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Research Article

The effect of multimodal balanced anaesthesia and long term gabapentin on neuropathic pain, nitric oxide and interleukin-1β following breast surgery

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KEYWORDS

Post breast therapy neuropathic pain;
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Gabapentin;
Nitric oxide and interleukin-1β

Abstract *Objectives:* To evaluate the effect of multimodal balanced anaesthesia and gabapentin (6 months) on neuropathic pain qualities, nitric oxide (NO) and interleukin 1-beta (IL-1β).
Methodology: This randomized study was conducted on 50 women scheduled for conservative breast surgery for cancer followed by chemotherapy and/or radiotherapy. Women enrolled into two groups; either to receive balanced general anaesthesia (GA) (control group) or ultrasound guided thoracic paravertebral with GA, multimodal balanced anaesthesia, (intervention group). Nociceptive pain was evaluated for 24 h. Neuropathic pain was evaluated using pain questionnaire 1 month postoperatively and neuropathic pain scale at 1, 3, 6 and 9 months. Gabapentin was prescribed to women reporting neuropathic pain 1 month postoperatively and for 6 months. NO and

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IL-1β were measured before operation, 1, 3, 6 & 9 months, postoperatively. Their relationship with neuropathic pain was assessed.

Results: Nociceptive pain was less in intervention group than control group immediately post operative, 4 h after surgery at rest and 8 h with movement. Neuropathic pain started few days postoperatively, in both groups. Its onset, sites, duration and precipitating factors did not differ between the groups. Sensitive, hot pain and unpleasantness reduced significantly 1 month postoperatively, in intervention group. Two months later, itchy, dull and sharp pain was significantly less in intervention group. At 6 months, most of neuropathic pain items except sharp and deep pain lowered significantly in intervention group. At 9 months, hot and superficial pain was still less in intervention group. NO decreased significantly 1 and 3 months postoperatively, while IL-1β was significantly lower through different times, in intervention group. IL-1β correlated well with neuropathic pain intensity and unpleasantness.

Conclusion: Breast surgery for cancer was associated with neuropathic pain that continued for 9 months after surgery. Multimodal balanced GA had positive impact on acute nociceptive and neuropathic pain. Gabapentin reduced almost all neuropathic pain qualities.

1. Introduction

Neuropathic pain following breast cancer surgery was thought to be rare. Accordingly, its prevention and management was neglected for a long time. The results of late studies suggested that, neuropathic pain following breast surgery was acute in nature, then progressed to persistent or chronic pain in 50% of the patients. Thirty percent of those patients reported no change or worsening of their neuropathic pain symptoms [1,2]. This finding might change physicians' attitude towards the management of postoperative neuropathic pain [3].

Neuropathic pain reported by patients can be transient or long-lasting, and has different expressions such as burning pain, numbness, pin prick, phantom sensations, and sensory loss or changes. According to the site of pain, four different types were identified; intercostobrachial neuralgia (ICN) or post-mastectomy pain syndrome, which is defined as pain accompanied by sensory changes in the distribution of the intercostobrachial nerve following breast surgery with or without axillary dissection, neuroma pain or scar pain (pain in the region of a scar on the breast, chest, or arm that is provoked or exacerbated by percussion), phantom breast pain (a sensory experience of a removed breast that is still present and is painful) and other neuropathic pain (pain outside the distribution of the intercostobrachial nerve consistent with damage to other nerves during breast surgery) [4,5].

Chemotherapy and radiotherapy can be additional risk factors for developing neuropathic pain and related symptoms and make diagnosis more difficult [6]. Persistent pain can be a source of considerable disability and psychological distress for patients. For example, it may lead to limited daily activity, sleep disturbance, persistent symptoms of depression and anxiety. These consequences reflect negatively on family and social life [7].

To date, the mechanism of neuropathic pain following breast therapy is still poorly understood. Recent investigations on chronic post surgical pain revealed that, both post surgical prolonged inflammation and excessive stretching and injuries to the nerves may lead to over stimulation of the spinal cord and result in central sensitization [8]. In inflammatory type of pain, local inflammatory mediators released from injured tissue stimulate peripheral sensory neurons. These in turn, produce repetitive firing to modulate and exaggerate dorsal horn mediators. Modulation at the level of spinal cord is not a simple process; it needs abnormal expression of transcription factors that alter the function of ion channels and receptors. Subsequent alteration in protein transcription in sensory neurons and in the spinal cord augments the release of excitatory transmitters and decreases inhibitory mediators resulting in central sensitization and spreading of spontaneous ongoing pain [9]. Concurrent nerve injuries during surgery produce central sensitization through structural and functional neural changes. Structure changes are due to direct nerve injury or formation of neuroma (entangling of nerve fibers into surrounding tissue), while functional changes are developed as a result of proliferation and activation of both tetrodotoxin sensitive and -resistant sodium channels following nerve injury that stimulate the release of excitatory mediators [10].

A growing body of evidence suggests that, nitric oxide (NO) and cytokines may be the main inflammatory mediators responsible for maintenance and exaggerating pain states after breast therapy [11]. Nitric oxide is an intracellular mediator responsible for numerous physiological processes in human body. It can exert pro- or anti-nociceptive effects depending on its concentration. Anti-nociceptive effects were evident in several animal studies when NO was injected in small amounts with NSAIDs [12,13]. On the other hand, pronociceptive effects were obvious when noxious stimuli induced significantly increased NO levels, either locally and at central levels. This pronociceptive effect was antagonized by NOS inhibitors [14,15].

Similarly, a number of pro and anti inflammatory cytokines are released in response to painful stimuli. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 beta (IL-1β), reduce thermal or mechanical pain thresholds, while anti-inflammatory ones, such as IL-4, IL-10, and IL-13 inhibit the production and action of the pro-inflammatory cytokines and possess anti hyperalgesic effect. The imbalance between both is responsible for pathological states [16].

To date, there is no evidence-based protocol for the management of chronic post breast therapy pain. Successful prevention and effective management may depend on minimizing risks for developing this type of pain. Psycho-education program, as well as encouraging family support may reduce the risk [17]. On the hand, better control of perioperative pain

using multimodal balanced general anaesthesia in form of regional and general balanced analgesia [18], in addition to attenuation of acute neuropathic pain intensity using analgesics, may reduce the incidence of developing persistent post operative pain [19].

Gabapentin [1-(aminomethyl) cyclohexane acetic acid], a structural analogue of γ-aminobutyric acid (GABA), was introduced as an antiepileptic drug, and is extensively used in the treatment of neuropathic pain. Gabapentin has been shown to reduce analgesic requirements for acute postoperative pain [20].

The present study aimed to evaluate the effect of multimodal balanced anaesthesia and long term use of gabapentin (6 months) on neuropathic pain intensity and its mediators; NO and IL1-β.

2. Patients and methods

After obtaining Ethical Committee approval and taking patients' consents, this study was conducted on 50 female patients between 20 and 59 years of age, admitted to the Clinical Surgery Department, Medical Research Institute Hospital, Alexandria University. All patients underwent surgical excision of tumor with adequate safety margin and axillary clearance, followed by either chemo and/or radiotherapy. After premedication with midazolam (0.01–0.04 mg/kg) intravenously, patients were divided into two groups. Patients in control group received the standard general anaesthesia, while those in the intervention group received multimodal balanced anaesthesia (US guided paravertebral block followed by the standard general anaesthesia). Three patients in control group and four patients in intervention group refused to continue in the research.

2.1. Inclusion and exclusion criteria

All patients were American Society of Anesthesiologists physical status II (ASA 11), and underwent conservative breast surgery for cancer. Patients with chronic pain, consuming analgesics, antidepressants, calcium channel blockers, antiepileptics, sedatives, hypnotics or received radiotherapy and/or chemotherapy prior to surgery were excluded from the study. Other exclusion criteria were submission to previous breast surgical operation, evidence of metastasis or refusing to give consent.

2.2. Anaesthesia

Ultrasound guided paravertebral block (PVB) was performed using SonoSite, S nerve, 2 D, Inc., USA machine and 60 mm curved probe 5–12 MHZ. The block was done in the sitting position using touhy needle 18 G and catheter 19 G at the level of ipsilateral 3rd thoracic vertebra Figs. 1 and 2. Twenty-five milliliter bupivacaine 0.25% was injected in paravertebral space at the ipsilateral site of surgery. Ipsilateral sensory block was assessed, 5–10 min after bupivacaine injection, at 2nd to 6th thoracic vertebrae by absent sensation to cold.

General anaesthesia in both groups was introduced by fentanyl 2 μg/kg, propofol 1–2 mg/kg, and cisatracurium 0.15 mg/kg for facilitation of tracheal intubation. Anaesthesia was maintained with isoflurane1–2%, air–oxygen mixture, and morphine 0.05 mg/kg/h intravenously. Cisatracurium 0.05 mg/kg was given to maintain one twitch of train of four using nerve stimulator. Postoperative pain was controlled using i.v acetaminophen (1 g/6 h) for 3 days, in addition to either i.v morphine PCA (Master PCA Fresenius KABI) at concentration of 1 mg/ml using 3 ml loading dose and 1 ml PCA with lock out time 6 min and a 20 ml maximum dose/4 h for 24 h in the control group or paravertebral PCA bupivacaine 0.125%, using 8 ml loading dose and a 6 ml/h infusion with a 4 mL bolus and 15-min lockout for 24 h, in the intervention group. Before discharging home, all patients were instructed to note the pain they might have at home and record the analgesic consumption. Non steroidal anti-inflammatory drugs (Meloxicam; 15 mg, once/day) and anti-inflammatory enzymes (Trypsin or Chymotrypsin, one tablet, three times/day, taken 1 h prior to meal) were prescribed to each patient for 10 days, postoperatively. Gabapentin was prescribed to any patient reporting neuropathic pain (VAS $\geqslant$ 4/10 points) 1 month after surgery and for 6 months in the intervention group. Gabapentin (300 mg, orally in divided doses) was given, and titrated up to 100 mg daily, to decrease pain intensity to less than four points (on scale 0–10 cm). Gabapentin maximum dose was 1800 mg. If excessive sedation, drowsiness or dizziness was reported, gabapentin was reduced to the previous dose.

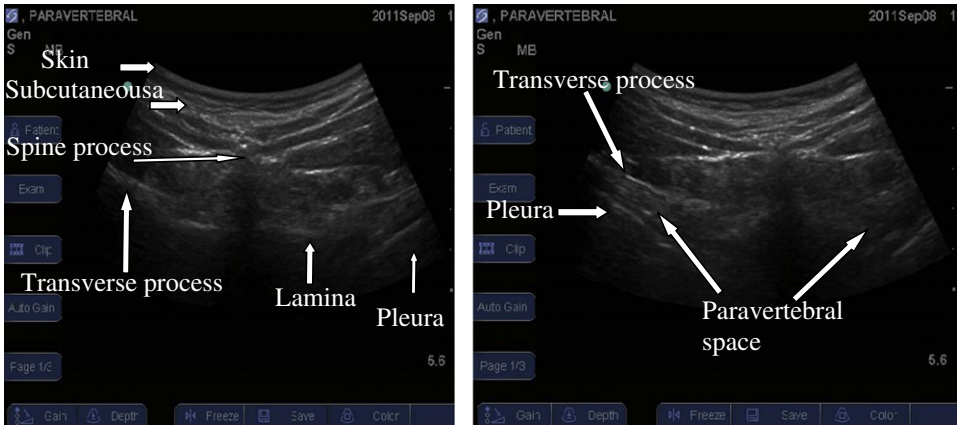


Figure 1 Ultrasound image of 3rd thoracic vertebra and paravertebral space.

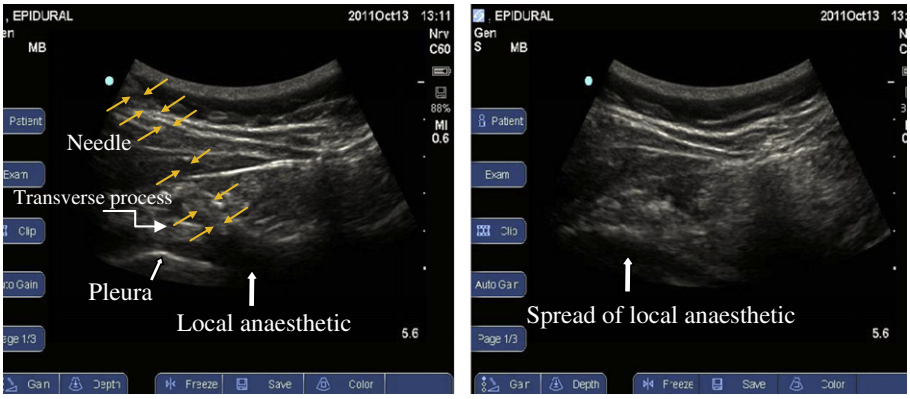


Figure 2 Local anaesthetic injection and its spread into paravertebral space.

2.3. Sample size

Using NCSS software, a sample size of 20 in each group was able to detect a difference of 1.00 ± 0.5 in pain scale of 0–10 points between the control and the intervention group with 90% power and at 5% level of significance.

2.4. Measurements

2.4.1. Outcome measures

The primary outcome was to detect the incidence of neuropathic pain after breast therapy for cancer. Secondary outcome was to measure the effect of multimodal balanced anaesthesia and gabapentin on the intensity and characters of neuropathic pain and its mediators.

2.5. Acute pain

- Acute postoperative pain after conservative breast surgery for cancer was evaluated using visual analogue scale (VAS) 0–10 cm with 0 = no pain and 10 = worst possible pain experienced. It was measured immediately after anaesthetic recovery at rest, then every 4 h for 24 h during rest and movement of ipsilateral arm.
- Additional analgesics taken after 10 days postoperatively were recorded.

2.6. Evaluation and measurement of neuropathic pain

Criteria for diagnosis of neuropathic pain were; presence of burning sensation, tingling, numbness, sensory loss, hyperalgesia and/or allodynia at ipsilateral breast or arm. Neuropathic pain was evaluated using pain questionnaire [21], neuropathic pain scale (NPS) [22] and sensory examination. The questionnaire assessed pain character, onset, location and duration of pain. It also evaluated a number of precipitating factors of pain and effect of pain on activity, sleep and mood (each item was rating on scale 0–4). (Appendix A) The NPS contains an introduction describing how people may experience pain sensations differently and how unpleasantness differs from intensity. The scale presents 10 domains of pain, including two items that assess global pain; pain intensity and pain unpleasantness and eight items that assess the specific qualities of neuropathic pain: sharp, hot, dull, cold, sensitive, itchy, deep, and surface. Patients were asked to rate each quality of pain on a scale of 0–10, where 0 = no pain and 10 the worst sensation imaginable. (Appendix B) NPS was evaluated at 1, 3, 6 and 9 months, postoperatively. Sensory examination was performed for surgical and contralateral side to confirm the neuropathic nature of pain. It was conducted to evaluate hypothesia, hyperalgesia and/or allodynia on area around breast scar, axillary scar and inner aspect of ipsilateral arm (distribution of intercostobrachial nerve) and/or outer aspect of arm (distribution of other nerves). Absent sensation to fine touch (piece of cotton) was used to detect hypothesia. Pain on slight touch to skin or repeated brushing of the skin indicated allodynia. Exaggerated response to pin prick sensation or cold sensation (alcohol swab) in comparison to other arm showed hyperalgesia.

2.7. Measurement of pain mediators

Venous blood samples were withdrawn from all patients participating in the current study, 1 day prior to operation and 1, 3, 6 and 9 months after operation for NO levels and IL1-β measurements. Blood samples were centrifuged and serum was collected and stored −50 °C till assay time. Plasma nitrate/nitrite (NO_x) content was determined using Griess reaction [23]. Serum IL1-β was measured using sandwich ELISA technique [24].

2.8. Difficulties encountered

At the beginning, this study aimed to evaluate the effect of continuous use of preemptive gabapentin for 6 months on the severity of post breast therapy neuropathic pain and its mediators; NO level and IL-1β. Since neuropathic pain started during gabapentin intake, patients did not believe in gabapentin efficacy and consequently discontinued treatment. It was easier to prescribe it after neuropathic pain perception to decrease its intensity.

2.9. Statistical analysis

Statistical analysis was performed using SPSS version 18.0. Normality testing was done through the Kolmogrov–Smirnov test. Normally distributed quantitative variables were described by mean and standard deviation, while not normally distributed data were described through the median and range.

Qualitative variables were described by their frequencies and %. Comparisons between the control and the intervention group were done through the independent *t*-test for normally distributed quantitative variables, while the Mann Whitney test was used for not-normally distributed variables. Qualitative variables were compared using the chi-squared test. In case of invalid Chi-square, the MonteCarlo *p* value was used. Correlations between pain scales, global items and the neuropathic pain mediators were done through the Spearman's rank correlation coefficient. All tests were two-sided and the significance was set at 5% level.

3. Results

Patients' characteristics were matched in both studied groups. No statistically significant differences were present between groups, neither in age, body weight, surgical duration, nor in type of therapy following surgery Table 1.

Acute nociceptive pain following surgery was reported by the patients in both studied groups at the breast, axilla and ipsilateral shoulder. Pain intensity measured by VAS at rest was less in the intervention group than control group, immediately post operative and 4 h later. However, pain was less during the first 8 h after surgery with the movement of ipsilateral arm Figs. 3 and 4.

One month after breast surgery, all women (100%) in both studied groups had abnormal sensation on the breast, axilla or the ipsilateral arm and described it as burning, tingling, numbness, hypersensitivity and/or dull pain. No one reported loss of sensation. They discovered the sensory loss in breast area, axilla and inner or outer aspect of arm during sensory examination. Pain started at average on the 10th or 11th day. The most common site of pain was ipsilateral arm in both studied groups. The distribution of acute neuropathic post surgical pain according to its onset sites and duration did not show significant differences between the control and intervention groups. Similarly, effort, hotness and/or coldness, that precipitated pain, pain interfered with activity, sleep and mood and meloxicam consumption at 1 month postoperative, did not differ in the studied groups Table 2.

Distribution of chronic neuropathic pain according to its site 9 months after breast surgery, showed that there was a large number of patients still complaining of pain, in both studied groups. Thirty-nine percent of patients in both groups were complaining of pain in the breast, meanwhile 27.9% of patients were complaining of pain in the axilla. Pain in the arm was present unfortunately in 72.1%, in both groups Table 3.

The global pain items of the neuropathic pain scale (pain unpleasantness and pain intensity) showed significantly lower

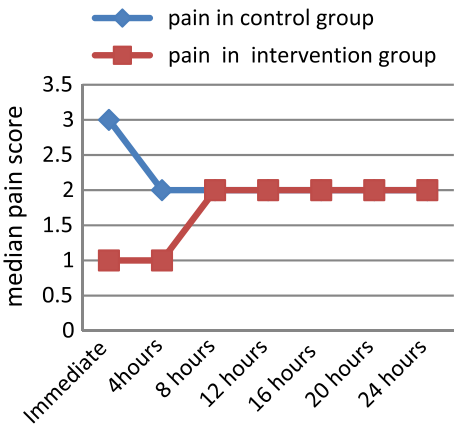


Figure 3 Pain at rest during the first 24 h post operative.

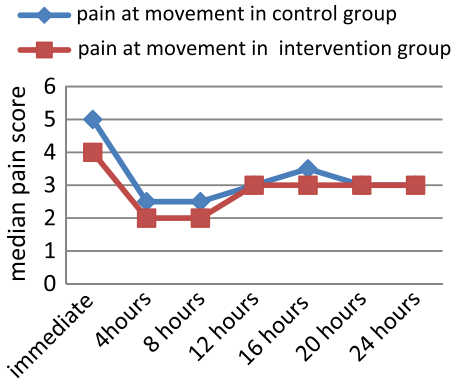


Figure 4 Pain at ipsilateral arm movement during the first 24 h post operative.

values in patients in the intervention group than those in the control group. For pain unpleasantness, significant lower median values were found after 1 month, 3 months and 6 months, postoperatively. Concerning pain intensity, significant lower median values existed, a little bit later, after 3 months, 6 and 9 months, postoperatively Table 4.

Some neuropathic pain characters were also significantly lower in the intervention group than in the control group (Table 4). One month after surgery, median values for sensitive and hot pain were significantly lower in the intervention than that of the control group. Two months later, median values for itchy pain, dull pain and sharp pain were significantly less in the intervention group. After 6 months most of neuropathic pain items, except sharp and deep pain were significantly lower

Table 1 Patients' characteristics in the control and the intervention groups.

	Control (n = 22)	Intervention (n = 21)	p
Age in years (means ± *SD*)	42 ± 8.1	41 ± 8.4	0.68
Weight in kg (means ± *SD*)	75 ± 18	76 ± 15	0.51
Duration of surgery in min. (means ± *SD*)	95 ± 13.9	90 ± 10.3	0.22
▲ Type of post-surgical therapy (%)			
Radiotherapy	2 (9.1)	1 (4.8)	1.00
Chemo and radiotherapy	20 (90.9)	20 (95.2)	

▲ MonteCarlo *p*.

Table 2 Neuropathic pain characteristics, precipitating factors and meloxicam consumption 1 month after breast surgery.

Variables	Control group	Intervention group	*p*
Number of patients reported abnormal sensation as a result of surgery (%)	22 (100%)	21 (100%)	1.00
Start of pain after surgery in days (means ± *SD*)	11.43 ± 3.58	9.90 ± 3.47	0.17
Site of pain (*n*) (%)			
Breast	10 (25.0)	11 (26.8)	0.65
Arm	17 (42.5)	16 (39.0)	0.93
Axilla	13 (32.5)	14 (34.2)	0.61
Duration of pain (h) (means ± *SD*)	2.45 ± 0.92	2.24 ± 0.89	0.44
▲ Precipitating factors			
Effort	2 (1–3)	2 (1–3)	0.61
Hotness	2 (1–3)	2 (1–3)	0.63
Coldness	2 (1–2)	2 (1–2)	0.56
▲ Interference with work	2 (1–3)	2 (1–2)	0.51
With sleep	2 (1–3)	2 (1–3)	0.63
With mood	2 (1–3)	2 (1–3)	0.62
Meloxicam rescue doses (mg) (means ± *SD*)	78 ± 29	65 ± 27	0.14

▲ Values are expressed as median (range).

Table 3 Site of neuropathic pain 3, 6 and 9 months after breast surgery in the control and the intervention groups.

Pain site	Control group (n = 22)	Intervention group (n = 21)	p Value
Breast			
3 months	11 (50.0)	10 (47.6)	0.65
6 months	10 (45.5)	10 (47.6)	0.89
9 months	8 (36.4)	9 (42.9)	0.66
Axilla			
3 months	11 (50.0)	11 (52.4)	0.88
6 months	7 (31.8)	9 (42.9)	0.45
9 months	7 (31.8)	5 (23.8)	0.44
Arm			
3 months	17 (77.3)	16 (76.2)	0.93
6 months	15 (68.2)	16 (76.2)	0.56
9 months	15 (68.2)	16 (76.2)	0.56

Values are expressed as frequencies and %.

in the intervention group. At 9 months postoperatively, hot and superficial pain were still less in the intervention group. None of the patients reported cold pain sensation.

Neuropathic pain mediators NO and IL-1β were significantly lower in the intervention group than in the control group (Table 5). For NO, significant lower values were detected after 1 and 3 months. Meanwhile, IL-1β median values were significantly lower in the intervention group through the different times.

The correlation between pain as represented by global pain unpleasantness, pain intensity and chronic pain mediators (NO and IL-1-β) were illustrated in Table 6. A significant direct correlation between pain unpleasantness and interleukin 1b was found after 3 and 6 months. Similarly, a significant direct correlation between pain intensity and IL-1-β was observed after 3, 6 and 9 months.

4. Discussion

Neuropathic post-surgical pain is influenced by two mechanisms: inflammatory mediators, which is the consequence of trauma to peripheral tissues and intraoperative nerve damage arising from nerve trans-section, crushing or other nerve injury. Both mechanisms result in changes in the sensitivity of the central nervous system that amplifies the peripheral signal and produces spontaneous ongoing pain. Neuropathic changes after tissue trauma seems to be short-lived and preventable, while those after nerve injuries are long lasting and need aggressive strategy for prevention and treatment [24]. Nowadays, it has been suggested that multimodal balanced anaesthesia using different classes of analgesic agents with different routes of administration can prevent neuroplastic changes after surgical peripheral tissue trauma and attenuate central neural excitation following nerve injuries [25].

The present study showed that acute pain after breast surgery for cancer was less in intervention group at rest for 4 h postoperatively and at movement of ipsilateral arm up to 8 h, postoperatively. This significantly lowered pain intensity could be explained by the effect of multimodal balanced anaesthesia using PVB in combination with traditional intraoperative opioid analgesics that was used in the intervention group. Paravertebral block provided tense block of dorsal root

Table 4 The neuropathic pain scale (NPS) (0–10 cm) in the control and the intervention groups at different times after breast surgery.

Neuropathic pain scale	Control (n = 22)	Intervention (n = 21)	p value
Unpleasantness			
1 month	5 (3–7)	4 (2–7)	0.05*
3 months	4 (3–8)	3 (0–6)	0.01*
6 months	4.5 (0–6)	3 (0–5)	0.00*
9 months	3 (2–5)	3 (0–4)	0.09
Intensity			
1 month	5 (3–7)	4 (3–7)	0.23
3 months	5 (3–7)	3 (0–5)	0.00*
6 months	4.5 (3–6)	3 (0–4)	0.00*
9 months	4 (2–7)	3 (2–3)	0.00*
Itchiness (poison oak/mosquito bite			
1 month	5 (3–7)	5 (3–7)	0.27
3 months	5 (2–6)	3 (0–5)	0.01*
6 months	0 (0–5)	0 (0–3)	0.05*
9 months	0 (0–0)	0 (0–0)	1.01
Sensitivity (sun burn/raw skin)			
1 month	6 (3–7)	5 (3–7)	0.03*
3 months	3 (2–6)	4 (0–5)	0.99
6 months	3 (1–5)	2 (0–4)	0.00*
9 months	0 (0–3)	0 (0–3)	0.12
Dullness (dull toothache/dull pain/aching/bruise)			
1 month	5 (4–7)	5 (3–7)	0.06
3 months	5 (2–7)	4 (2–5)	0.05*
6 months	4 (0–6)	3 (0–5)	0.00*
9 months	3 (0–3)	3 (0–3)	0.19
Sharpness (knife/spike/jabbing/jolts)			
1 month	6 (3–8)	5 (4–8)	0.32
3 months	5 (3–7)	4 (3–6)	0.02*
6 months	4 (2–5)	3 (2–5)	0.32
Hotness (burring – fire)			
1 month	3 (2–5)	3 (2–4)	0.00*
9 months	3 (2–4)	3 (0–4)	0.00*
Superficial			
1 month	7 (5–10)	6 (5–10)	0.07
3 months	5.5 (5–9)	4 (3–8)	0.00*
6 months	4.5 (2–6)	3 (1–6)	0.00*
9 months	3 (1–3)	1 (1–3)	0.00*
Deep			
1 month	3 (1–3)	3 (1–3)	0.3
3 months	3 (3–4)	3 (2–4)	0.32
6 months	3 (1–5)	3 (1–5)	0.51
9 months	4 (3–6)	3 (2–5)	0.23

* $P \leqslant 0.05$ for Mann Whitney was considered statistically significant. Values expressed as median (range).

ganglions, and sympathetic chain, in addition to somatic nerves in paravertebral space. Subsequently, it prevented sensitization of the central nervous system, N-methyl-D-aspartate receptor activation and inhibited 'wind up' phenomena [26]. Opioids are power analgesics acting on opioid receptors, peripherally and at the central level and add synergistic analgesic effect [27].

In consistence with the present result, Dabbagh and Elyasi [28] and El Nasr et al. [29] reported that the thoracic PVB provided lower visual analogue scale (VAS) for pain than did GA, for the first 6 h, postoperatively. Previous meta analysis study evaluated fifteen randomized control researches, including 877 patients and concluded that thoracic PVB alone or in combination with GA reduced severity of postoperative pain at less than 2 h and provided better postoperative pain relief at 2–24 h, with little complications than general anaesthesia [30].

In the current study, better postoperative pain control under the influence of multimodal balanced anaesthesia did not give a positive impact on meloxicam consumption 1 month after surgery. This could be explained by the developing of a new pain (neuropathic pain) a few days after surgery, that did not respond to meloxicam treatment. In agreement with the present result, Kairaluoma et al. [31] reported that preoperative PVB did not reduce 14-day consumption of analgesics, but it lowered the intensity of chronic pain as late as 1 year after breast cancer surgery.

Table 5 Nitric oxide (NO) and interleukin 1 β – (IL 1-β) in the control and the intervention groups at different times, after breast surgery.

Chronic pain mediators	Control (n = 22)	Intervention (n = 21)	p
Nitric oxide			
▲Pre operative	2.5 ± 0.54	2.6 ± 0.41	0.37
▲1 month	4.0 ± .86	3.2 ± .74	0.00*
3 months	4.7 (2.9–6.9)	3.5 (2–4.1)	0.00*
▲6 months	2.5 ± .50	2.5 ± .46	0.82
▲9 months	3.4 ± .89	3.1 ± .64	0.36
Interleukin1-B			
▲Pre operative	8.6 ± 3.91	9.2 ± 2.88	0.59
1 month	11 (6–32)	5 (1–12)	0.00*
3 months	8 (5–25)	4 (2–12)	0.00*
6 months	7 (2–10)	2 (2–6)	0.00*
9 months	5 (2–12)	3 (2–5)	0.00*

▲ Values expressed as mean ± *SD*.
* $P \leqslant 0.05$ for Mann Whitney was considered statistically significant. Values are expressed as median (range).

Acute neuropathic pain which started a few days after surgery was moderate in intensity and intermittent in duration, in both studied groups. This moderate neuropathic pain intensity interfered to some extent with activity, sleep, and mood, without significant difference between groups. The delayed onset of neuropathic pain after breast surgery could be explained by a mixed nature of pain (nociceptive and neuropathic) associated with surgery. The higher nociceptive pain intensity may hide the less neuropathic pain sensation at the beginning. But after a few days, nociceptive type of pain resolved by tissue healing, while nerves needed longer time to recover and continued sending messages to higher centers. Therefore, patients started to be aware with it [24].

A large number of patients (72.1%) in both groups had persisting neuropathic pain in the arm up to 9 months, postoperatively. In consistence with the present result, Tasmuth et al. [32] reported that most women that underwent mastectomy or conservative breast surgery with axillary clearance had mild to moderate neuropathic pain in the breast area or ipsilateral arm, a month after surgery. One year after conservative breast, 82% of women were still complaining of neuropathic pain. Eighty percent of those women reported parathesia in breast area, while all patients reported ipsilateral arm parathesia.

Although the intensity of neuropathic pain in the present study did not show significant difference between the groups 1 month after surgery, the degree of unpleasantness, sensitive and hot pain sensation were reduced significantly under the influence of multimodal balanced anaesthesia. Three earlier studies evaluated PVB combined GA versus GA alone, on the development of chronic postoperative pain. They concluded that PVB lowered the prevalence and intensity of chronic pain at1, 2, 6 and 12 months after breast surgery for cancer [33–35].

In the current study, 3 months after surgery and 2 months after taking gabapentin, global neuropathic pain intensity, itchy, dull and sharp pain reduced significantly in the intervention group. After 6 months postoperatively, most of neuropathic pain items were influenced positively in the intervention group. At 9 months, hot and superficial sensations were less in intervention group. Deep pain was not affected either by paravertebral block or gabapentin at any time of measurement. The mechanism of gabapentin-induced analgesia could be attributed to inhibition of calcium currents that reduce neurotransmitter release and attenuate postsynaptic excitability [36].

Earlier studies supported the result of the current study and reported that, gabapentin and pregabalin reduced postoperative neuropathic pain intensity [37,38]. The efficacy of gabapentin in reducing pain intensity and burning sensation after 4 weeks treatment in patients with spinal cord injury was reported by Tai et al. [39].

The inhibitory effect of gabapentin on pain sensitivity (sensation of raw skin or sun burn) that made skin over the affected area very painful on touch may be similar to its effect on tactile allodynia in a previous study [40]. The authors evaluated the differences between two types of tactile allodynia (static and dynamic allodynia) in mice with herpetic or post herpetic pain and documented that gabapentin markedly inhibited both static and dynamic allodynia, at herpetic and post herpetic periods.

Levendoglu et al. [41] evaluated the effect of gabapentin on 20 patients with neuropathic spinal cord injury-related pain and found that, gabapentin reduced significantly global pain intensity and unpleasantness, as well as sharp, hot, deep, and surface pain, at 4 and 8 weeks. But unlike the present finding, they reported that gabapentin did not influence dull, sensitive, or itchy pain. The effect of gabapentin (1800 mg) on post herpetic neuropathic pain condition was evaluated by Jensen et al. [42]. They reported that a significant effect was documented on sharp, dull, sensitive, and itchy pain. Few effects were found on hot, cold, deep or surface pain qualities.z

The discrepancy of the efficacy of gabapentin in different pain condition may be explained by the fact that different neuropathic pain characters may arise as a result of different neuropathic pain conditions. Sharp, superficial, sensitive and itchy pain may be mostly obvious in peripheral neuropathy, while deep pain is the key component of neuropathic pain after amputation or osteoarthritis [43–45]. Gabapentin in the present study attenuated most of neuropathic pain characters, whereas it did not influence deep pain which may arise from interference with lymphatic system of the breast and ipsilateral arm after breast surgery and radiotherapy for cancer [46].

Table 6 Correlations between pain unpleasantness, pain intensity, nitric oxide and interleukin 1-β at different times, after breast surgery.

Times	Pain mediators	Pain unpleasantness	Pain intensity
1 month	NO	−0.11	0.11
	IL 1-β	0.12	0.08
3 months	NO	0.29	0.29
	IL 1-β	0.40**	0.45**
6 months	NO	0.06	−0.03
	IL 1-β	0.50***	0.58***
9 months	NO	0.06	0.10
	IL 1-β	0.25	0.54***

Values are correlation coefficients.
** $p < 0.01$.
*** $p < 0.001$.

The current study showed that, significantly less NO and IL-1β readings were found in intervention group in comparison to the control group. For NO, significant less values were detected after 1 and 3 months in patients experiencing less pain intensity under the influence of PVB and gabapentin treatment. Meanwhile, IL-1β median values were significantly less in the intervention group through the different times. A significant direct correlation between pain unpleasantness and pain intensity and IL-1β at 3, 6 and 9 months postoperatively, was also detected. However, there was no correlation with NO.

The presence of high levels of NO in chronic pain conditions was documented in previous studies [47,48]. The attenuated effect of PVB on NO release after breast surgery was investigated by Iohom et al. [33]. They concluded that, NO values 48 h postoperatively were greater in patients receiving a standard intraoperative and postoperative analgesic regimen (morphine sulfate, diclofenac, dextropropoxyphene hydrochloride and acetaminophen) compared with those receiving a continuous PVB (for 48 h), acetaminophen and parecoxib (followed by celecoxib up to 5 days). Lower levels of NO under the effect of gabapentin was reported by Oka et al. [49]. They showed that gabapentin inhibited Ca^{2+} channels involving the activation of NO synthetase that in turn reduced NO production.

Elevated serum concentrations of anti-inflammatory cytokines in patients with chronic pain conditions, such as juvenile rheumatoid arthritis [50], fibromyalgia [51], cervicogenic headache [52], or migraneurs [53] were detected in previous studies.

Koch et al. [54] investigated a number of cytokines and NO in the plasma of chronic pain patients (neuropathic, nociceptive and mixed pain conditions) and found that pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IFN-g and TNF-a) correlated with increasing pain intensity and that plasma levels of NO increased significantly in patients with chronic pain. Similarly, correlations between tissue levels of cytokines and a number of painful conditions were detected in some studies [55,56].

The relationship between NO release and IL-1β was not exactly clear. Few studies examined the effect of NO on pro-inflammatory cytokines. One study evaluated pain in human immunodeficiency virus-1 (HIV-1) and reported that, HIV-1stimulated pro-inflammatory cytokine-mediated pain was carried out through activation of *n*-NOS [57]. Another study showed that NO may facilitate the hyperalgesia induced by pro-inflammatory cytokines using the cAMP second messenger pathway and may also possess an independent cGMP-dependent hyperalgesic effect [58]. Chen et al. [59] reported that intraperitoneal injection of NOS inhibitors attenuated thermal hyperalgesia induced by intraplantar injection of hyperalgesic substance (complete Freund's adjuvant) in mice. They also concluded that pretreatment with NOS inhibitors prevented the increased TNF and IL-1β values under the influence of inflammatory stimulus.

Taken together, data of the present study showed that breast surgery for cancer was associated with acute neuropathic pain in 100% of the cases. This pain continued at ipsilateral arm in 72.1% of the cases for 9 months following surgery. Multimodal balanced anaesthesia in the form of PVB in combination with GA had positive impact on acute nociceptive and neuropathic pain. Gabapentin reduced almost all neuropathic pain qualities with exception of deep pain. Nitric oxide did not correlate with neuropathic pain intensity or unpleasantness; however IL-1β showed a good correlation. Further studies are required to reveal the role played by neuropathic pain mediators (NO and IL-1β) in an attempt to develop a better therapeutic strategy towards pain control.

Appendix A. Questionnaire for evaluation of neuropathic pain

Do you have any abnormal sensation (burning, tingling, numbness, or soreness) that could bother you as a result of your breast surgery?	Yes	No		
When did this sensation commerce after your surgery?	Days	Weeks	Months	
Where is the site of your pain?	In my breast	In my arm	Axilla	
Duration of pain	Seconds	Minutes	Hours	Days
Precipitating factors	Not at all	A little	To some extent	A lot
Physical activity				
Weighting heavy objects				
Hot weather				
Cold weather				
How much your pain interferes with work (scale 0-4)?	Not at all	A little	To some extent	A lot
With Sleep, (scale 0-4)?	Not at all	A little	To some extent	A lot
With Mood (scale 0-4)?	Not at all	A little	To some extent	A lot

Appendix B. Neuropathic pain scale

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

Not sharp | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **hot** sensation imaginable ("on fire")

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

Not cold | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sen-sitive | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **itchy** sensation imaginable ("like poison oak")

8. Which of the following best describes the **time** quality of your pain? Please check only one answer.

( ) I feel a background pain all of the time **and** occasional flare-ups (break-through pain) some of the time.

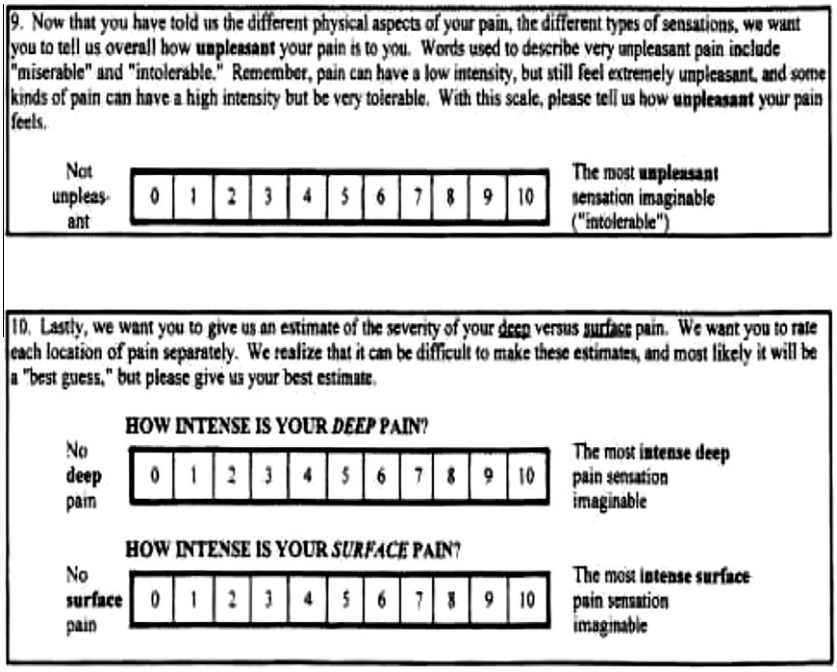
Describe the background pain: _____

Describe the flare-up (break-through) pain: _____

( ) I feel a single type of pain all the time. Describe this pain: _____

( ) I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain: _____



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