Interfascial block at the serratus muscle plane versus conventional analgesia in breast surgery: a randomized controlled trial

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ABSTRACT

Background and objectives In the context of opioid-sparing perioperative management, there is still little evidence from randomized controlled trials regarding the effectiveness of interfascial thoracic blocks. This study hypothesizes that receiving a serratus plane block reduces opioid requirements, pain scores, and rescue medication needs.

Methods This double-blind, randomized controlled study was conducted on 60 adult females undergoing oncologic breast surgery. After general anesthesia, patients were randomly allocated to either conventional analgesia (control group, n=30) or single-injection serratus block with L-bupivacaine 0.25% 30mL (study group, n=30). First 24-hour total morphine consumption (primary outcome), pain scores at 1, 3, 6, 12, and 24 hours, time-to-first opioid rescue analgesia, and adverse effects were recorded.

Results Median 24 hours' opioid dose was greater in the control group (median difference 9 mg (95% CI 4 to 14.5 mg); p<0.001). Proportional odds model showed that the study group has a lower probability of receiving opioid drugs (OR=0.26 (95% CI 0.10 to 0.68); p<0.001), while mastectomies have a higher probability of receiving them (OR=4.11 (95% CI 1.25 to 13.58); p=0.002). Pain scores in the study group were significantly lower throughout the follow-up period (p<0.001). Control group subjects needed earlier morphine rescue and had a higher risk of rescue dose requirement (p=0.002).

Conclusions Interfascial serratus plane block reduces opioid requirements and is associated with better pain scores and lower and later rescue analgesia needs in the first 24 hours, compared with conventional intravenous analgesia, in breast surgery.

Trial registration number NCT02905149.

INTRODUCTION

There is growing interest in opioid-sparing methods in perioperative pain management, given an ongoing epidemic of opioid use and misuse that is causing significant morbidity and mortality.[1] While misuse occurs more frequently among chronic pain patients, the perioperative period is often the patient's first exposure to these medications.[2]

Breast cancer is one of the most frequent cancers among women,[3] and surgical treatment remains a keystone in its management. The need for an opioid prescription may extend beyond a few months after surgery in 10% of patients undergoing breast reconstructive surgery,[4] and long-term use may ultimately lead to complications. The development of a chronic pain syndrome as a complication is not uncommon and can occur in 20%–60% of patients.[5]

Although definitive evidence is lacking, it seems that regional anesthesia techniques can play a crucial role in opioid-sparing perioperative pain management. Thoracic paravertebral block (PVB) remains the gold standard analgesic technique in breast surgery; however, despite the advantage of ultrasound (US) guidance, severe potential complications (eg, total spinal block or pneumothorax) still exist.[6]

US-guided serratus plane block (SPB) was first described in 2013.[7 8] SPB deposits local anesthetic in a plane superficial to or underneath the serratus anterior muscle in the midaxillary line at the fourth rib level, causing a blockade of the sensory nerves of the axillomammary area.[7–10] Even with partial dermatome spreading, the simplicity and low rate of complications can make SPB a first-choice technique in breast surgery.

Currently, regional anesthesia in oncologic breast surgery achieves better analgesia, fewer side effects, and higher patient satisfaction, compared with conventional analgesia.[11 12] However, to our knowledge, randomized controlled trial-based evidence regarding the effectiveness of the SPB and interfascial thoracic blocks remains scarce. The hypothesis of this trial is that an interfascial block at the serratus plane muscle has a higher analgesic efficacy, compared with conventional intravenous analgesia. The aim of this study was to compare perioperative morphine consumption, proving the efficacy of SPB as an opioid-sparing method, and to determine whether the block affects postoperative pain scores, morphine-related side effects, and patient satisfaction during the first 24 hours after surgery.

METHODS

This double-blind, randomized clinical trial was conducted after obtaining approval from the Hospital's Institutional Review Board (30 June 2015, file number 358, Chairman Dr Rodriguez Capellan), and was conducted in compliance with the Helsinki Declaration. Written informed consent was obtained from every subject. The trial was registered at ClinicalTrials.gov before patient enrollment (NCT02905149, principal investigator: GM.

Date of registration: 19 September 2016). Sixty adult females, who were scheduled for elective oncologic breast surgery, were included.

Inclusion criteria were as follows: (A) patients ≥18 years old; (B) American Society of Anesthesiologists (ASA) risk scale <IV; and (C) oncologic breast surgery, with or without reconstruction, with at least 24 hours' hospital stay (eg, mastectomy or partial mastectomy, also known as lumpectomy, with axillary regional or radical lymph node dissection). Exclusion criteria were as follows: (A) patients with ASA risk scale ≥IV; (B) body mass index (BMI) >40; (C) neurologic impairment; (D) inability to give informed consent; (E) contraindications to nerve block, such as coagulopathy and local infection at the site of the block; (F) local anesthetic allergy; and (G) chronic opioid treatment.

Before surgery, all participants received education regarding the visual analog scale (VAS) pain score (0 mm=no pain and 100 mm=worst imaginable pain) and the use of electronic patient-controlled analgesia (PCA) pumps. After performing standard monitoring with pulse oximeter, ECG, non-invasive blood pressure (GE Healthcare, Chicago, Illinois, USA), bispectral index module (BIS module, GE Healthcare, Helsinki, Finland), and TOF-Watch-S (Organon Teknika, Oss, The Netherlands), general anesthesia was induced with intravenous midazolam 0.01–0.03 mg/kg, fentanyl 1 µg/kg, and propofol 2 mg/kg. A laryngeal mask was introduced after the administration of intravenous rocuronium bromide 0.6 mg/kg for muscle relaxation. The lungs were ventilated to maintain an end-tidal carbon dioxide of 35 mm Hg. Anesthesia was maintained with an oxygen fraction (FiO_2) of 0.4 and propofol continuous intravenous infusion to keep BIS index between 40 and 60.

After anesthesia induction, patients were randomly allocated into two groups (1:1 allocation ratio) by a random sequence generated from a pseudorandom number seed (!RNDSEQ V.2011.09.0, JMDomenech); these sequences were kept in sealed and consecutively numbered opaque envelopes, which were opened after informed consent was obtained. Patients in the study group received SPB with the midaxillary line approach, using levobupivacaine 0.25% 30 mL, while those in the control group did not. An anesthetist with experience in interfascial blocks performed the US-guided technique using a linear probe

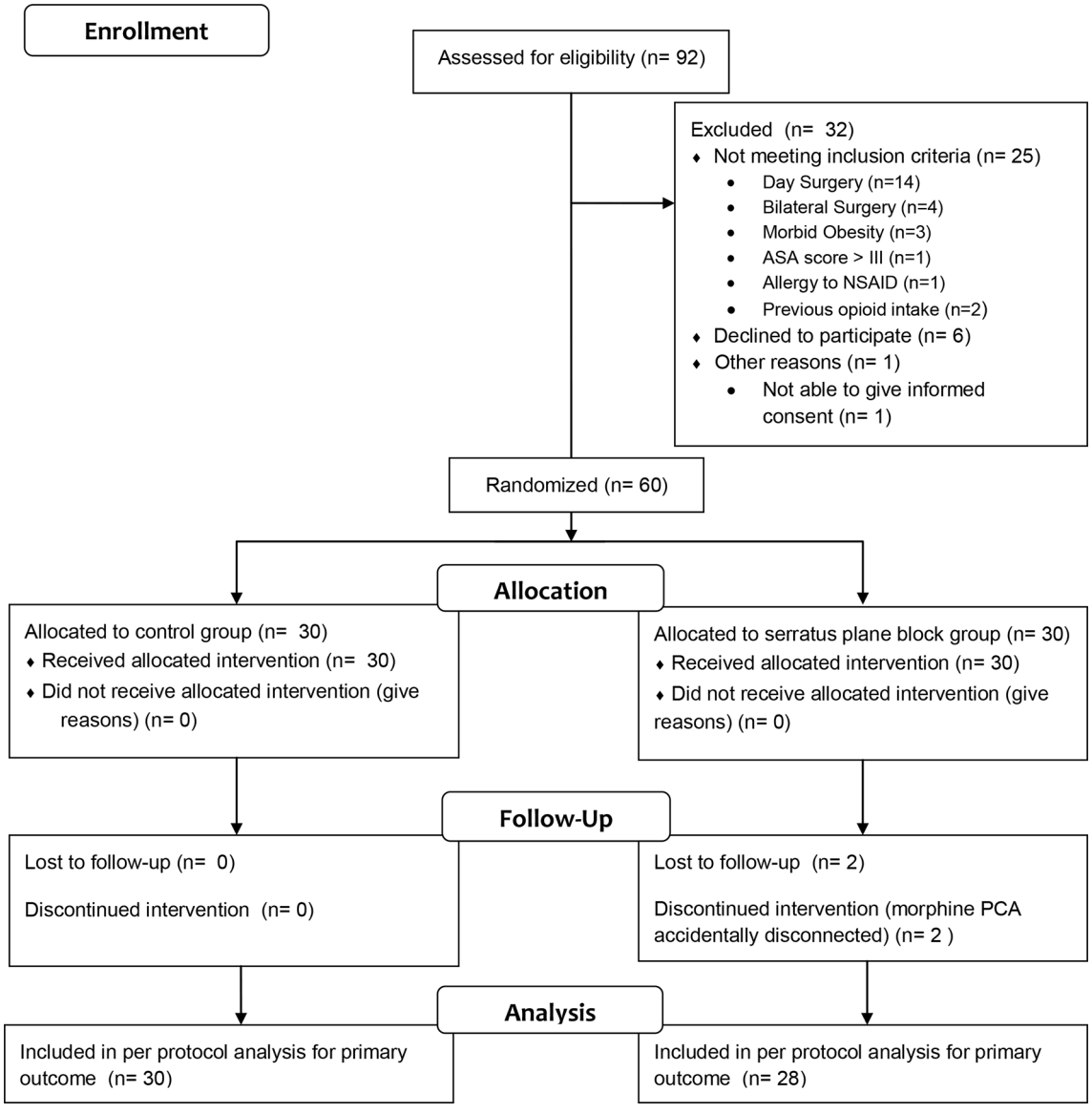

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ASA, American Society of Anesthesiologists; NSAID, non-steroidal anti-inflammatory drug; PCA, patient-controlled analgesia.

Table 1 Baseline characteristics of patients included in the study. Values are mean (SD) or count (percentage)

	Control group (n= 30)	Block group (n= 28)
Age (years)	59.5 (12.5)	60.2 (11.9)
BMI (kg/m^2)	26.7 (4.4)	27.9 (4.1)
Duration of surgery (min)	78 (30)	73 (17)
ASA		
I	9 (30)	7 (25)
II	18 (60)	18 (64)
III	3 (10)	3 (10)
Type of surgery		
Partial mastectomy/quadrantectomy	21 (70)	25 (89)
Mastectomy	9 (30)	3 (19)
Axillary lymphadenectomy		
Regional lymph node resection	20 (67)	21 (75)
Radical lymph node resection	10 (33)	7 (25)
Site of surgery		
External quadrants	13 (43)	15 (56)
Interquadrantic line	2 (7)	4 (14)
Internal quadrants	6 (20)	6 (21)
Mastectomy	9 (30)	3 (11)

ASA, American Society of Anesthesiologists physical status; BMI, body mass index.

(8–13 MHz), a US machine (M-Turbo, SonoSite, Bothell, Washington, USA), and a 22 G, 50 mm echogenic needle (Stimuplex D; B Braun, Melsungen, Germany). With the patient lying supine and the arm abducted at 90°, the US probe was positioned in a sagittal plane at the midaxillary line. The fascial plane between the serratus anterior muscle and external intercostal muscles was identified between the fourth and fifth ribs[7 9] in the midaxillary region.[9] The gauge was advanced in-plane, and the local anesthetic was placed by hydrodissecting the interfascial space in a caudal to cranial fashion.

Following the initial bolus of fentanyl during induction, perioperative analgesia was achieved by administering a bolus of 1 µg/kg fentanyl if blood pressure and/or heart rate increased ≥20% from baseline measurement (first operating room assessment). Thirty minutes before the end of surgery, intravenous paracetamol 1 g was administered in both groups. At the end of surgery, intravenous granisetron 40 µg/kg and dexamethasone 4 mg were administered; muscle relaxation was reversed if needed.

During the postoperative period, all patients received intravenous opioid medication on demand via an electronic PCA pump (CADD Solis, Smiths Medical, Minneapolis, Minnesota, USA). The pump was set to deliver a bolus dose of 1 mg, with a lockout interval of 10 min, and maximum dose of 6 mg/hour without continuous perfusion. The patient was instructed to press the PCA button whenever pain increased to VAS≥40 mm. Moreover, intravenous paracetamol 1 g/8 hours and dexketoprofen 50 mg/8 hours were administered in both groups, as part of multimodal analgesia management.

We recorded age, BMI, type, site and duration of surgery, type of lymphadenectomy (radical vs regional/sentinel lymph node), intraoperative fentanyl (µg), postoperative morphine (mg), and time-to-opioid first rescue dose. First 24 hours' total opioid requirements (intraoperative+postoperative, primary outcome) were calculated by converting fentanyl used intraoperatively into morphine equivalents (fentanyl conversion factor; 10 µg fentanyl=1 mg morphine). The participants were blinded to group allocation, as the blocks were performed after induction of general anesthesia. The healthcare provider (attending anesthesiologist) who administered the opioid was blinded to subject allocation as he was not present in the operating room during the standard time used by the investigator to perform the block, even for control subjects who did not receive any block. When attending anesthesiologist was called back to the operating room, the same equipment was present (US machine and disposable items needed to perform the technique, such as syringes and vials) and a white dressing that prevented injection identification was placed on all subjects.

In the postoperative period, pain was assessed by the VAS at 1, 3, 6, 12, and 24 hours after surgery. The occurrence of side effects (nausea, pruritus, apnea, urinary retention, or paralytic ileus), block-related complications, and Pain Out questionnaire answers[13] were recorded at 24 hours after surgery. The data collector for the postoperative data was a different investigator from the one who performed the block and was blinded to the subjects' study group allocation.

Statistical analysis

Continuous variables were reported as medians with IQRs or means with SDs where applicable; categorical variables were reported as counts and percentages. We checked for the normality of continuous variables by using the Shapiro-Wilk test.

Since this was a single-center investigation with a relatively limited pool of recruitable subjects (roughly 80–100 cases per year), we performed a power analysis for sample size estimation to test the feasibility of the study. We based the calculation on data from a previous study[14] where mean opioid requirements in the first 24 hours in patients undergoing breast cancer surgery with conventional analgesia were 25 mg with 8 mg (SD). Assuming a 40% reduction in morphine equivalents as clinically significant, a sample size of 56 patients has a power of 99% with a 5% alpha error to detect significant differences (online supplementary efigure 1). We increased the sample size to 60 patients (30 per group) to cover possible sample losses without compromising study feasibility in the available recruitment period (1 year). Analyses were performed per protocol.

Difference in overall opioid dose between groups in the first 24 hours postoperatively was assessed by Wilcoxon rank-sum test. We performed a post hoc analysis, controlling for the effect of type of surgery, by fitting a proportional odds model with cumulative opioid dose in 24 hours as the dependent variable, and group and type of surgery as independent variables (with

Table 2 Intraoperative and postoperative opioid requirements by group

	Control	Study	P values
Total opioid 24 hours' dose (mg)	30 (26 to 35)	18.5 (17 to 24)	<0.001
Intraoperative fentanyl (µg)	225 (174 to 300)	155 (100 to 247)	0.038
Postoperative morphine (mg)	6 (3 to 7)	2 (2 to 4)	<0.001

Values are median (95% CI).

Table 3 Proportional odds model with 24-hour opioid requirements as dependent variable

	Estimate	SE	OR	Lower 95% CI	Upper 95% CI
Study group	−1.35	0.50	0.26	0.10	0.67
Mastectomy	1.41	0.61	4.11	1.25	13.58

Table 4 Cumulative link mixed regression model with pain scores as dependent variable

	Estimate	SE	OR	Lower 95% CI	Upper 95% CI	P values
Pain scores at rest						
Study group	−2.441	0.73	0.09	0.02	0.37	<0.001
Hour	−0.090	0.02	0.91	0.88	0.95	<0.001
Opioid dose	−0.007	0.03	0.99	0.94	1.04	0.77
Group*hour	−0.055	0.04	0.95	0.87	1.03	0.20
Pain scores at movement						
Study group	−2.247	0.68	0.11	0.03	0.4	0.001
Hour	−0.058	0.02	0.94	0.91	0.98	0.002
Opioid dose	−0.010	0.03	0.99	0.94	1.04	0.70
Group*hour	−0.048	0.03	0.95	0.90	1.01	0.10

control group as reference category in the group variable and with partial mastectomy as reference category in the type of surgery variable).[15]

VAS pain score differences between groups were assessed by fitting a cumulative link mixed regression model with VAS pain scores as the dependent variable, patient as random effect and group, and the opioid dose in 24 hours and interaction between study group and postoperative hour as independent variables. Postoperative hour main effect was introduced in the model to maintain the hierarchy.

Time-to-first postoperative opioid rescue dose was assessed by Kaplan-Meier estimator; a Cox regression model was fitted with first opioid rescue dose as the dependent variable, and group and intraoperative fentanyl dose as covariates. Stata V.13 (StataCorp, College Station, Texas, USA) and R statistical software V.3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses; two-sided statistical significance was set at $p<0.05$.

RESULTS

We assessed for eligibility 92 patients between September 2016 and June 2017; after checking for exclusion criteria, we randomized 60 patients either to the study or control group (figure 1). Two patients were excluded from analysis because morphine PCA was discontinued by the ward nurse without medical indication. Patient characteristics are shown in table 1.

The median 24 hours' cumulative opioid doses were 30 mg (21–41) and 18.5 mg (14.5–29) of morphine equivalents in the control and study groups, respectively ($p<0.001$). Table 2 shows intraoperative and postoperative opioid requirements by group as well as total opioid 24 hours' requirements. Proportional odds model fitting showed that the study group had a statistically significant lower OR to receive a bigger opioid dose and that patients undergoing mastectomy had a statistically significant higher OR, compared with partial mastectomy/quadrantectomy (table 3).

Cumulative link mixed regression is shown in table 4 and figure 2. The study group's pain scores, even after controlling for interindividual variability, opioid dose, and hour of assessment in the model, were significantly lower throughout the follow-up period. Figure 3 shows a graphical distribution of pain scores.

There was no statistical difference in the percentage of patients with postoperative nausea and vomit (PONV) between groups ($p=0.22$). No block-related complications or other side effects were reported.

Kaplan-Meier estimator of first opioid rescue dose by group is shown in figure 4. Control group subjects required earlier morphine rescue ($p=0.002$). Cox regression model showed that risk of opioid rescue dose requirement in the control group was 2.17, compared with the study group (95% CI 1.13 to 4.15, $p=0.02$, online supplementary etable 1). Median time to

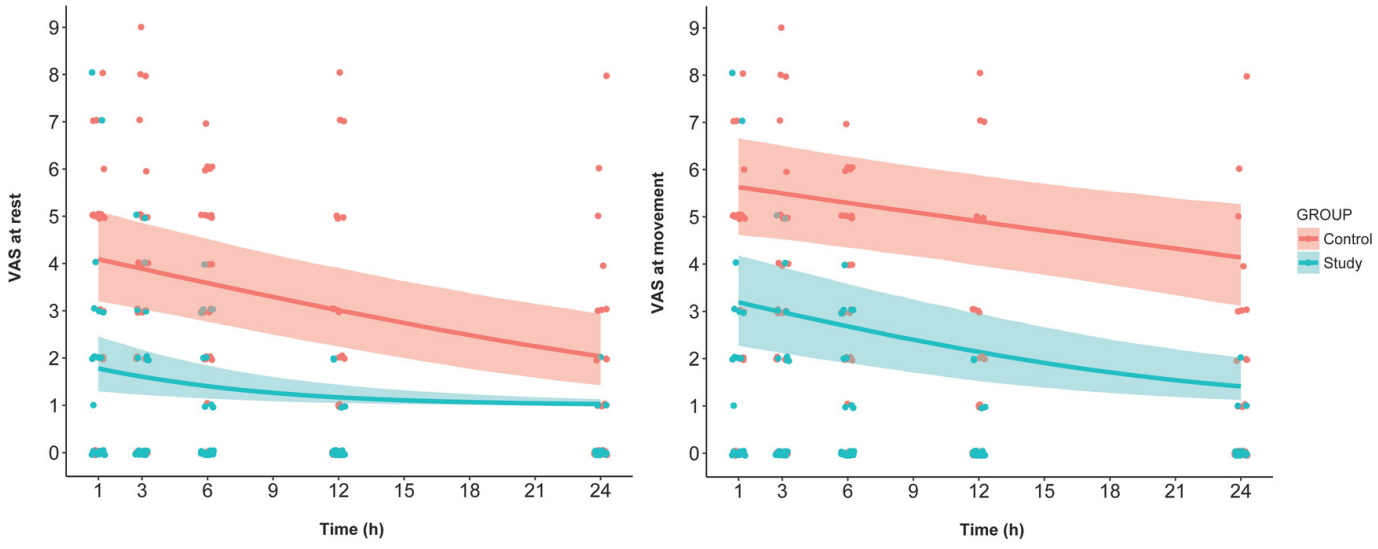

Figure 2 Cumulative link mixed regression model. Visual analog scale (VAS) pain (movement and rest) evolution, 24 hours postoperatively. Solid line: median tendency. Fade color area: 95% confidence area. Jitter was added to each value's points to improve visibility.

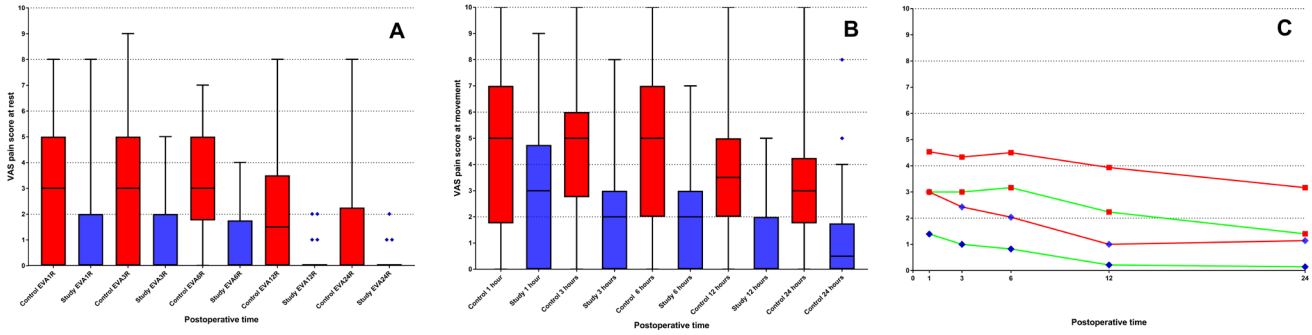

Figure 3 Distribution of pain scores with Tukey's box plot at rest (A) and movement (B) and mean pain scores at different time points (C). (A, B) Red boxes, control group; blue boxes, study group. (C) Red squares, control group; blue diamonds, study group; red lines, pain at movement; green lines, pain at rest. VAS, visual analog scale (0 to 10 scale).

opioid rescue dose was significantly shorter in the control group (median difference 2 hours, 95% CI 1 to 3, p<0.001).

Pain Out questionnaire answers by group are reported in supplemental digital content (online supplementary etable 2).

DISCUSSION

This study shows that performing an SPB for breast cancer surgery significantly reduces the opioid requirements during surgery and in the first 24 hours postoperatively. This effect remains significant even after controlling for the type of surgery.

Cumulative link mixed model showed that patients in the study group had lower VAS pain scores at every recorded time point during the 24 hours' follow-up period, although higher morphine doses were administered in the control group. Moreover, survival function analysis applied to first opioid administration showed that the control group required rescue analgesia significantly sooner, even after considering the intraoperative fentanyl dose interaction. Our results show that interfascial plane block was effective on multiple levels (analgesic requirements and pain), since subjects in the control group, even if they received a higher overall dose of opioid and earlier rescue medication administration, experienced higher pain both at rest and on movement.

Proportional odds model with study group and type of surgery as covariates showed that patients who underwent mastectomy had an OR of 4.11 (95% CI 1.25 to 13.58) for requiring more opioid medication. The model suggests that the opioid-sparing feature of an interfascial serratus block could be even more significant in cases of more aggressive surgical indications. Nevertheless, we chose to include surgical indications other than mastectomy to increase the external validity of the results, since breast-conserving surgery with neoadjuvant radiation is an increasingly used alternative with promising short-term and long-term oncologic outcomes.[16] We chose to perform this post hoc analysis because we suspected that block and type of surgery interaction was an important aspect worth exploring.

SPB is a relatively new interfascial thoracic technique,[7 9] and definitive evidence regarding its efficacy remains to be gathered. However, our randomized controlled trial data are consistent with those of a recent large retrospective study[17] that showed a reduction in opioid requirements and side effects with SPB block, compared with conventional analgesia.

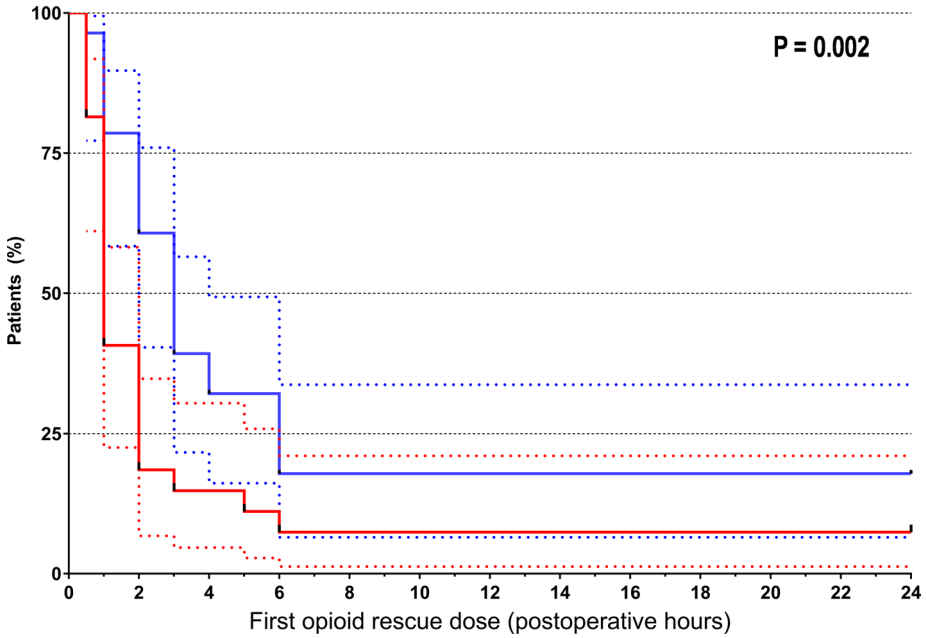

Figure 4 Kaplan-Meier graph. Solid line: survival function. Dashed lines: 95% confidence boundaries.

Moreover, we compared with conventional analgesia because PVB for breast surgery is not commonplace in our environment,[18] probably due to anesthetists' concerns regarding infrequent but potentially catastrophic complications.[19 20] While PVB has proven to be a safe technique with few and rare complications,[21 22] SPB could provide a better risk-benefit ratio, especially for less invasive or ambulatory surgeries. Indeed, we did not observe any complications related to the fascial blockade performed in our study, although our sample size admittedly does not allow any definitive conclusion.

Anatomical studies conducted in cadavers show that an SPB performed with a volume of 20 mL of methylene blue and latex, spread across five to six dermatomes,[23] with 30 mL of saline and air, could reach the second intercostal space.[24] We used 30 mL volume to maximize spread and efficacy of the block, although we did not assess it anatomically. Furthermore, clinical assessment was unfeasible since the block was performed on anesthetized subjects due to blinding. We chose this specific block approach[9] over the original one[7] on practical grounds because we find that it is simpler to perform (particularly in obese patients), and that it has the theoretical advantage of blocking both lateral and anterior branches of intercostal nerves[9]; however, this is based on assumptions and requires further anatomical corroboration. To our knowledge, there is no definitive proof in the literature regarding the superiority of one approach over the other.

Although almost two-thirds of the total opioid dose was due to intraoperative fentanyl administration, the control group had significantly greater requirements for both intraoperative fentanyl and postoperative morphine. Despite receiving a significantly greater dose of postoperative morphine, control subjects had higher pain scores throughout the follow-up period, even after taking into account the potential effects of previously administered opioid dose and interindividual variability. These results show that the interfascial block was effective, independent of when the opioid was administered or who performed the administration.

Our postoperative medication route of administration (intravenous PCA) was selected to ensure that morphine dose was not investigator dependent and that the data were easily and readily retrievable; further, the intravenous route is currently common practice in our center. Despite the provision of information regarding PCA usage and their increased opioid administration, patients in the control group did not use sufficient medication to achieve lower (<4) VAS scores postoperatively. PCA has been associated with adverse features[25] from the patient's perspective (fear of overdose, addiction, and adverse outcome) that lead them to distrust this route of administration; providing additional information does not avoid this shortcoming.[26] It could be that, despite the reporting of high (>4) pain scores, the relatively low postoperative morphine administration may be related to the multimodal analgesia protocol. Every patient received paracetamol and dexketoprofen postoperatively, thus likely diminishing opioid requirements.

Our data showed no statistical difference in PONV or other side effects between groups. These results are similar to other trials that assessed SPB or similar interfascial blocks.[27] Furthermore, the low incidence of PONV in our data could be explained by the choice of anesthetic technique (total intravenous anesthesia) and preventive intraoperative use of two synergistic antiemetics (dexamethasone and granisetron), as the multimodal antiemetic regimen has been proven to be effective in eradicating PONV.[28]

The strengths of our study are the broader inclusion criteria, in terms of the type of surgery, enabling investigation of SPB efficacy, and methodology design in a manner that included controls for the type of surgery in opioid consumption and rescue dose; additionally, it included a repeated measures analysis with a mixed regression model to adjust for intersubject and intrasubject variability.[29]

Nevertheless, some limitations must be acknowledged. The blinding method chosen cannot entirely exclude ascertainment bias. The opioid drug was mainly administered intraoperatively, and the follow-up was short. We found no differences in PONV or opioid-related postoperative complications; apart from intravenous anesthesia, this was probably due to the lack of statistical power in our sample. The questionnaire we chose to assess postoperative recovery was perhaps outdated; a better choice could have been a performance quality rating scale to better assess the multidimensionality of pain experience.[30] Hydrodissection during block was not standardized, and the sensory block was not evaluated, due to the chosen blinding method. Patients' PCA usage was suboptimal, despite the information given, resulting in a probable underestimation of the difference in opioid requirements. We decided to compare interfascial block with conventional intravenous analgesia in patients without basal opioid medication; thus, analgesic efficacy with other simple measures, such as local wound infiltration or in a different population of patients, remains to be determined. Finally, to analyze the influence of the type of surgery on the efficacy of the block, and due to the 24 hours' total opioid requirement variable distribution, we had to choose a method (proportional odds model) in which interpretation is not intuitive; nevertheless, the results are valid.

CONCLUSIONS

In conclusion, serratus interfascial plane block reduces opioid requirements and is associated with better pain scores in the first 24 hours postoperatively, compared with conventional intravenous analgesia in breast surgery. The roles of this block and thoracic interfascial techniques in the anesthetist's therapeutic arsenal are yet to be fully determined.

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Patient consent Patient gave their written informed consent prior to study enrolment

Ethics approval Hospital's Institutional Review Board.

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