Chronic pain after breast surgery: incidence, associated factors and impact on quality of life, an observational prospective study

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Research
Abstract

Background. Chronic pain after breast surgery (CPBS) has a disabling impact on postoperative health status. Mainly because of the lack of a clear definition, inconsistency does exist in the literature concerning both the actual incidence and the risk factors associated to CPBS. The aim of this prospective, observational study is to describe the incidence of and risk factors for CPBS, according to the definition provided by the IASP taskforce. The impact of CPBS on patients’ function and quality of life is also described.

Methods. Adult female patients scheduled for oncological or reconstructive breast surgery at the Breast Unit of Careggi Hospital (Florence, Italy) were prospectively observed. Postoperative pain was evaluated at 2 months (“pain becoming chronic”) and at 3 months (CPBS) after surgery. Preoperative, intraoperative, and postoperative factors were compared in CPBS and No-CPBS groups through multivariate logistic regression analysis.

Results. Among the 307 patients considered in this study, the incidence of “pain becoming chronic” was 25.4% [95%CI 20.6%-30.7%], while that of CPBS was 28% [95%CI 23.1%-33.4%]. The presence of pain at 2 months concords with the presence of CPBS at 3 months (Cohen k coefficient 0.63, IC95% 0.54-0.73). Results from the logistic regression analysis suggest that axillary surgery (OR [95%CI], 2.99 [1.13-7.87], p=0.03), preoperative use of pain medications (OR [95%CI], 2.04 [1.20-3.46], p=0.01), and higher dynamic NRS values at 6 hours postoperatively (OR [95%CI], 1.28 [1.05-1.55], p=0.01) were all independent predictors for CPBS.

Conclusions. Chronic pain after breast surgery is a frequent complication. The presence of early pain at 2 months after surgery concords with the occurrence of CPBS. The possibility to early detect persistent pain, particularly in those patients at high risk for CPBS, might help physicians to more effectively prevent pain chronicization. In our cohort, long-term use of analgesics for preexisting chronic pain, axillary surgery, and higher dynamic NRS values at 6 hours postoperatively were all factors associated with increased risk of developing CPBS.

Trial registration: clinicalTrials.gov registration NCT04309929

Background

Chronic pain is recognized as one of the most relevant complications associated with breast surgery(Odle 2014; Peuckmann et al. 2009). Chronic pain after breast surgery (CPBS) usually ranges from mild to moderate in intensity and presents with neuropathic characteristics (burning, stabbing, pulling, hypoesthesia/anaesthesia, phantom breast/nipple)(Jung et al. 2003). It can last for months or years after surgery(Caffo et al. 2003), with 5-10% of patients experiencing severe pain intensity(Schug and Bruce 2018). Chronic pain has a disabling impact on health status and negatively affects the quality of life of breast cancer survivors(Belfer et al. 2013), mainly interfering with sleep, work, daily life, and relationships(Miaskowski et al. 2012).
The pathophysiology of CPBS is extremely complex and not completely understood (Lavand’homme 2017). Several pathophysiological theories have been postulated to explain why CPBS is so common, including traumatic nerve injury, inflammation, and peripheral and central sensitization (Uríts et al. 2020). Based on pathophysiological mechanisms of CPBS, a multimodal approach – involving, for instance, use of anti-inflammatory drugs (for preventing primary hyperalgesia) or locoregional anaesthesia (nerve blocks or epidural anaesthesia, for preventing secondary hyperalgesia and central nervous system sensitization) – is nowadays suggested to limit the transition from acute to chronic pain (Uríts et al. 2020).

Several efforts have been made to identify preoperative (Bell et al. 2014; Gartner et al. 2009; Mejdahl et al. 2013; Poleshuck et al. 2006; Spivey et al. 2018; Wang et al. 2018), intraoperative (Mejdahl et al. 2013; Spivey et al. 2018), and postoperative (Fassoulaki et al. 2009; Hamood et al. 2018; Schou Bredal et al. 2014; Wang et al. 2018) factors potentially associated with CPBS. Nonetheless, results are inconsistent, and uncertainty does exist on the definition of those patients susceptible to CPBS. Interestingly, conflicting results are reported in the literature concerning the estimated incidence of CPBS. Although recognised as a frequent complication, the occurrence of CPBS varies across the different studies from 25% to 60% (Gartner et al. 2009), mainly because of the lack of a clear definition, unequal follow-up time points, and case-mix heterogeneity (Brummett 2011). Only recently, the International Association for the Study of Pain (IASP) Taskforce for the Classification of Chronic Pain has provided a final, unambiguous definition for CPBS (Schug et al. 2019), defining it as “pain that develops or worsens after a surgical procedure in the breast area (anterolateral chest wall and, in some cases, the ipsilateral axillary region) and persists at 3 months after surgery” (Schug et al. 2019).

Taking into consideration this new and widely accepted definition, the aim of this prospective, observational study is to describe the incidence of and risk factors for CPBS in a cohort of female patients undergoing surgery for breast cancer. The intensity and impact of CPBS on patients’ daily activities will be also described. Finally, the concordance between CPBS and early postoperative pain will be examined.

**Methods**

All adult (age ≥ 18 years) female patients scheduled for breast surgery during a 3 months period at the Breast Unit of Careggi Hospital, a large tertiary care teaching hospital in Florence, Italy, were prospectively observed for this study. The study was approved by the Ethical Committee of Area Vasta Toscana Centro before enrolment of the first patient (N° OSS.16.246, clinicalTrials.gov registration NCT04309929). Each patient gave her consent for participation in this study and publication of the results.

According to local routine practice, all patients were preoperatively taught how to correctly identify and treat acute postoperative and chronic pain. In particular, the signs and symptoms associated with CPBS (e.g. burning, stabbing, pulling, hypoesthesia/anaesthesia, phantom breast/nipple) and the use of Patient-Controlled-Analgesia (PCA) and rescue analgesia was explained to all breast surgery candidates.
Each patient was prospectively observed during the entire perioperative period (from preoperative anesthesia evaluation to postoperative and post hospital discharge). In particular, comorbidities, demographic, and baseline clinical variables were recorded before surgery. Intraoperative surgical and anaesthesiologic variables were prospectively recorded right after the surgical procedure. Finally, use of analgesic drugs was recorded at 0hrs, 3hrs, 6hrs, 12hrs, 24hrs, 48hrs after surgery. Acute postoperative pain was assessed at the same time points using the Numerical Rating Scale (NRS) – ranging from 0 (no pain) to 10 (worst pain) – both in resting conditions (static pain) and during active ipsilateral arm abduction or cough (dynamic pain). Each patient was re-evaluated at 2 and 3 months postoperatively for the presence of signs and symptoms of pain that develops or worsens in the breast area. Using a yes/no question, patients were asked to self-report the presence and level of pain, based on their subjective experience. According to the IASP definition (Schug et al. 2019), the presence of signs and symptoms of pain at 3 months was considered CPBS. On the other hand, the presence of signs and symptoms of pain at 2 months postoperatively was considered as early pain – defined here as “pain becoming chronic” – that may be treated proactively to prevent chronicization. Although some central and peripheral sensitization may already be present at 2 months postoperatively, an earlier assessment of somatic pain is uncommonly feasible in several centres. Furthermore, particularly in those patients who had underwent surgery for oncological disease, earlier assessment of somatic pain might be unreliable due to interfering factors, such as limitation of movement due to band-aid, anxiety related to waiting for histological results, and consciousness of body changes after surgery.

To reduce assessment biases, an anaesthesiologist not involved in the surgical procedure assessed pain both postoperatively and during follow-up. Preoperative, intraoperative, and postoperative variables statistically associated with CPBS were evaluated. Finally, for those patients with “pain becoming chronic” and/or CPBS, pain intensity and pain interference with daily functions were assessed through the Italian validated version of the Brief Pain Inventory (BPI) questionnaire (Bonezzi et al. 2002; Daut et al. 1983). This is a multidimensional 10-item questionnaire aimed at exploring the impact of pain on each item, with values ranging between 0 and 10 (0 = minimal impact, 10 = invalidating impact). Patients with missing preoperative, intraoperative and postoperative data were excluded from the analysis.

**Statistical analysis**

According to data available in the literature (Vilholm et al. 2008), we calculated the sample size required to expect CPBS in 24% of the subjects included (CI95% interval width 0.1), with 90% statistical power and 0.05 level of significance.

Continuous variables are expressed as means ± standard deviation or medians and interquartile range, according to the data distribution (normality assessed through Shapiro-Wilk test). The CPBS and the No-CPBS groups of patients were compared for statistical differences using the unpaired Student’s t-test and the Wilcoxon’s test for normally and not-normally distributed variables, respectively. Categorical variables are expressed as a percentage; statistical differences between the two groups were evaluated through a Chi-square or Fisher’s exact test. The level of agreement between patients with “pain becoming chronic”
at 2 months and patients with CPBS at 3 months is expressed through the Cohen's kappa coefficient. The difference in frequency of patients with persistent pain at 2 months and at 3 months was assessed through a McNemar's test. A \( p<0.05 \) was considered as the cut-off for significance. A multivariate logistic regression model was designed considering quantitative and qualitative variables significantly associated with CPBS in the univariate analysis (\( p\text{-value}<0.2 \)). A backward selection procedure based on the AIC was used to select the variables in the final model. Results are expressed in terms of \( p\)-value, Odds ratio (OR) and 95% confidence interval (95%CI). The capability of the final model to predict CPBS at 3 months was assessed with a ROC Analysis and expressed as a ROC-AUC. Statistical analysis was performed using R© software version 3.5.1.

**Results**

Three hundred and fifty-three patients underwent breast surgery in the study period and were all prospectively observed perioperatively. Of these, 37 (10.5%) and 46 (13%) dropped out of the study at 2 months and 3 months follow-up, respectively, because they were not contactable for assessment; 307 patients were thus considered for the analysis (Figure 1).

The incidence of “pain becoming chronic” at 2 months after surgery was 25.4% [95%CI 20.6%-30.7%] (median NRS 4[3-7]), while that of CPBS at 3 months was 28% [95%CI 23.1%-33.4%] (median NRS 5[3-7]). Among patients (n=86) who developed CPBS at 3 months, 60 (69.8%) had signs or symptoms of pain at 2 months postoperatively (“pain becoming chronic”) (Figure 1). Among patients (n=221) who did not develop CPBS at 3 months, 203 (91.9%) had no signs or symptoms of pain at 2 months postoperatively (“pain becoming chronic”). The presence of pain at 2 months concords with the presence of CPBS at 3 months (Cohen k coefficient 0.63, IC95% 0.54-0.73). McNemar’s test revealed no significant differences in the classification of patients with pain at 2 months and at 3 months postoperatively (\( p=0.23 \)).

Table 1 displays patients’ baseline characteristics, and surgical and anaesthesiologic factors. Most patients underwent mastectomy or breast conservative surgery, alone or in combination with other surgical procedures (e.g. cosmetic reconstruction and/or axillary surgery), as described in table 1. All surgical procedures were performed under general anaesthesia alone (total intravenous or inhaled anaesthesia) or in association with other forms of regional anaesthesia (PECS block or local anaesthetics infiltration). A combination of morphine, ketorolac tromethamine, and paracetamol was used for analgesia at the end of surgery.

Drugs used for postoperative analgesia are shown in table 2. About half of the patients were prescribed paracetamol 1gr or 500mg q.i.d. (according to the patient's weight) and morphine (administered with PCA set up to deliver a bolus of 1mg of morphine with a lockout interval of 15 minutes). The remaining patients were prescribed paracetamol in combination with tramadol or ketorolac tromethamine as rescue analgesic. Static and dynamic NRS values are shown in table 3, both for CPBS and No-CPBS groups.

All variables statistically associated with CPBS with \( p\text{-value}<0.2 \) in the univariate analysis were considered for multivariate logistic regression analysis. In the final model, variables independently
associated with CPBS were: axillary surgery (Sentinel Node Biopsy and/or Axillary Lymph Node Dissection) (OR [95%CI], 2.99 [1.13-7.87], \( p = 0.03 \)); preoperative use of pain medications (OR [95%CI], 2.04 [1.20-3.46], \( p = 0.01 \)); higher dynamic NRS values at 6hrs postoperatively (OR [95%CI], 1.28 [1.05-1.55] \( p = 0.01 \)). This model was able to identify the development of CPBS at 3 months postoperatively with a ROC-AUC of 0.67 (95%CI [0.61-0.74]).

All pain intensity and interference scores measured through the BPI questionnaire are presented in Figure 2. BPI scores at 3 months are also reported in the supplementary table 1.

**Discussion**

In this prospective, monocentric, observational study performed in a large tertiary care teaching hospital, we have observed a 28% [95%CI 23.1%-33.4%] incidence of CPBS in a cohort of female patients undergoing surgery for breast cancer. Axillary surgery, preoperative use of pain medications, and higher dynamic NRS values at 6hrs postoperatively have been identified as independent predictors of CPBS. The presence of early signs and symptoms of pain, assessed at 2 months after surgery (“pain becoming chronic”), concords with CPBS at 3 months.

Chronic pain is a very well-known complication of breast surgery (Alves Nogueira Fabro et al. 2012; De Oliveira et al. 2014; Tasmuth et al. 1996; Wang et al. 2018). Despite increasing recognition of chronic pain and the multidisciplinary efforts made to prevent this complication, the occurrence of persistent pain after breast surgery still remains high (Humble et al. 2018). The incidence of CPBS found in our cohort of patients (28%) falls within the range of values reported in previous studies (i.e. 25-60% (Gartner et al. 2009; Wang et al. 2018)). This wide variability in CPBS incidence mainly derives from the lack of a specific definition of CPBS, only recently provided by the IASP task force (Schug et al. 2019). The main significance of the present study lies in the fact that it provides estimates of the incidence of CPBS based on the IASP definition. Accordingly, in contrast with previous studies where CBPS was usually detected at 12-24 months postoperatively (Bell et al. 2014; Mejdahl et al. 2013), we have evaluated CPBS at 3 months follow-up. Furthermore, in order to avoid confounding factors or misinterpretation of signs or symptoms, each patient enrolled in this study was preoperatively taught how to correctly identify body areas (i.e. breast/anterolateral chest wall, axilla, ipsilateral arm) and symptoms of persisting postoperative pain (including neuropathic characteristics). Finally, follow-up assessment of pain at 2 and 3 months was carried out after the scheduled postoperative surgical and physiotherapy evaluations, so as to exclude other confounding causes of postoperative pain (e.g. seroma, hematoma, prosthesis infection, previous arm-shoulder pain). All these aspects have contributed to improve the reliability of CPBS incidence estimated in this study.

Interestingly, 69.8% of patients with CPBS already had signs or symptoms of pain at 2 months postoperatively (“pain becoming chronic”), while 91.9% of those without CPBS did not experienced signs or symptoms of pain at 2 months postoperatively. To the best of our knowledge, this is the first study to report a concordance between early pain (at 2 months) after breast surgery and CPBS. The possibility to
early detect pain might help physicians to more effectively prevent pain chronicization. A follow-up assessment of persistent pain right after surgery might allow early detection of “pain becoming chronic” and favour the implementation of proactive pharmacologic and non-pharmacologic approaches to prevent CPBS, particularly in high risk patients.

There is, however, no clear consensus about the definition of “high risk patients” for CPBS, thus making it difficult to identify those subjects who might benefit the most from careful, early pain assessment. A complex multidisciplinary, multiparametric approach involving also psychosocial and genetic factors has been suggested to perioperatively stratify patients and identify those at high risk of developing CPBS (Bortsov et al. 2020; James 2017). Nevertheless, because genotyping is expensive and usually unfeasible in routine clinical practice, strategies for risk stratification are currently based on the evaluation of those clinical and anamnestic, pre- and intraoperative predictors of CPBS that have already been identified in the literature. Given the observational nature of this study, it was not possible to explore genetic susceptibility in our cohort of patients. On the other hand, to the best of our knowledge, this is the first study evaluating selective pectoral muscle denervation as a potential risk factor for CPBS. Although denervation is a major risk factor for chronic neuropathic pain, none of the 19 patients undergoing selective pectoral muscle denervation for aesthetic purposes developed CPBS.

In contrast with previous studies, we have not observed an association between CPBS and patient age (Gartner et al. 2009; Vilholm et al. 2008), previous breast surgery (Vilholm et al. 2008), reconstructive surgery (Roth 2018) or implant-device placement (both above or below the pectoralis major muscle) (Wallace et al. 1996). On the other hand, our study confirms that there is little evidence to suggest CPBS might be influenced by type of anaesthesia (Cho et al. 2013; Steyaert et al. 2016; Veevaete and Lavand’homme 2014). However, it should be recognised that anaesthesiologic factors considered in this study are biased towards totally intravenous anaesthesia, thus calling for caution when interpreting the results. Similarly, the numbers of PECS Blocks and local anaesthetics infiltration performed in this cohort is relatively small, thus potentially affecting our results. Although PECS block II has already been recognised as a protective factor for pain chronicization (De Cassai et al. 2020), we have not observed this effect in our cohort. Furthermore, other techniques (such as paravertebral blocks or epidural analgesia) (Andreae and Andreae 2013) and other drugs (such as ketamine, or i.v. lidocaine) (Crousier et al. 2008; Grigoras et al. 2012) known to have benefits in reducing chronic pain have not been used in this cohort of patients, and thus their role has not been explored in this study. The lack of information on the effects of locoregional anaesthesia and adjuvant analgesics in reducing CPBS should be recognised as a limitation of this study.

Independently associated factors predicting CPBS in our cohort of patients were: long-term use of analgesics for preexisting chronic pain, axillary surgery, and higher values of dynamic NRS at 6hrs postoperatively.

Preoperative breast pain and/or preexisting chronic pain before surgery are well-known risk factors for chronic postoperative pain, particularly for CPBS (Gartner et al. 2009; Wang et al. 2018). In this study,
nearly a third of patients had preoperative pain, mainly low-back pain or migraine (52.6% and 44.2% of cases respectively). Preoperative painful conditions seem to predispose patients to the development of chronic post-surgical pain/CPBS, probably because the postoperative transition from acute to chronic pain is facilitated by long-term central and peripheral pain sensitization (Ji R, Nackley A, Huh Y, Terrando N 2018). In this study, preoperative chronic pain was not found to be an independent risk factor for CPBS, except for the most severe cases requiring chronic analgesic drugs for pain management. As far as we are aware, this is the first study reporting a correlation between the use of preoperative painkillers and CPBS, although the possibility that use of analgesics before surgery may just reflect hypochondriacal behaviour should also be considered. Unfortunately, we do not have enough data on patients’ psychological features to explore the role of pathologic behaviours in preoperative use of analgesics and possible development of CPBS. In our cohort of patients, migraine (treated with paracetamol and NSAIDs), low-back pain (treated with paracetamol, NSAIDs, and corticosteroids), and chronic dental pain (treated with NSAIDs and gabapentin) were the main causes for long-term use of analgesics. No patients had pre-existing breast or axillary pain.

The association between axillary surgery and CPBS has already been reported in the literature. In particular, conclusions produced from a meta-analysis study including more than 19,000 patients have highlighted a 21% increased risk of developing CPBS in those subjects who underwent axillary surgery (Wang et al. 2018). In this study, axillary surgery was associated with a 93% increased risk of developing CPBS. A likely explanation is the use of different follow-up time frames for evaluating the correlation between axillary surgery and CPBS. Among the studies evidencing a correlation between axillary lymph node dissection (ALND) and CPBS, three explored this correlation within 6 months postoperatively (Alves Nogueira Fabro et al. 2012; Karen K et al. 2002; De Oliveira et al. 2014), and the remaining two within 12 months (Meretoja et al. 2014; Thornton et al. 2013). A higher likelihood of surgery-related nerve injury – more frequent during ALND than sentinel node biopsy – has been advocated as the most probable cause of this association. Interestingly, differences between sentinel node biopsy and ALND as risk factors for CPBS have not emerged in our cohort of patients, probably because of the low rate of ALND included in this study (15.3% vs >30% in other studies) (Wang et al. 2018). To the best of our knowledge, no study has so far evaluated the possible role of sentinel node biopsy as a risk factor for CPBS. Furthermore, it should be underlined that, beside the effects of single surgical procedures (as reported in table 1), the combination of different procedures might also have a synergic/additive role in determining CPBS. This issue has not been explored in this study.

Higher dynamic NRS values at 6 hours postoperatively play a role as independent factors to predict CPBS in our cohort of patients. Several studies have recognised the presence and severity of acute postoperative pain as risk factors for postoperative chronic pain (Palotie et al. 2013; Tasmuth et al. 1996), particularly for CPBS (Fassoulaki et al. 2009). Our results suggest that one-point increase in dynamic NRS values corresponds to a 27% increased risk of developing CPBS. Median postoperative NRS values reported in this study, both at rest and during movement, suggest that adequate postoperative management of pain was generally achieved in the enrolled population. It is worth noting that patients who developed CPBS at 3 months exhibited higher NRS values than those who did not. In particular,
statistically significant differences were observed between CPBS and No-CPBS groups in terms of dynamic and static NRS values at 3hrs, 6hrs, 12hrs and 24hrs postoperatively.

Pain intensity and pain interference with daily functions were assessed through the Italian validated version of the BPI questionnaire. This is a reliable, multidimensional tool for evaluating also non-oncological chronic pain and has already been used for CPBS (Bonezzi et al. 2002; De Oliveira et al. 2014). Analysis of BPI scores by item showed that in most cases chronic pain was of mild to moderate intensity. In 18 (20.9%) patients with CPBS, the median NRS values recorded during movement were greater than five, therefore reflecting moderate to severe chronic pain. These results are in line with those reported in the literature (Andersen and Kehlet 2013; Leysen et al. 2018; Peuckmann et al. 2009). Finally, according to the BPI questionnaire, CPBS had a profound impact on sleep quality, mood and perception of happiness.

It is plausible that a number of limitations may have influenced the results of this study. First, this is a monocentric study carried out in a single teaching-hospital. Second, our cohort of patients was quite small and therefore our findings need to be validated in a larger population. Third, we were not able to evaluate other factors such as psychological or genetic features as potential predictors of CPBS. A further limitation is that neither the numbers and levels of sentinel node biopsy nor the preservation vs cut of the intercostobrachial nerve were recorded. Finally, we were not able to evaluate the role of acupuncture and other non-pharmacologic analgesic therapies or interventional procedures in modulating CPBS.

Conclusions

Chronic pain after breast surgery is a frequent complication that interferes with patients daily activities. In this study, evaluation of CPBS according to the IASP definition resulted in a 28% incidence at 3 months postoperatively. Interestingly, the presence of early pain at 2 months after surgery (“pain becoming chronic”) concords with the occurrence of CPBS. The possibility to early detect persistent pain, particularly in those patients at high-risk for CPBS, might help physicians to more effectively prevent pain chronicization. In our cohort of adult surgical female patients, long-term use of analgesics for preexisting chronic pain, axillary surgery, and higher dynamic NRS values at 6 hours postoperatively were statistically associated with a higher risk of developing CPBS. A timely follow-up right after surgery, aimed at recognising “pain becoming chronic” in high-risk patients, might thus allow the implementation of proactive pharmacologic and non-pharmacologic approaches to prevent CPBS.

Declarations

Ethics approval and consent to participate

The institutional review boards of the centre (“Comitato Etico Area Vasta Toscana Centro”) reviewed and approved the study protocol for the Azienda Ospedaliero Universitaria Careggi in Florence (OSS.16.246).
Because of the retrospective nature of this study, written consent for analysis and publication of clinical data was waived from the IRB. All methods of consent were approved by the appropriate ethics committees.

**Consent for publication**

Not Applicable.

**Availability of data and materials**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

Dr. Gianluca Villa has received honoraria for lectures from Baxter and Pall Italia. Prof. Stefano Romagnoli has received honoraria for lectures/consultancy from Baxter, Orion Pharma, Vygon, intensive care unit medical, MSD and Medtronic and funds for travel expenses, hotel accommodation and registration to meetings from Baxter, BBraun, Pall International, Medigas and Vygon. Prof. Angelo Raffaele De Gaudio has received research grants from MSD Italia, Baxter and Pall International. The remaining authors disclose that they do not have any potential conflict of interest.

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**Authors’ contributions**

G.V.: This author was responsible for all aspects of the study thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved; R.M.: This author helped with analysis and interpretation of data; C.S.C.: This author helped with analysis and interpretation of data; V.R.: This author substantially contribute to study conception and design, acquisition of data, analysis and interpretation of data; M.D.D.: This author substantially contributed to study conception and design, acquisition of data, analysis and interpretation of data; D.P.M.: This author substantially contributed to study conception and design, acquisition of data, analysis and interpretation of data; L.P.: This author substantially contributed to study conception and design, acquisition of data, analysis and interpretation of data; A.R.D.G.: This author contributed to draft the manuscript and review it critically; S.R.: This author substantially contributed to study conception and design, and approved the final version of the manuscript.
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Abbreviations

CPBS: Chronic pain after breast surgery

IASP: International Association for the Study of Pain

NRS: Numerical Rating Scale

BPI: Brief Pain Inventory

PCA: Patient-controlled-analgesia

ALND: Axillary lymph node dissection

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Tables
### Patient characteristics

|                   | Total (n=307) | No-CPBS (n=221) | CPBS (n=86) | OR [95%CI] | p   |
|-------------------|--------------|----------------|-------------|------------|-----|
| **Age (yrs)**     | 56.2±12.4    | 55.3±12.4      | 53.6±11.2   | 0.99 [0.97-1.01] | 0.275 |
| **Height (cm)**   | 163.5±6.3    | 163.6±6.6      | 163.4±5.3   | 0.99 [0.96-1.04] | 0.824 |
| **Weight (kg)**   | 64.5±12.5    | 55.3±5.9       | 55.2±4.8    | 0.10 [0.99-1.03] | 0.212 |
| **BMI (Kg/m2)**   | 24.1±4.4     | 23.9±4.1       | 24.7±4.9    | 1.04 [0.98-1.10] | 0.168 |
| **Preoperative pain** | 95 (30.9%) | 56 (25.3%) | 39 (45.3%) | 1.13 [0.64-1.97] | 0.686 |
| **Chronic use of pain drugs** | 19 (6.2%) | 9 (4.1%) | 10 (11.6%) | 3.10 [1.21-7.92] | 0.018 |
| **Anxiety/Depression** | 43 (14%) | 33 (14.9%) | 10 (11.6%) | 0.75 [0.35-1.60] | 0.446 |
| **Fibromyalgia**   | 2 (0.7%)     | 1 (0.5%)       | 1 (1.2%)    | 2.59 [0.16-41.90] | 0.511 |
| **Neoadjuvant-CHT** | 23 (7.5%) | 15 (6.8%) | 8 (9.3%) | 1.41 [0.58-3.45] | 0.461 |
| **Preop. hormone-therapy** | 37 (12.1%) | 28 (12.7%) | 9 (10.5%) | 0.81 [0.36-1.79] | 0.589 |
| **Neoadjuvant-RT** | 1 (0.33%) | 1 (0.5%) | 0 (0.0%) | - | - |
| **Previous ipsilateral breast surgery** | 108 (35.18%) | 78 (35.3%) | 30 (34.9%) | 0.98 [0.58-1.66] | 1.000 |
| **School education** | | | | | 0.517 |
| Primary school    | 30 (9.77%)   | 24 (10.9%)     | 6 (7.0%)    | 0.79 [0.28-2.24] | |
| Secondary school  | 57 (18.57%)  | 40 (18.1%)     | 17 (19.8%)  | 1.35 [0.62-2.93] | |
| High school       | 145 (47.23%) | 100 (45.2%)    | 45 (52.3%)  | 1.42 [0.75-2.69] | |
| University        | 75 (24.43%)  | 57 (25.8%)     | 18 (20.9%)  | Ref. | |

### Surgical factors

|                  | Total (n=307) | No-CPBS (n=221) | CPBS (n=86) | OR [95%CI] | p   |
|------------------|--------------|----------------|-------------|------------|-----|
| **Breast-conserving surgery** | 149 (48.5%) | 110 (49.8%) | 39 (45.3%) | 0.84 [0.51-1.38] | 0.526 |
| Procedure                                                                 | Count | Percentage | Reference Count | Reference Percentage | Odds Ratio [95% CI] | P-value |
|---------------------------------------------------------------------------|-------|------------|------------------|----------------------|---------------------|---------|
| Mastectomy                                                                | 91(29.6%) | 61(27.6%) | 30(34.9%)        |                      | 1.41 [0.83-2.39]    | 0.214   |
| Implant-based reconstructive surgery (tissue-expanders or prosthesis)    | 113(36.8%) | 81(36.7%) | 32(37.2%)        |                      | 1.02 [0.61-1.72]    | 0.928   |
| Pre-pectoral prosthesis                                                   | 23(7.5%)  | 17(21.0%)  | 6(18.8%)         |                      | Ref.                | -       |
| Under-pectoral prosthesis or tissue-expander                              | 47(15.3%) | 32(39.5%) | 15(46.9%)        |                      | 1.33 [0.44-4.05]    | 0.618   |
| Tissue-expander substitution with prosthesis                              | 43(14.0%) | 32(39.5%) | 11(34.4%)        |                      | 0.97 [0.31-3.09]    | 0.964   |
| Axillary surgery                                                          | 146(47.6%) | 95(43.0%) | 51(59.3%)        |                      | 1.93 [1.17-3.21]    | 0.011   |
| Sentinel Node Biopsy                                                      | 99(32.3%) | 64(29.0%) | 35(40.7%)        |                      | 0.94 [0.46-1.96]    | 0.877   |
| Axillary lymph node dissection                                            | 47(15.3%) | 31(14.0%) | 16(18.6%)        |                      | Ref.                | -       |
| Cosmetic surgery                                                          | 68(22.2%) | 48(21.7%) | 20(23.3%)        |                      | 1.09 [0.60-1.98]    | 0.762   |
| Dorsal-flap reconstructive surgery                                        | 1(0.3%)   | 1(0.5%)   | 0(0.0%)          |                      | Ref.                | -       |
| Bilateral surgery                                                         | 103(33.6%) | 70(31.8%) | 33(38.4%)        |                      | 1.33 [0.79-2.24]    | 0.276   |
| Selective pectoral nerves dissection                                      | 19(6.2%)  | 12(5.5%)  | 7(8.1%)          |                      | 1.53 [0.58-4.02]    | 0.390   |

**Anesthesiologic factors**

| Anesthetic Type               | Count | Percentage | Reference Count | Reference Percentage | Odds Ratio [95% CI] | P-value |
|------------------------------|-------|------------|------------------|----------------------|---------------------|---------|
| Total Intravenous Anesthesia | 251(81.8%) | 180(81.4%) | 71(82.6%)        |                      | 0.93 [0.48-1.78]    | 0.821   |
| PROPOFOL                     | 251(81.8%) | 180(81.4%) | 71(82.6%)        |                      | 1.08 [0.56-2.07]    | 0.821   |
| REMIFENTANIL                 | 221(72.0%) | 157(71.0%) | 64(74.4%)        |                      | 1.19 [0.67-2.09]    | 0.554   |
| SUFENTANIL                   | 29(9.5%)  | 22(10.0%)  | 7(8.1%)          |                      | 0.80 [0.33-1.95]    | 0.626   |
| FENTANIL                     | 14(4.6%)  | 9(4.1%)    | 5(5.8%)          |                      | 1.45 [0.47-4.47]    | 0.513   |
| Inhaled Anesthesia           | 56(18.2%) | 41(18.6%)  | 15(17.4%)        |                      | 1.07 [0.56-2.07]    | 0.999   |
| SEVORANE                     | 40(13%)   | 29(13.1%)  | 11(12.8%)        |                      | 0.88 [0.23-3.32]    | 0.846   |
| DESFLURANE                   | 16(5.2%)  | 12(5.4%)   | 4(4.7%)          |                      | 1.14 [0.30-4.29]    | 0.846   |
| Anesthesia Type                  | CPBS  | No-CPBS | OR   [95%CI] | p-value |
|---------------------------------|-------|---------|---------|---------|
| REMIFENTANIL                    | 32 (10.4%) | 22 (10.0%) | 10 (11.6%) | 0.58 [0.16-1.94] | 0.384 |
| FENTANIL                        | 24 (7.8%) | 19 (8.6%) | 5 (5.8%) | 1.73 [0.50-5.95] | 0.384 |
| Regional Anesthesia             | 66 (21.5%) | 53 (24.0%) | 13 (15.1%) | 0.56 [0.29-1.10] | 0.092 |
| PECS 1                          | 28 (9.1%) | 22 (10.0%) | 6 (7.0%) | 0.68 [0.27-1.74] | 0.418 |
| PECS 2                          | 17 (5.6%) | 12 (5.4%) | 5 (5.8%) | 1.08 [0.37-3.15] | 0.895 |
| Local anesthetics infiltration  | 21 (6.8%) | 19 (8.6%) | 2 (2.3%) | 0.25 [0.03-1.09] | 0.075 |
| **Intraoperative analgesia**    |       |         |         |         |         |
| PARACETAMOL                     | 265 (86.3%) | 188 (85.1%) | 77 (89.5%) | 1.50 [0.69-3.29] | 0.309 |
| KETOROLAC                       | 49 (16.0%) | 33 (14.9%) | 16 (18.6%) | 1.30 [0.68-2.51] | 0.431 |
| MORPHINE                        | 242 (7.8%) | 169 (76.5%) | 73 (84.9%) | 1.73 [0.89-3.37] | 0.108 |

**Table 1. Patients’ baseline characteristics, surgical, and anesthesiologic factors in CPBS and No-CPBS groups**

Among anesthesiologic factors, specific drugs used for total intravenous anesthesia and inhaled anesthesia are described for both CPBS and No-CPBS groups. For patients treated with Locoregional anesthesia, use of Pectoralis and Serratus Plane Blocks (PECS1 and PECS2) and of Local anesthetics infiltration is reported. For variables with more than two levels, OR [95%CI] are expressed with respect to the level used as reference (Ref.). Wald test p-values are 0.774 for Implant-based reconstructive surgery and 0.517 for school education. Among patients who underwent axillary surgery, differences between those treated with sentinel node biopsy and those treated with axillary lymph node dissection were evaluated with a chi-squared test (OR [95% CI]=0.94 [0.46-1.96], p-value=0.877).
Table 2
Analgesics used postoperatively

| Prescribed for postoperative analgesia | Total (n = 307) | No-CPBS (n = 221) | CPBS (n = 86) | OR [95%CI]   | p   |
|--------------------------------------|----------------|------------------|--------------|--------------|-----|
| Paracetamol                          | 307 (100%)     | 221 (100%)       | 86 (100%)    | -            | -   |
| Morphine (PCA)                       | 142 (46.3%)    | 101 (45.7%)      | 41 (47.7%)   | 1.08 [0.64–1.84] | 0.799 |
| Tramadol rescue                      | 95 (30.9%)     | 62 (28.1%)       | 33 (38.8%)   | 1.62 [0.93–2.84] | 0.074 |
| Ketorolac rescue                     | 70 (22.8%)     | 54 (24.4%)       | 16 (21.1%)   | 0.83 [0.41–1.60] | 0.639 |

Actually administered for postoperative analgesia

| At 3 hrs                              | Total (n = 307) | No-CPBS (n = 221) | CPBS (n = 86) | OR [95%CI]   | p   |
|---------------------------------------|----------------|------------------|--------------|--------------|-----|
| Currently using PCA                  | 142/142 (100%) | 101/101 (100%)   | 41/41 (100%) | -            | -   |
| Doses requested                       | 1 [0; 21]      | 0 [0; 21]        | 1 [0; 9]     | 1.05 [0.91–1.21] | 0.472 |
| Doses administered                   | 1 [1; 6]       | 0 [0; 6]         | 1 [0; 5]     | 1.05 [0.79–1.39] | 0.751 |
| Tramadol rescue                       | 4/95 (4.2%)    | 3/62 (4.8%)      | 1/33 (3.0%)  | 0.67 [0.07–6.72] | 0.731 |
| Ketorolac rescue                      | 3/70 (4.3%)    | 3/54 (5.6%)      | 0/16 (0%)    | -            | -   |

| At 6 hrs                              | Total (n = 292) | No-CPBS (n = 208) | CPBS (n = 84) | OR [95%CI]   | p   |
|---------------------------------------|----------------|------------------|--------------|--------------|-----|
| Currently using PCA                  | 139/142 (97.9%)| 99/101 (98.0%)   | 40/41 (97.6%)| -            | -   |
| Doses requested                       | 1 [0; 26]      | 1 [0; 26]        | 1.50 [0; 15] | 1.08 [0.98–1.18] | 0.133 |
| Doses administered                   | 1 [0; 11]      | 1 [0; 11]        | 2 [0; 10]    | 1.16 [0.98–1.36] | 0.078 |
| Tramadol rescue                       | 1/81 (1.2%)    | 0 (0%)           | 1/26 (3.8%)  | -            | -   |
| Ketorolac rescue                      | 1/57 (1.8%)    | 1/46 (2.2%)      | 0 (0%)       | -            | -   |

At the different time points, the percentages of patients on the surgical ward using PCA and/or tramadol and ketorolac tromethamine as prescribed rescue analgesics are reported over time. Requested and administered doses are expressed as median and minimum-maximum values.

Among patients treated with PCA in the No-CPBS and CPBS groups, those receiving less than 3 doses (1 dose = morphine 1 mg) were respectively 94 (93.1%) and 40 (97.6%) in the first 3 hrs postoperatively, 84 (84.8%) and 31 (77.5%) in the first 6 hrs postoperatively; those receiving less than 6 doses in the first 12 hrs postoperatively were 67 (88.2%) and 26 (86.7%), respectively; those receiving less than 10 doses in the first 24 hrs were 28 (87.5%) and 14 (93.3%), respectively; those receiving less than 15 doses in the first 48 hrs postoperatively were 1 (100%) and 3 (100%), respectively.
|                          | Total (n = 307) | No-CPBS (n = 221) | CPBS (n = 86) | OR [95%CI] | p    |
|--------------------------|----------------|-------------------|---------------|------------|------|
| Currently using PCA     | 106/142 (74.7%) | 76/101 (75.2%)    | 30/41 (73.2%) |            |      |
| Doses requested          | 2 [0; 28]       | 2 [0; 28]         | 4 [0; 25]     | 1.06 [0.99–1.14] | 0.119 |
| Doses administered       | 2 [0; 14]       | 2 [0; 13]         | 3.50 [0; 14]  | 1.11 [0.98–1.25] | 0.097 |
| Tramadol rescue          | 2/69 (2.9%)     | 1/46 (2.2%)       | 1/23 (4.3%)   | 2.05 [0.12–34.3] | 0.619 |
| Ketorolac rescue         | 5/54 (9.3%)     | 4/44 (9.1%)       | 1/10 (10.0%)  | 1.11 [0.11–11.2] | 0.929 |
| At 24 hrs                |                |                   |               |            |      |
| Currently using PCA     | 47/110 (42.7%)  | 32/79 (40.5%)     | 15/31 (48.4%) |            |      |
| Doses requested          | 3 [0; 35]       | 3 [0; 23]         | 4 [1; 35]     | 1.05 [0.96–1.15] | 0.298 |
| Doses administered       | 3 [0; 17]       | 3 [0; 17]         | 4 [1; 14]     | 1.06 [0.91–1.24] | 0.292 |
| Tramadol rescue          | 0/26 (0%)       | 0 (0%)            | 0 (0%)        | -          | -    |
| Ketorolac rescue         | 2/33 (6.1%)     | 2/27 (7.4%)       | 0 (0%)        | -          | -    |
| At 48 hrs                |                |                   |               |            |      |
| Currently using PCA     | 4/142 (2.82%)   | 1/24 (4.2%)       | 3/17 (17.6%)  |            |      |
| Doses requested          | 12 [4; 13]      | 11                | 13 [4; 13]    | 0.92 [0.47–1.82] | 0.817 |
| Doses administered       | 6.5 [4; 11]     | 11                | 4 [4; 9]      | -          | -    |
| Tramadol rescue          | 0/8 (0%)        | 0 (0%)            | 0 (0%)        | -          | -    |
| Ketorolac rescue         | 1/9 (11.1%)     | 0 (0%)            | 1 (100%)      | -          | -    |

At the different time points, the percentages of patients on the surgical ward using PCA and/or tramadol and ketorolac tromethamine as prescribed rescue analgesics are reported over time. Requested and administered doses are expressed as median and minimum-maximum values.

Among patients treated with PCA in the No-CPBS and CPBS groups, those receiving less than 3 doses (1 dose = morphine 1 mg) were respectively 94 (93.1%) and 40 (97.6%) in the first 3 hrs postoperatively, 84 (84.8%) and 31 (77.5%) in the first 6 hrs postoperatively; those receiving less than 6 doses in the first 12 hrs postoperatively were 67 (88.2%) and 26 (86.7%), respectively; those receiving less than 10 doses in the first 24 hrs were 28 (87.5%) and 14 (93.3%), respectively; those receiving less than 15 doses in the first 48 hrs postoperatively were 1 (100%) and 3 (100%), respectively.
Table 3
Static and dynamic postoperative NRS in both CPBS and No-CPBS groups.

| Pain intensity                  | Total (n = 307) | No-CPBS (n = 221) | CPBS (n = 86) | OR [95%CI]     | \( p \) |
|---------------------------------|-----------------|-------------------|---------------|----------------|-------|
| At 0hrs                         |                 |                   |               |                |       |
| NRS at rest                     | 1 [0; 9]        | 1 [0, 9]          | 1 [0, 8]      | 1.13 [1.00-1.28] | 0.075 |
| NRS during movement             | 1 [0; 10]       | 1 [0, 10]         | 2 [0, 9]      | 1.12 [1.01-1.25] | 0.051 |
| At 3hrs                         | Total (n = 306) | No CPBS (n = 220) | CPBS (n = 86) |                |       |
| NRS at rest                     | 1 [0; 7]        | 1 [0, 5]          | 1 [0, 7]      | 1.28 [1.02-1.62] | 0.034 |
| NRS during movement             | 2 [1; 8]        | 2 [0, 6]          | 2 [0, 8]      | 1.31 [1.08-1.59] | 0.004 |
| At 6hrs                         | Total (n = 292) | No CPBS (n = 208) | CPBS (n = 84) |                |       |
| NRS at rest                     | 1 [0; 5]        | 1 [0, 5]          | 1 [0, 5]      | 1.24 [0.98-1.56] | 0.101 |
| NRS during movement             | 2 [1; 7]        | 2 [0, 5]          | 2 [0, 7]      | 1.27 [1.06-1.54] | 0.041 |
| At 12hrs                        | Total (n = 254) | No CPBS (n = 180) | CPBS (n = 74) |                |       |
| NRS at rest                     | 1 [0; 6]        | 1 [0, 6]          | 1 [0, 5]      | 1.26 [0.99-1.58] | 0.036 |
| NRS during movement             | 2 [0; 7]        | 2 [0, 6]          | 2 [0, 7]      | 1.24 [1.04-1.48] | 0.024 |
| At 24hrs                        | Total (n = 156) | No CPBS (n = 111) | CPBS (n = 45) |                |       |
| NRS at rest                     | 1 [0; 5]        | 1 [0, 4]          | 1 [0, 5]      | 1.36 [0.98-1.90] | 0.110 |
| NRS during movement             | 1 [0; 6]        | 1 [0, 5]          | 2 [0, 6]      | 1.35 [1.06-1.71] | 0.024 |
| At 48hrs                        | Total (n = 58)  | No CPBS (n = 35)  | CPBS (n = 23) |                |       |
| NRS at rest                     | 1 [0; 4]        | 1 [0, 4]          | 1 [0, 2]      | 0.86 [0.47-1.56] | 0.817 |
| NRS during movement             | 2 [0; 6]        | 2 [0, 5]          | 2 [0, 6]      | 1.26 [0.90-1.75] | 0.279 |