Systematic Review/Meta-analysis

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Prescription of pregabalin for prevention of acute post-mastectomy pain syndrome (APMPS): a systematic review and meta-analysis of randomized controlled trials

Rohit Ganduboina, MBBS[a], Palak Dutta, MD[b,*], Shubhadarshini G. Pawar, MBBS, MPH[c], Indraneil Mukherjee, MD[d]

Background: Mastectomy is generally considered the most effective treatment option for breast cancer. However, it is linked to a variety of complications that contribute to an elevated morbidity. Acute Post Mastectomy Pain Syndrome (APMPS) is 2 months or more of neuropathic pain after mastectomy. Pregabalin, a powerful central nervous system inhibitor is commonly prescribed for the relief of neuropathic pain. This study evaluates its efficacy in curing neuropathic pain and enhancing mastectomy pain management.

Methods: We conducted a comprehensive literature search comparing pregabalin with placebo using relevant syntaxes. Postoperative acute pain scores, 24-hour morphine use, dizziness, and sedation were evaluated. A *P*-value of less than 0.05 was considered statistically significant.

Results: Ten studies with a total of 719 patients were included. The pregabalin group exhibited significantly lower acute pain scores compared to the placebo group (standard mean difference: –0.61; 95% confidence interval: –1.02 to –0.20; $P < 0.01$). No statistically significant differences were observed in 24-hour morphine consumption (standardized mean difference, –2.74; 95% CI, –6.27; –0.79, $P > 0.05$, $I^2 = 97.6\%$), dizziness (RR, 1.49; 95% CI, 0.82; 2.71, $P > 0.05$, $I^2 = 1.0\%$) or sedation (RR, 1.38; 95% CI, 0.11; 17.84, $P > 0.05$, $I^2 = 0.0\%$) between the groups. The acute pain scores showed significant heterogeneity, with an I^2 value of 78.6%.

Discussion: This meta-analysis indicates that pregabalin may be effective for managing APMPS. However, due to the heterogeneity and limitations of the included studies, the findings should be interpreted with caution. Future research should focus on larger sample sizes, incorporating potential moderating factors to more precisely determine pregabalin's role in APMPS.

Keywords: acute postmastectomy pain syndrome (APMPS), mastectomy, meta-analysis, postoperative pain scores, pregabalin

Introduction

Breast cancer, which makes up about 25% of all cancer cases worldwide, is the most prevalent form of cancer and one of the two leading causes of death for malignant tumors in women[1,2]. Axillary dissection is a crucial component of the surgical management of breast cancer[3]. Although surgery is typically regarded as the most effective treatment option, it is coupled with an array of complications that add to increased morbidity. Postoperative hyperalgesia is a substantial factor that contributes to postoperative morbidity[4].

Studies have indicated that a surgical incision may trigger hyperalgesia, which may aggravate postoperative pain[5]. Post-mastectomy pain syndrome (PMPS) is an increasingly prevalent neuropathic pain disease that occurs following breast surgery. According to reports, the occurrence rate varies from 4% to 100%. The problem is localized to the precise region where the procedure was conducted and its immediate vicinity. The post-operative period extends beyond three months and has a substantial negative impact on the general state of well-being in women who have undergone the procedure[6-8]. The symptoms associated with breast cancer pain are greatly influenced by several sensory problems, including burning, numbness, persistent feelings, heightened pain sensitivity, and pain triggered by non-painful stimuli (allodynia). Furthermore, there is a correlation between pain and supplementary interventions such as chemotherapy and radiotherapy. Additional risk factors for post-mastectomy pain syndrome (PMPS) might involve the severity of early postoperative pain, psychological state, age (especially people aged 40 and older), and prior breast pain[9-11]. Previous research has demonstrated that proficiently

[a]NRI Institute of MEDICAL SCIENCES, Visakhapatnam, India, [b]Kyiv Medical University, Kyiv, Ukraine, [c]Cedars Sinai Medical Center, Los Angeles, USA and [d]Staten Island University Hospital – Northwell Health, Staten Island, New York, USA

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*Corresponding author. Address: Kyiv Medical University, Kyiv, Ukraine. E-mail: duttapalak05@gmail.com (P. Dutta).

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controlling acute pain following surgery can substantially enhance both acute illness and chronic long-term pain[12].

Pregabalin is commonly prescribed for the relief of neuropathic pain[13,14]. Multiple clinical trials have been conducted to evaluate this therapy's efficacy and potential adverse effects in reducing postoperative acute pain. Administering pregabalin postoperatively yielded marginal enhancements in outcomes for individuals with hyperalgesia. Nevertheless, additional investigations have presented results that are inconsistent due to variations in drug dosage, dosing frequency, pain severity, and type of pain[15]. This meta-analysis seeks to assess the effectiveness of pregabalin in the treatment of acute hyperalgesia following mastectomy, with a specific focus on its potential to enhance postoperative morbidity.

Methodology

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) criteria and AMSTAR 2 checklists were followed, and established techniques were used to conduct this study[16,17].

Definition and outcomes

Currently, the optimal pregabalin doses for managing postmastectomy pain remain uncertain. Existing studies indicate that a common dose of 150 mg of pregabalin leads to improved outcomes with fewer adverse effects. Our primary outcomes were acute pain scores, 24-hour morphine requirements, chronic pain scores, and adverse effects.

Search strategy and study selection

We systematically searched PubMed, Cochrane, Web of Science, Scopus, Clinical Trials, and Google Scholar for articles until 5 January 2024. The following MeSH terms were used "postmastectomy pain" AND "pregabalin"; "mastectomy pain" AND "pregabalin"; "postmastectomy pain syndrome" AND "pregabalin"; "postmastectomy pain" OR "mastectomy pain" AND "pregabalin"; "postmastectomy pain" [Title/Abstract] OR "mastectomy pain" [Title/Abstract]) AND "pregabalin" [Title/Abstract]; "postmastectomy pain" [MeSH Terms] OR "mastectomy pain" [MeSH Terms] AND "pregabalin" [MeSH Terms]. The methodological quality of eligible reports was evaluated. Two writers assessed the publications' abstracts and titles to determine their credibility for the study. Any inclusion-related discrepancy was managed by the senior author (I.M.). Only articles in English with full text were included.

Eligibility criteria

A thorough examination of the effects of post-mastectomy pregabalin administration was performed, compared to a placebo. Our study focused on adult patients aged >18 and used a variety of study designs, including multicenter, case-control, observational, and randomized clinical trials. We ensured that each study had detailed baseline characteristics and closely monitored results. Our analysis excluded non-original studies such as literature reviews, systematic reviews, commentaries, letters, animal studies, and those published in languages other than English. We also excluded studies that involved pediatric patients, lacked a comparator arm, or had outcomes that did not meet our research criteria. This stringent selection process was designed to ensure the reliability and validity of our results.

Data extraction and statistical analysis

Data from the eligible selected studies were meticulously extracted, including demographics, comorbidities, risk factors, and outcomes for both groups. This process was carried out by two authors. Additionally, two investigators independently assessed the risk of bias using version 2 of the Cochrane risk of bias tool for randomized controlled trials (RCTs). Baseline continuous variables were summarized in mean (SD), whereas dichotomous variables were described in frequencies. We performed a conventional meta-analysis for primary and secondary outcomes and adopted the random-effects model for the study variations. We considered a two-tailed *P*-value of less than 0.05 to be statistically significant. In addition, we assessed the between-study heterogeneity using the I^2 tests and considered the results to be below (<25%), moderate (25–50%), and High (>50%)[18].

Publication bias was performed for outcomes with at least six studies and was assessed through a funnel plot and quantified using Egger's test[19]. All statistical work, including analyses and graphical illustrations, was conducted using R Studio 4.3.2.

Quality assessment

We assessed the quality of the included studies using the Jadad Scale for randomized clinical trials[20]. In cases of disagreement, senior author consensus was involved. The details of the quality assessment are presented in Supplementary Digital Content, Table 1, http://links.lww.com/MS9/A705.

Results

Study selection

Using the specified syntaxes, a preliminary search of the database resulted in 255 publications. After checking duplicate entries, 60 duplicates were eliminated. 173 studies were subsequently excluded following the initial review of titles and abstracts, based on our criteria for inclusion and exclusion, as well as the comparison between the pregabalin and placebo groups. A comprehensive review was done for the remaining 22 publications that were identified. Four studies were removed as their data could not be retrieved, and 8 studies were removed due to either having an inappropriate target group, not being primary research publications, or lacking heterogeneity. Therefore, our meta-analysis included a total of ten research papers that satisfied the eligibility criteria. The PRISMA flow diagram has been shown in Fig. 1.

Patient and study demographics

Ten studies with a total of 719 patients—360 patients in the pregabalin group and 359 patients in the placebo group were included in the meta-analysis. The baseline demographics of the study participants are summarized in Table 1. The mean ages of the pregabalin and placebo groups were 51.8 and 52.2 years, respectively. The participants were female. The participants

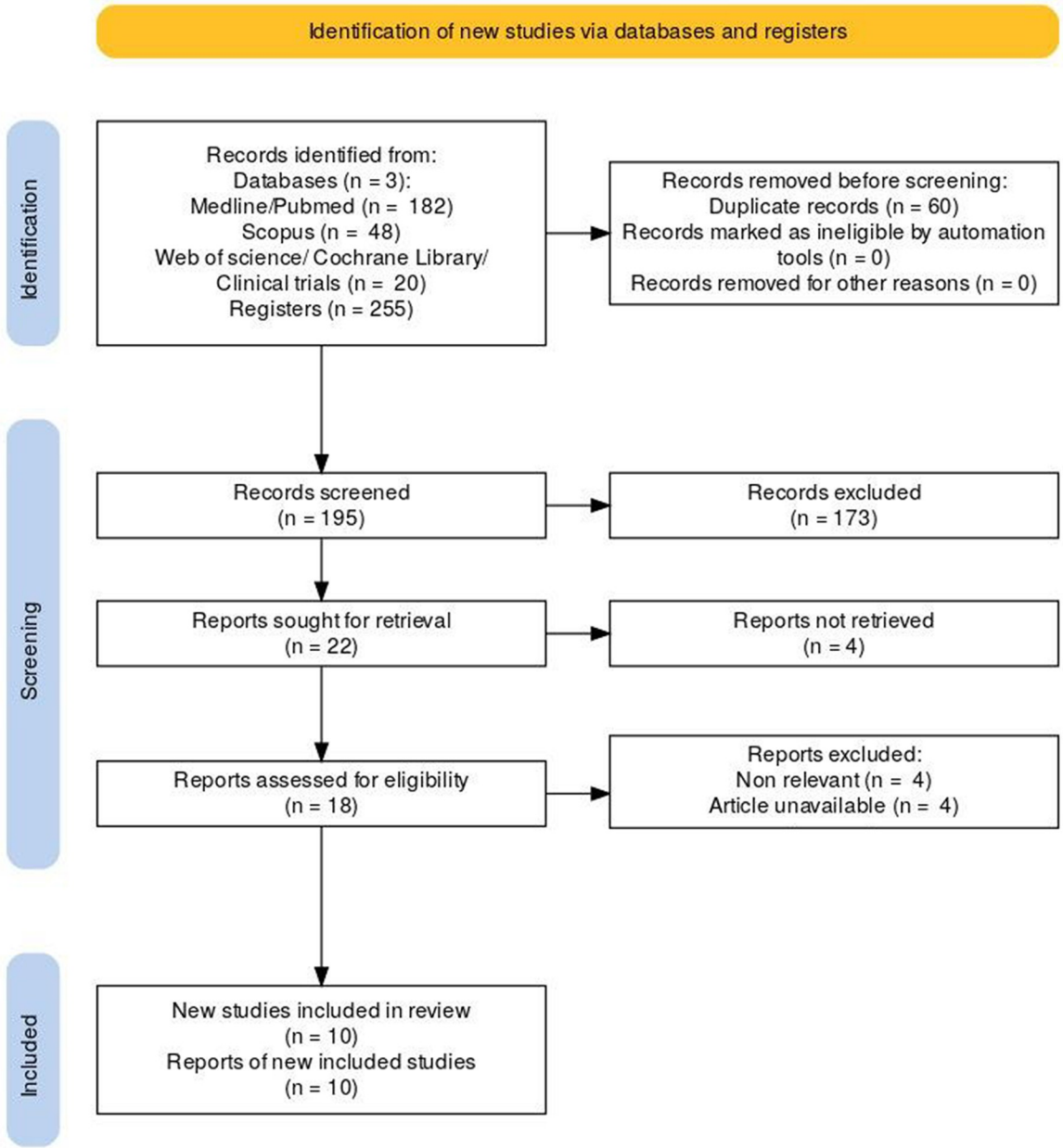

Figure 1. PRISMA Chart.

chosen for the studies were individuals diagnosed with breast cancer. Average BMI of both groups; 26.4 kg/m^2 in the pregabalin group and 27.2 kg/m^2 in the control group.

Risk of bias assessment

The majority of the studies included in the analysis do not exhibit significant bias. Out of the 10 studies, only 4 exhibited a risk bias, with 2 demonstrating a high risk of bias and the remaining studies having an unclear risk. Ten studies were conducted to evaluate the bias present in the randomization process. Two studies exhibited a significant bias in the assessment of outcomes. The RoB assessment of the studies has been shown in Supplementary Digital Content, Figures 1a and b, http://links.lww.com/MS9/A705[21].

Meta-analysis of outcomes

The pooled analysis of primary outcomes showed the pregabalin group is associated with lower acute pain scores (standardized mean difference [SMD], −0.61; 95% CI, −1.02; −0.20, $P < 0.01$, I^2 = 78.6%) in comparison to placebo. However, substantial variation existed between studies, indicated by the high heterogeneity (I^2 = 78.6%) (Fig. 2a).

There was no significant association with secondary outcomes of 24 hr morphine intake (mg) (SMD, −2.74; 95% CI,

Table 1

Baseline demographic characteristics

Author, year	Country	Surgery	Sample size	Age[a]	BMI[a]	Pregabalin dose(mg)	Follow-up
			Pregabalin/ placebo	Pregabalin/ placebo	Pregabalin/ placebo		
Araújo JN *et al*, 2022[30]	Brazil	Mastectomy with axillary dissection	40 20/20	-	26.3/28.1	150 mg	24 h
Vig S *et al*, 2019[4]	India	Modified radical mastectomy (MRM)	71 35/36	56.9/55.5	26.6/26.8	75 mg/150 mg/300 mg	3 months
Khan JS *et al*, 2019[31]	Canada	Unilateral/bilateral mastectomy or lumpectomy	100 50/50	54.2/54.4	-	300 mg 1 dose, 150 mg, 75 mg 2 day post-op	3 months
Reyad RM *et al*, 2019[29]	Egypt	MRM/conservative breast surgery, with axillary dissection	181 92/89	49.8/51	-	150 mg	24 weeks
Athitarn Earsakul *et al*, 2018[23]	Thailand	MRM/mastectomy with axillary dissection	30 16/14	-	-	75 mg	48 h
Hetta DF *et al*, 2016[15]	Egypt	Modified radical mastectomy (MRM)	57 27/30	46.1/47.4	27.7/27.8	75 mg/150 mg/300 mg	24 h
Mahran E *et al*, 2015[27]	Egypt	Modified radical mastectomy (MRM)	60 30/30	53.5/53.9	27.4/28.6	150 mg	24 h
Mansor SH *et al*, 2015[22]	Malaysia	Mastectomy with/without axillary dissection	49 25/24	51.5/52	24.7/25.3	150 mg	24 h
Babatunde A. O *et al*, 2014[32]	United States	Unilateral modified mastectomy/lumpectomy with axillary dissection	47 23/24	-	-	150 mg	3 months
Kim SY *et al*, 2011[33]	Korea	Partial or total mastectomy with/without axillary dissection	84 42/42	50/50	23.2/22.7	75 mg × 2	1 week

[a]Mean value, (#) in hours.

–6.27; –0.79, $P > 0.05$, $I^2 = 97.6\%$) was less among pregabalin group in comparison to placebo (Fig. 3).

There was no significant association to prove adverse effects of dizziness (RR, 1.49; 95% CI, 0.82; 2.71, $P > 0.05$, $I^2 = 1.0\%$) and sedation (RR, 1.38; 95% CI, 0.11; 17.84, $P > 0.05$, $I^2 = 0.0\%$) were high among the pregabalin group (Fig. 4a and 4b).

Sensitivity analysis

Sensitivity analyses were performed for acute pain scores owing to high heterogeneity (>75%). Upon excluding one study at a time, results for acute pain scores remained significant in terms of magnitude and direction (Supplementary Digital Content, Figure 2, http://links.lww.com/MS9/A705). In addition, we used an approach based on Galbraith's plot to identify studies that could influence the total effect estimate. This plot visually evaluates the relationship between study size and effect magnitude, and studies that deviate significantly from the expected trend may impact the overall results. Under the guidance of Galbraith's plot & leave-one-out analysis (Supplementary Digital Content, Fig. 3, http://links.lww.com/MS9/A705), studies by Hetta DF *et al*, Mansor SH *et al*, and Athitarn Earsakul et. al were excluded[15,22,23], Acute pain scores remained significantly reduced in the pregabalin group (SMD, –0.25; 95% CI, –0.47; –0.24, $P < 0.05$, $I^2 = 29.2\%$), with a significant reduction in heterogeneity from 78.6% to 29.2% (Fig. 2b).

Publication bias

Minor funnel plot asymmetry with non-significant Egger's test ($P > 0.05$) was detected for acute pain scores, suggesting that we cannot rule out publication bias (Supplementary Digital Content, Figure 4, http://links.lww.com/MS9/A705)[24].

Discussion

This meta-analysis explores the effectiveness of pregabalin in managing acute hyperalgesia after mastectomy. Our study findings suggest that the use of pregabalin is associated with a notable decrease in acute pain scores, in comparison to the use of a placebo. However, no statistically significant impact was found on the 24-hour morphine intake and the occurrence of adverse effects such as dizziness and sedation. Pregabalin's effectiveness in lowering postoperative pain has been thoroughly investigated and substantiated. Previous studies have provided evidence showing a reduction in opioid usage and relief from acute postoperative pain[25,26]. The analgesic properties are likely due to its ability to modify calcium channels in neurons, which may decrease the release of excitatory neurotransmitters involved in pain pathways[13]. Nevertheless, the absence of a substantial decrease in the amount of morphine used throughout 24 hours in our study necessitates additional investigation. This may be attributed to variables such as the time of pregabalin administration or potential interactions with other pain drugs administered concurrently[27].

In a meta-analysis conducted by Chang *et al*, the effectiveness of pregabalin in treating acute and chronic postpartum pain was demonstrated[28]. The findings of our study are consistent with these findings, as well as with the findings of other studies[13,14,28]. It suggests that pregabalin may be a valuable intervention for addressing post-mastectomy pain. However, the substantial heterogeneity ($I^2 = 78.6\%$) indicates a notable variation in effect sizes across the studies. Due to the small sample sizes within subgroups, it was not possible to conduct a thorough analysis to determine the exact sources of this variation. Variations in baseline pain levels, surgical techniques, and

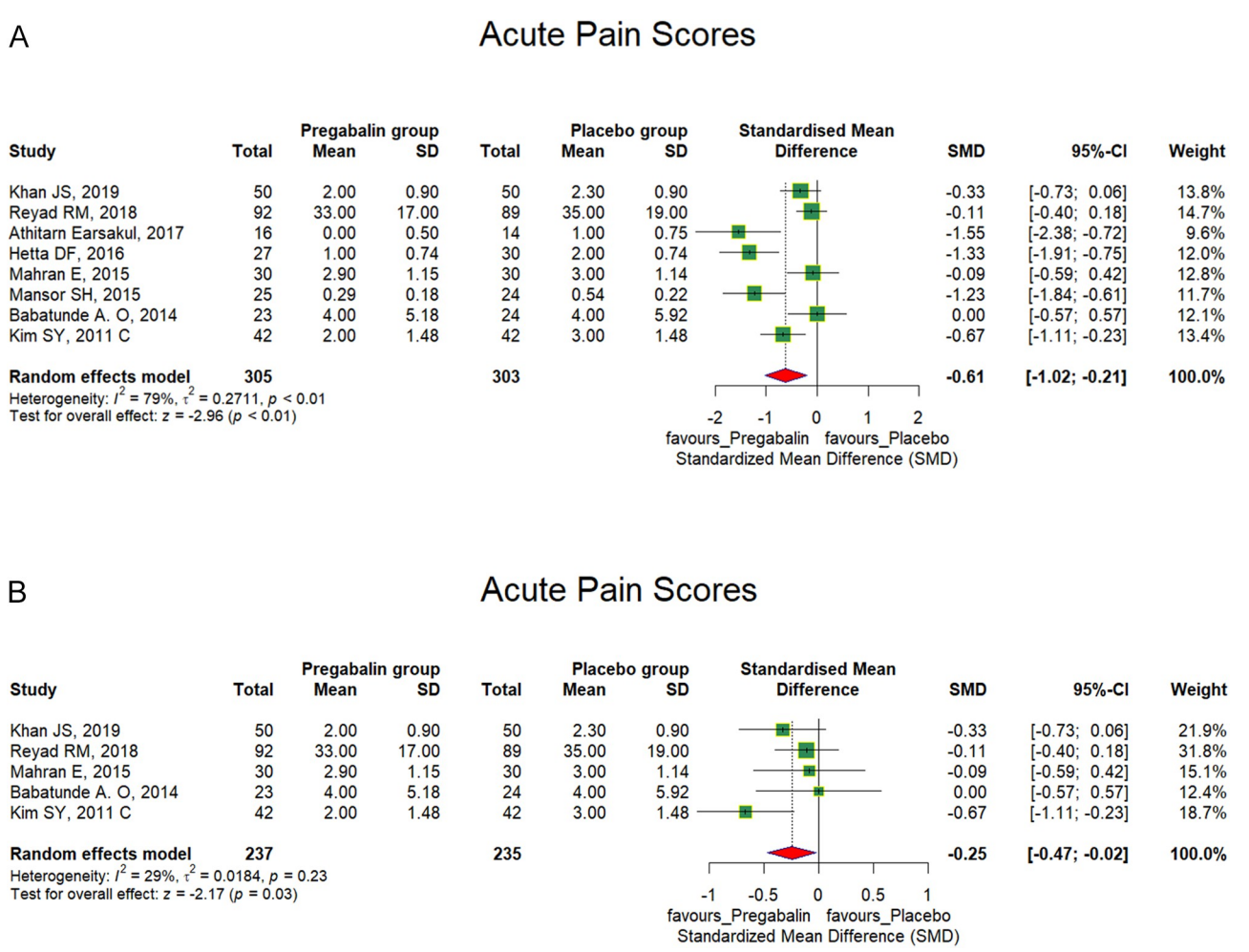

Figure 2. (A) Forest plot of acute postoperative pain scores (un-adjusted). (B) Forest plot of acute postoperative pain scores (adjusted).

co-administration of analgesics may also contribute to this variability. Upon excluding three studies, the sensitivity analysis revealed a significant reduction in heterogeneity (from 78.6% to 29.2%) for acute pain scores. It seems that these studies may have been unique instances that had a significant influence on the overall dispersion. However, it is important to approach this finding with caution considering the potential for exclusion bias and the limited amount of available data.

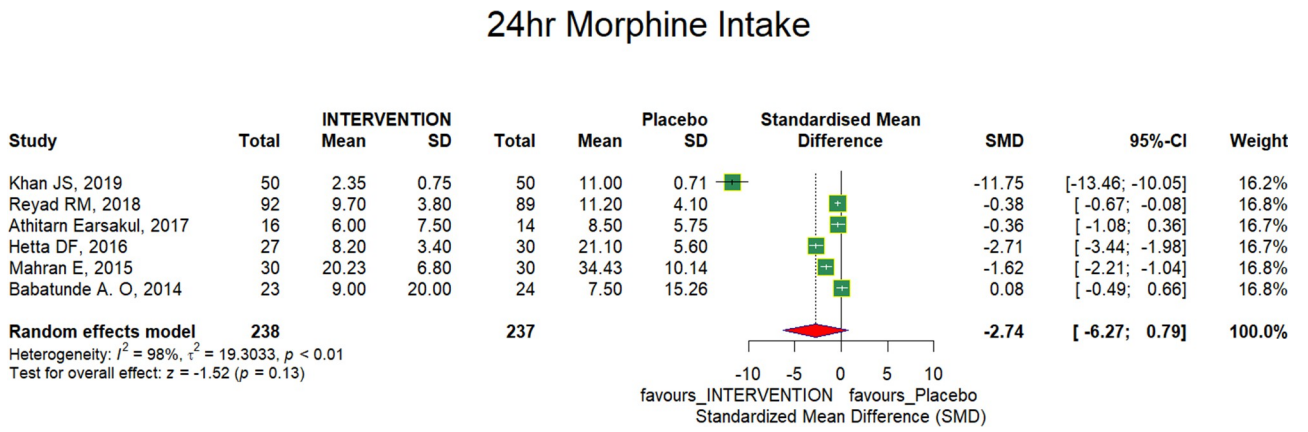

Figure 3. Forest plot of 24-hr morphine intake.

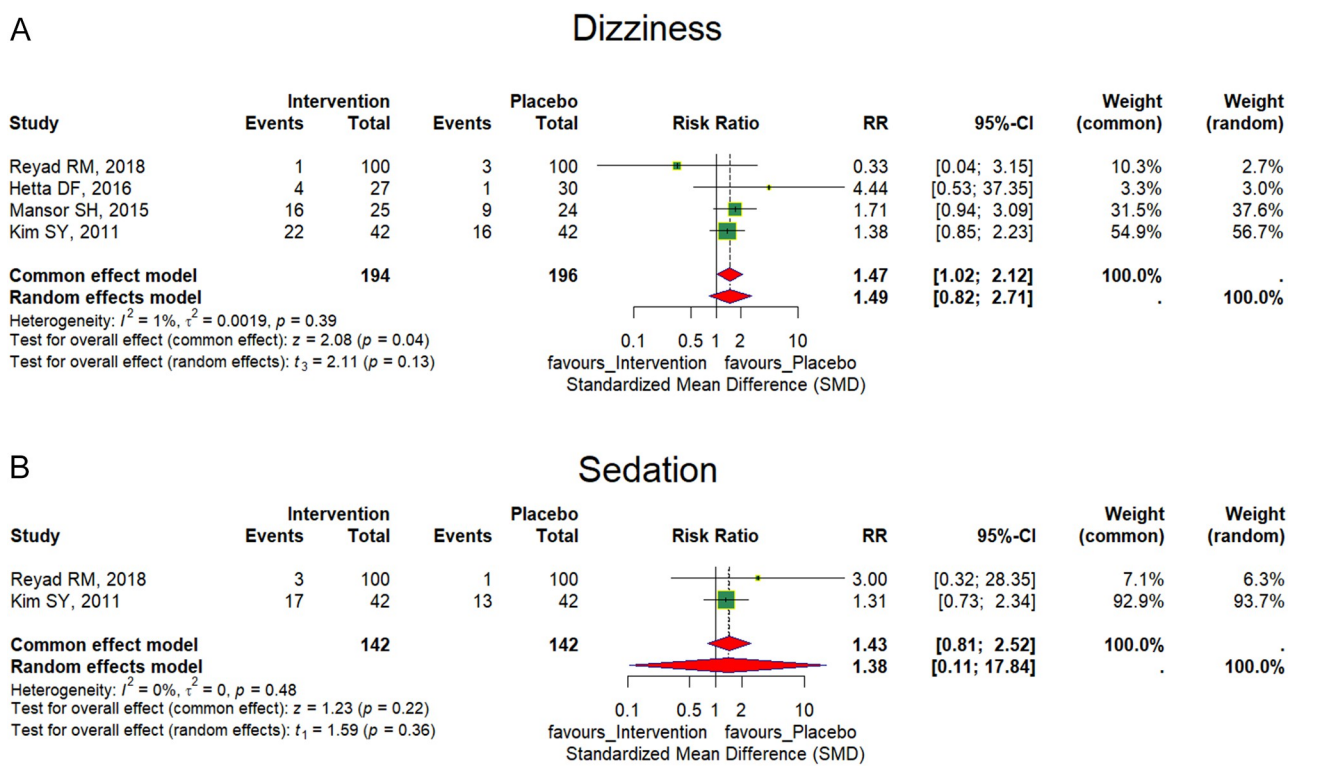

Figure 4. (A) Forest plot of adverse effect dizziness. (B) Forest plot of adverse effect sedation.

While there is a significant decrease in acute pain scores observed with the use of pregabalin, it is crucial to acknowledge that we cannot definitively claim that pregabalin reduces acute pain scores after mastectomy. This is because there is significant heterogeneity and a risk of bias present in the studies. However, even with these limitations, the observed reduction in pain scores may indicate clinically meaningful benefits, such as improved patient comfort and potentially a lower risk of developing chronic pain syndromes as previously stated by Reyad *et al*[29]. Further investigations using more extensive, standardized trials and precise inclusion criteria are required to validate our results and investigate the causes of heterogeneity. Performing subgroup analyses that take into account characteristics such as dosage, surgical technique, and baseline pain could yield more precise and detailed information on the effectiveness of pregabalin for different types of patients. Additionally, it would be beneficial to investigate the possible beneficial interactions with other medications that are commonly administered after surgery.

Limitations

Despite conducting a thorough analysis, our study does possess certain potential limitations. The observed heterogeneity in acute pain scores (I^2 = 78.6%) indicates that the treatment effects of pregabalin may differ based on several factors, including surgical techniques, participants' initial pain levels, and the administration of supplementary analgesics. Furthermore, the scarcity of studies eligible for inclusion amplifies the likelihood of bias and raises doubts about the credibility of our findings. The interpretation of results is further complicated by the presence of publication bias and quality limitations in study design.

Conclusion

Our meta-analysis demonstrates that pregabalin is highly effective in reducing acute hyperalgesia following mastectomy. However, the presence of heterogeneity and biases within the included studies must be acknowledged when assessing the potential benefits of pregabalin in managing acute post-surgical pain. Based on our research, pregabalin can relieve pain after surgery. Nevertheless, it is imperative to carry out additional extensive research to substantiate this result.

Given the evidence we have gathered, it is challenging to reach a conclusive determination regarding the influence of pregabalin on morphine intake or safety. The main reason is the broad range of confidence intervals for adverse effects. Additional research is necessary to determine the safety of pregabalin after surgery, given the current lack of information on this topic.

In light of these drawbacks, our analysis offers compelling evidence in favor of pregabalin's usage in the treatment of postoperative pain in patients with breast cancer. Recognizing and addressing the limitations of our study is crucial for future research to strengthen the evidence and offer recommendations for clinical practice. Improving pain management following mastectomy may significantly

improve the quality of life for individuals diagnosed with breast cancer.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

There is no funding to disclose.

Author's contributions

Conceptualization: R.G., P.D., I.M., S.G.P.; Methodology: R. G., P.D.; Validation: R.G., P.D.; Formal analysis, Investigation: R.G.; Data curation: R.G., P.D.; Writing-Original draft: R.G., P. D., I.M., S.G.P.; Visualization: R.G., P.D., I.M.; Writing-Review and editing: R.G., P.D., I.M., S.G.P.; Editing: R.G., I. M.; Supervision, Project administration: I.M.

Conflicts of interest disclosure

There are no conflicts of interest to disclose.

Research registration unique identifying number (UIN)

A predetermined study protocol has been registered on Prospero in October 2023 (ID=CRD42023472289). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023472289.

Guarantor

Rohit Ganduboina.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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