doi: 10.48095/cccg2025447

Postoperative analgesia in breast cancer surgeries – anesthetic techniques and the role of cytokines

Pooperační analgezie při operacích karcinomu prsu – anestetické techniky a role cytokinů

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Summary: Objectives: To examine the relationships between postoperative pain and anesthetic technique and analgesic use, to compare preoperative and postoperative serum cytokine levels, and to determine the influence of the anesthetic technique on these levels in patients undergoing breast cancer surgery. **Materials and methods:** Thirty-six patients undergoing oncological breast surgery were allocated to general anesthesia only (G; N = 20) and general anesthesia with erector spinae plane block (ESPB, E; N = 16) groups. Postoperative pain intensity was evaluated using a visual analogue scale at three periods (M): 2, 24, and 48 hours after the end of surgery (M2, M24, and M48, resp.). Blood was collected preoperatively, before the induction of general anesthesia (M0), and at M24 and M48. Plasma interleukin (IL)-1, IL-8, and tumor necrosis factor-α (TNF-α) levels were determined by enzyme-linked immunosorbent assay. Associations between categorical variables were evaluated using the Fisher's exact test. Pain scores and cytokine levels were compared between groups G and E and between patients undergoing mastectomy and quadrantectomy using repeated-measures analysis of variance. The significance level adopted for all tests was 5.0%. **Results:** Moderate to severe pain was more frequent in group G than in group E at M24 ($P = 0.016$). The IL-8 level was lower in group E than in group G ($P = 0.029$). In the whole cohort, TNF-α level was reduced at M48 ($P = 0.010$), IL-8 level was reduced at M24 ($P < 0.001$), and IL-1 level was increased at M48 ($P < 0.001$). **Conclusions:** ESPB is an effective alternative in cases with contraindications or technical difficulties with other anesthetic techniques, such as epidurals. Its use could improve women's quality of life and health after breast cancer surgery.

Key words: mastectomy – segmental mastectomy – cytokines – neuromuscular blockade – general anesthesia

Souhrn: Cíle: Zkoumat vztahy mezi pooperační bolestí, anesteziologickou technikou a použitím analgetik, porovnat předoperační a pooperační hladiny cytokinů v séru a určit vliv anesteziologické techniky na tyto hladiny u pacientek podstupujících operaci rakoviny prsu. **Materiály a metody:** Celkem 36 pacientek podstupujících onkologickou operaci prsu bylo rozděleno do skupin pouze s celkovou anestezií (G; n = 20) a s celkovou anestezií ESPBE (erector spinae plane block, E; n = 16). Intenzita pooperační bolesti byla hodnocena pomocí vizuální analogové stupnice ve třech okamžicích (M): 2, 24 a 48 hod po ukončení operace (M2, M24 a M48). Krev byla odebrána před operací, před indukcí celkové anestezie (M0) a v M24 a M48. Hladiny plazmatického interleukinu (IL)-1, IL-8 a tumor nekrotizujícího faktoru α (TNF-α) byly stanoveny pomocí enzymově vázaného imunosorbentního testu. Souvislosti mezi kategoriálními proměnnými byly hodnoceny pomocí Fisherova exaktního testu. Skóre bolesti a hladiny cytokinů byly porovnány mezi skupinami G a E a mezi pacientkami podstupujícími mastektomii a kvadrantektomii pomocí analýzy rozptylu s opakovanými měřeními. Hladina významnosti použitá pro všechny testy byla 5,0 %. **Výsledky:** Středně silná až silná bolest byla častější ve skupině G než ve skupině E v M24 ($p = 0{,}016$). Hladina IL-8 byla ve skupině E nižší než ve skupině G ($p = 0{,}029$). V celé kohortě byla hladina TNFα snížena v M48 ($p = 0{,}010$), hladina IL-8 byla snížena v M24 ($p < 0{,}001$) a hladina IL-1 byla zvýšena v M48 ($p < 0{,}001$). **Závěry:** ESPB je účinnou alternativou v případech s kontraindikacemi nebo technickými obtížemi s jinými anestetickými technikami, jako je epidurální anestezie. Jeho použití by mohlo zlepšit kvalitu života a zdraví žen po operaci rakoviny prsu.

Klíčová slova: mastektomie – segmentální mastektomie – cytokiny – neuromuskulární blokáda – celková anestezie

Introduction

Breast surgery is a crucial part of breast cancer treatment, and it has become more conservative over time [1]. Almost 60% of patients undergoing breast surgery have severe acute postoperative pain [2]. Inadequately treated postoperative pain is associated with the activation of the sympathetic nervous system and increased perioperative use of opioids, and may be associated with cancer recurrence and reduced survival [3]. Moreover, women who undergo mastectomy or quadrantectomy may present chronic postoperative pain and neuropathic syndromes [4]. Thus, pain management is of paramount importance to reduce postoperative complications, hospitalization times, and the occurrence of chronic pain [5].

The use of opioids as anesthesia and to treat postoperative pain is common [6]. However, opioids have undesirable effects such as respiratory depression and may increase neuroinflammation, leading to persistent pain. They also precipitate neurocognitive decline in frail and elderly patients. Recent findings confirm that acute pain treatments that modulate nociceptive and inflammatory pain should be used with caution, as drugs that inhibit inflammation, such as nonsteroidal anti-inflammatory drugs and corticosteroids, can interfere with natural recovery processes [7].

In the context of major breast surgery, regional anesthesia such as that induced with an epidural, paravertebral block, pectoral nerve block, fascial blocks, and/or local anesthetic wound infiltration should be considered for additional pain relief. Indeed, regional analgesia is recommended as a key component of multimodal analgesia techniques for major oncological procedures. It is associated with reductions in the severity and impact of pain at 3, 6, and 12 months after mastectomy surgery [8]. In this context, the administration of epidural anesthetics and opioids has been considered to be the gold standard. Epidural analgesia is of indisputable efficacy but has limitations such as technical difficulty, hemodynamic changes triggered by sympathetic blockade, and side effects, particularly late respiratory depression. New techniques for peripheral nerve blockade have recently emerged. With the development of ultrasound guidance, a higher success rate, fewer complications, and a simpler and more effective postoperative analgesia effect have been achieved [2].

While the possibilities for anesthesia have increased, so has confusion about which technique to use and when. The paravertebral block is a peripheral nerve block of moderate difficulty that can be challenging to perform even with the use of ultrasound. It requires specific training that is not always included in routine learning schedules [9], but it is the second most widely recognized anesthetic technique for postoperative analgesia, after the epidural, for breast surgery. Other blocks used for breast surgery are type I and type II pectoral blocks (PECS I and PECS II, respectively) [10]. Some studies suggest that the ultrasound-guided PECS II block is the best option for perioperative pain relief and the reduction of intraoperative and postoperative opioid use [11].

The erector spinae plane block (ESPB) is a relatively new technique that provides excellent analgesia for breast surgery [12]. Its mechanisms of action include neural blockade and central nervous system inhibition through the direct spread of the local anesthetic to the paravertebral or epidural space. The local anesthetic spreads to the ventral branch of the spinal nerves and involves the dorsal branch; epidural spread is observed less commonly. A systemic effect of the local anesthetic is also plausible, but unlikely to be a major contributor to analgesic efficacy. This block is associated with reduced risks of neurovascular and pleural injury and systemic local anesthetic toxicity, and is characterized by relative technical simplicity compared with epidural and paravertebral blocks. It has been used in the management of acute perioperative pain in a variety of clinical applications, including breast, thoracic, and abdominal surgeries and trauma. It is guided by ultrasound, reduces the need for postoperative analgesic use, and avoids the use of more invasive techniques, such as paravertebral block [13].

Cytokines are involved in the initiation and persistence of pathological pain through the direct activation of nociceptive sensory neurons. They are also involved in the central sensitization induced by nerve damage or inflammation and are related to the development of hyperalgesia and allodynia [14]. In cases of acute trauma, such as surgery, persistently high levels of pro-inflammatory cytokines prolong the hyperalgesia needed to preserve the injured area, which may explain the development of chronic pain syndrome [15]. Pro-inflammatory cytokines are produced predominantly by activated macrophages and are involved in the upregulation of inflammatory reactions. Abundant evidence indicates that pro-inflammatory cytokines such as interleukin (IL)-1, IL-8, and tumor necrosis factor-α (TNF-α) are involved in the pathological pain process [14].

The objectives of this study were to examine the relationship of postoperative pain to the anesthetic technique and analgesics used, to compare preoperative and postoperative serum cytokine levels, and to determine the influence of the anesthetic technique on these levels in patients undergoing surgery for breast cancer.

Patient population and methodology

Patients and study design

Thirty-six patients aged 27–79 years who were diagnosed with breast cancer with surgical treatment indication and were treated at the mastology outpatient clinic of the Department of Gynecology and Obstetrics and the Discipline of Anesthesiology, Federal University of Triângulo Mineiro (UFTM), between May 2021 and December 2022 were included in this study. The patients were divided into two groups according to the anesthetic technique: those undergoing general anesthesia (group G), and those undergoing general anesthesia with ESPB (group E).

This was a longitudinal, prospective, double-blind study, as the patients and the researcher responsible for data collection were unaware of the anesthetic technique used. The anesthetic technique was selected before patient allocation using a random draw program (http://www.randomization.com) and a pre-established sequence.

The inclusion criteria were the diagnosis of breast cancer, indication for mastectomy or quadrantectomy with an axillary approach, and age > 18 years. Patients with impaired cognition or other clinical conditions preventing comprehension of the visual analogue scale (VAS), those with other immunosuppressive diseases and/or who were using immunosuppressive drugs, those whose last chemotherapy cycles had ended fewer than 30 days previously, and those who were pregnant were excluded.

The Research Ethics Committee of UFTM approved this study (CAAE: 44131621.2.0000.5154).

Anesthetic technique

Two techniques were performed: balanced general anesthesia with no regional block (group G) and balanced general anesthesia with ultrasound-guided ESPB (group E). General anesthesia was standardized to 2–3 μg/kg fentanyl, 1.5 mg/kg lidocaine, 2–3 mg/kg propofol depending on the patient's previous hemodynamic condition, and 0.6 mg/kg intravenous rocuronium. Postoperative analgesia was standardized for all patients to intravenous dipyrone (2 g before the end of surgery and 1 g every 6 hours in the postoperative period), 100 mg intravenous ketoprofen [a non-steroidal anti-inflammatory drug (NSAID)] every 12 hours, and, when necessary, 100 mg intravenous tramadol (a weak opioid dose) every 8 hours and analgesic rescue with 2 mg morphine upon patient request.

ESPB

ESPB procedures were performed by resident physicians in anesthesiology under the supervision of experienced anesthesiologists to ensure the maintenance of technical quality. Each patient was placed in a sitting position under standard monitoring, including electrocardiography, pulse oxygen saturation tracking, and non-invasive blood pressure measurement. After the laterality of the surgery was confirmed, 3 cm were marked lateral to the spinous processes of the fourth (T4) and fifth thoracic vertebrae using a Mindray® linear ultrasound probe at 6–13 Hz. The patient's skin was disinfected with 0.5% alcoholic chlorhexidine. The ultrasound probe was covered with a sterile sheath, the transverse process of T4 and the overlying erector spinae muscle were visualized, and a needle (22 gauge, 50 mm; B. Braun®) was inserted in plane in the craniocaudal direction until its tip contacted the transverse process of T4. The needle was then withdrawn slightly, and 30 mL 0.5% ropivacaine was injected.

Pain evaluation and clinicodemographic data collection

The intensity of postoperative pain was evaluated using a VAS ranging from 0 (absence of pain) to 10 (maximum pain felt by the patient). VAS scores of 0–2 were classified as mild pain and those of 3–10 were classified as moderate to severe pain. Evaluation was performed at three moments (M): 2, 24, and 48 hours after the end of surgery (M2, M24, and M48, resp.). Using a researcher autonomy questionnaire, the following data were collected: age, weight, height, body mass index, physical status according to the American Society of Anesthesiologists (ASA), procedure performed, anesthetic and analgesic techniques used, and use of analgesic drugs (common analgesics, weak and strong opioids) during the first 24 and 48 hours after the procedure.

Blood collection for cytokine analysis

Blood was collected from the patients preoperatively, before the induction of general anesthesia (M0), and at M24 and M48. The blood was collected into tubes containing separator gel using a vacuum system (BD Vacutainer®). After 30 min coagulation, the samples were centrifuged for 10 min at 4 °C and 2,000 rpm, and the sera were stored in 250-μL aliquots at –70 °C until use.

Serum cytokine measurement by ELISA

Serum IL-1, IL-8, and TNF-α levels were determined by enzyme-linked immunosorbent assay (ELISA). Diluted samples and standards corresponding to the respective curves (100 μL each) were added to the wells of the ELISA plate and coated with capture monoclonal antibodies for IL-1, IL-8, and TNF-α, blanks and samples. The ELISA plate was covered with an adhesive sealant and incubated for 2 h at room temperature (RT) on a microplate shaker. Then, the wells were aspirated and washed five times with 300 μL wash buffer using automatic multichannel micropipettes. The plate was then inverted on absorbent paper to remove any residual buffer, followed by the addition of 100 μL working solution (detection antibodies for IL-1, IL-8, and TNF-α with streptavidin peroxidase conjugate) and incubation for 1 h at RT. Aspiration and washing were repeated as described above, 100 μL substrate solution (tetramethylbenzidine and hydrogen peroxide) was added, and the plate was incubated in a microshaker for 30 min in the dark. Then, 50 μL stop solution (1 M H_3PO_4) was added to each well. Optical density at 450 nm was determined using a microplate

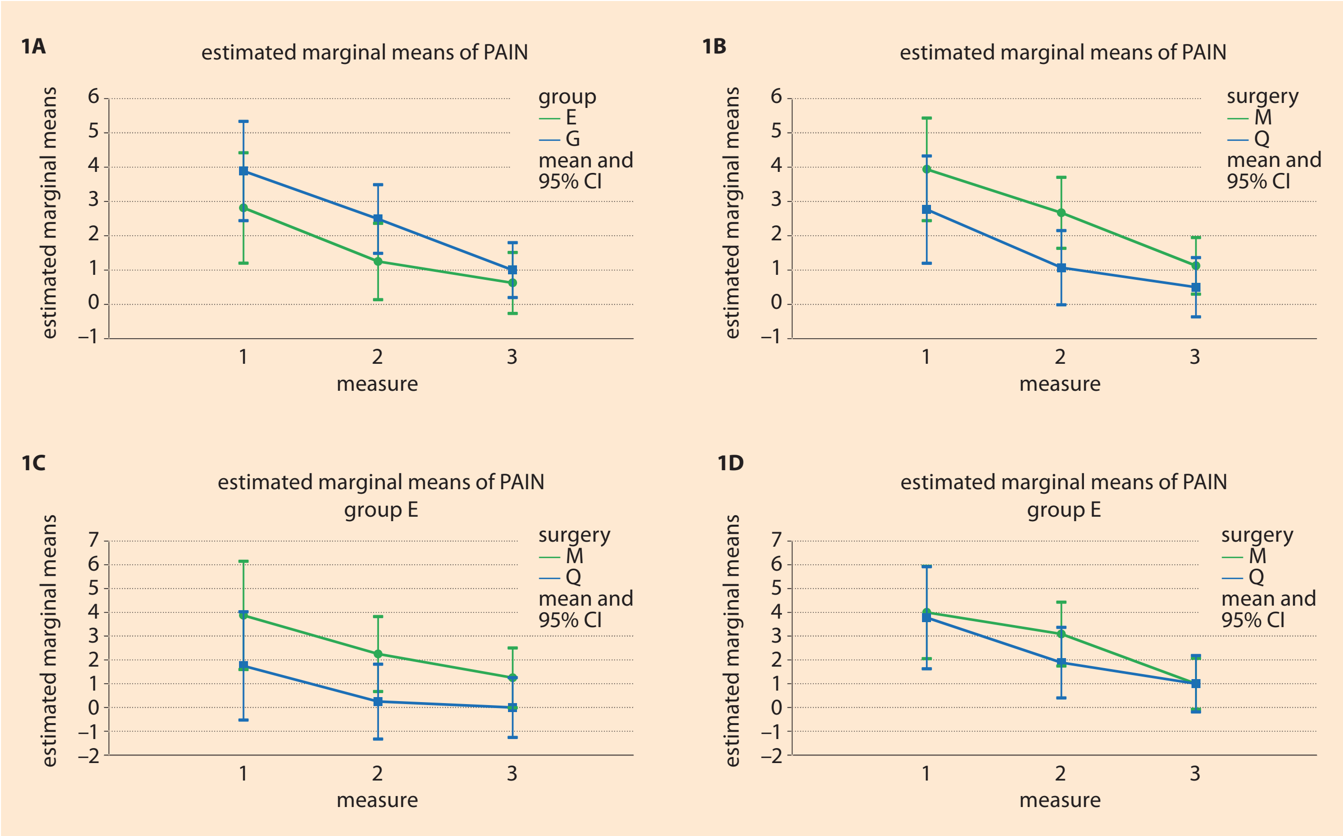

Fig. 1. A) Pain and anesthetic technique. B) Pain and type of surgery. C) Pain and type of surgery in group E. D) Pain and type of surgery in group G.

Obr. 1. A) Bolest a anestetická technika. B) Bolest a typ operace. C) Bolest a typ operace ve skupině E. D) Bolest a typ operace ve skupině G.

reader. The test had a limit of detection of 1 pg/mL, 8–10% inter-assay precision, and 4–6% intra-assay precision. The concentrations (in pg/mL) were calculated through comparison with their standard curves.

Statistical analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences (version 20). Absolute frequencies and percentages were calculated for categorical variables, and means and standard deviations were calculated for quantitative variables. Anthropometric data were compared between groups G and E using Student's independent-samples T test. Associations between categorical variables were evaluated using Fisher's exact test. Repeated-measures analysis of variance was used to compare pain scores and TNF-α, IL-1, and IL-8 concentrations between groups G and E, between patients who underwent mastectomy and those who underwent quadrantectomy, and among measurement timepoints. The significance level was set to $\alpha = 0.050$.

Results

Of the 36 participants, 16 received general anesthesia with ESPB (group E) and 20 received general anesthesia alone (group G). All (100%) patients in group E and 17 (85%) patients in group G were ASA2; 3 (15%) patients in group G were ASA3. Eight (50%) patients each in group E underwent mastectomy and quadrantectomy; in group G, 11 (55%) patients underwent mastectomy and 9 (45%) patients underwent quadrantectomy. Fifteen (75%) patients in group G and 10 (62.5%) patients in group E received opioids in the postoperative period as a rescue treatment for pain ($P = 0.424$). All patients received dipyrone and all but one patient who was allergic received NSAIDs.

Mean pain scores declined over time in the postoperative period ($P < 0.001$). They were consistently lower in group E than in group G, but this difference was not significant ($P = 0.548$; Fig. 1A). Similarly, the mean pain scores of patients who underwent quadrantectomy were consistently lower than those of patients who underwent mastectomy, but this difference was not significant ($P = 0.512$; Fig. 1B); it remained non-significant after patient segregation according to the anesthesia technique ($P = 0.775$).

In group E, the mean pain scores of patients who underwent quadrantectomy were consistently lower than those of patients who underwent mastectomy, but this difference was not significant. In

Tab. 1. Prevalence of the number of patients with mild or moderate to severe pain according to the VAS, in relation to the type of surgical technique, mastectomy (M) or quadrantectomy (Q) and anesthetic technique, groups E (ESPB with general) and G (general), of the patients seen with a diagnosis of malignant neoplasm of the breast.
Tab. 1. Prevalence počtu pacientek s mírnou nebo středně silnou až silnou bolestí dle VAS ve vztahu k typu chirurgické techniky, mastektomii (M) nebo kvadrantektomii (Q) a anesteziologické technice, skupiny E (ESPB s obecnou diagnózou) a G (obecná), u pacientek vyšetřených s diagnózou maligního nádoru prsu.

	M		Q	
	E N = 8	G N = 11	E N = 8	G N = 9
M2 – 2 hours after surgery				
light	3 (8.33%)	3 (8.33%)	6 (16.67%)	4 (11.11%)
moderate or intense	5 (13.89%)	8 (22.22%)	2 (5.56%)	5 (13.89%)
M24 – after 24 hours				
light	5 (13.89%)	3 (8.33%)	8 (22.22%)	7 (19.44%)
moderate or intense	3 (8.33%)	8 (22.22%)	0 (0%)*	2 (5.56%)
M48 – after 48 hours				
light	7 (19.44%)	9 (25.00%)	8 (22.22%)	8 (22.22%)
moderate or intense	1 (2.78%)	2 (5.56%)	0 (0%)	1 (2.78%)

Pain prevalence at M2 (P = 0.307), Fisher's exact test; *Pain prevalence at M24 (P = 0.016), Fisher's exact test; Pain prevalence at M48 (P = 0.783), Fisher's exact test.
E – general anesthesia associated with ESPB, ESPG – rector spinae plane block, G – general anesthesia, M – mastectomy surgery, N – number, Q – quadrantectomy surgery, VAS – visual analogue scale

Tab. 2. Confidence intervals (CI) of pain moments related to TNF-α serum cytokine levels.
Tab. 2. Intervaly spolehlivosti (CI) momentů bolesti souvisejících s hladinami cytokinů TNF-α v séru.

Comparisons	Mean difference (I–J) ± standard deviation	P	95% CI	
			lower bound	upper bound
Preoperative moment (M0) (I) versus				
Moment 24h (J)	0.161 ± 13.493	1.000	**–33.990**	**34.312**
Moment 48h (J)	24.350 ± 10.010	0.063	**–0,983**	**49.684**
Time 24 hours postoperatively (M24) (I) versus				
Moment 0h (J)	–0.161 ± 13.493	1.000	**–34.312**	**33.990**
Moment 48h (J)	24.189 ± 7.560*	0.010	**5.055**	**43.323**
Moment 48 hours postoperatively (M48) (I) versus				
Moment 0h (J)	–24.350 ± 10.010	0.063	**–49.684**	**0.983**
Moment 24h (J)	–24.189 ± 7.560*	0.010	**–43.323**	**–5.055**

Moment 0h – TNF-α preoperative, Moment 24h – TNF-α after 24 hours postoperatively, Moment 48h – TNF-α after 48 hours postoperatively, P – ANOVA test of repeated measures
*P < 0.05.

group G, the pain scores of patients who underwent quadrantectomy were lower than those of patients who underwent mastectomy at M2 and M24; they did not differ according to the surgery type at M48 (Fig. 1C, 1D).

In the immediate postoperative period, 13 (65%) patients in group G and 7 (43.8%) patients in group E had moderate to severe pain (P = 0.313). Pain intensity (mild vs. moderate to severe) also did not differ significantly between groups E and G at M24 (p = 0.083) or M48 (p = 0.613). At M24, significantly fewer patients who underwent quadrantectomy than those who underwent mastectomy had moderate to severe pain (P = 0.006). No such difference was observed at M2 (P = 0.179) or M48 (P = 0.605). Only at M24 was there a significant difference in pain intensity among groups defined by both the surgery type and anesthesia technique (P = 0.016; Tab. 1).

The mean TNF-α concentration declined significantly over time (P = 0.049). It was similar at M0 and M24, but significantly lower at M48 (P = 0.010; Tab. 2).

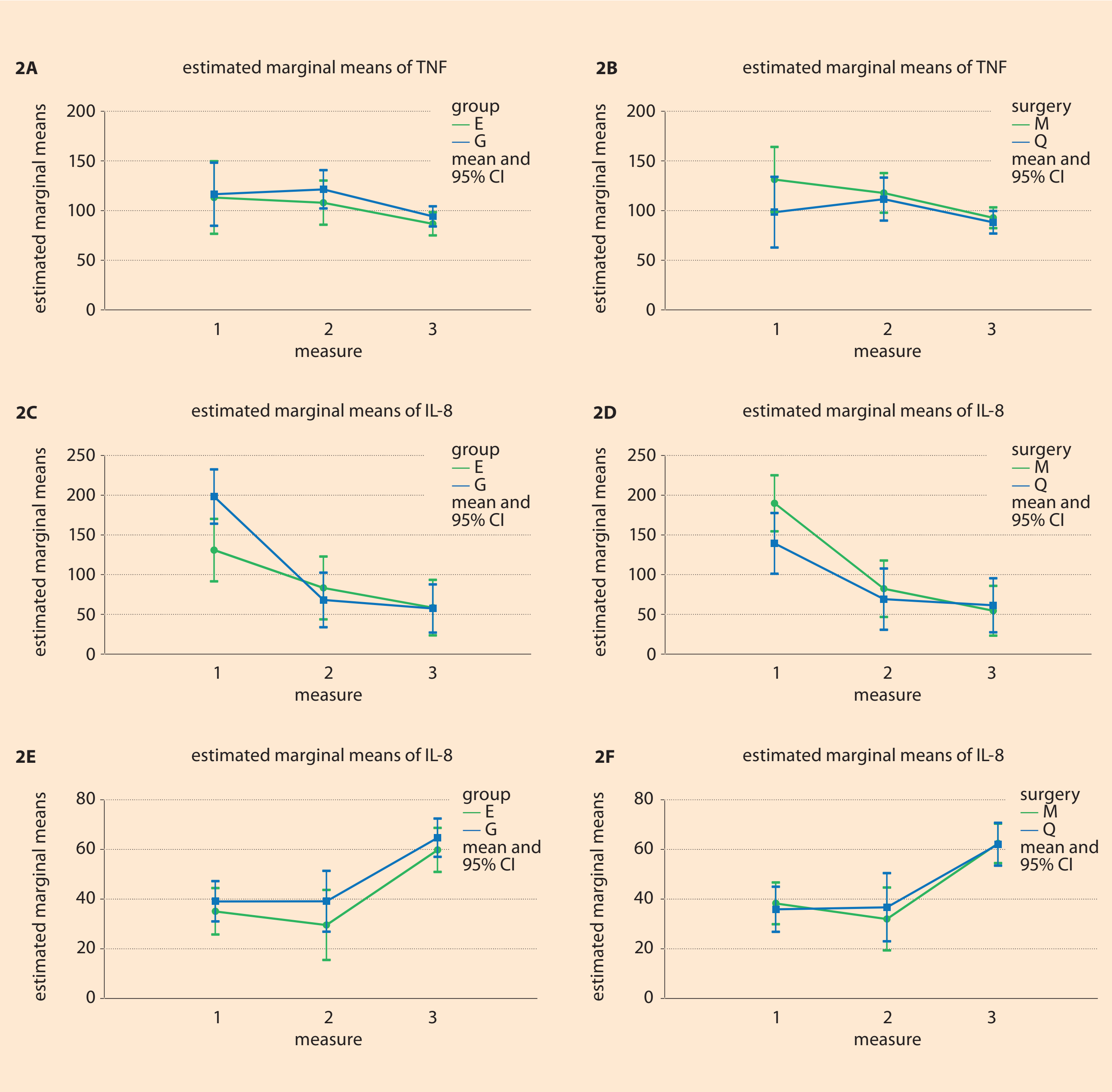

Fig. 2. A) TNF-α values in groups E and G. B) TNF-α values in relation to the type of surgery M and Q. C) IL-8 values in groups E and G. D) IL-8 values in relation to the type of surgery M and Q. E) IL-1 values in groups E and G. F) IL-1 values in relation to the type of surgery M and Q.

Obr. 2. A) Hodnoty TNF-α ve skupinách E a G. B) Hodnoty TNF-α ve vztahu k typu operace M a Q. C) Hodnoty IL-8 ve skupinách E a G. D) Hodnoty IL-8 ve vztahu k typu operace M a Q. E) Hodnoty IL-1 ve skupinách E a G. F) Hodnoty IL-1 ve vztahu k typu operace M a Q.

This concentration did not differ according to the anesthetic technique (P = 0.849) or surgery type (P = 0.324), although it was lower in group E than in group G and in patients undergoing quadrantectomy than in those undergoing mastectomy (Fig. 2A, 2B). The mean IL-8 concentration declined over time, with a significant difference between M0 and M24 (P < 0.001; Tab. 3). It was significantly lower in group E than in group G (P = 0.029), but did not differ significantly according to the surgery type (Fig. 2C, 2D). The mean IL-1 concentration increased over time; it differed significantly between M0 and M48 and between M24 and M48 (both P < 0.001; Fig. 2E, 2F; Tab. 4). It did not differ

Tab. 3. Confidence intervals (CI) of pain moments related to IL-8 serum cytokine levels.
Tab. 3. Intervaly spolehlivosti (CI) momentů bolesti souvisejících s hladinami cytokinů IL-8 v séru.

Comparisons	Mean difference (I–J) ± standard deviation	P	95% CI	
			lower bound	upper bound
Pre-surgical moment (M0) (I) versus				
Moment 24h (M24) (J)	88.817 ± 14.588*	0.000	**51.897**	**125.738**
Moment 48 (M48) (J)	106.576 ± 14.727*	0.000	**6.303**	**143.849**
Time 24 after surgery (M24) (I) versus				
Moment 0h (M0) (J)	–88.817 ± 14.588*	0.000	**–125.738**	**–51.897**
Moment 48h (M48) (J)	17.759 ± 11.442	0.392	**–11.200**	**46.718**
Time 48h after surgery (M48) (I) versus				
Moment 0h (M0) (J)	–106.576 ± 14.727*	0.000	**–143.849**	**–69.303**
Moment 24h (M24) (J)	–17.759 ± 11.442	0.392	**–46.718**	**11.200**

Moment 0h – IL-8 preoperative, Moment 24h – IL-8 after 24 hours postoperatively, Moment 48h – IL-8 after 48 hours postoperatively,
P – ANOVA test of repeated measures
*P < 0.05.

Tab. 4. Confidence intervals (CI) of pain moments related to IL-1 serum cytokine levels.
Tab. 4. Intervaly spolehlivosti (CI) momentů bolesti souvisejících s hladinami cytokinů IL-1 v séru.

Comparisons	Mean difference (I–J) ± standard deviation	P	95% CI	
			lower bound	upper bound
Moment 0h – preoperative (M0h) (I) versus				
Moment 24h (M24) (J)	2.737 ± 4.015	1.000	**–7.424**	**12,898**
Moment 48h (M48) (J)	–25.151 ± 4.847*	0.000	**–37.418**	**–12.885**
Moment 24h after surgery (M24) (I) versus				
Moment 0h (M0h) (J)	–2.737 ± 4.015	1.000	**–12.898**	**7.424**
Moment 48h (M48) (J)	–27.889 ± 5.723*	0.000	**–42.372**	**–13.405**
Time 48h after surgery (M48) (I) versus				
Moment 0h (M0) (J)	25.151 ± 4.847*	0.000	**12.885**	**37.418**
Moment 24h (M24) (J)	27.889 ± 5.723*	0.000	**13.405**	**42.372**

Moment 0h – IL-1 preoperative, Moment 24h –IL-1 after 24 hours postoperatively, Moment 48h – IL-1 after 48 hours postoperatively,
P – ANOVA test of repeated measures
*P < 0.05.

according to the surgery type or anesthetic technique.

Discussion

In the context of breast cancer surgery, postoperative analgesia remains challenging, as many patients have moderate to severe postoperative pain and most patients require high doses of opioids to alleviate acute postoperative pain [16]. This pain burden can reduce the quality of life of patients already suffering from the disease, the often mutilating surgery, and the side effects of chemotherapy. Most postoperative mastectomy pain occurs within the first 24 hours after surgery [17]. The inadequate management of acute postoperative pain is well known to be an important risk factor for the development of chronic pain [18]. Thus, the identification of an effective analgesia technique that is easy to perform, has few side effects, and reduces the incidence of chronic postoperative pain is extremely important.

ESPB is relatively simple and safe to execute [19]. Its effectiveness for thoracic surgeries and its opioid-sparing effect have been demonstrated [20,21], but its contribution to postoperative pain control has been reported to be limited [14]. A cadaver study showed that paravertebral spread after ESPB depends on the anesthetic volume injected, with volumes > 30 mL injected below the erector spinae muscle reaching multiple levels of the paravertebral space [22]. In the present study, ESPB was performed with 30 mL local anesthetic, and the results obtained were satisfactory.

We found that more patients in group G than in group E received opioids in the postoperative period, but this difference was not significant. This result contrasts with the previous finding that ESPB significantly reduces postoperative opioid administration [23].

Mean pain scores decreased over time during the postoperative period in this study. In the immediate postoperative period, intense tissue damage is present and pro-inflammatory cytokines such as IL-1 are released; cytokine levels peak and decrease over time. More pro-inflammatory cytokines are produced during the active phase of inflammation [24], and these cytokines play important roles in pain perception. Thus, pro-inflammatory cytokine modulation is vital for pain control and tissue recovery. Mean pain scores were lower in our group E than in group G, but this difference was not significant. Local anesthetics used in regional anesthesia prevent the excitation of nerve endings and action potential formation in peripheral nerves, thereby inhibiting pain. ESPB achieves this goal by blocking the conduction of surgical nociceptive stimuli [25]. Our finding is not consistent with the expectation that there would be less pain in the group that received regional anesthesia, as demonstrated previously [23]. Pain scores were higher in this group only at M24, suggesting that the maximum effect of ESPB occurs after more than 2 h, despite the previous finding that the thoracic ESPB onset of action occurs within 30 min [26]. After 48 hours, ESPB no longer has an effect and pain decreases over time.

The two study groups were subdivided according to the surgical technique (mastectomy or quadrantectomy) due to the observation that moderate to severe pain was much more common in patients undergoing mastectomy under general anesthesia, and under the assumption of independence between variables. Moderate to severe pain was more common in group G than in group E at M24, regardless of the surgery type, confirming the previous finding that ultrasound-guided ESPB effectively reduces pain intensity in the first 24 hours after breast cancer surgery compared with general anesthesia alone [27].

We expected to observe reductions in pro-inflammatory cytokine levels over time and according to the anesthetic technique employed, with lower levels in the group that received ESPB, as shown previously [28]. The local anesthetic employed with this technique should block the propagation of nociceptive stimuli and the release of inflammatory mediators and pro-inflammatory cytokines, and protect against the hyperalgesia that leads to chronic pain syndrome. We observed a reduction only in the IL-8 level. In the whole cohort, the TNF-α level was significantly reduced only at M48, and the IL-1 level showed a peculiar increase at M48. The roles of IL-1 in acute and chronic pain have been elucidated [29–32]. The cytokine IL-1β is produced in large quantities in animal models of and patients with multiple sclerosis, arthritis, and osteoarthritis, and causes pain associated with these diseases [30]. Significantly elevated spinal and circulating levels of IL-1β were also found in mice with oropharyngeal squamous cell carcinoma [31]. IL-1 inhibitors may be used in patients with acute gout pain [29,32].

Recent studies have demonstrated the effectiveness of ESPB in preventing acute and chronic pain after various types of surgery [33–35]. In patients undergoing video-assisted thoracoscopic lobectomy, ESPB significantly reduced acute postsurgical pain and the severity, but not the incidence, of chronic postsurgical pain [33]. In patients undergoing breast cancer surgery, the combination of ESPB and posterior quadratus lumborum block significantly reduced the impact of moderate to severe pain and the need for rescue analgesia within 24 hours after surgery compared with conventional intravenous analgesia [34]. In the context of urological surgery, ESPB provided effective analgesia, reduced opioid consumption, and maintained hemodynamic stability [35]. These data reinforce our results, which suggest that ESPB is a good option in breast cancer surgery.

One limitation of this study was the performance of the ESPB by different professionals. The sample size is another limitation, and could explain the results reflecting only tendencies toward significance. Furthermore, heterogeneity in the extent of the surgeries performed, including the axillary approach, is a limitation. Another important consideration is that the study was conducted during the COVID-19 pandemic. The isolation of patients and family members during this period could have influenced their psychological states and potentially altered patients' perceptions of postoperative pain. The examination of relationships between pro-inflammatory cytokine levels and the use of ultrasound-guided regional anesthesia, which has received limited research attention, is a study strength. Serum levels of pain-related cytokines are more objective than pain scores for the assessment of analgesia.

The results of this study suggest that changes in the analgesia protocol for breast surgery are warranted, given the effectiveness of ESPB. This alternative anesthesia technique is easy to perform, has easy access, and is practically free of complications; its use could reduce postoperative complications and hospitalization durations and costs.

Conclusion

In this study, pain was reduced in group E at M24, regardless of the surgery type. The IL-8 level was also lower in this group than in group G at M24. Thus, ESPB is an effective alternative in cases with contraindications or technical difficulties with other anesthetic techniques, such as the epidural. Its use could improve women's quality of life and health after breast cancer surgery.

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Publication ethics: The Editorial Board declares that the manuscript met the ICMJE uniform requirements for biomedical papers.

Publikační etika: Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

Conflict of interests: The authors declare they have no potential conflicts of interest concerning the drugs, products or services used in the study.

Konflikt zájmů: Autoři deklarují, že v souvislosti s předmětem studie/práce nemají žádný konflikt zájmů.

Dedication: The work was supported by CNPq (National Council for Scientific and Technological Development – Brazil, process No.: 01115/2018-4 and research grant for Rosekeila Simões Nomelini process No.: 303086/2022-0), FAPEMIG (Minas Gerais Research Funding Foundation, process No.: APQ-00888-21 and RED-00011-14), FUNEPU (Uberaba's Teaching and Research Foundation, process No.: 02 2011), and CAPES (Brazilian Federal Agency fot the Support and Evaluation of Graduate Education, process No.: 32012012001P5 and Proex).

Dedikace: Práce byla podpořena CNPq (Národní rada pro vědecký a technologický rozvoj – Brazílie, číslo procesu: 01115/2018-4 a výzkumný grant pro Rosekeila Simões Nomelini, číslo procesu: 303086/2022-0), FAPEMIG (Nadace pro financování výzkumu Minas Gerais, číslo procesu: APQ-00888-21 a RED-00011-14), FUNEPU (Nadace pro výuku a výzkum Uberaby, číslo procesu: 02 2011) a CAPES (Brazilská federální agentura pro podporu a hodnocení postgraduálního vzdělávání, číslo procesu: 32012012001P5 a Proex).

Acknowledgments: We would also like to thank Sérgio Antônio Zullo (Administrative Analyst EBSERH – HC/UFTM) for his support in carrying out the statistical analyses.

Poděkování: Rádi bychom také poděkovali Sérgiovi Antôniovi Zullovi (administrativní analytik EBSERH – HC/UFTM) za jeho podporu při provádění statistických analýz.

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Submitted/Doručeno: 25. 3. 2025
Accepted/Přijato: 5. 8. 2025

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