REVIEW

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Novel Prevention Approaches of Breast Cancer Surgery Related Complications: Systematic Review and Network Meta-Analysis

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Abstract

Background: Breast cancer surgery related complications are a complex condition influenced by interactions among nerve pathways and the physiological responses to breast surgery. The intensity of this complications displays substantial heterogeneity, dependent on individual patient characteristics, the extent of the surgical procedure performed, and various contributing factors. **Methods:** A comprehensive search of electronic databases was conducted to identify relevant randomized controlled trials (RCTs) investigating interventions for post-mastectomy pain syndrome (PMPS). A network meta-analysis was performed to integrate direct and indirect evidence, enabling comparisons of multiple interventions across different outcome measures. **Results:** The systematic search yielded a total of 26 RCTs investigating 4 groups of different interventions for PMPS. The interventions included pharmacological agents, nerve blocks, physical therapy, and anesthesia regimens. Nerve blocks (OR: 0.34; 95% CrI: 0.24–0.46) and anesthesia (OR: 0.39; 95% CrI: 0.26–0.56) demonstrated improvements in functional outcomes and quality of life. **Conclusion:** This systematic review and network meta-analysis provide a comprehensive evaluation of interventions for PMPS, highlighting their varying efficacy in alleviating pain and improving functional outcomes and quality of life. However, further research with large-scale, well-designed RCTs is warranted to strengthen the evidence base and validate the effectiveness of these interventions in managing PMPS effectively.

Keywords: Oncology- breast cancer surgery- complications- post-mastectomy pain syndrome

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Introduction

Breast cancer (BC) is the primary cause of mortality in women and ranks as the fifth leading cause of cancer-related deaths worldwide. It accounted for 2.3 million new cases in 2020, representing 11.7% of all cancer cases, and caused 684,996 deaths [1]. Notably, Asia had the highest incidence with 1,026,684 cases (45.4%) and the highest number of deaths with 345,559 (50.4%) [1, 2]. In Kazakhstan alone, an estimated 4,896 new cases of invasive breast cancer will be diagnosed in 2030 [3]. Moreover, the number of breast cancer-related deaths is set to double by 2040 in many countries, suggesting a concerning escalation in the future burden of BC [4, 5].

Based on data from the CONCORD-2 study, BC patients diagnosed between 2005 and 2009 had 5-year survival rates of at least 85% [6]. However, a significant concern in survivorship is persistent pain after breast cancer treatment, with 10-20% of survivors reporting moderate to severe pain that can last for several years after surgery [7]. The growing number of survivors highlights the need to improve the quality of life for breast cancer patients whose lives are extended by treatment. Unfortunately, intractable post-mastectomy pain negatively affects the quality of life for many patients [8, 9].

The persistent pain is commonly known as post-mastectomy pain syndrome (PMPS), which is described by the International Association for the Study of Pain (IASP) as enduring pain in the anterior thorax, axilla, and/or upper arm for more than three months after completing treatment. PMPS may result from nociceptor or nerve fiber of peripheral nerves damage during mastectomy or adjuvant therapy, indicating that it mainly exhibits neuropathic pain characteristics [10]. The exact incidence of PMPS varies in the literature, with estimates ranging from 20% to 60% of mastectomy patients experiencing chronic pain after surgery [11-13]. The classic PMPS itself has a lower incidence (23.9%) in comparison with

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lymphedema and musculoskeletal pain (47% and 42%) in patients undergoing breast surgery [9, 12, 14].

Certain risk factors have been identified to increase the likelihood of developing PMPS. These include younger age, pre-existing painful conditions, more extensive surgeries involving lymph node removal, radiation therapy, and psychological vulnerability, anxiety and depression [15]. One of the most reliable factors associated with the development of persistent postoperative pain is the presence of pre-existing pain, as indicated by a recent meta-analysis [16]. The study revealed that among women who had pre-operative pain, the odds of experiencing PMPS increased to 1.29 (95% CI = 1.01-1.64) [16]. Some authors suggest that pain sensitivity and/or central sensitization might predispose surgical patients to chronic pain after surgery [17-19].

The primary aim of this review is to identify the most effective treatment modality for chronic pain after breast cancer-related surgery.

Materials and Methods

This systematic review was designed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

Information sources and selection of studies

The researchers captured all pertinent trials specific to treatments for PMPS. The search was conducted through MEDLINE (PubMed), Embase (Elsevier), Cochrane Central Register of Controlled Trials (Wiley), Clinicaltrials.gov, and Web of Science (Clarivate) databases from 1 January 2010 to 1 July 2023. All results were exported to EndNote for further deduplication and evaluation. Search strings contained MESH terms and key words such as: "breast neoplasm/surgery; mastectomy; lumpectomy; segmentectomy; postoperative pain/adverse reactions; perioperative treatment; neuralgia; chronic pain; neuropathic pain; neurofibrositis; neurosensory pain; pain syndrome; persistent pain; nerve damage; post-operative pain; post-surgery pain; post-mastectomy pain syndrome". After that, all unique articles meeting criteria of inclusion were exported to online platform to independent screening by review team (investigators from author list). Additional articles identified by searching the references of eligible articles. No restrictions of language or geographical location were placed. Search strategies included searching for articles in other languages. When such an article was included, it was translated by a qualified translator.

Selection of studies

Included in the synthesis were full-text articles with outcomes of our interest, such as presence of chronic (> 1 months) pain after mastectomy. Definitions, such as "breast surgery", "persistent pain" were outlying for selection. RCTs with sample sizes greater than 10 patients in every arm were included. To avoid selection bias, inclusion criteria were agreed before data extraction and NMA. Full-text screening was performed by two investigators with uncertainties resolved by senior author.

Inclusion criteria

- Full-text, original articles in peer-reviewed journals;
- Reporting outcomes of impact of intervention on PMPS after breast cancer surgery;
- Randomized Controlled Trials with sample size > 10 patients.

Exclusion criteria

- Case reports, letters, commentaries, expert opinions, books, narrative and systematic reviews, abstracts;
- Uncompleted trials;
- Animal studies, cell studies;
- Follow-up period <3 months.

Data extraction and assessment

Data from studies that met the eligibility criteria was validated to extraction and exported to Excel spreadsheet. Data fields of interest included: (1) first author, publication year and country of study; (2) study design and prevention approach; (3) sample size; (4) follow-up period; (5) outcomes; (6) instrument for outcome measurement. This information was obtained for both experimental and control groups. The primary outcomes were considered to patient's self-reported pain condition, comparing the PMPS incidence in the main and control groups. The quality of RCTs was assessed by using the Jadad scale [21]. Studies were evaluated according to study design, including availability of randomization and blinding methods, as well as description of any withdrawals in the follow-up period. We graded studies as having a high (0-2 points) or low risk of bias (3-5 points).

The feasibility assessment via NMA evaluated whether RCTs were comparable in terms of outcomes and timepoints at which outcomes were assessed. Connected networks that included control and comparators are presented in Figure 1. Comparisons between interventions were compared indirectly via Bayesian NMA.

Bayesian Analysis and NMA Approach

In every analysis, the comparisons between the control group and each treatment of interest were determined using long-established Bayesian Network Meta-Analysis (NMA) techniques. Bayesian NMA used to explore the potential impact of prevention modalities across trial populations, within variety subgroups of treatment methods. Heterogeneity across studies was proceeded using Cochrane Q-statistic ($p \leq 0.05$ was set as statistically significant) and heterogeneity of studies was confirmed with I^2=96%. The following ranking was used: I^2=0%-25% - no heterogeneity; I^2=25%-50% - moderate heterogeneity; I^2=50%-75%, - large heterogeneity; I^2=75%-100% - extreme heterogeneity.

We used random-effects (RE) models to determine the overall intervention effect, taking into account heterogeneity among trials. For continuous outcomes (pain severity), the overall pooled estimates were reported as weighted standardized mean difference (SMD) with 95% confidence intervals (CI), to take into account the differences in sample sizes across studies. Among the studies that met our selection criteria, pain was evaluated using either the visual analogue scale (VAS) with a range

of 0 to 100 or the numeric rating scale (NRS) with a range of 0 to 10. All pain scores were converted to the NRS format, which ranges from 0 to 10.

All analyses were performed using the RevMan Web (v 1.22.0, The Cochrane Collaboration, 2020) and MetaInsight software (v 1.1, National Institute for Health Research) [22]. NMA was conducted with usage of with 50,000 iterations and a burn-in period of size 10,000. Forest plots with odds ratios and their 95% CI were used to visualize all results. Each NMA yielded an assessment of the relative treatment effect, represented as an odds ratio (OR) for incidence of PMPS. Along with these estimates, a 95% credible interval (CrI) was provided. In the results section, the term 'statistically' was used to indicate cases where the 95% CrIs for OR did not encompass the 1.

Ethics approval and consent to participate

Not required as data is not individualized, and primary data need to be collected.

Consent for publication

The corresponding author accepts responsibility for releasing this material on behalf of all co-authors.

Results

Systematic Literature Review

Study Selection

The comprehensive search identified 4,128 records for the title and abstract screening after duplicate removal. Of these, 509 articles were screened for full-text eligibility and 26 publications meeting inclusion criteria were involved in qualitive synthesis and Bayesian NMA. Of the 86 RCTs identified by researchers, 60 trials were excluded for the following reasons: 49 trials investigated short follow-up after intervention with time-points at 24h and 4 weeks, 33 trials did not contain any outcomes of interest, 4 trials included multi-arm stratification with varying doses of medications. Subsequently, a total of 26 RCTs were included in the NMA, as presented in the flow diagram, in Figure 2.

Risk of Bias Assessment

Among the included studies, the most frequently found bias was performance bias; only 7 studies (out of 26) were unblinded (Figure 3).

Treatment and patient characteristics

A summary of the trials characteristics and treatment approaches is provided in Table 1. The 26 studies included in the NMA assessed monotherapy options. The evaluated treatments and their frequencies across the RCTs were as follows: nerve blocking (nine studies), anesthesia (five studies), oral medications (five studies), physical methods (seven studies).

A total of 2669 patients were included in the 26 RCTs. Sample sizes ranged from 18 to 190. All patients have been diagnosed with metastatic BC or locally advanced BC and received prior treatment, such as radical or partial mastectomy. Trial samples were generally similar, including sex, age and type of prior treatment. Range of average age estimated from 50 to 60 years.

Prevention Modalities

Nerve Blocks

Ten studies were RCTs on the efficacy of perioperative nerve blocks in the prevention of PMPS met inclusion criteria (Table 1). The total study population involved

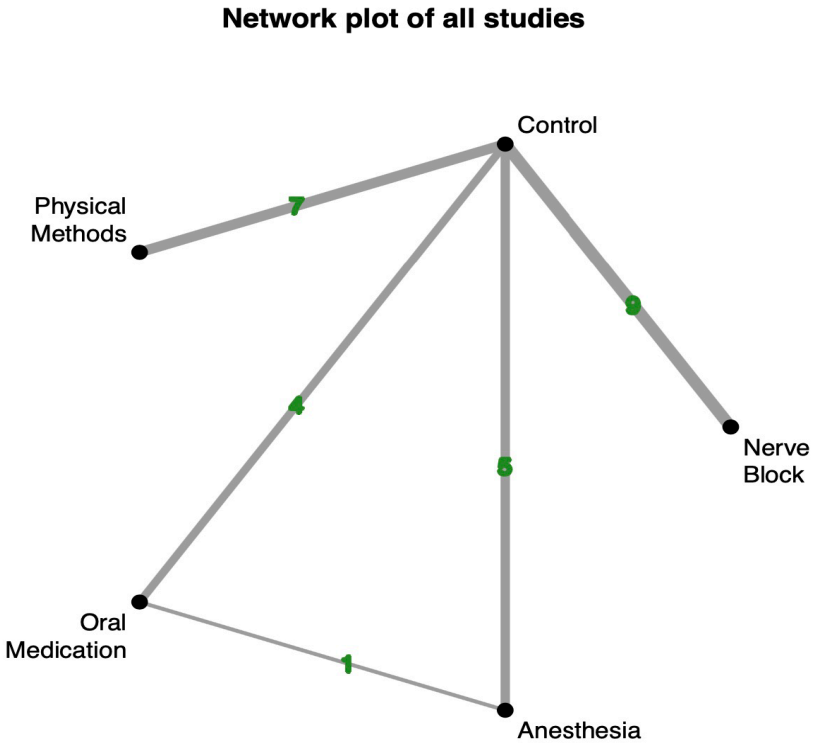

Figure 1. Netawork Plot of All Studies with a Number of each Comparison Pairs.

Table 1. Characteristics of Included Studies.

First author, year, country of study	Mean age of participants (SD); sample size of each group	Intervention	Control	Outcome measure(s)	Jadad Scale Assessment
Nerve Block					
Fujii et al., 2019, Japan	Exp = 58.4 (12.7) Cont = 57.9 (13.4) Exp = 40 Cont = 40	PECS II Block: 10 ml ropivacaine 0.5% between the pectoralis muscles and 20 ml ropivacaine 0.5% above the serratus anterior muscle	SAP Block: 30 ml ropivacaine 0.5% between the serratus anterior and latissimus dorsi muscles	- pain assessment on a 0–100 mm VAS score - morphine consumption in postoperative period - % of patients, who is pain-free at 6 months after intervention	High (3 points)
Abbas et al., 2018, Egypt	Exp = 50.0 (13.0) Cont = 47.6 (7.5) Exp = 40 Cont = 40	Thermal RF neurolysis at a temperature of 80o C	Pulsed RF at a temperature of 42o C and voltage of 60–70 v	-changes in VAS (0-100 mm) for pain assessment -self-reported functional improvement - analgetic consumption - impact on QoL of patients - disability level	High (5 points)
Salman et al., 2021, Egypt	Exp = 51.5 (11.7) Cont = 52.4 (11.8) Exp = 40 Cont = 40	Ultrasound-guided stellate ganglion block one hour before surgery using five mL of 0.5% bupivacaine and multimodal systemic analgesia	Multimodal systemic analgesia	- grading system for neuropathic pain (GSNP) -opioid consumption in the first 24 hours -numeric rating scale (NRS) -functional capacity evaluation via the Eastern Cooperative Oncology Group (ECOG) score	Low (2 points)
Karmakar et al., 2014, China	Exp = 53 (8) Cont = 51 (9) Exp = 60 Cont = 60	General Anesthesia + Continuous thoracic paravertebral block (TPVB) with ropivacaine (2 mg/kg) and epinephrine (5 μg/mL)	General Anesthesia	-VRS pain score -incidence and severity of chronic pain -HRQOL via SF-36	High (5 points)
Gacio et al., 2016, Portugal	Exp = 55.1 (9.8) Cont = 52.68 (8.9) Exp = 40 Cont = 40	Paravertebral block: single-injection at the T4 level with 0.5% ropivacaine + adrenaline 3 μg mL−1	General Anesthesia: propofol (1.5 mg kg−1 h−1) + fentanyl (2 μg kg−1)	-VAS -DN4 Scale -HADS Scale - EORTC QLQ-C30	Low (1 point)
Qian et al., 2019, China	Exp = 52 (NA) Cont = 51 (NA) Exp = 90 Cont = 89	SAP block with ropivacaine 0.5%	0.9% saline	-NRS -QoR -PACU stay	High (5 points)
Hetta et al., 2021, Egypt	Exp = 50.8 (5.3) Cont = 50.7 (6.6) Exp = 30 Cont = 31	RF thoracic sympathectomy	Sham	-VAS	High (3 points)
Ilfeld1 et al., 2015, USA	Exp = 48 (8) Cont = 49 (9) Exp = 30 Cont = 30	Prolonged paravertebral nerve block with 0.5% ropivacaine	0.9% saline	- NRS -Brief Pain Inventory	High (4 points)
Mendonça et al., 2023, Brazil	Exp = 57.6 (NA) Cont = 59.5 (NA) Exp = 27 Cont = 26	Pectoserratus plane block (PSPB) with 20mL of 0.5%	General balanced inhaled anesthesia with sevoflurane and fentanil	-NRS -pain assessment in follow-up period	
Ilfeld2 et al., 2022, USA	Exp = 43 (NA) Cont = 42 (NA) Exp = 31 Cont =29	Ultrasound-guided percutaneous cryoneurolysis	Sham ultrasound-guided percutaneous cryoneurolysis	-NRS -Brief Pain Inventory	High (5 points)
Anesthesia					
Terkawi et al., 2015, USA	Exp = 55.2 (10.9) Cont = 55.0 (13.7) Exp = 34 Cont = 27	Lidocaine infusion at 2 mg/kg/hr (to a maximum upper limit of 200 mg/hr)	0.9% NaCl	-Original questionnaire on pain severity	High (5 points)
Wang et al., 2020, China	Exp = 52.1 (9.0) Cont = 49.1 (9.9) Exp = 37 Cont = 37	10 ml 0.5% ropivacaine in drainage exit's sites	10 ml 0.9% saline	-VAS -PONV	High (5 points)
Kendall et al., 2018, USA	Exp = NA Cont = NA Exp = 74 Cont = 74	1.5 mg/kg bolus of intravenous lidocaine followed by a 2 mg/kg/hour infusion	Normal saline at the same bolus and infusion rate	Evaluated at 3 and 6 months for the presence of chronic persistent postsurgical pain	High (4 points)

Table 1. Continued

First author, year, country of study	Mean age of participants (SD); sample size of each group	Intervention	Control	Outcome measure(s)	Jadad Scale Assessment
Anesthesia					
Kim et al., 2016, Republic of Korea	Exp = 48.7 (6.4) Cont = 49.0 (6.9) Exp = 39 Cont = 39	Lidocaine was administered at 2 mg/kg	Same volume saline	-NRS -PONV -PACU stay -Short- form McGill pain questionnaire	High (5 points)
Kang et al., 2020, Republic of Korea	Exp = 50.8 (8.4) Cont = 49.7 (7.2) Exp = 82 Cont = 81	Bolus (0.5 mg/kg of ketamine), followed by a continuous infusion (0.12 mg/kg/h of ketamine)	0.9% normal saline	-NRS -Sedation assessment -Recovery time -Cumulative morphine consumption -PONV	High (5 points)
Oral Medication					
Morel et al., 2016, France	Exp = 51.6 (NA) Cont = 57.3 (NA) Exp = 20 Cont = 20	Memantine during one month, starting two weeks before surgery.	Placebo (lactose) during one month starting two weeks before mastectomy	-NRS -six months post-mastectomy the pain intensity -the analgesic concomitant medications -the impact of treatment on cognitive function, QoL	High (5 points)
Vig et al., 2019, India	Exp = 48.54 (10.03) Cont = 50.28 (10.43) Exp = 35 Cont = 36	Pregabalin (Lyrica, Pfizer) 75 mg. BD starting from the morning of surgery and continued for 1 week	Placebo capsules at identical time intervals	-incidence of chronic postmastectomy pain (at 3 months postoperatively)	High (5 points)
Reyad et al., 2019, Egypt	Exp = 49.8 (11.6) Cont = 51.0 (8.4) Exp = 100 Cont = 100	Pregabalin (Lyrica, Pfizer, NY) 75 mg with a sip of water one hour before induction of anesthesia and repeated 12 hourly for seven days	Placebo capsules at the same time points with the same steps	-Grading System for Neuropathic Pain (GSNP) -VAS -Daily drug consumption	High (5 points)
Na et al., 2016, Republic of Korea	Exp = 52.5 (9.5) Cont = 53.9 (12.0) Exp = 41 Cont =42	20 mg of nefopam infused in 100 ml of normal saline	100 mL of normal saline	-NRS -administration of rescue analgesic drugs	High (3 points)
Khan et al., 2019, Canada	Exp = 54.2 (9.5) Cont = 55.2 (11.6) Exp = 50 Cont = 51	Perioperative pregabalin	Intravenous lidocaine	-NRS -DN4 Scale - McGill pain questionnaire	High (4 points)
Physical Methods					
Ammitzbøll et al., 2019, Denmark	Exp = 53 (10) Cont = 52 (10) Exp = 82 Cont = 76	Progressive resistance training exercise program supervised by physiotherapist 3 Times/week	Usual care Mobility exercise and manual therapy	-NPRS	High (5 points)
De Groef et al., 2017, Belgium	Exp = 53.9 (11.5) Cont = 54.7 (11.9) Exp = 72 Cont = 75	8 sessions of myofascial therapy	Usual care	-VAS -McGill pain questionnaire -DASH questionnaire	High (5 points)
Hammond et al., 2020, Canada	Exp = 56.3 (9.9) Cont = 53.0 (10.3) Exp = 22 Cont = 26	Nerve gliding exercise - 5–10 min×3 times daily Stretching and ROM exercise - Neck & UL and axillary webbing exercise	Usual care	-NRPS -DASH questionnaire -Self-report version of Leeds Assessment for Neuropathic Symptoms and Signs	High (4 points)
Lu Z et al., 2021, China	Exp = 48.2 (9.0) Cont = 48.2 (8.2) Exp = 190 Cont =188	TEAS at bilateral PC6 (Neiguan, a key acupoint of the hand-jueyin pericardium meridian) and CV17 (Danzhong, a key acupoint of the Ren meridian).	Electrode attachment but without stimulation	-NRS	High (5 points)
Hansdorfer-Korzon et al., 2016, Poland	Exp = 62.4 (12.9) Cont = 62.5 (12.0) Exp = 19 Cont = 18	Low-pressure compression corsets - 7 months	Usual care	-VAS	Low 2 points)

Table 1. Continued

First author, year, country of study	Mean age of participants (SD); sample size of each group	Intervention	Control	Outcome measure(s)	Jadad Scale Assessment
Physical Methods					
Lu W et al., 2020, USA	Exp = 54.0 (NA) Cont = 53.5 (NA) Exp = 14 Cont = 17	Acupuncture - 30 min × 18 sessions × 8 weeks Week 1: manual acupuncture Week 2–8: electro acupuncture	No acupuncture	-PNQ -FACT-NTX scores -BPI-SF pain severity -pain interference -QLQ-C30	High (3 points)

*PECS, pectoral nerves; SAP, serratus anterior plane; VAS, Visual Analogue Scale; RF, radiofrequency; QoL, quality of life; HADS, Hospital Anxiety and Depression scale.

837 patients.

Inefficiency of wound irrigation with local analgetics via catheter/injection prompted to search new nerve blocking techniques [23]. However, higher doses of opioid analgetics for regional irrigation led to decrease in pain severity ($p<0.006$), but had limitations, including respiratory depression, sedation, nausea, vomiting, constipation, and high tolerance [24].

The PECS II block is an ultrasound-guided technique targeting the inter-fascial plane between the pectoralis major muscle and the pectoralis minor muscle, with a deeper block affecting the serratus anterior muscle (SAM) [25]. Compared to the original PECS method, the modified PECS II procedure showed more effective results. A study comparing PECS and PECS II found that the latter reduced opioid use in the first 12 hours and resulted in shorter post-anesthesia care unit stays and overall hospitalization time [26]. Study included in this NMA showed higher rate of pain-free women at six postoperative months after PECS II block compared to the SAP block ($p = 0.03$) [27].

The use of thoracic paravertebral block (TPVB) in breast surgery has been well-known in previous studies, showing reductions in opioid use and postoperative pain. In study performed by Karmakar et al. (2014) [28], the single-injection TPVB technique requires less time to perform and is less labor-intensive compared to the

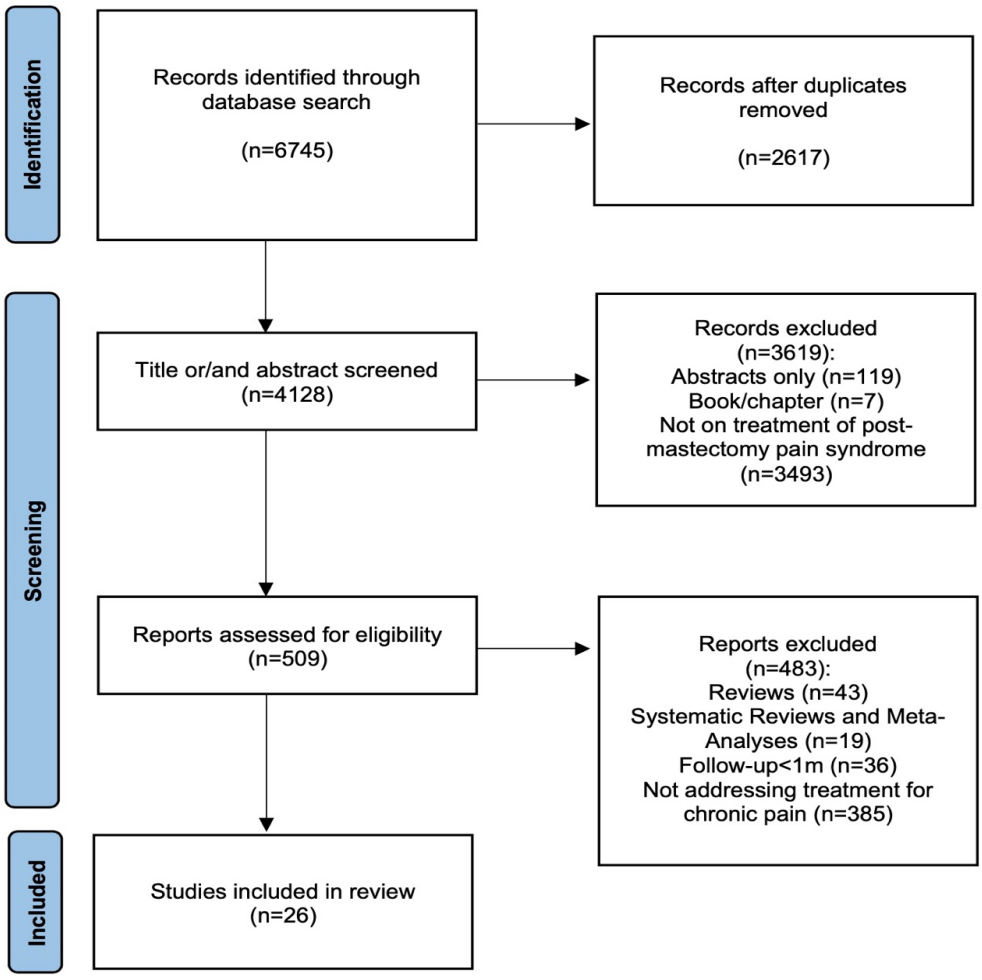

Figure 2. PRISMA-P Flow Diagram. This diagram demonstrates the method of identifying articles for the systematic review.

multiple-injection technique or paravertebral catheters. However, it should be noted that TPVB may be regional and not affect axilla (T1 nerve distribution).

Anesthesia

Five studies investigating the efficacy of anesthesia in preventing PMPS were included in this review, comprising

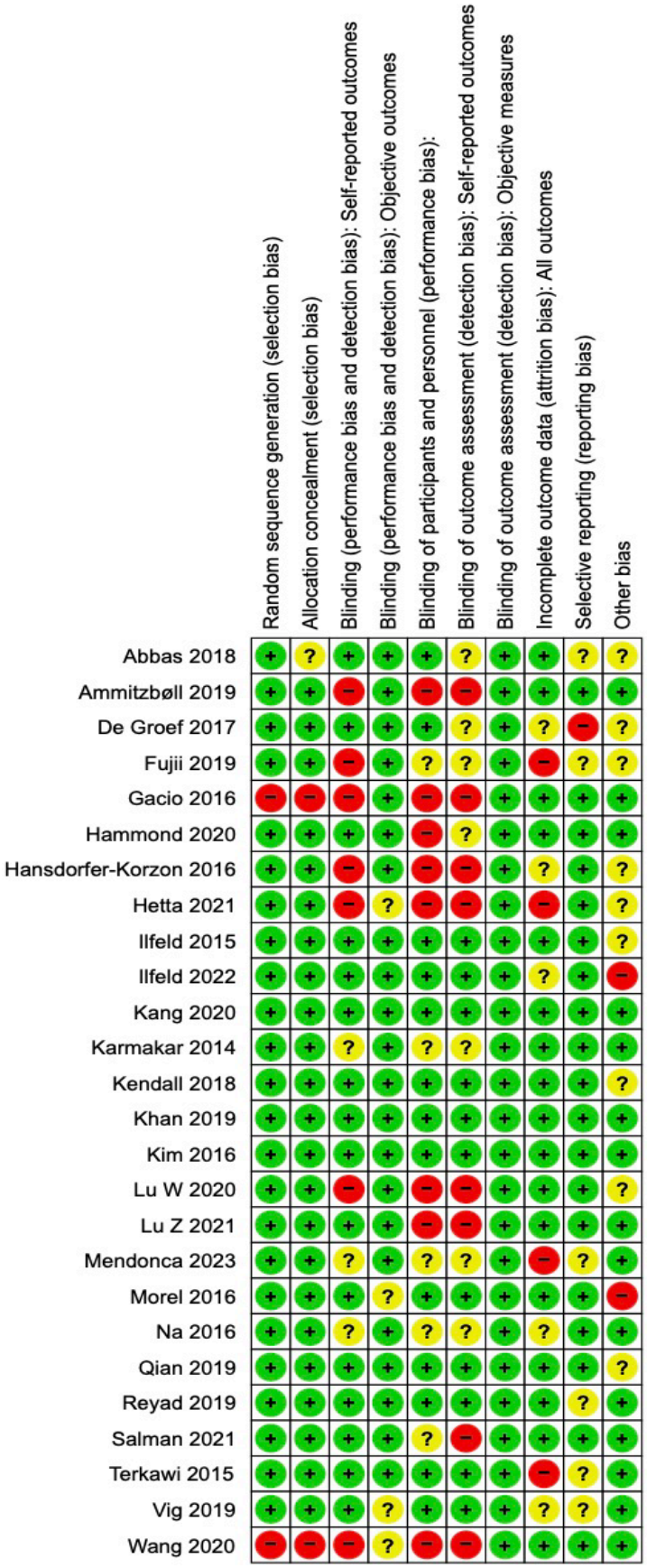

Figure 3. Risk of Bias assessment Using Cochrane Criteria.

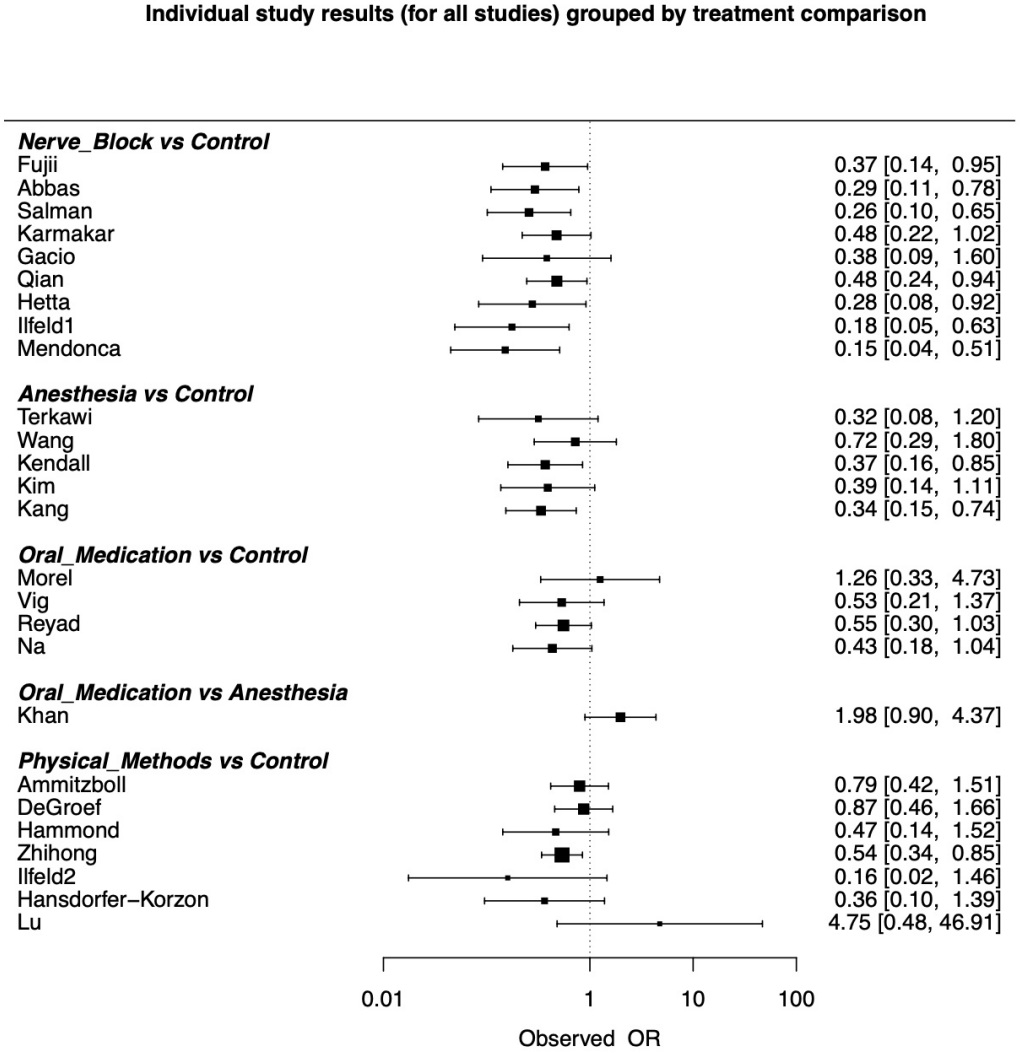

Figure 4. Forest Plot of PMPS Incidence Comparison. Estimates derived from individual study results. Included references: Anesthesia (Terkawi 2015; Wang 2020; Kang 2020; Kim 2016; Kendall 2018), Nerve_Block (Fujii 2019; Abbas 2018; Salman 2021; Karmakar 2014; Gacio 2016; Qian 2019; Hetta 2021, Ilfeld 2014, Mendonça 2023; Ilfeld 2022;), Oral_Medication (Morel 2016; Vig 2019; Reyad 2019; Na 2016; Khan 2019), Physical Methods (Ammitzbøll 2019; De Groef 2017; Hammond 2020; Zhihong 2021; Hansdorfer-Korzon 2016; Lu 2020). Abbreviations: OR – odds ratio; 95% CrI – 95% credential interval.

a total study population of 529 patients (Table 1).

Lidocaine exhibits several properties that make it a potentially useful drug for preventing chronic postsurgical pain, including sodium channel blockade, anti-inflammatory effects, and anti-hyperalgesic properties. Terkawi et al. (2015) [29] conducted a double-blind, placebo-controlled study and found that perioperative lidocaine infusion reduced the incidence of PMPS (12%) compared to the placebo group (30%). However, there was no statistically significant difference in acute post-operative pain or morphine consumption between the lidocaine and placebo groups in this study population. Kendall et al. (2018) [30] reported no differences in the quality of recovery, pain burden, or opioid consumption between groups at 24 hours. However, at 6 months after surgery, 29% of patients in control group had pain attributed to surgery compared to 13% in experimental group ($p = 0.04$).

Kang et al. (2020) [31] found that intraoperative low-dose ketamine reduced pain incidence at 3 months postoperatively compared to the control group, but this effect did not persist at 6 months ($p = 0.121$). However,

Table 2. Ranking Results

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	SUCRA (%)
Anesthesia	0.28	0.68	0.04	0.00	0.00	80.95
Nerve Block	0.71	0.28	0.01	0.00	0.00	92.66
Oral Medication	0.00	0.03	0.56	0.40	0.00	40.66
Physical Methods	0.00	0.02	0.39	0.59	0.00	35.61

Higher SUCRA (Surface Under the Cumulative Ranking Curve) values indicate better performance of therapy method.

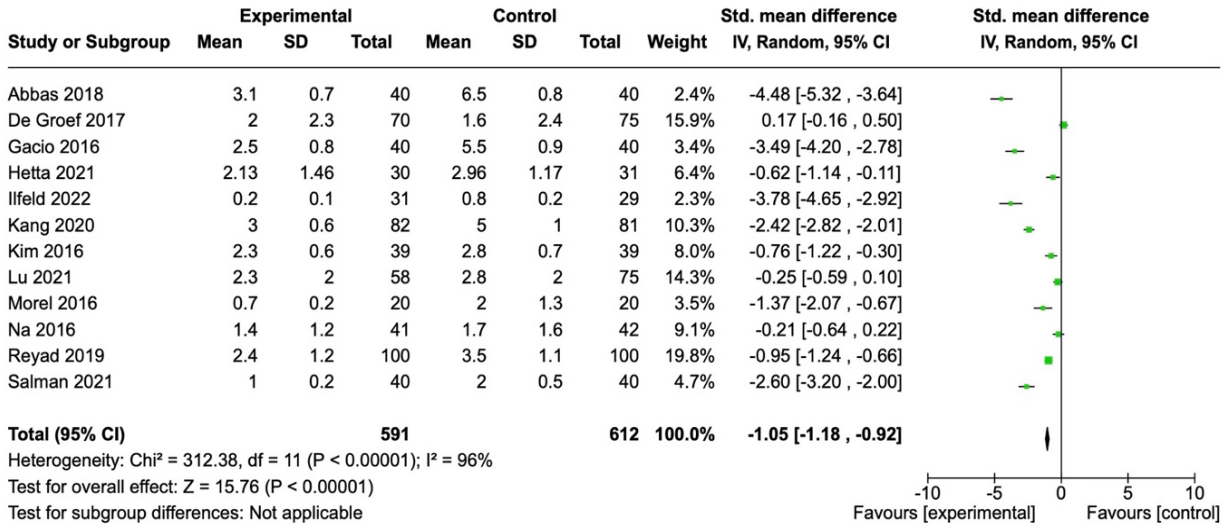

Figure 5. Forest Plot for chronic pain severity, based on VAS/NRS pain assessment after 3 months of the follow-up. The observed effects, based on the random-effects model, are indicated with the green square with the outer edges indicating the 95% confidence interval limits. The size of each square is proportional with the weight of that particular study in the meta-analysis.

Table 3. League Table. The estimates from the network meta-analysis.

	Anesthesia	Control	Nerve Block	Oral Medications	Physical Methods
Anesthesia	Anesthesia	2.65 (1.81-3.88)	0.87 (0.52-1.43)	1.59 (0.98-2.54)	1.69 (1.05-2.72)
Control	0.38 (0.26-0.55)	Control	0.33 (0.24-0.45)	0.6 (0.41-0.87)	0.64 (0.47-0.85)
Nerve Block	1.15 (0.7-1.91)	3.06 (2.22-4.23)	Nerve Block	1.83 (1.11-3.01)	1.95 (1.27-3.02)
Oral Medications	0.63 (0.39-1.02)	1.67 (1.14-2.45)	0.55 (0.33-0.9)	Oral Medications	1.06 (0.66-1.72)
Physical Methods	0.59 (0.37-0.96)	1.57 (1.17-2.11)	0.51 (0.33-0.79)	0.94 (0.58-1.51)	Physical Methods

This table contain estimates from Bayesian meta-analysis with indirect evidence. The data are considered consistent due to the high heterogeneity of the studies included in the NMA.

subanesthetic ketamine doses may be associated with serious psychotomimetic complications, and guidelines caution against its use due to potential adverse effects.

Systemic lidocaine, on the other hand, not only improved acute postoperative pain scores but also positively influenced emotional state and pain sub-

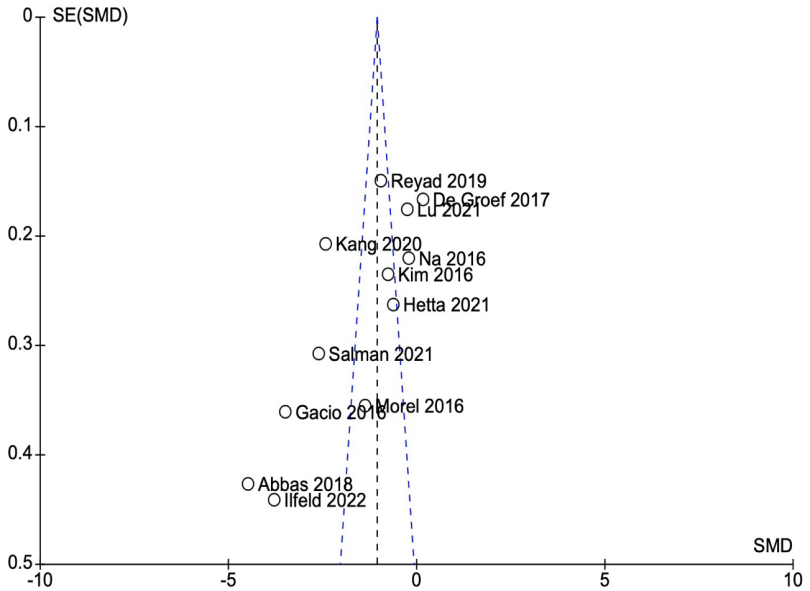

Figure 6. The Funnel Plot in the Pooled Analysis of Pain Severity in Patients with PMPS.

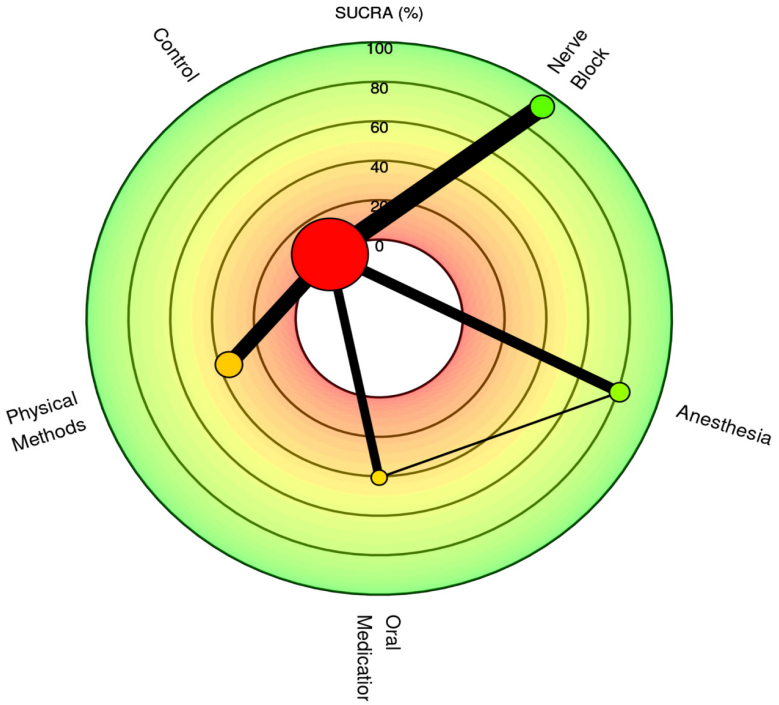

Figure 7. Ranking Results. SUCRA (Surface Under the Cumulative Ranking Curve) values, varying from 0 to 100%, indicate the probability of a therapy being in the top rank or among the top ranks. A higher SUCRA value, closer to 100%, signifies a greater likelihood of the therapy ranking higher. Conversely, a lower SUCRA value, closer to 0, suggests a higher likelihood of the therapy being in the bottom rank or among the lower ranks.

scores of the Quality of Recovery-40 (QoR-40) [32]. Additionally, systemic lidocaine reduced the intensity of chronic pain at 3 months post-surgery, as evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ). No significant differences were observed between the magnesium and control groups (p = 0.164) [32].

Wang et al. (2020) [33] found that ropivacaine infiltration of two drainage exit sites effectively reduced postoperative acute pain and analgesic requirements within 24 hours. However, at the 3-month follow-up, no significant differences were detected in the incidence of chronic pain between the ropivacaine and control groups.

Oral Medications

Five RCTs investigating the efficacy of oral medications in managing PMPS met the inclusion criteria (Table 1), comprising a total population of 495 patients.

Morel et al. (2016) [34] conducted a randomized, pilot clinical trial and found that patients in the memantine group reported significantly less pain than those in the placebo group (p = 0.017). Moreover, only 5% of patients in the memantine group required neuropathic pain treatment compared to 30% in the placebo group (p = 0.04). This innovative trial suggests that pre-surgery memantine may prevent the occurrence of pain three months after mastectomy and potentially reduce dysesthesia and paresthesia induced by chemotherapy.

Studies investigating the efficacy of pregabalin yielded controversial results [35, 36]. Vig et al. (2019) [36] reported no difference in the severity of chronic pain (numeric rating scale ≥ 4) between the pregabalin and control groups (p = 0.307). In contrast, Reyad et al. (2019) [35] found that pregabalin decreased the incidence and intensity of chronic pain at 6 months postoperatively.

Nefopam was found to be effective in reducing acute postoperative pain and analgesic drug consumption [37]. Notably, significantly fewer patients in the nefopam group experienced postoperative pain compared to the control group at 3 months postoperatively (36.6% vs. 59.5%, p = 0.04). However, in nefopam group NRS points was low and comparable between the two groups.

Physical Methods

Six randomized controlled trials (RCTs) assessed the impact of physical therapy (PT) on the incidence and severity of post-mastectomy pain syndrome (PMPS), involving a total study population of 808 patients.

According to Ammitzbøll et al. (2020) [38], implementing a 1-year progressive resistance training program did not yield any notable advantages over usual care in terms of reducing the incidence or intensity of chronic pain. Pain scores mostly showed insignificant decreases from baseline to 20 weeks, which remained consistent at the 12-month follow-up. De Groef et al. (2017) [39] found that including an 8-session myofascial therapy program in a standard PT regimen did not result in any additional benefits. The addition of myofascial therapy did not show any extra advantageous effects on pain prevalence rate, pain intensity, or pain quality in the early postoperative stage after breast cancer surgery [39]. Hammond et al. (2020) [40] demonstrated that the treatment group, after attending four PT sessions, experienced a significant reduction in pain over time (OR 0.85, 95% CI 0.76-0.94; p = 0.002).

Surgical Methods

Targeted muscle reinnervation could potentially alleviate persistent neuroma pain following mastectomy and/or axillary lymph node dissection (ALND). Nerve allografts might serve as grafts placed between nearby nerve segments. Additionally, the use of fat grafting could reduce the likelihood of developing PMPS [26].

The use of autologous fat graft may lead to improvements in tissue differentiation and scar softness, which can positively impact nerve entrapment and contribute to successful clinical outcomes [41]. The effectiveness of fat grafting in addressing PMPS is based on the principles of regenerative medicine. Specifically, the stromovascular component of fat tissue contains crucial mesenchymal stem cells (ADSC) [41]. These ADSCs play a significant role in sustaining the viability of grafted fat cells by secreting various cytokines and growth factors, leading to neoangiogenesis, immunomodulation, and anti-inflammatory effects.

Meta-Analysis

To evaluate the efficacy in decreasing PMPS incidence by variety of treatment modalities we visualized two forest plots. We calculated odds ratios with a random-effects meta-analysis of the incidence of PMPS between treated and control groups.

Individual study results grouped by treatment comparison are shown in Figure 4. Estimates for nerve block and anesthesia studies across the remaining subgroup comparisons significantly favored these methods. Thus, OR for nerve blocks ranged from 0.15 (95% CrI 0.04-0.51) to 0.48 (95% CrI 0.24-0.94), P<0.0001. Anesthesia-treated patients also had statistically lower PMPS incidence with OR ranged from 0.32 (95% CrI: 0.08–1.20) to 0.72 (95% CrI: 0.29–1.80), P<0.0001. Comparisons of oral medications were not statistically different overall (Figure 4).

Pain Severity

Data from 12 RCTs, including 1,203 patients (591 in the experimental groups and 612 in the control groups), were used for the meta-analyses of chronic pain. Only these studies reported pain scores in VAS or NRS scales assessment after 3 months. Results indicated a reduction in the incidence of PMPS at 3 months (OR 0.55 [0.39 to 0.87], P = 0.04).

Chronic pain was modestly but statistically significantly less for patients in the experimental groups than for those in control groups (SMD = -1.05, 95%CI = -1.18 to -0.92, P < 0.00001) (Figure 5). Pain severity scores after 3 months were less in the nerve blockers group than for those in the control group (Abbas 2018: SMD = -4.48, 95%CI = -5.32 to -3.64; Ilfeld 2022: SMD = -3.78, 95%CI = -4.65 to -2.92; Gacio 2016: SMD = -3.49, 95%CI = -4.20 to -2.78, P < 0.0001). The test for heterogeneity for the model was significant, suggesting variability of the true effects for pain between experimental and control groups among studies (Figure 5).

Pain was significantly less for patients in the bolus ketamine followed by a continuous infusion (SMD = -2.42, 95%CI = -2.82 to -2.01, P<0.0001). Memantine during one month, starting two weeks before surgery was effective preventing PMPS in the 3 months of the follow-up (SMD = -1.37, 95%CI = -2.07 to -0.67, P<0.0001) (Figure 5).

According to the Hedges' g and funnel plot, publication bias occurred in the results of the studies to determine the pain severity in patients with PMPS because of heterogeneity of studies included in meta-analysis (the weight of each study, the sample size, the inverse of the variance) (P: 0.002; Figure 6).

Network Meta-Analysis

Figure 7 shows range in treatment modalities calculated by NMA and estimated in SUCRA value. Thus, the most effective methods were nerve blocking with SUCRA 92,66% and anesthesia with SUCRA 80.95% (Figure 7; Table 2). Oral medication and physical methods ranked 3 and 4 (40.66% and 35.61%, respectively) % (Figure 7; Table 2).

In Bayesian analysis, there was a trend toward nerve blocks reducing incidence across all comparators, with statistical advantages compared with anesthesia (OR: 0.87; 95% CrI: 0.52–1.43), oral medications (OR: 0.55; 95% CrI: 0.33–0.9), and physical methods (OR: 0.51; 95% CrI: 0.33–0.79) (Table 3).

Oral medications and physical methods were statistically unsignificant in any comparisons with other treatment modalities. However, there was significant difference in these two methods itself. Thus, oral medications were effective in comparison to physical methods (OR: 0.94; 95% CrI: 0.58-1.51). Anesthesia was associated with a significantly lower PMPS incidence compared with oral medications (OR: 0.63; 95% CrI: 0.64–0.90) and physical methods (OR: 0.59; 95% CrI: 0.37–0.96) (Table 3).

Discussion

Post-mastectomy pain syndrome is a challenging and distressing condition that affects a considerable number of breast cancer survivors. Many studies have been carried out to investigate the efficacy of various PMPS prevention modalities and breast cancer surgery. In this study, we first evaluated indirect comparisons between treatment groups, the efficacy of each comparator itself, and its influence on PMPS incidence through a systematic review and network meta-analysis.

Our findings demonstrated that PMPS management requires a multidimensional approach, as the specific pain experienced by patients may vary based on individual characteristics, the extent of surgery, and other contributing factors. The efficacy of interventions varied, with some showing promising results in reducing pain intensity, while others demonstrated improvements in functional outcomes and quality of life. The pooled analysis of data from included trials of high methodological quality showed a significant effect of nerve blocks and anesthesia compared with other approaches on the general and physical components of women with PMPS.

Pharmacological agents, particularly nerve pain medications and anti-inflammatory drugs, emerged as

potential options for alleviating PMPS-related pain. Their ability to target neuropathic pain mechanisms may explain their favorable outcomes. Memantine inhibits neuropathic pain through impairment of NMDA-receptors activity. The key impact of NMDA-antagonists in neuropathic pain is to inhibit downstream protein expression and phosphorylation of tyrosine 1472 on the NR2B subunit of NMDAr in two structures of the limbic system, the hippocampus and the insular cortex, leading to a decrease in the central sensitization component of persistent pain. Thus, patients who received memantine had minimal adverse effects (dizziness and somnolence). Studies included in this NMA add to the evidence that using pregabalin as a preventive analgesic may not reduce the incidence of chronic postmastectomy pain. In a systematic review, Larsson et al., (2017) [42] showed that tricyclic antidepressants are effective in neuropathic pain, but included studies were non-randomized cohort studies and didn't meet our criteria. Although, they stated that anti-epileptic drugs didn't show any positive effect on pain reduction.

Yuksel et al., (2021) [43] systematic review evaluated that perioperative IV lidocaine had the most positive effect on PMPS incidence; however, differences in pain assessment through all studies can affect the final results. Nefopam in Na et al. [37] study enhanced the efficacy of fentanyl, ketorolac, and meloxicam. The analgetics consumption was comparable during the first 6 h. So, we can conclude, that adding nefopam to other drugs can reduce persistent pain more than the acute one immediately after operation. There is no RCTS meeting NMA criteria on the usage of capsaicin. However, some authors stated that capsaicin is very effective in the postoperative period with minimal adverse effects (burning sensations) [44, 45]. After analyzing RCTs on anesthesia regimens, it was revealed that modulation of acute pain isn't sufficient to prevent chronic pain. Thus, we highly recommend controlling the patient's follow-up in PACU and combining two or three methods for PMPS prevention.

Physical therapy interventions, such as exercises targeting a range of motion and strengthening, may address muscular and biomechanical factors contributing to pain. Acupuncture is gaining substantial support as an effective approach for managing chronic issues among cancer survivors, encompassing chemotherapy-induced nausea and vomiting, anxiety, and post-treatment fatigue [46]. Class I compression corsets serve as a dual-purpose solution: not only are they effective in treating lymphedema, but they can also be employed for preventive measures against edema in patients who have undergone axillary lymph node removal and radiotherapy. Kannan et al., (2021) [47] investigated only physical methods in alleviating chronic pain. However, as stated earlier resistance training was very effective in these patients. Thus, there is no evidence proofing the efficacy of new physical methods, including water exercises and nerve gliding in PMPS prevention. Generally, any type of perioperative exercise or postoperative program are safe interventions for women. We can recommend perioperative intervention of physical methods or mental preparation programs for decrease PMPS incidence.

Furthermore, nerve blocks and complementary therapies demonstrated potential benefits in managing PMPS. Nerve blocks may offer targeted pain relief by interrupting pain signals from affected nerves. Thoracic paravertebral blocks (TPVB) achieve immediate but short-term pain relief (<1 month). Pectoral nerves block with steroid injection showed an initial slower response but longer lasting (6 months) relief [48]. Blocks may be useful in cases where immediate pain relief is needed. The PECS II block is comparable in quality to TPVB in pain scores and opioid consumption, with both methods being superior to systemic analgesia alone. However, one significant advantage of PECS II is its safety in the postoperative period and the duration of action without the need for additional medications (e.g., steroids). Potential disadvantages of PECS II include potential intravascular spread by the pectoral branch of the thoracoacromial artery. Compared to TPVB, the PECS II block is peripheral in nature and carries a lower risk of sympathetic blockade and major bleeding. However, there is a lack of high-quality evidence and RCTs comparing the various technical approaches and their efficacy.

Cryoneurolysis stands out due to its prolonged effects, lasting for weeks and months after a single administration. This method also offers an advantage by avoiding systemic side effects associated with opioid use, such as nausea, sedation, and respiratory depression [49]. Furthermore, it presents no risk of misuse, dependence and overdose. Paravertebral nerve block, lasting 6-8 hours with an option for continuous infusion via catheter, may lead to adverse effects (sympathetic blockade, hemodynamic instability). The serratus plane block's effects last from 2 to 3 days up to 12 weeks; however, it should be noted that it carries the risk of pneumothorax, but widely used in plastic surgery cases for easiest further flap fixation.

This meta-analytic review has several strengths. We identified significant benefits for several treatment modalities in reducing pain severity in women with PMPS. Also, we provided indirect comparison within modalities due to a lack of RCTs with head-to-head comparisons.

The current meta-analysis has some limitations: the small sample sizes and overall patient count in some of the included trials. It is noteworthy that the complexity of PMPS posed certain challenges to our analysis. Variability in outcome measures and patient populations may have influenced the results.

In conclusion, further research and high-quality RCTs are necessary to consolidate these findings and guide the development of evidence-based guidelines for PMPS management, ultimately improving the lives of breast cancer survivors facing this challenging condition. By implementing evidence-based interventions, both surgeons and anesthesiologists can optimize pain relief, functional outcomes, and overall quality of life for breast cancer survivors experiencing PMPS.

Author Contribution Statement

Conceptualization: DN, MA; methodology: DN, AB; software: DN; validation: DA, MM; Qualitative data

collection and analysis: DN, GK; investigation: DN, SK; data curation: MA; writing—review and editing: DN, KD, AB. All authors have read and agreed to the published version of the manuscript.

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Any conflict of interest

The authors declare no potential conflict of interest.

How the ethical issue was handled

Not required as data is not individualized, and primary data need to be collected.

Availability of data

The datasets created and analyzed during this study are publicly available due to their availability. They can be obtained from the corresponding author upon request.

Consent for publication

All authors have given consent for publication.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. Available from: https://doi.org/10.3322/caac.21660.
2. Ferlay J, Ervik M, Lam F. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer (cited 2023 June 25). Available from: https://gco.iarc.fr/today.
3. Igissinov N, Toguzbayeva A, Telmanova Z, Baibusunova A, Abdykalikova A, Igissinova G, et al. Evaluation of Breast Cancer Incidence Trends in the Karaganda Region of Kazakhstan. Iran J Public Health. 2022;51(10):2308-16. Available from: https://doi.org/10.18502/ijph.v51i10.10989.
4. Li N, Deng Y, Zhou L, Tian T, Yang S, Wu Y, et al. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Hematol Oncol. 2019;12(1):140. Available from: https://doi.org/10.1186/s13045-019-0828-0.
5. Ferlay J LM, Ervik M. Global Cancer Observatory: Cancer Tomorrow. Lyon, France: International Agency for Research on Cancer (cited 2023 June 25). Available from: https://gco.iarc.fr/tomorrow.
6. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977-1010. Available from: https://doi.org/10.1016/s0140-6736(14)62038-9.
7. Glare P, Aubrey K, Gulati A, Lee YC, Moryl N, Overton S. Pharmacologic Management of Persistent Pain in Cancer Survivors. Drugs. 2022;82(3):275-91. Available from: https://doi.org/10.1007/s40265-022-01675-6.
8. Frost MH, Schaid DJ, Sellers TA, Slezak JM, Arnold PG, Woods JE, et al. Long-term satisfaction and psychological and social function following bilateral prophylactic mastectomy. JAMA. 2000;284(3):319-24. Available from: https://doi.org/10.1001/jama.284.3.319.
9. Peuckmann V, Ekholm O, Rasmussen NK, Groenvold M, Christiansen P, Møller S, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. Eur J Pain. 2009;13(5):478-85. Available from: https://doi.org/10.1016/j.ejpain.2008.05.015.
10. Schug S, Pogatzki-Zahn E. Chronic pain after surgery or injury. Pain Clin Updates. 2011;19:1-5.
11. Carpenter JS, Andrykowski MA, Sloan P, Cunningham L, Cordova MJ, Studts JL, et al. Postmastectomy/postlumpectomy pain in breast cancer survivors. J Clin Epidemiol. 1998;51(12):1285-92. Available from: https://doi.org/10.1016/s0895-4356(98)00121-8.
12. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. Br J Cancer. 2008;99(4):604-10. Available from: https://doi.org/10.1038/sj.bjc.6604534.
13. Alves Nogueira Fabro E, Bergmann A, do Amaral ESB, Padula Ribeiro AC, de Souza Abrahão K, da Costa Leite Ferreira MG, et al. Post-mastectomy pain syndrome: incidence and risks. Breast. 2012;21(3):321-5. Available from: https://doi.org/10.1016/j.breast.2012.01.019.
14. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA. 2009;302(18):1985-92. Available from: https://doi.org/10.1001/jama.2009.1568.
15. Chappell AG, Bai J, Yuksel S, Ellis MF. Post-Mastectomy Pain Syndrome: Defining Perioperative Etiologies to Guide New Methods of Prevention for Plastic Surgeons. World J Plast Surg. 2020;9(3):247-53. Available from: https://doi.org/10.29252/wjps.9.3.247.
16. Wang L, Guyatt GH, Kennedy SA, Romerosa B, Kwon HY, Kaushal A, et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. CMAJ. 2016;188(14):E352-e61. Available from: https://doi.org/10.1503/cmaj.151276.
17. Kaunisto MA, Jokela R, Tallgren M, Kambur O, Tikkanen E, Tasmuth T, et al. Pain in 1,000 women treated for breast cancer: a prospective study of pain sensitivity and postoperative pain. Anesthesiology. 2013;119(6):1410-21. Available from: https://doi.org/10.1097/aln.0000000000000012.
18. Langford DJ, Paul SM, West C, Abrams G, Elboim C, Levine JD, et al. Persistent arm pain is distinct from persistent breast pain following breast cancer surgery. J Pain. 2014;15(12):1238-47. Available from: https://doi.org/10.1016/j.jpain.2014.08.013.
19. Meretoja TJ, Leidenius MHK, Tasmuth T, Sipilä R, Kalso E. Pain at 12 months after surgery for breast cancer. JAMA. 2014;311(1):90-2. Available from: https://doi.org/10.1001/jama.2013.278795.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Available from: https://doi.org/10.1136/bmj.n71.
21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds

DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. Available from: https://doi.org/10.1016/0197-2456(95)00134-4.
22. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Synth Methods. 2019;10(4):569-81. Available from: https://doi.org/10.1002/jrsm.1373.
23. Strazisar B, Besic N. Comparison of continuous local anaesthetic and systemic pain treatment after axillary lymphadenectomy in breast carcinoma patients - a prospective randomized study. Radiol Oncol. 2013;47(2):145-53. Available from: https://doi.org/10.2478/raon-2013-0018.
24. Mohamed SA, Abdel-Ghaffar HS, Kamal SM, Fares KM, Hamza HM. Effect of Topical Morphine on Acute and Chronic Postmastectomy Pain: What Is the Optimum Dose? Reg Anesth Pain Med. 2016;41(6):704-10. Available from: https://doi.org/10.1097/aap.0000000000000496.
25. 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(9):470-5. Available from: https://doi.org/10.1016/j.redar.2012.07.003.
26. Bashandy GM, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40(1):68-74. Available from: https://doi.org/10.1097/aap.0000000000000163.
27. Fujii T, Shibata Y, Akane A, Aoki W, Sekiguchi A, Takahashi K, et al. A randomised controlled trial of pectoral nerve-2 (PECS 2) block vs. serratus plane block for chronic pain after mastectomy. Anaesthesia. 2019;74(12):1558-62. Available from: https://doi.org/10.1111/anae.14856.
28. Karmakar MK, Samy W, Li JW, Lee A, Chan WC, Chen PP, et al. Thoracic paravertebral block and its effects on chronic pain and health-related quality of life after modified radical mastectomy. Reg Anesth Pain Med. 2014;39(4):289-98. Available from: https://doi.org/10.1097/aap.0000000000000113.
29. Terkawi AS, Sharma S, Durieux ME, Thammishetti S, Brenin D, Tiouririne M. Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: a double-blind, placebo-controlled randomized trial. Pain Physician. 2015;18(2):E139-46.
30. Kendall MC, McCarthy RJ, Panaro S, Goodwin E, Bialek JM, Nader A, et al. The Effect of Intraoperative Systemic Lidocaine on Postoperative Persistent Pain Using Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials Criteria Assessment Following Breast Cancer Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial. Pain Pract. 2018;18(3):350-9. Available from: https://doi.org/10.1111/papr.12611.
31. Kang C, Cho AR, Kim KH, Lee EA, Lee HJ, Kwon JY, et al. Effects of Intraoperative Low-Dose Ketamine on Persistent Postsurgical Pain after Breast Cancer Surgery: A Prospective, Randomized, Controlled, Double-Blind Study. Pain Physician. 2020;23(1):37-47.
32. Kim MH, Lee KY, Park S, Kim SI, Park HS, Yoo YC. Effects of systemic lidocaine versus magnesium administration on postoperative functional recovery and chronic pain in patients undergoing breast cancer surgery: A prospective, randomized, double-blind, comparative clinical trial. PLoS One. 2017;12(3):e0173026. Available from: https://doi.org/10.1371/journal.pone.0173026.
33. Wang B, Yan T, Kong X, Sun L, Zheng H, Zhang G. Ropivacaine infiltration analgesia of the drainage exit site enhanced analgesic effects after breast Cancer surgery: a randomized controlled trial. BMC Anesthesiol. 2020;20(1):257. Available from: https://doi.org/10.1186/s12871-020-01175-8.
34. Morel V, Joly D, Villatte C, Dubray C, Durando X, Daulhac L, et al. Memantine before Mastectomy Prevents Post-Surgery Pain: A Randomized, Blinded Clinical Trial in Surgical Patients. PLoS One. 2016;11(4):e0152741. Available from: https://doi.org/10.1371/journal.pone.0152741.
35. Reyad RM, Omran AF, Abbas DN, Kamel MA, Shaker EH, Tharwat J, et al. The Possible Preventive Role of Pregabalin in Postmastectomy Pain Syndrome: A Double-Blinded Randomized Controlled Trial. J Pain Symptom Manage. 2019;57(1):1-9. Available from: https://doi.org/10.1016/j.jpainsymman.2018.10.496.
36. Vig S, Kumar V, Deo S, Bhan S, Mishra S, Bhatnagar S. Effect of Perioperative Pregabalin on Incidence of Chronic Postmastectomy Pain Syndrome: A Prospective Randomized Placebo-Controlled Pilot Study. Indian J Palliat Care. 2019;25(4):508-13. Available from: https://doi.org/10.4103/ijpc.Ijpc_85_19.
37. Na HS, Oh AY, Koo BW, Lim DJ, Ryu JH, Han JW. Preventive Analgesic Efficacy of Nefopam in Acute and Chronic Pain After Breast Cancer Surgery: A Prospective, Double-Blind, and Randomized Trial. Medicine (Baltimore). 2016;95(20):e3705. Available from: https://doi.org/10.1097/md.0000000000003705.
38. Ammitzbøll G, Andersen KG, Bidstrup PE, Johansen C, Lanng C, Kroman N, et al. Effect of progressive resistance training on persistent pain after axillary dissection in breast cancer: a randomized controlled trial. Breast Cancer Res Treat. 2020;179(1):173-83. Available from: https://doi.org/10.1007/s10549-019-05461-z.
39. De Groef A, Van Kampen M, Vervloesem N, De Geyter S, Christiaens MR, Neven P, et al. Myofascial techniques have no additional beneficial effects to a standard physical therapy programme for upper limb pain after breast cancer surgery: a randomized controlled trial. Clin Rehabil. 2017;31(12):1625-35. Available from: https://doi.org/10.1177/0269215517708605.
40. Andersen Hammond E, Pitz M, Steinfeld K, Lambert P, Shay B. An Exploratory Randomized Trial of Physical Therapy for the Treatment of Chemotherapy-Induced Peripheral Neuropathy. Neurorehabil Neural Repair. 2020;34(3):235-46. Available from: https://doi.org/10.1177/1545968319899918.
41. Caviggioli F, Maione L, Forcellini D, Klinger F, Klinger M. Autologous fat graft in postmastectomy pain syndrome. Plast Reconstr Surg. 2011;128(2):349-52. Available from: https://doi.org/10.1097/PRS.0b013e31821e70e7.
42. Larsson IM, Ahm Sørensen J, Bille C. The Post-mastectomy Pain Syndrome-A Systematic Review of the Treatment Modalities. Breast J. 2017;23(3):338-43. Available from: https://doi.org/10.1111/tbj.12739.
43. Yuksel SS, Chappell AG, Jackson BT, Wescott AB, Ellis MF. "Post Mastectomy Pain Syndrome: A Systematic Review of Prevention Modalities". JPRAS Open. 2022;31:32-49. Available from: https://doi.org/10.1016/j.jpra.2021.10.009.
44. Holzer P. The pharmacological challenge to tame the transient receptor potential vanilloid-1 (TRPV1) nocisensor. Br J Pharmacol. 2008;155(8):1145-62. Available from: https://doi.org/10.1038/bjp.2008.351.
45. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107(4):490-502. Available from: https://doi.org/10.1093/bja/aer260.
46. Deng G. Integrative Medicine Therapies for Pain Management in Cancer Patients. Cancer J. 2019;25(5):343-8. Available

from: https://doi.org/10.1097/ppo.0000000000000399.
47. Kannan P, Lam HY, Ma TK, Lo CN, Mui TY, Tang WY. Efficacy of physical therapy interventions on quality of life and upper quadrant pain severity in women with post-mastectomy pain syndrome: a systematic review and meta-analysis. Qual Life Res. 2022;31(4):951-73. Available from: https://doi.org/10.1007/s11136-021-02926-x.
48. Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien). 2011;153(4):763-71. Available from: https://doi.org/10.1007/s00701-010-0881-5.
49. Nezami N, Behi A, Manyapu S, Meisel JL, Resnick N, Corn D, et al. Percutaneous CT-Guided Cryoneurolysis of the Intercostobrachial Nerve for Management of Postmastectomy Pain Syndrome. J Vasc Interv Radiol. 2023;34(5):807-13. Available from: https://doi.org/10.1016/j.jvir.2022.12.465.
50. Gacio MF, Lousame AM, Pereira S, Castro C, Santos J. Paravertebral block for management of acute postoperative pain and intercostobrachial neuralgia in major breast surgery. Braz J Anesthesiol. 2016;66(5):475-84. Available from: https://doi.org/10.1016/j.bjane.2015.02.007.
51. Qian B, Fu S, Yao Y, Lin D, Huang L. Preoperative ultrasound-guided multilevel paravertebral blocks reduce the incidence of postmastectomy chronic pain: a double-blind, placebo-controlled randomized trial. J Pain Res. 2019;12:597-603. Available from: https://doi.org/10.2147/jpr.S190201.
52. Salman AS, Abbas DN, Elrawas MM, Kamel MA, Mohammed AM, Abouel Soud AH, et al. Postmastectomy pain syndrome after preoperative stellate ganglion block: a randomized controlled trial. Minerva Anestesiol. 2021;87(7):786-93. Available from: https://doi.org/10.23736/s0375-9393.21.15112-0.
53. Abbas DN, Reyad RM. Thermal Versus Super Voltage Pulsed Radiofrequency of Stellate Ganglion in Post-Mastectomy Neuropathic Pain Syndrome: A Prospective Randomized Trial. Pain Physician. 2018;21(4):351-62.
54. Hetta DF, Mohamed AA, Hetta HF, Abd El-Hakeem EE, Boshra MM, El-Barody MM, et al. Radiofrequency Thoracic Sympathectomy for Sympathetically Maintained Chronic Post-Mastectomy Pain, a Preliminary Report: 6-Month Results. Pain Pract. 2021;21(1):54-63. Available from: https://doi.org/10.1111/papr.12933.
55. Ilfeld BM, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, et al. Persistent postmastectomy pain and pain-related physical and emotional functioning with and without a continuous paravertebral nerve block: a prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study. Ann Surg Oncol. 2015;22(6):2017-25. Available from: https://doi.org/10.1245/s10434-014-4248-7.
56. Mendonça FT, Nascimento LFC, Veloso NM, Basto GCP. Long-term Efficacy of Pectoserratus Plane Block (PSPB) for Prevention of Post-mastectomy Pain Syndrome: Extended Follow-up From a Randomized Controlled Trial. Clin J Pain. 2023;39(7):334-9. Available from: https://doi.org/10.1097/ajp.0000000000001118.
57. Ilfeld BM, Finneran JJ, Swisher MW, Said ET, Gabriel RA, Sztain JF, et al. Preoperative Ultrasound-guided Percutaneous Cryoneurolysis for the Treatment of Pain after Mastectomy: A Randomized, Participant- and Observer-masked, Sham-controlled Study. Anesthesiology. 2022;137(5):529-42. Available from: https://doi.org/10.1097/aln.0000000000004334.
58. Khan JS, Hodgson N, Choi S, Reid S, Paul JE, Hong NJL, et al. Perioperative Pregabalin and Intraoperative Lidocaine Infusion to Reduce Persistent Neuropathic Pain After Breast Cancer Surgery: A Multicenter, Factorial, Randomized, Controlled Pilot Trial. J Pain. 2019;20(8):980-93. Available from: https://doi.org/10.1016/j.jpain.2019.02.010.
59. Hansdorfer-Korzon R, Teodorczyk J, Gruszecka A, Wydra J, Lass P. Relevance of low-pressure compression corsets in physiotherapeutic treatment of patients after mastectomy and lymphadenectomy. Patient Prefer Adherence. 2016;10:1177-87. Available from: https://doi.org/10.2147/ppa.S108326.
60. Lu W, Giobbie-Hurder A, Freedman RA, Shin IH, Lin NU, Partridge AH, et al. Acupuncture for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Survivors: A Randomized Controlled Pilot Trial. Oncologist. 2020;25(4):310-8. Available from: https://doi.org/10.1634/theoncologist.2019-0489.
61. Lu Z, Wang Q, Sun X, Zhang W, Min S, Zhang J, et al. Transcutaneous electrical acupoint stimulation before surgery reduces chronic pain after mastectomy: A randomized clinical trial. J Clin Anesth. 2021;74:110453. Available from: https://doi.org/10.1016/j.jclinane.2021.110453.