Systematic Review

Does Gabapentin Decrease Post-Mastectomy Acute And Chronic Pain? A Systematic Review Of Clinical Trials

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Abstract

Introduction: Mastectomy is associated with moderate to severe pain. Researchers are recently exploring new modalities and drugs to avoid numerous side effects associated with prescribed narcotics. For treatment, gabapentin is a widely used medication, but there is no comprehensive report on the post-mastectomy effects of this medication. Thus, this study aims to evaluate the effects of gabapentin on managing acute pain after surgery.

Methods: This was a systematic review (PRISMA checklist) study in which clinical trial articles published between 2000-2020 using the Cochrane checklist in PubMed, OVID, Medline, Scopus, Web Of Science with breast keywords cancer, gabapentin, postoperative pain, mastectomy, breast surgery, postoperative analgesia, ERAS, multimodal therapy were sought to evaluate the effect of gabapentin on post-mastectomy pain.

Results: In the initial search, 288 articles were found. Twenty-one articles were ultimately selected by repeated trading off, including reviewing texts and abstracts, outcomes, results, and the general conclusion, and included in this meta-analysis; The results of most studies have shown that gabaanthin can lead to Acute and Chronic Pain Decrease Post-Mastectomy. Gabapantin also reduced the need for drugs to control pain.

Conclusion: Dispensing gabapentin as a single treatment or in combination with other therapies meaningfully alleviates pain and diminishes drug use after breast surgery.

Keywords: Breast cancer, Mastectomy, Pain, Gabapentin

Submitted:

Introduction

Narcotics are currently the most commonly prescribed drug [1] and accepted as the first line of therapy in postoperative pain control [2, 3]. However, outcomes and side effects caused by excessive administration entail taking precautionary measures [4]. Choosing drugs does not merely depend on their pain-alleviating effects, but the side effects are also strongly in play. Thus, dispensing other drugs

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with narcotics can decrease pain, diminish the volume of narcotics and associated side effects [5].

Mastectomy is one of the most common procedures in Iran and worldwide [6]. The majority of these operations are done to treat breast cancer, which is the most common cancer in women [7, 8]. Other procedures are done on benign diseases, cosmetic settings, and also breast reconstruction after mastectomy. Mastectomy is among operations with moderate to severe postoperation pain [9]. It has been found that about 40 to 60 percent of women who undergo mastectomy experience acute postoperative pain. Likewise, about 10 to 60 percent of women experience chronic pain after surgery [10]. Importantly, the severity of acute pain after mastectomy is a strong predictor of chronic pain [11].

In Iran, gabapentin is widely administrated for neuropathic pain, but it is rarely used in the treatment of acute postoperative pain [12, 13]. Studies on the effects of gabapentin on pain control (acute and chronic) have been performed, the majority of which have confirmed the effectiveness of this drug; However, in a small number of articles, the effects of this drug compared to placebo have not been able to significantly lead to pain management; Because chronic pain after a mastectomy can be more severe in patients seeking complementary therapies such as chemotherapy and radiotherapy, and pain management in these patients must be determined, the effects of gabapantin need to be addressed in an article. Be collected and presented systematically; Because most breast cancer experts do not know exactly this[7, 9]. Since breast surgery is among the most common operations in Iran, it is crucial to control drug use in the treatment of postoperative pain [14]. Thus, we attempt to determine the effect of gabapentin on the prescription of narcotics, associated side effects, and control of acute pain after mastectomy. The purpose is to evaluate the effectiveness of gabapentin for use in this type of surgery.

Methods

This was a systematic review (PRISMA checklist) conducted by searching clinical trial published articles from 2000 to 2020 in Pubmed , Embase ، Cochrane Library ،Scopus ،Web of Science . The keywords recorded by the two chief researchers included breast cancer, gabapentin, postoperative pain, mastectomy, breast surgery, postoperative analgesia, ERAS, and multimodal therapy, which were searched with Boolean operators "AND" and "OR" in the databases. Keywords were selected according to Mesh.

The keywords breast cancer, gabapentin, postoperative pain, mastectomy, breast surgery, postoperative analgesia, ERAS, and multimodal therapy with Boolin operators were searched for the following: breast cancer AND gabapentin; gabapentin AND postoperative pain; breast surgery AND

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postoperative analgesia; multimodal therapy AND breast surgery; gabapentin AND breast surgery; breast surgery OR breast cancer; gabapentin OR postoperative pain; multimodal therapy OR postoperative pain.

Inclusion criteria were articles published in Persian or English between 2000 and 2020, randomize clinical trial articles, and full-text articles. Exclusion criteria were articles irrelevant to the main topic of our study, articles reporting no outcome (pain), low-quality articles (Cochrane tool was used to evaluate the quality), and articles presented at conferences partially.

Keywords were searched by two separate researchers by the above operators. Articles were found within a week by two main researchers and entered into EndNote. Databases of articles found in the first stage were further analyzed to finding more relevant articles. Then, the relevant articles were searched among all articles, and those reporting on consequences of post-mastectomy pain and the effects of gabapentin on its control were listed. In the next step, the clinical trial articles were picked, and ultimately, the articles with full text were included in this systematic review. PRISMA (Preferred Reporting Items for systematic Meta-Analysis Reviews and) checklist was used to evaluate the quality of the articles; Based on this, study selection, data collection process or data extraction, risk of bias, synthesis of results were examined by the researchers.

In this study, Cochrane tool was used to evaluate the quality of articles. This tool examines clinical trial studies for randomization, allocation concealment, blinding, selective outcome reporting, outcome reporting, and other biases. Due to the fact that in this study, the reviewed articles were heterogeneous, the findings were reported systematically. Finally, the data were analyzed using PRISMA instructions.

Results

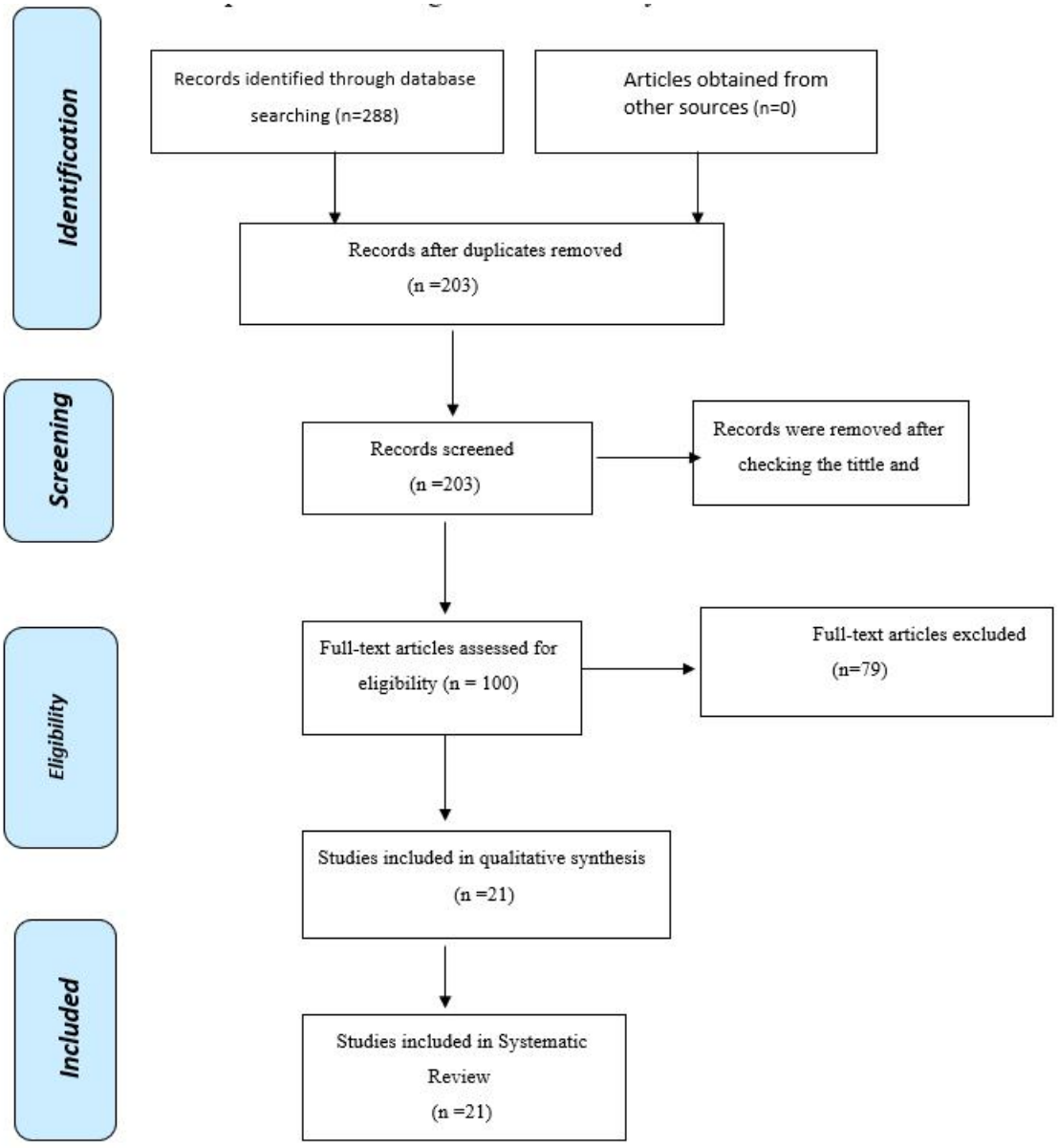
In the initial search, 288 studies were found, which were reviewed at different stages, including review of texts and abstracts, review of consequences, review of reported results, and review of general conclusions. Finally, 21 studies were included in this systematic review. [15-35]. Flowchart 1 shows the process of including studies in a systematic review. A summary of the study results is described below and due to the similarity of the study results, it was not presented by the table.

In 13 studies, the effect of gabapentin was compared with placebo to estimate its effect on surgical pain in a clinical trial. In 10 articles out of 21, gabapentin was compared with placebo alone, of which one study showed no change in postoperative pain while in the remaining the reduction in pain was observed. In four studies, patients were evaluated in three groups, a group receiving

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placebo and the other two groups receiving medication. Metry et al. showed that pre-and postoperative administration is effective in reducing pain during movement and rest as compared to the placebo group. Gosai et al. reported alleviated pre-and postoperative pain upon dispensing gabapentin.



Flowchart 1. The process of entering articles into the systematic review

In other studies, gabapentin only reduced pain during movement, e.g., compared to venlafaxine in the study by Amr and Yousef, and mexiletine in the study by Bharti and et al. In four studies, gabapentin was not prescribed as a single drug but simultaneously with other drugs at varying intervals after surgery, or with nerve blocks, and compared with the second group. In their 2005 study, Fassoulaki

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et al. used gabapentin with a local anesthetic cream and brachial plexus and intercostal nerve block. In the control group, oral placebo, topical placebo cream, and injectable normal saline were used alternatively. Gartner et al. prescribed gabapentin before the surgery, paracetamol, dextromethorphan, and celecoxib preoperatively, and dexamethasone and ondansetron intraoperatively in the case group, and did not use any treatment or modality in the control group. Chiu et al. used no medication in the control group. In the case group, however, they administrated acetaminophen, scopolamine, regional anesthesia, and paravertebral block with gabapentin preoperatively, and dexamethasone and ondansetron intraoperatively. Barker et al. prescribed gabapentin with acetaminophen or celecoxib in group I, injectable acetaminophen in group II, and no drug in group III (the control group). All four studies have evaluated the effect of gabapentin on pain relief and diminishing uses of narcotics.

Some other works have studied the amount of anesthetic required with and without gabapentin. In all these studies, the demand for anesthetics has been reported to be reduced. Intraoperative use of fentanyl isoflurane, propofol, and remifentanil has been reported to be decreased (e.g., see Doha et al., Bharti et al., And Azemati et al.).

Discussion

Knowing the underlying mechanisms of postoperative pain enables us to find effective strategies and use various modalities. Similar to other surgeries, various methods are used for post-mastectomy pain control, such as dispensing oral drugs or injecting medications, single or in combination with other drugs [36, 37]. Each drug and the way of its use has its advantages and side effects. Furthermore, considering the anatomy and residence of the breast as an intradermal gland on ribs, and since its main nerves are coming from the intercostal nerves 2 to 6, invasive techniques such as local anesthetic injections, intercostal block, epidural chest anesthesia, and paravertebral block are often practiced to control pain after mastectomy.

Gabapentin is among anticonvulsants and was originally used to treat seizures caused by epilepsy. Gabapentin is structurally similar to Gammabutyric Acid but does not convert to gamma-aminobutyric acid or its agonists in the body. Additionally, gabapentin does not degrade gamma-butyric acid or inhibit its reabsorption. Gabapentin shows negligible binding to proteins and is excreted via the kidneys with undergoing little or no metabolism. It also shows no pharmacokinetic interactions with other drugs due to the lack of hepatic metabolism and ineffectiveness in inhibiting or inducing liver enzymes. Today, gabapentin has become the first-line drug for the treatment of neuropathic pain, especially diabetic neuropathy and herpetic neuralgia,

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due to its good therapeutic effect on neuropathic pain. Gabapentin uniquely affects voltage-dependent receptors of calcium channels (α2-δ1 subunit) and inhibition of calcium flow. These receptors are present in the dorsal root ganglia of the nerves (peripheral part of the nervous system). By inhibiting these receptors and calcium current, gabapentin prevents the transmission of pulses to the neurons of the posterior horn of the spinal cord (central part of the nervous system) and ultimately alleviates pain. Thus, gabapentin assists control pain by acting on both the peripheral nerves and the central nervous system.

Numerous studies have shown that dispensing gabapentin before surgery reduces pain intensity and drug use after surgery. In their 2016 study, Arumugam et al. systematically reviewed the effect of gabapentin on drug use in the first 24 hours after elective surgeries. Seventeen RCT studies were analyzed, including the data on 1793 patients who were candidates for elective surgery (including 20 mastectomy patients). They reported a significant reduction in drug use in the first 24 hours after surgery, increased drowsiness compared with placebo, and no difference in the rate of nausea and vomiting.

In their 2018 systematic survey, HU et al. similarly reviewed 79 RCT studies including 6201 patients candidates for various types of surgery, regardless of the type of operation. It was found that a higher dose of gabapentin leads to more reduction in drug use in the first 24 hours after surgery. Moreover, using a high dose of gabapentin (more than 900 mg) remarkably reduces the severity of pain during rest in the first 24 hours than lower doses (300 to 600 mg).

The results of our study showed that the use of papappantin can significantly reduce chronic pain after mastectomy; The use of this drug can also significantly reduce the need for analgesics. In a meta-analysis study by Fabritius et al., Researchers stated that gabapantin could not be useful in controlling chronic postoperative pain. On the other hand, another meta-analysis study by Fabritius et al found that Gabapentin cannot reduce the need for postoperative analgesia; In these two studies, more than 100 clinical trial articles were evaluated and the effects of this drug on pain control and its effects on reducing the need for analgesics in different surgeries were investigated, which seems to be the main reason for the difference in our results. Be with the results of these two studies [38, 39].

Other studies have specifically examined the effect of gabapentin on pain and drug use after mastectomy (separately or in combination with other surgeries). Rai et al. reviewed and meta-analyzed studies to evaluate the effect of pregabalin and gabapentin, including 8 RCT studies on gabapentin with a total of 516 candidates for breast cancer surgery. All the patients had received oral gabapentin before surgery to evaluate its effect on acute pain and

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postoperative morphine use. Gabapentin positively controlled acute postoperative pain and reduced morphine use after surgery, while it did not affect chronic postoperative pain. Jiang et al. systematically reviewed 9 RCT studies with a total of 576 patients who were candidates for mastectomy. They included all the results reported by Rai et al., as well as a 2010 RCT study. Systematic review results showed that using 300 to 1200 mg gabapentin before surgery diminishes morphine consumption by 4.9 mg, alleviates pain immediately and 24 hours after surgery, and reduces chronic pain and nausea. Fabritius et al. systematically reviewed 47 RCT studies evaluating the effect of oral gabapentin prescription before mastectomy, cholecystectomy, hysterectomy, and arthroplasty on postoperative pain and drug use. Ten studies, out of 47, evaluated 667 patients who were candidates for mastectomy. The sample size in these studies was larger than the study by Jiang et al. and two other 2010 and 2015 RCT studies, while it was lower than a similar 2002 study. The difference was in excluding or including older studies related to inclusion criteria. The results included a general reduction in pain intensity as well as a reduction in pain 6 hours after surgery at rest, 6 hours after surgery during movement, 24 hours after surgery during movement, and 24 hours after surgery at rest with gabapentin. At the same time, a decrease in drug use was observed in the first 24 hours after surgery.

In a review study by Felder et al. Examining the effects of gabapentin on pain control after cesarean section, the researchers found that there was no statistically significant difference between placebo and gabapentin at 6 hours before surgery but at 12 and 6 hours after surgery , This drug was able to significantly reduce pain and control pain; Therefore, it was recommended that this drug be used to treat pain after cesarean section; The results of their study are similar to the results of our study; Several other studies have shown similar results, in which gabapantin has been shown to reduce severity after various surgeries[40, 43].

Studies confirm the positive effect of gabapentin on pain relief, especially pain during movement, and reduction of postoperative drug use. Importantly, considering the advantages of combination therapy in postoperative pain control, gabapentin can be efficient as a single drug or as part of the combination therapies prescribed. It also affects postoperative complications, so that many studies have reported decreased, or at least not increased, postoperative nausea and vomiting. Such side effects, however, may appear upon using narcotics. Gabapentin additionally reduces intraoperative drug use, which may indicate an increase in pain threshold.

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One of the limitations of our study was access to the full text of the articles, which was tackled except in one case. Second, two articles were not in English and thus excluded from the study. And the third limitation was the non-uniformity of variables (e.g., the dose of drugs, the type of drug in the control group, and the side effects studied in the studies).

Conclusion

Studies show that gabapentin may be useful in controlling pain after mastectomy, so as a practical conclusion, it is recommended that this drug be used as one of the effective drugs in controlling acute pain after breast surgery. ; However, this issue needs further investigation. . Furthermore, given the necessity to prevent chronic pain after mastectomy, it is recommended to evaluate the effect of gabapentin on chronic pain after such surgeries in Iran. Gabapentin's efficiency in reducing drug consumption during anesthesia is also recommended to be investigated in a separate study.

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