats. Clin Exp Pharmacol Physiol. 2018;45(6):536–546. DOI:10.1111/1440-1681.12915
[11] Weber CJ, O'Dorisio TM, McDonald TJ, et al. Gastrin-releasing peptide-, calcitonin gene-related peptide-, and calcitonin-like immunoreactivity in human breast cyst fluid and gastrin-releasing peptide-like immunoreactivity in human breast carcinoma cell lines. Surgery. 1989;106(6): 1134–1140. discussion 9-40.
[12] Ito A, Takeda M, Yoshimura T, et al. Anti-hyperalgesic effects of calcitonin on neuropathic pain interacting with its peripheral receptors. Mol Pain. 2012;8:42.
[13] Yousef AA, Aborahma AM. The preventive value of epidural calcitonin in patients with lower limb amputation. Pain Med. 2017;18(9):1745–1751.
[14] Chin KJ, Adhikary S, Sarwani N, et al. The analgesic efficacy of pre-operative bilateral erector spinae plane (ESP) blocks in patients having ventral hernia repair. Anaesthesia. 2017;72(4):452–460.
[15] Gabopoulou Z, Vadalouca A, Velmachou K, et al. Epidural calcitonin: does it provide better postoperative analgesia? an analysis of the haemodynamic, endocrine, and nociceptive responses of salmon calcitonin and opioids in epidural anesthesia for hip arthroplasty surgery. Pain Pract. 2002;2(4):326–331.
[16] Maytorena A, Rogers J, Sierra O. Subarachnoid and epidural calcitonin in patients with metastatic cancer pain. Reg Anesthesia J Neural Blockade Obstet Surg Pain Control. 1993;18(Suppl 2):50.
[17] Guay J, Suresh S, Kopp S. The use of ultrasound guidance for perioperative neuraxial and peripheral nerve blocks in children: a cochrane review. Anesth Analg. 2017;124(3):948–958.
[18] Peters CM, Ririe D, Houle TT, et al. Nociceptor-selective peripheral nerve block induces delayed mechanical hypersensitivity and neurotoxicity in rats. Anesthesiology. 2014;120(4):976–986.
[19] Li L, Ye XP, Lu AZ, et al. Hyperglycemia magnifies bupivacaine-induced cell apoptosis triggered by mitochondria dysfunction and endoplasmic reticulum stress. J Neurosci Res. 2013;91(6):786–798. DOI:10.1002/jnr.23216
[20] Takakura K, Mizogami M, Morishima S, et al. The inhibitory effects of local anesthetics on primary sensory nerve and parasympathetic nerve in rabbit eye. Anesth Analg. 2006;103(3):615–619.
[21] Picetti R, Ho A, Butelman ER, et al. Dose preference and dose escalation in extended-access cocaine self-admini stration in Fischer and Lewis rats. Psychopharmacology. 2010;211(3):313–323.
[22] Michelet D, Andreu-Gallien J, Bensalah T, et al. A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. Anesth Analg. 2012;114(2):393–406. DOI:10.1213/ANE.0b013e31823d0b45