What is the role of locoregional anesthesia in breast surgery? A systematic literature review focused on pain intensity, opioid consumption, adverse events, and patient satisfaction.

Pasquale Sansone, Assoc. Prof.[1], Luca Gregorio Giaccari, M.D.,[1] Mario Faenza, M.D. PhD,[2] Pasquale Di Costanzo, M.D.,[2] Sara Izzo, M.D.,[2] Caterina Aurilio, Prof.,[1] Francesco Coppolino, M.D.,[1] Maria Beatrice Passavanti, M.D. PhD,[1] Vincenzo Pota, M.D. PhD,[1] Maria Caterina Pace, Prof.,[1]

[1]Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Napoli – Italy.
[2]Multidisciplinary Departement of Medical Surgical and Dental Sciences – Plastic Surgery Unit, University of Campania "Luigi Vanvitelli", Napoli – Italy.

Corresponding author:
Pasquale Sansone
Telephone: +39 0815665180
E-mail: pasquale.sansone@unicampania.it
Address: Università degli Studi della Campania "Luigi Vanvitelli". Piazza Luigi Miraglia, 2. Napoli – Italy.

ABSTRACT

Background: Breast surgery in the United States is common. Pain affects up to 50% of women undergoing breast surgery and can interfere with postoperative outcomes. General anesthesia is the conventional, most frequently used anaesthetic technique. Various locoregional anesthetic techniques are also used for breast surgeries. A systematic review of the use of locoregional anesthesia for postoperative pain in breast surgery is needed to clarify its role in pain management.

The aim of this study was to establish the efficacy and the safety of locoregional anesthesia used in the treatment of pain after breast surgery.

Methods: Embase, MEDLINE, Google Scholar and Cochrane Central Trials Register were systematically searched in Mars 2020 for studies examining locoregional anesthesia for management of pain in adult after breast surgery. The methodological quality of the studies and their results were appraised using the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) checklist and specific measurement properties criteria, respectively.

Results: Nineteen studies evaluating locoregional anesthesia were included: 1058 patients underwent lumpectomy/mastectomy, 142 breast augmentation and 79 breast reduction. Locoregional anesthesia provides effective anesthesia and analgesia in the perioperative setting. After mastectomy, the use of locoregional anesthesia techniques seems to reduce pain, especially in the first hour after the end of the surgery. Other potentially beneficial effects of locoregional anesthesia emerged from our review include decreased need for opioids, decreased postoperative nausea and vomiting, fewer complications and increased patient satisfaction. All this improves postoperative recovery and shortens hospitalization stay.

Conclusion: The results of this study support the technique of locoregional anesthesia for breast surgery.

Key Words (MesH): breast surgery, mastectomy, locoregional anesthesia, pain intensity, opioid consumption, adverse events, patient satisfaction.

BACKGROUND

Rationale. Breast surgery in the United States is common. In 2020, an estimated 276,480 new cases of invasive breast cancer will be diagnosed among women and approximately 80% of patients will have surgery to remove their primary tumour.[1] In addition, an increasing number of women are turning to plastic surgeons for interventions of cosmetic: among these breast augmentation is the first procedure performed in the United States.[2]

Pain affects up to 50% of women undergoing breast surgery and can interfere with postoperative outcomes. Breast pain is one of the factors determining patient distress, long hospital stay, and an increase in post-surgical admissions to the hospital.[3]

Nociceptive/inflammatory pain is caused by tissue damage, whereas neuropathic pain is the consequence of a central and peripheral nerve damage,[4] in most cases a lesion of intercostal nerves from T2 to T6. Neuropathic pain typically begins immediately after breast surgery and can be persistent, lasting even for months sometimes.[3]

The control of pain is the main objective for anesthesia in breast surgery. The correct management of acute postoperative pain is essential to improve patient outcome and satisfaction.

At present various anesthetic agents, devices, and strategies are available. For a long time, intravenous analgesia has been the main avenue to relieving postoperative pain. Over the years, the growing number of surgical procedures for breast cancer and cosmetic treatment has however stimulated the development of new anesthetic techniques with improved pain reduction and safety, and fewer complications.

The international guidelines recommended the use of a multimodal analgesia.[5,6] Regional anesthetic techniques are effective as a component of multimodal analgesia for management of postoperative pain associated with a number of surgical procedures. These techniques can be administered as a single shot or a continuous catheter, both prior to surgical incision or after surgery.[5,6] Also local anesthetics infiltration shows benefit for the surgical procedure. Wound infiltration can be performed either as a single injection of local anesthetic typically at the conclusion of surgery or as a continuous infusion of local anesthetic through a catheter at the incision site prior to skin closure.[5,6] Finally, the international guidelines suggest the use of intravenous (IV) lidocaine, especially in

patients underwent open or laparoscopic abdominal surgical procedures.[5,6] Perioperative lidocaine infusion may be considered for patients undergoing mastectomy.[7]

Objectives. The aim of the current study was to conduct a systematic literature review to establish the efficacy and the safety of locoregional anesthesia used in the treatment of pain after breast surgery.

METHODS

Protocol and registration. We performed a systematic review based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[8] and following a protocol written prior to start the review.

Eligibility criteria. The population, intervention, comparison, and outcome (PICO) criteria were applied to the research question. Patients of at least 18 years undergoing breast surgery were considered as the population (P); the intervention (I) was postoperative analgesia with locoregional anesthesia techniques; the comparison (C) concept was standard pain treatment provided in each study; pain intensity, opioid consumption, adverse events (AEs), and patient satisfaction were considered the outcomes (O) for this systematic review. We included randomized controlled trial published from 2010 to the present.

Table 1. *PICO criteria for including studies.*

Literature search. We identified the articles by searching electronic databases (Embase, MEDLINE, Google Scholar and Cochrane Central Trials Register). Other relevant studies were identified from the reference lists of systematic reviews and meta-analyses.
We used a combination of terms for *"breast augmentation"*, *"breast reduction"*, *"mastectomy"*, *"mastopexy"*, *"local anesthetic agent"*, *"postoperative pain"* and *"randomized clinical trial"*.
We applied no language restrictions in searches. The initial search was performed in Mars 2020.

The studies included in this review evaluated adult patients undergoing breast surgery and receiving any type of locoregional anesthesia to treat postoperative pain.

Primary outcomes. Pain scores and opioid consumption in the first 48 hours postoperatively were the primary outcomes of interest. Pain intensity was assessed via a Numeric Rating Scale (NRS) at 1, 6, 12, 24 and 48 hours after surgery. Pain intensity data assessed by means other than a zero to 10 NRS were normalized to such a scale. The other primary outcome was the average per patient opioid consumption in Post-Anesthesia Care Unit (PACU) and up to 48 h after surgery. Opioid consumption was converted to morphine sulfate equivalents.[9]

Secondary outcomes. We extracted data on the following secondary outcomes:

1. Adverse Events, such as nausea and vomiting, were recorded. Complications during wound healing were also analyzed.
2. Patient Satisfaction.

Selection of studies. We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy our inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement by discussion.
The methodological quality of the included studies was evaluated and rated using the COSMIN checklist, which has a 4-point rating scale.

Data extraction and management. Data extracted included the following:

- Age, weight, height and body mass index (BMI) of participants;
- Number of participants enrolled and completing the study;
- Type of operation;
- Regional anesthesia technique (local anesthetic and dose);
- Pain intensity for all-time points at which it was measured;
- Opioid consumption;
- Patient satisfaction;
- Severity or incidence of adverse events.

RESULTS

The flow diagram (see **Figure 1**) shows the results from the literature search and the study selection process. Nineteen studies met the eligibility criteria: 14 concerned lumpectomy/ mastectomy, 3 breast augmentation, and 2 breast reduction.

According to the COSMIN checklist, all studies included in this review showed an excellent-to-good quality. The majority of clinical trials had a low risk of bias.

Table 2A, 2B and **2C** display the nineteen papers included in this review.

Figure 1. *Flow diagram study selection process.*

Table 2A, 2B, 2C. *Studies characteristics.*

LUMPECTOMY/MASTECTOMY. In the included studies 1058 patients underwent lumpectomy/mastectomy. There were no demographic differences between the two groups as shown in **Table 3**.

Table 3. *Personal and clinical characteristics.*

The largest studies involved 140 patients (*Mohamed et al., 2013; Versyck et al., 2017*), while the smallest consisted of 44 patients (*Couceiro et al., 2014*). All analyzed studies were conducted in inpatient settings.

Patients underwent mastectomy, while lumpectomy was performed in 4 studies (*Campbell et al., 2014; Cros et al., 2018; Gürkan et al., 2018; Versyck et al., 2017*). *Lanier et al 2018* and *Wang et al 2018* reported immediate tissue expander or implant based breast reconstruction. Surgical treatment for breast cancer was associated with a sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) in 10 papers (*Campbell et al., 2014; Cros et al., 2018; Gürkan et al., 2018; Ilfeld et al., 2014; Lanier et al., 2018; Mohamed et al., 2013; Neethu et al., 2018; Versyck et al. 2017;Wang et al., 2018; Yao et al., 2019*).

Regional anesthetic techniques were performed ten times: the most common procedure was pectoralis nerve (Pecs) block type I and II (5 studies: *Cros et al., 2018; Neethu et al., 2018; Versyck et al. 2017; Wang et al., 2018; Wang et al., 2019*), followed by serratus plane block (SPB) (2 studies: *Wang et al., 2019; Yao et al., 2019),* erector spinae plane (ESP) block

(*Gürkan et al., 2018*), and paravertebral block (PVB) (*Ilfeld et al., 2014*). In *Lanier et al 2018,* intraoperative nerve blocks of intercostal and pectoral nerves were performed under direct visualization by the attending plastic surgeon at the completion of the mastectomy.
Local infiltration was reported in 3 studies. In *Campbell et al 2014,* patients received 20 mL of bupivacaine 0.25% with or without adrenaline to be infiltrated into the breast wound and a further 20 mL of bupivaciane 0.25% with adrenaline to be infiltrated into the axilla wound when applicable. In *Mohamed et al 2013,* 5 ml of bupivacaine 0.5% with or without clonidine were diluted with saline 0.9% to 15 mL volume and irrigated into the surgical field before skin closure. An infusion pump of levobupivacaine 0.50% for approximately 48 hours was evaluated in *Ferreira Laso et al 2014.*
Couceiro et al 2014 and *Terkawi et al 2014* investigated i.v. lidocaine infusion. In the first paper, bolus dose of lidocaine was not administered and, after incision, lidocaine infusion at 3 mg/kg was started. In the other study, lidocaine was administered as a bolus to all patients before anesthetic induction, at a dose of up to 1.5 mg/kg, followed by a lidocaine infusion at 2 mg/kg/h until 2 hours after arrival in PACU.
Almost all studies were conducted under general anesthesia, except for *Ilfeld et al 2014* conducted under sedation. General anesthesia was induced and then maintained with opioids, such as alfentanyl (*Ferreira Laso et al., 2014*), fentanyl (*Couceiro et al., 2014; Gürkan et al., 2018; Ilfeld et al., 2014; Mohamed et al., 2013; Neethu et al., 2018; Terkawi et al., 2014; Wang et al., 2018*), remifentanil (*Wang et al., 2019*) and sufentanil (*Versyck et al., 2017; Wang et al., 2019; Yao et al., 2019*). For the postoperative pain management, four studies (*Couceiro et al., 2014; Cros et al., 2018; Ferreira Laso et al., 2014; Ilfeld et al., 2014*) provided infiltration of the chest wall ipsilateral to the mastectomy with local anesthetic; acetaminophen and other NSAIDs were systematically administered. Two studies did not report the anesthesia protocol (*Campbell et al., 2014; Lanier et al., 2018*).

Pain Intensity. Different investigators recorded this outcome on different scales and at different intervals. We normalized all NRS to a zero to 10 range (see **Table 4**). The majority of authors reported pain intensity at 1, 6, 12, 24 and 48 hours after surgery.

Table 4. *NRS at 1, 6, 12, 24 and 48 hours after surgery.*

As shown in **Figure 2**, the average NRS score was 1.83 ± 0.81 at 1 h, 2.02 ± 1.03 at 6 h, 1.92 ± 1.57 at 12 h, 1.74 ± 1.29 at 24 h and 1.51 ± 1.03 at 48 h in the intervention group; in the placebo group were recorded NRS scores of 3.36 ± 1.65 at 1 h, 3.10 ± 1.29 at 6 h, 2.35 ± 1.14 at 12 h, 2.37 ± 1.27 at 24 h and 2.77 ± 1.12 at 48 h.

Figure 2. *NRS at 1, 6, 12, 24 and 48 hours after surgery.*

One study, *Couceiro et al 2014*, did not report NRS at any interval: only 2 (9.09%) *vs* 3 (13.6%) patients in the lidocaine and placebo groups, respectively, experienced severe to very severe pain 24 hours after surgery.

Opioid consumption. The most frequently used opioids were codeine (*Campbell et al., 2014; Couceiro et al., 2014*), fentanyl (*Neethu et al., 2018*), oxycodone (*Campbell et al., 2014*), piritramide (*Versyck et al. 2017*), tramadol (*Campbell et al., 2014; Mohamed et al., 2013; Versyck et al. 2017*), and sufentanil (*Yao et al., 2019*). Morphine was used in the other studies.

At discharge from PACU, the overall mean amounts of morphine consumed in the intervention and placebo groups were 3.0 ± 3.63 mg and 4.87 ± 5.76 mg, respectively, with the difference being not statistically significant ($p = 0.51$).

After 48 hours, the overall mean amounts of morphine consumed in the intervention and placebo groups were, respectively, 2.68 ± 0.88 mg and 4.94 ± 4.61 mg ($p = 0.18$). Among regional anesthetic techniques, postoperative opioid consumption for the first 48 hours was respectively 2.14 ± 1.52 mg and 4.84 ± 4.63 mg; no statistically significant difference was observed ($p = 0.16$). The average per patient opioid consumption up to 48 h after surgery was 1.33 ± 1.49 mg *vs* 3.01 ± 3.05 mg ($p = 0.52$) among patients treated with local infiltration.

Table 5 shows the mean amounts of morphine consumed in the intervention and placebo groups.

Table 5. *Average per patient opioid consumption in PACU and up to 48 h after surgery.*

In *Couceiro et al 2014,* opioid consumption in the first 24 hours after surgery was similar in the lidocaine and placebo groups.

Adverse Events (AEs). An adverse event is defined as any undesirable experience associated with the use of a medical product in a patient. A total of 379 AEs were recorded. Three studies (*Couceiro et al., 2014; Ilfeld et al., 2014; Versyck et al., 2017)* did not report the number of AEs. The most frequently reported AEs were nausea, vomiting and postoperative nausea and vomiting (PONV), pruritus, dizziness, hematoma/bleeding, seroma and bruising (see **Table 6** and **Figure 3**). Some studies did not specify the timing of adverse events.

Table 6. *Number of adverse events (AEs).*

Figure 3. *Distribution of adverse events (AEs) among intervention group.*

Nausea, vomiting and PONV. Nausea, vomiting and PONV were the most frequent AEs (235 events, 62% of AEs). 96 *vs* 139 episodes were respectively recorded in intervention *vs* placebo group (p = 0.25). In 9 studies (*Cros et al., 2018; Ferreira Laso et al., 2014; Gürkan et al., 2018; Lanier et al., 2018; Neethu et al., 2018; Terkawi et al., 2014; Versyck et al. 2017; Wang et al., 2018; Yao et al., 2019*) prophylaxis was administered; in the others studies prescription of antiemetic drugs was missed or not reported.

Pruritus. A total of 23 cases of pruritus was reported in two studies (*Ferreira Laso et al., 2014; Wang et al., 2019*). No statistically significant difference was observed (7 *vs* 16, p = 0.47).

Dizziness. Fifteen episodes were recorded among patients not receiving treatment; only two patients reported dizziness in the intervention group. No statistically difference (p = 0.06) was observed in these 3 studies (*Ferreira Laso et al., 2014; Wang et al., 2019; Yao et al., 2019*).

Hematoma/Bleeding. Three studies (*Campbell et al., 2014; Cros et al., 2018; Ferreira Laso et al.*) reported a total of 21 episodes (10 *vs* 11, $p = 0.85$).

Seroma. Seroma was found in 10 cases in the intervention group *vs* 11 cases in the placebo group (*Campbell et al., 2014; Ferreira Laso et al., 2014*) with no statistically significant difference ($p = 0.91$).

Bruising. *Campbell et al 2014* reported 36 episodes of bruising (20 *vs* 16, $p = 0.70$).

Others. Hemodynamic changes were rarely reported. Hypotension was reported in 3 studies (*Cros et al., 2018; Ferreira Laso et al., 2014; Mohamed et al., 2013*) for a total of 7 AEs (5 *vs* 2, $p = 0.25$). *Ferreira Laso et al 2014* reported a case of hypertension. Two episodes of bradycardia were reported from *Mohamed et al 2013.*

Infection was observed, respectively, 3 *vs* 2 times in intervention and placebo groups in two studies (*Campbell et al., 2014; Ferreira Laso et al.*); no statistically significant difference was noticed ($p = 0.69$). Deep vein thrombosis (DVT), pulmonary thromboembolism (PTE) and acute respiratory infection were equally distributed (1 *vs* 1, $p = 1.0$) in *Ferreira Laso et al 2014.*

Patient satisfaction. Patient satisfaction results were presented as different degrees subjective satisfaction levels. We normalized all to "satisfied / not satisfied".

Only 5 studies (*Cros et al., 2018; Ferreira Laso et al., 2014; Lanier et al., 2018; Neethu et al., 2018; Wang et al., 2019;*) were available for analysis of satisfaction (see **Table 7** and **Figure 4**).

Table 7. *Patient satisfaction.*

Figure 4. *Patient satisfaction.*

Among intervention group, there were 164 satisfied patients *vs* 14 not satisfied patients; in the placebo group 149 patients were satisfied and 40 not satisfied. No statistically significant difference was observed between the two groups.

In *Versyck et al 2017,* both patient-groups were very satisfied about their management; while in *Yao et al 2019,* patient satisfaction scores were higher in the SPB group.

BREAST AUGMENTATION. 142 patients underwent breast augmentation. As shown in **Table 8**, the groups were similar in age, weight, height and body mass index.

Table 8. *Personal and clinical characteristics.*

All patients underwent subpectoral bilateral cosmetic breast augmentation.
Regional anesthetic techniques were performed in two studies: PVB in *Gardiner et al 2012;* association of Pecs type II and PSB in *Schuitemaker et al 2019.* In the other study, *Picard et al 2017,* a local infiltration was performed.
Patients received general anesthesia in *Schuitemaker et al 2019,* and sedation in *Gardiner et al 2012.* In both studies patients received fentanyl. *Picard et al 2017* did not report the anesthesia protocol.

Pain Intensity. Different investigators recorded this outcome on different scales and at different intervals. We normalized all NRS to a zero to 10 range (see **Table 9**). The majority of authors reported pain intensity at 1, 6, 24 and 72 hours after surgery.

Table 9. *NRS at 1, 6, 24 and 72 hours after surgery.*

As shown in **Figure 5**, the average NRS score was 3.4 ± 0.5 at 1 h, 3.0 at 6 h, 3.65 ± 1.15 at 24 h and 3.05 ± 0.25 at 72 h in the intervention group; in the placebo group were recorded NRS scores of 5.25 ± 0.05 at 1 h, 3.0 at 6 h, 3.65 ± 1.15 at 24 h and 4.2 ± 0.5 at 72 h.

Figure 5. *NRS at 1, 6, 24 and 72 hours after surgery.*

Opioid consumption. In *Gardiner et al 2012,* 6 patients in the placebo group required supplementary opioid use. No patient received opioids in intervention group.
After 24 hours in *Schuitemaker et al 2019*, the overall mean amounts of morphine consumed in the intervention and placebo groups were 0.2 ± 0.8 mg and 0.6 ± 1.2 mg, respectively, with the difference being not statistically significant ($p = 0.29$).

No data on opioid consumption was available in *Picard et al 2017.*

Adverse Events (AEs). A total of 19 (9 *vs* 10) AEs were recorded .
Gardiner et al 2012 reported 12 episodes of nausea and vomiting (5 *vs* 7, $p = 0.36$). In this study, hypotension occurred 3 times among patients in the intervention group and once in placebo group. A single case of bradycardia occurred in both groups.
No differences were observed between groups concerning the appearance of AEs in *Schuitemaker et al 2019.*
No adverse effects were reported in *Picard et al 2017.*

Patient satisfaction. Only *Schuitemaker et al 2019* reported data about patient satisfaction: after 24 hours, 80% *vs* 53% of patients in intervention and placebo groups were satisfied.

BREAST REDUCTION. 79 patients underwent breast reduction. The mean age was 38.28 ± 2.71years *vs* 38.78 ± 3.21 years (see **Table 10**).

Table 10. *Personal and clinical characteristics.*

All patients underwent breast reduction surgery.
Tumescent anesthesia was performed in *Christie et al 2017;* in *Valente et al 2014,* patients received local infiltration. All patients in these studies underwent general anesthesia.

Pain Intensity. Different investigators recorded this outcome on different scales and at different intervals. We normalized all NRS to a zero to 10 range (see **Table 11**). The authors reported pain intensity at 24 hours after surgery.

Table 11. *NRS at 24 hours after surgery.*

The average NRS score was 2.55 ± 1.72 in the intervention group; in the placebo group was recorded NRS score of 2.85 ± 1.14 ($p = 0.89$).

Opioid consumption. After 24 hours in *Christie et al 2017*, the overall mean amounts of morphine consumed in the intervention and placebo groups were 0.58 mg and 0.64 mg, respectively, with the difference being not statistically significant (p = 0.71).
No data on opioid consumption is available in *Valente et al 2014.*

Adverse Events (AEs). There was no significant difference in occurrence of nausea or vomiting in the first 24 hours between the two groups in *Christie et al 2017*. No adverse effects were reported in *Valente et al 2014.*

Patient satisfaction. Level of satisfaction was not reported in these studies.

DISCUSSION

LUMPECTOMY/MASTECTOMY.

Pain intensity. Pain intensity on a numeric rating scale (NRS) was lower in intervention group than in placebo group at 1, 6, 12, 24 and 48 hours after surgery. The difference of NRS at 1 hour between the groups was statistically significant (p = 0.02); no statically difference was reported at other intervals.
In the first hour after surgery, all patients in intervention group reported NRS lower than 4; instead in the placebo group, two studies (*Ferreira Laso et al., 2014; Wang et al., 2018*) experienced, respectively, a mean pain intensity of 6.7 and 4.3. In the placebo group we also found NRS higher than 4 in *Wang et al 2019* after 6 hours and in *Ferreira Laso et al 2014* after 24 hours.
We considered NRS lower than 4 as optimal cut-off point between mild and moderate pain. This cut-off was identified as the tolerable pain threshold.[29]

Opioid consumption. Postoperative use of opioids was lower in the interventional group both upon discharge from the PACU and after 48 hours, although there was no statistically significant difference. The difference in opioid use was statistically significant in three studies (*Ferreira Laso et al., 2014; Ilfeld et al., 2014; Versyck et al. 2017*) at the time of discharge from the PACU. Eight studies (*Campbell et al., 2014; Ferreira Laso et al., 2014;*

Gürkan et al., 2018; Mohamed et al., 2013; Neethu et al., 2018; Versyck et al. 2017; Wang et al., 2018; Yao et al., 2019) reached statistical significance after 48 hours from surgery.

Safety. No statistically significant difference was noticed ($p = 0.74$) between interventional and placebo groups. Among interventional group a total of 163 AEs was reported. Nausea, vomiting or PONV were the most common (59%), followed by bruising (14%), hematoma/bleeding (6%), seroma (6%), pruritus (4%) and hemodynamic alterations (4%), such as hypotension, hypertension or bradycardia.

Patient satisfaction. Patient satisfaction was high, minimum 92% of satisfaction among patients treated with locoregional anesthesia. The satisfaction rate was also high in the placebo group (79%).

BREAST AUGMENTATION.

Pain intensity on a numeric rating scale (NRS) was lower in intervention group than in placebo group at 1, 6, 24 and 72 hours after surgery. No statically difference was reported at these intervals.

Postoperative use of opioids was lower in the interventional group after 24 hours, although there was no statistically significant difference.

Concerning safety, no difference was noticed between interventional and placebo groups.

BREAST REDUCTION.

Pain intensity on a numeric rating scale (NRS) was lower in intervention group than in placebo group after 24 hours. No statically difference was reported.

Postoperative use of opioids was lower in the interventional group after 24 hours, although there was no statistically significant difference.

No difference was noticed between interventional and placebo groups about AEs incidence.

General anesthesia is the conventional, most frequently used anesthetic technique. Various locoregional anesthetic techniques are also used for breast surgeries. These include local wound infiltration,[30] tumescent anesthesia,[31] regional anesthetic techniques, such as pectoralis nerve (Pecs) blocks type 1 and 2,[32,33] serratus plane block (SPB),[34] and parasternal block (PSB),[35] pain pump,[36,37] and intravenous regional block.[38,39]

Locoregional anaesthesia provides effective anesthesia and analgesia in the perioperative setting. The beneficial analgesic effect of regional block is well known, and also confirmed in our analysis. After mastectomy, the use of locoregional anesthesia techniques seems to reduce pain especially in the first hour after the end of the surgery.

Other potentially beneficial effects of locoregional anaesthesia and analgesia on other perioperative outcomes emerged from our review include decreased need for opioids for controlling post-operative pain, decreased post-operative nausea and vomiting, fewer complications and increased patient satisfaction. The effective management and relief of postoperative pain plays a vital role in overall surgical outcome. Untreated pain has been linked to prolonged hospital stays, deep venous thrombosis, pulmonary embolus, pneumonia, bowel dysmotility, insomnia, and impaired wound healing.[40] Reduced occurrence of nausea and vomiting is related to better analgesia and opioids/inhalational anaesthetics sparing effect by regional blocks.[41,42] All this improves post-operative recovery and shortens hospitalization stay.

CONCLUSION

In summary, the results of this study support the technique of locoregional anesthesia for breast surgery. The most important findings of this analysis are the significant association with reduced pain scores, lower postoperative opioids consuption, lower incidence of PONV and other AEs, and good patient satisfaction.

LIST OF ABBREVIATIONS

- AEs, Adverse Events;
- ALND, Axillary Lymph Node Dissection;
- BMI, Body Mass Index;
- DVT, Deep Vein Thrombosis;
- ESP, Erector Spinae Plane;
- IV, Intravenous;
- NRS, Numeric Rating Scale;
- PACU, Post-Anesthesia Care Unit;
- Pecs, Pectoralis nerve;
- PONV, Postoperative Nausea and Vomiting;
- PTE, Pulmonary Thromboembolism;
- PVB, Paravertebral Block;
- SLNB, Sentinel Lymph Node Biopsy;
- SPB, Serratus Plane Block.

DECLARATIONS

Ethics approval and consent to participate. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication. Not applicable.

Availability of data and materials. Dataset derived from public resources and are available on request.

Competing interests. The authors declare that they have no competing interests.

Funding. No funding or sponsorship was received for this study or publication of this article.

Authors Contributions. PS helped design the study, conduct the study, analyze the data, and write the manuscript; LGG helped design the study, conduct the study, analyze the data, and write the manuscript; MF helped design the study and analyze the data; PDC helped design the study and analyze the data; SI helped design the study and analyze the data; CA helped design the study and analyze the data; FC helped design the study and analyze the data; MBP helped design the study and analyze the data; VP helped design the study and analyze the data; MCP helped design the study, conduct the study and analyze the data.

Acknowledgements. Not applicable.

Disclosures. Luca G. Giaccari, Francesco Coppolino, Caterina Aurilio, Pasquale Di Costanzo, Mario Faenza, Sara Izzo, Maria Caterina Pace, Maria Beatrice Passavanti, Vincenzo Pota and Pasquale Sansone have nothing to disclose.

REFERENCES

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. *CA A Cancer J Clin.* 2000;70:7-30.
2. American Society of Plastic Surgeons. Plastic Surgery Statistics Report. https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf. Accessed Avril 13, 2020.
3. Broyles JM, Tuffaha SH, Williams EH, Glickman L, George TA, Lee Dellon A. Pain after breast surgery: etiology, diagnosis, and definitive management. *Microsurgery.* 2016;36(7):535-8.
4. Pace MC, Mazzariello L, Passavanti MB, Sansone P, Barbarisi M, Aurilio C. Neurobiology of Pain. *J Cell Physiol.* 2006; 209(1):8-12.
5. Chou R, Gordon DB, de Leon-Casasola OA et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The Journal of Pain. 2016;*17(2):131-57.
6. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. *JAMA Surg.* 2017;152(7):691–7.
7. Dunn LK, Durieux ME; Perioperative Use of Intravenous Lidocaine. *Anesthesiology* 2017;126(4):729-37.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *BMJ* 2009;339:b2535.
9. Equivalent Opioid Calculator (EOC). Available at http://clincalc.com/Opioids/. Accessed Avril 6, 2020.
10. Campbell I, Cavanagh S, Creighton J, et al. Local anaesthetic in breast surgery. A*NZ J Surg.* 2015;85:353-7.
11. Couceiro TC, Lima LC, Burle LM, Valença MM. Intravenous lidocaine for postmastectomy pain treatment: randomized, blind, placebo controlled clinical trial. *Braz J Anesthesiol.* 2015;65(3):207-12.
12. Cros J, Sengès P, Kaprelian S, et al. Pectoral I Block Does Not Improve Postoperative Analgesia After Breast Cancer Surgery: A Randomized, Double-Blind, Dual-Centered Controlled Trial. *Reg Anesth Pain Med.* 2018;43:596-604.
13. Ferreira Laso L, Lopez-Picado A, Lamata L, et al. Postoperative Analgesia by Infusion of Local Anesthetic into the Surgical Wound after Modified Radical Mastectomy. *Plast Reconstr Surg.* 2014;134(6):p862e-870e.
14. Gürkan Y, Aksu C, Kuş A,Yörükoğlu UH, Kılıç CT. Ultrasound guided erector spinae plane block reduces postoperative opioid consumption following breast surgery: A randomized controlled study. *J Clin Anesth.* 2018;50:65-8.

15. Ilfeld BM, Madison SJ, Suresh PJ, et al. Treatment of postmastectomy pain with ambulatory continuous paravertebral nerve blocks: a randomized, triple-masked, placebo-controlled study. *Reg Anesth Pain Med*. 2014;39(2):89–96.

16. Lanier ST, Lewis KC, Kendall MC, et al. Intraoperative Nerve Blocks Fail to Improve Quality of Recovery after Tissue Expander Breast Reconstruction: A Prospective, Double-Blinded, Randomized, Placebo-Controlled Clinical Trial. *Plast Reconstr Surg*. 2018;141(3):590-7.

17. Mohamed SA, Abdel-Ghaffar HS. Effect of the addition of clonidine to locally administered bupivacaine on acute and chronic postmastectomy pain. *J Clin Anesth.* 2013;25(1):20-7.

18. Neethu M, Pandey RK, Sharma A, et al. Pectoral nerve blocks to improve analgesia after breast cancer surgery: A prospective, randomized and controlled trial. *J Clin Anesth.* 2018;45:12-7

19. Terkawi AS, Durieux ME, Gottschalk A, et al. Effect of Intravenous Lidocaine on Postoperative Recovery of Patients Undergoing Mastectomy: A Double-Blind, Placebo-Controlled Randomized Trial. *Reg Anesth Pain Med.* 2014;39:472-7.

20. Versyck B, van Geffen CJ, Van Houwe P. Prospective double blind randomized placebo-controlled clinical trial of the pectoral nerves (Pecs) block type II. *J Clin Anesth.*2017;40:46-50.

21. Wang K, Zhang X, Zhang T, et al.The Efficacy of Ultrasound-guided Type II Pectoral Nerve Blocks in Perioperative Pain Management for Immediate Reconstruction After Modified Radical Mastectomy: A Prospective, Randomized Study. *Clin J Pain.* 2018;34(3):231-6.

22. Wang W, Song W, Yang C,et al. Ultrasound-Guided Pectoral Nerve Block I and Serratus-Intercostal Plane Block Alleviate Postoperative Pain in Patients Undergoing Modified Radical Mastectomy. *Pain Physician.* 2019;22(4):E315-E323.

23. Yao Y, Li J, Hu H, Xu T, Chen Y. Ultrasound-guided serratus plane block enhances pain relief and quality of recovery after breast cancer surgery. *Eur J Anaesthesiol.* 2019;36(6):436-41.

24. Gardiner S, Rudkin G, Cooter R, Field J, Bond M. Paravertebral Blockade for Day-Case Breast Augmentation. *Anesth Analg.* 2012;115(5):1053-9.

25. Picard F, Niddam J, De Runz A, Chaouat M, Mimoun M, Boccara D. Intraoperative instillation of ropivacaine during the placement of sub-muscular cosmetic breast implants: Is there a clinical benefit? *Ann Chir Plast Esth.* 2018;63(1):20-4.

26. Schuitemaker RJB, Sala-Blanch AP. Sánchez Cohen LA, López-Pantaleon JT, Mayoral R, Cubero M. Analgesic efficacy of modified pectoral block plus serratus plane block in breast augmentation surgery: A randomised, controlled, triple-blind clinical trial. *Rev Esp Anestesiol Reanim.* 2019;66(2):62-71.

27. Christie BM, Kapur S, Kempton SJ, Hanson SE, Ma Y, Rao VK. A Prospective Randomized Trial Comparing the Effects of Lidocaine in Breast Reduction Surgery. *Plast Reconstr Surg.* 2017;139(5):1074e-1079e.

28. Valente DS. Preemptive Analgesia with Bupivacaine in Reduction Mammaplasty, *Plast Reconstr Surg.* 2014;134(4):581-6.

29. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W. Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods. *Br J Anaesth.* 2011;107(4):619-26.

30. Mustoe TA, Buck DW, Lalonde DH. The safe management of anesthesia, sedation and pain in plastic surgery. *Plast Reconstr Surg Journal.* 2010, 126(4):165e-176e.

31. Khater A, Mazy A, Gad M, Taha Abd Eldayem O, Hegazy M. Tumescent mastectomy: the current indications and operative tips and tricks. *Breast cancer - targets and therapy.* 2017;9:237-43.

32. Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. *Anaesthesia.* 2011;66:840-52.

33. Blanco R, Fajardo M, Parras Maldonado T. Ultrasound description of Pecs II (modified Pecs I): A novel approach to breast surgery. *Rev Esp Anestesiol Reanim*. 2012;59:470-5.

34. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. *Anaesthesia.* 2013;68(11):1107-13.

35. Fusco P, Scimia P, Petrucci E, DI Carlo S, Marinangeli F. The ultrasound-guided parasternal block: a novel approach for anesthesia and analgesia in breast cancer surgery. *Minerva Anestesiol.* 2017;83(2):221-2.

36. Chandran GJ, Lalonde DH. A review of pain pumps in plastic surgery. *Can J Plast Surg.* 2010;18(1):15-8.

37. Monahan AM, Ilfeld BM. Continuous peripheral nerve blocks. In: Hadzic A. *Hadzic's textbook of regional anesthesia and acute pain management*. 2th ed. United States: McGraw Hill Companies; 2017:1180-6.

38. Dunn LK, Durieux ME. Perioperative Use of Intravenous Lidocaine. *Anesthesiology.* 2017;126(4):729-37.

39. Chang YC, Liu CL, Liu TP, Yang PS, Chen MJ, Cheng SP. Effect of perioperative intravenous lidocaine infusion on acute and chronic pain after breast surgery: a meta-analysis of randomized controlled trials. *Pain practice.* 2017;17(3):336-43.

40. Carr DB, Goudas L. Acute pain. *Lancet.* 1999;353:2051

41. Calì Cassi L, Biffoli F, Francesconi D, Petrella G, Buonomo O. Anesthesia and analgesia in breast surgery: The benefits of peripheral nerve block. *Eur Rev Med Pharmacol Sci.* 2017;21:1341-5.

42. Becker DE. Nausea, vomiting, and hiccups: A review of mechanisms and treatment. *Anesth Prog.* 2010;57:150-6.

Table 1. *PICO criteria for including studies.*

POPULATION	Patients of at least 18 years undergoing breast surgery.
INTERVETION	Postoperative analgesia with locoregional anesthesia techniques.
COMPARATOR	Standard pain treatment.
OUTCOMES	Pain Intensity, Opioid Consumption, Adverse Events, Patient Satisfaction.
STUDY TYPE	Randomized Controlled Trial.
TIME	From 2010 to present.

Table 2A, 2B, 2C. *Studies characteristics.*

LUMPECTOMY/MASTECTOMY						
Author, year	**Study**	**Sites**	**No.**	**Type of surgery**	**Anesthesia**	**Intervention**
Campbell et al.,[10] 2014	SB-RCT	New Zeland, 1	79	Lumpectomy/ Mastectomy ± ALND	?	Local Infiltration
Couceiro et al.,[11] 2014	DB-RCT	Brazil, 1	44	Mastectomy	GA	IV lidocaine
Cros et al.,[12] 2018	DB-RCT	France, 1 Canada, 1	127	Lumpectomy/ Mastectomy ± SLNB/ALND	GA	Pecs I
Ferreira Laso et al.,[13] 2014	DB-RCT	Spain, 1	73	Mastectomy	GA	Infusion pump
Gürkan et al.,[14] 2018	SB-RCT	Turkey, ?	50	Lumpectomy/ Mastectomy ± SLNB/ALND	GA	ESP
Ilfeld et al.,[15] 2014	DB-RCT	US, ?	60	Mastectomy ± ALND	Sedation	PVB
Lanier et al.,[16] 2018	DB-RCT	US, ?	45	Mastectomy + reconstruction ± SLNB/ALND	?	Intercostal + pectoral nerve blocks
Mohamed et al.,[17] 2013	DB-RCT	Egypt, ?	140	Mastectomy ± ALND	GA	Local infiltration
Neethu et al.,[18] 2018	RCT	India, 1	60	Mastectomy ± SLNB/ALND	GA	Pecs I - II
Terkawi et al.,[19] 2014	DB-RCT	US, ?	71	Mastectomy	GA	IV lidocaine
Versyck et al.,[20] 2017	DB-RCT	Belgium, 1	140	Mastectomy/ tumorectomy ±SLNB/ALND	GA	Pecs II
Wang et al.,[21] 2018	SB-RCT	China, ?	64	Mastectomy + reconstruction ± ALND	GA	Pecs II
Wang et al.,[22] 2019	RCT	China, ?	61	Mastectomy	GA	Pecs I + SPB
Yao et al.,[23] 2019	DB-RCT	China, 1	72	Mastectomy ± ALND	GA	SPB

SB-RCT, Single-Blind Randomized Controlled Trial; **DB-RCT**, Double-Blind Randomized Controlled Trial; **SLNB**, Sentinel Lymph Node Biopsy; **ALND**, Axillary Lymph Node Dissection; **GA**, General Anesthesia; **Pecs,** Pectoralis nerve block; **ESP**, Erector Spinae Plane block; **PVB**, ParaVertebral Block; **SPB**, Serratus Plane Block.

BREAST AUGMENTATION						
Author, year	**Study**	**Sites**	**No.**	**Type of surgery**	**Anesthesia**	**Intervention**
Gardiner et al.,[24] 2012	SB-RCT	Australia, ?	40	BA	Sedation	PVB
Picard et al.,[25] 2017	SB-RCT	France, ?	72	BA	?	Local infiltration
Schuitemaker et al.,[26] 2019	DB-RCT	Spain, ?	30	BA	GA	Pecs II + SPB
SB-RCT, Single-Blind Randomized Controlled Trial; **DB-RCT**, Double-Blind Randomized Controlled Trial; **BA**, Breast Augmentation; **GA**, General Anesthesia; **Pecs,** Pectoralis nerve block; **PVB**, ParaVertebral Block; **SPB**, Serratus Plane Block.						

BREAST REDUCTION						
Author, year	**Study**	**Sites**	**No.**	**Type of surgery**	**Anesthesia**	**Intervention**
Christie et al., [27] 2017	DB-RCT	US, 1	40	BR	GA	Tumescent Anaesthesia
Valente et al.,[28] 2014	DB-RCT	Brazil, ?	39	BR	GA	Local infiltration
B-RCT, Double-Blind Randomized Controlled Trial; **BR**, Breast Reduction; **GA**, General Anesthesia.						

Table 3. *Personal and clinical characteristics.*

	Patients (n=)		***Age (years)***		***Weight (kg)***		***Height (cm)***		***BMI (kg/m^2)***	
	Group I	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***
Campbell et al., 2014	45	34	59.4	61.7	80.7	73.8	163.3	162.3	30.2	28.1
Couceiro et al., 2014	22	22	47.0	52.4	--	--	--	--	28.1	28.2
Cros et al., 2018	62	66	60.5	62.0	63.6	65.0	160.0	160.0	24.8	25.6
Ferreira Laso et al., 2014	34	39	54.8	57.7	67.2	66.7	--	--	--	–
Gürkan et al., 2018	25	25	49.5	49.8	72.4	73.1	161.0	161.0	27.8	28.2
Ilfeld et al., 2014	30	30	48.0	49.0	62.0	61.0	165.0	166.0	23.0	24.0
Lanier et al., 2018	23	22	48.0	50.0	67.0	70.0	160.0	170.0	26.0	26.0
Mohamed et al., 2013	105	35	39.9	38.9	70.2	69.8	160.6	158.5	27.4	27.9
Neethu et al., 2018	30	30	50.5	45.6	--	--	--	--	--	--
Terkawi et al., 2014	34	37	53.0	54.0	--	--	--	--	26.2	28.2
Versyck et al., 2017	45	40	59.6	58.8	67.3	67.0	165.0	165.0	24.7	24.6
Wang et al., 2018	30	30	46.8	47.4	--	--	--	--	25.4	24.8
Wang et al., 2019	32	29	51.3	55.3	58.7	57.6	162.5	161.0	22.3	22.2
Yao et al., 2019	34	34	46.5	47.7	57.2	56.2	160.9	160.8	22.3	21.9
TOTAL	**585**	**473**	**51.05 ± 5.6**	**52.16 ± 6.3**	**66.65 ± 6.5**	**66.03 ± 5.8**	**162.04 ± 1.8**	**162.74 ± 3.3**	**25.71 ± 2.3**	**25.83 ± 2.2**

Table 4. *NRS at 1, 6, 12, 24 and 48 hours after surgery.*

	Up to 1h		***Up to 6h***		***Up to 12h***		***Up to 24h***		***Up to 48h***	
	Group I	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***
Campbell et al., 2014	–	–	1.75	2	–	–	2.3	1.7	1.8	1.25
Couceiro et al., 2014	–	–	–	–	–	–	–	–	–	–
Cros et al., 2018	3	3	–	–	–	–	–	–	–	–
Ferreira Laso et al., 2014	1.6	6.7	–	–	–	–	0.8	4.2	0.4	3.3
Gürkan et al., 2018	2	2	2	2	0	1	0	1	–	–
Ilfeld et al., 2014	–	–	–	–	–	–	3.6	3.7	–	–
Lanier et al., 2018	3	5	4	5	5	4	4	4	–	–
Mohamed et al., 2013	2.67	3.7	2.43	3.6	2.53	3.8	2.43	3.7	2.43	3.8
Neethu et al., 2018	1.78	3.08	0.43	0.76	1.20	1.40	0.5	0.53	–	–
Terkawi et al., 2014	–	–	2.94	3.88	–	–	2.91	2.66	2.72	3.9
Versyck et al., 2017	0.38	0.20	–	–	–	–	–	–	–	–
Wang et al., 2018	1.65	4.3	2.45	3.9	1.8	1.9	1	1	–	–
Wang et al., 2019	1	3	0.8	4.4	1	2	0.5	1.8	0.2	1.6
Yao et al., 2019	1.3	2.7	1.4	2.4	–	–	1.2	1.8	–	–
TOTAL	**1.83 ± 0.81**	**3.36 ± 1.65**	**2.02 ± 1.03**	**3.10 ± 1.29**	**1.92 ± 1.57**	**2.35 ± 1.14**	**1.74 ± 1.29**	**2.37 ± 1.27**	**1.51 ± 1.03**	**2.77 ± 1.12**
p	**0.02***		**0.08**		**0.63**		**0.29**		**0.13**	

Table 5. *Average per patient opioid consumption in PACU and up to 48 h after surgery.*

	PACU			***Up to 48h***		
	Group I	***Group C***	***p***	***Group I***	***Group C***	***p***
Campbell et al., 2014	–	–		3.42	7.33*	
Couceiro et al., 2014	–	–		–	–	
Cros et al., 2018	1.5	3		1.5	3	
Ferreira Laso et al., 2014	0	0.7*		0	0.7*	
Gürkan et al., 2018	1	1		5	16*	
Ilfeld et al., 2014	1	2.4*		2.5	5.7	
Lanier et al., 2018	8	17		4	5.18	
Mohamed et al., 2013	–	–		0.58	1*	
Neethu et al., 2018	–	–		1.46	2.03*	
Terkawi et al., 2014	9.35	9.69		11.02	11.61	
Versyck et al., 2017	0.18	0.33*		0.20	0.37*	
Wang et al., 2018	–	–		1.75	5.42*	
Wang et al., 2019	–	–		–	–	
Yao et al., 2019	–	–		0.73	1.03*	

TOTAL	**3.0 ± 3.63**	**4.87 ± 5.76**	**0.51**	**2.68 ± 0.88**	**4.94 ± 4.61**	**0.18**
* Difference statistically significant.						

Table 6. *Number of adverse events (AEs).*

AEs	Group I (n =)	Group C (n =)	*p*
Nausea/Vomiting/PONV	96	139	*0.25*
Pruritus	7	16	*0.47*
Hypotension	5	2	*0.25*
Hypertension	0	1	*0.32*
Dizzness	2	15	*0.06*
Bradycardia	2	0	*0.32*
Hematoma/Bleeding	10	11	*0.85*
Seroma	10	11	*0.91*
Alteration of healing	2	3	*0.78*
Infection	3	2	*0.69*
DVT	1	1	*1.00*
PTE	1	1	*1.00*
Acute respiratory infection	1	1	*1.00*
Bruising	23	13	*0.70*
TOTAL	**163**	**216**	***0.74***

Table 7. *Patient satisfaction.*

	Group I		Group C	
	Satisfied	Not satisfied	Satisfied	Not satisfied
Campbell et al., 2014	–	–	–	–
Couceiro et al., 2014	–	–	–	–
Cros et al., 2018	*61*	*1*	*64*	*1*
Ferreira Laso et al., 2014	*32*	*2*	*37*	*2*
Gürkan et al., 2018	–	–	–	–
Ilfeld et al., 2014	–	–	–	–
Lanier et al., 2018	*23*	0	23	0
Mohamed et al., 2013	–	–	–	–
Neethu et al., 2018	*25*	*5*	*10*	*20*
Terkawi et al., 2014	–	–	–	–
Versyck et al., 2017*	–	–	–	–
Wang et al., 2018	–	–	–	–

Wang et al., 2019	*23*	*6*	*15*	*17*
Yao et al., 2019**	–	–	–	–
TOTAL	***164***	***14***	***149***	***40***
* Both patient-groups were very satisfied about their management (9.6 ± 0.6 and 9.1 ± 1.8 on a 10-point scale, $p = 0.21$). **Patient satisfaction scores were higher in the SPB group.				

Table 8. *Personal and clinical characteristics.*

	Patients (n=)		***Age (years)***		***Weight (kg)***		***Height (cm)***		***BMI (kg/m²)***	
	Group I	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***
Gardiner et al., 2012	20	20	33.4	34.9	–	–	–	–	20.5	20.1
Picard et al., 2017	29	43	32.4	34.6	–	–	–	–	–	–
Schuitemaker et al., 2019	15	15	33.0	33.0	52.0	54.0	163.0	163.0	20.0	20.0
TOTAL	**64**	**78**	**32.93 ± 0.41**	**34.16 ± 0.83**	**52.0**	**54.0**	**163.0**	**163.0**	**20.25 ± 0.25**	**20.05 ± 20.04**

Table 9. *NRS at 1, 6, 24 and 72 hours after surgery.*

	Up to 1h		***Up to 6h***		***Up to 24h***		***Up to 72h***	
	Group I	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***
Gardiner et al., 2012	3.9	5.2	–	–	–	–	3.3	4.7
Picard et al., 2017	–	–	–	–	4.8	5.1	2.8	3.7
Schuitemaker et al., 2019	2.9	5.3	3.0	3.0	2.5	3.0	–	–
TOTAL	**3.4 ± 0.5**	**5.25±0.05**	**3.0**	**3.0**	**3.65± 1.15**	**4.05±1.05**	**3.05±0.25**	**4.2 ± 0.5**
p	**0.06**		**–**		**0.82**		**0.17**	

Table 10. *Personal and clinical characteristics.*

	Patients, n		***Age, years***		***Weight, kg***		***Height, cm***		***BMI, kg/m²***	
	Group I	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***	***Group I***	***Group C***
Christie et al., 2017	20	20	41.0	42.0	–	–	–	–	33.0	31.0
Valente et al., 2014	18	20	35.57	35.57	–	–	–	–	–	–
TOTAL	**38**	**40**	**38.28 ± 2.71**	**38.78 ± 3.21**	**–**	**–**	**–**	**–**	**33.0**	**31.0**

Table 11. *NRS at 24 hours after surgery.*

	Up to 24h

	Group I	***Group C***
Christie et al., 2017	4.28	4.00
Valente et al., 2014	0.83	1.71
TOTAL	**2.55 ±1.72**	**2.85 ± 1.14**
p	**0.89**	

Figure 1. *Flow diagram study selection process.*

Figure 2. *NRS at 1, 6, 12, 24 and 48 hours after surgery.*

Figure 3. *Distribution of adverse events (AEs) among intervention group.*

Figure 4. *Patient satisfaction.*

Figure 5. *NRS at 1, 6, 24 and 72 hours after surgery.*