



# **Efficacy of Preemptive Analgesia with Pregabalin in Orthognathic Surgery-A Systematic Review**

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Orthognathic surgery is a treatment approach that is used for correcting the congenital or developmental anomalies of maxilla and mandible as well as secondary deformities of trauma. During these procedure saws, chisels, separators, and plate screw systems are used. Postoperative pain is an acute pain that is accompanied by the inflammatory process that occurs as a result of surgical trauma, and gradually decreases with tissue recovery. The analgesic prevents the establishment of the central sensitization due to incisional injury (only covers the surgical period) and prevents the establishment of the central sensitization (covering the surgical and early postoperative periods). Pregabalin is a structural gama-aminobutyric acid (GABA) analogue. It has been shown in recent studies that pregabalin, which is involved in chronical pain treatment, can also be involved in acute postoperative pain treatment.

**Objectives:** The aim of this systematic review is to assess the efficacy of preemptive analgesia with pregabalin on postoperative pain in orthognathic surgery.

**Materials and Methods:** The Data Bases of PubMed, Cochrane and Google scholar were searched for the related topics along with a complimentary manual search of all oral surgery journals till September 2019. Articles were selected based on the inclusion criteria, which included all RCTs.

**Results:** From this systematic review it is concluded that pre-emptive analgesia with pregabalin is effective in lowering acute postoperative pain in the patients who have undergone orthognathic surgery.

**Conclusion:** In this systematic review we have concluded that, on average, a single dose of pregabalin was shown to decrease post-operative pain. More studies have to be done to evaluate the efficacy of the drug.

*Keywords: Preemptive analgesia; pregabalin; orthognathic surgery; pain; gaba analogue.*

## 1. INTRODUCTION

Orthognathic surgery is a well established method to correct various forms of dentofacial deformities (Aziz, 2004). With the current standards of surgery and anesthesia, this procedure is considered relatively safe with good results. But it can also be sometimes less satisfying due to complications associated with the procedure. Among the post-operative sequelae,

Pain is a horrifying experience which a person wants to avoid and it is pain associated with the procedure which makes a person very anxious about these procedures [1].

Introducing the concept of pre-emptive analgesia is a rewarding experience not only for the operator but also for the patient. Different explanations have been made for pre-emptive analgesia [2,1].

The analgesic prevents the establishment of the central sensitization due to incisional injury (only covers the surgical period) and prevents the establishment of the central sensitization due to incisional inflammatory injury (covering the surgical and early postoperative periods) [3,4,5]. Pre-emptive analgesia has been shown to significantly decrease acute post-operative pain [6].

Pregabalin is an oral medication known to have antiallodynic and anti-hyperalgesic properties useful for treating neuropathic pain in adults and been shown to be effective in pre-emptively reducing postoperative pain, opioid consumption, and opioid-related adverse effects. Pregabalin is a structural gamma-aminobutyric acid (GABA) analogue.

The mechanism of pregabalin is not completely known. Pregabalin also reduces the release of many neurotransmitters including glutamate, noradrenalin, P substance, and calcitonin gene related peptide [7,8,9]. From this study it is

concluded that pre-emptive analgesia with pregabalin is effective in lowering acute postoperative pain in the patients who have undergone orthognathic surgery. The aim of this systematic review was to analyse the existing literature to assess the efficacy of preemptive analgesia with pregabalin on post operative pain following orthognathic surgery.

## 2. STRUCTURED QUESTION

Is preemptive analgesia with pregabalin effective in lowering post operative pain following orthognathic surgery.

### 2.1 PICO Analysis

**Population:** Patients undergoing orthognathic surgery.

**Intervention:** Pregabalin.

**Comparison:** Placebo, NSAIDS.

**Outcome:** Postoperative control of pain.

## 3. MATERIALS AND METHODS

### 3.1 Search Methodology

#### 3.1.1 Inclusion criteria

*3.1.1.1 Criteria for considering studies for the Review*

#### **Types of studies:**

- . Randomized controlled trials
- . Clinical trials.

**Types of Participants:** Patients undergoing orthognathic surgery.

**Types of Intervention:** Postoperative discomfort is evaluated using pregabalin as a pre-emptive analgesic agent for the patients undergoing orthognathic surgery.

**Types of Comparison:** Postoperative discomfort is evaluated using placebo for the patient undergoing orthognathic surgery.

**Types of Outcome Measures:** Post-operative pain was evaluated using VAS scale for the patient undergoing orthognathic surgery.

### 3.1.2 Exclusion criteria

#### 3.1.2.1 The following studies were excluded

- Review articles
- Animal studies
- Invitro studies
- Studies not meeting inclusion criteria
- Languages other than English

### 3.1.3 Sources used

The Data Bases of PubMed, Cochrane and Google scholar were searched for the related topics.

We used free-text terms to search the following journals”.

- British Journal of Oral and Maxillofacial Surgery
- International Journal of Oral and Maxillofacial Surgery
- Journal of Oral and Maxillofacial Surgery
- Journal of Cranio Maxillofacial Surgery
- Quintessence International Journal

Only articles in English and human species were applied during the electronic search to include all the possible clinical trials that are relevant for the search phase of the systematic review. Reference list of the identified randomized trials were also checked for possible additional studies.

## 4. RESULTS AND DISCUSSION

Table 1 represents Variables of interest which is Pain scale. Table 2 represents General characteristics of the studies included. Fig. 2 represents post operative pain score in both the groups.

Adequate post-operative analgesia is a prerequisite for successful ambulatory surgery. The production of noxious stimuli and post-operative pain is a known entity in maxillofacial surgery that has been attempted to be alleviated by pre-emptive analgesia [3,1,2]. Postoperative pain management provides post-surgery early

mobilization, shortened hospitalization, reduced hospital expenses, and increased patient satisfaction.

Post BSSO postoperative pain was reported to be more intense than soft tissue surgery [10]. Furthermore, the possibility of inferior alveolar nerve injury after BSSRO leads to unpleasant sensations such as allodynia, hyperalgesia, dysesthesia and particularly a constant hyperalgesia and neuralgia is experienced in the lower part of the face [11].

Pre-emptive analgesia is one of the postoperative pain management methods. Pre-emptive analgesia is the analgesic application preceding painful stimulant beginning [12]. Many local and systemic agents were used for pre-emptive analgesia. Clonidine, ketorolac, ibuprofen, gabapentin, and more recently pregabalin can be listed among the systemic medications used for this purpose [13,14]. The premise behind these studies has been that the diminishment of pain at the site of noxious stimulation will decrease transmission to the brain and therefore decrease pain perception post-operatively. The production of noxious stimuli in surgical procedures produces neurogenic and inflammatory mediators that may propagate post-operative pain. The gate control theory of pain, put forward by Melzack and Wall [15], is the idea that physical pain is not a direct result of activation of pain receptor neurons, but rather its perception is modulated by interaction between different neurons. If the neurogenic and inflammatory mediators produced during surgery can be blocked or reduced prior to being perceived by the patient as pain, then there may be a decrease in post-operative pain. This may ultimately lead to a decrease in the amount of narcotic pain medicine consumed as well as an improved quality of life.

Pregabalin is an oral medication known to have antiallodynic and a n t i hyperalgesic properties useful for treating neuropathic pain in adults. Pregabalin binds to and modulates the alpha-two-delta subunit of the voltage• dependent calcium channel in the central nervous system exerting its intended effect to reduce neuropathic pain.

Several studies [15,16,17] have shown that post-operative pain following orthognathic surgery is one of the main sequela that is most concerning to patients. Finding a regimen of appropriate pre-operative anti-allodynic and anti-inflammatory

medications that are effective enough to block the neurogenic and inflammatory mediators of post-operative pain would be extremely beneficial in all aspects of surgery [18,19]. There have been no known prospective randomized

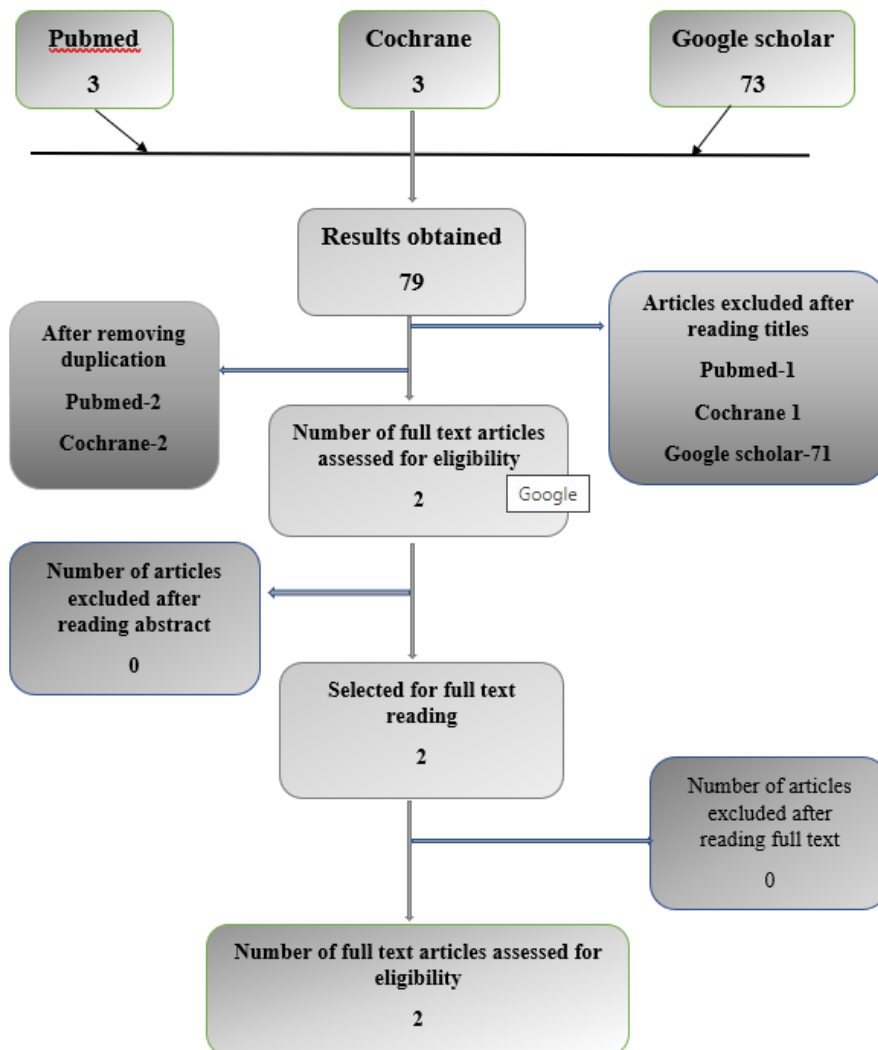
double blind placebo control clinical studies that have focused on the pre-emptive analgesic efficacy in orthognathic surgery, particularly those involving pregabalin.

**Table 1. Variables of interest**

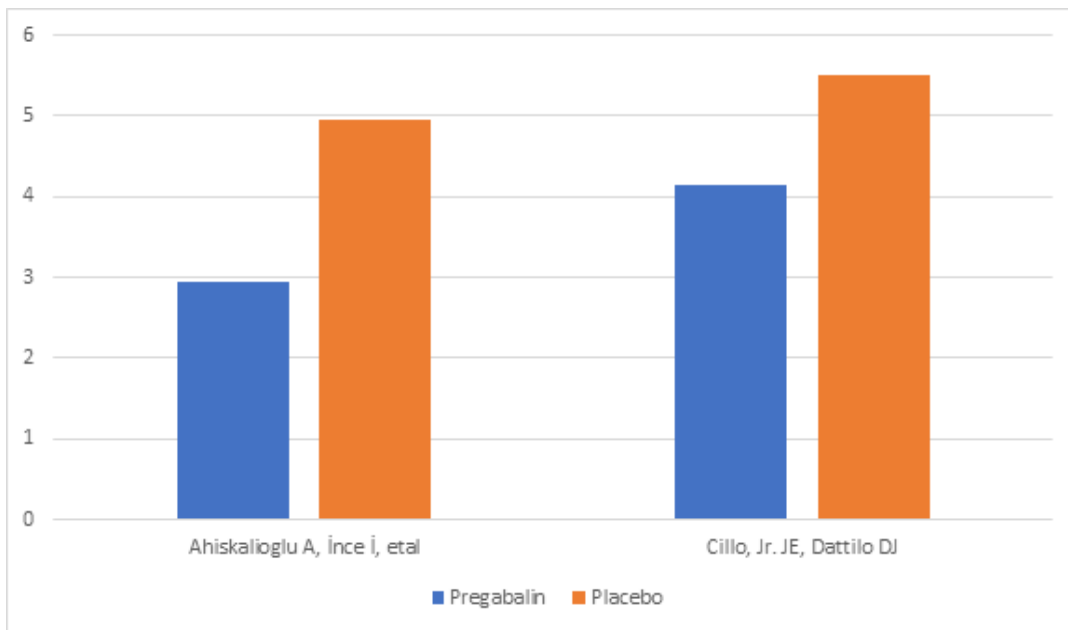
S No	Outcome measures
Clinical Parameter	Post-operative pain (Visual Analog Scale)

**Table 2. General characteristics of the studies**

S No	Author& Year	Study design	Sample Size	Age	Method of evaluation
1	Ahiskalioglu A Ince I et al. 2015	RCT	N=20	18-45 years	Post -operative pain using VAS Scale
2	Cillo Jr. JE, Dattilo 2014	RCT	N=40	18-60 years	Post -operative pain using VAS Scale



**Fig. 1. Schematic diagram**



**Fig. 2. Comparison of post operative pain using vas scale**

Fig. 2 represents Postoperative pain following Orthognathic surgery where X-Axis represents Groups (Pregabalin Group and Control Group) And Y-Axis represents Visual Analog Scale. This graph concludes there is a reduction in postoperative pain in Pregabalin group compared to Control group  $p < 0.05$  and it is statistically significant

The gabapentinoids, which are offered to market as antiepileptic and are effective by connecting to voltage dependent calcium channels, prevent central sensitization as well as hyperalgesia development, and are commonly used in the treatment of neuropathic pain [20]. There are studies that show the analgesic effectiveness of gabapentin in different surgical Groups [21,22].

Being a new derivative, pregabalin has a better pharmacokinetic profile and potency, in addition studies have been reported in different doses and surgeries which show its effectiveness in preventing postoperative pain. Pregabalin has antihyperalgesic, anticonvulsant, and anxiolytic properties similar to gabapentin, and has fewer side-effects and dose independent absorption. Pregabalin has antiallodynic and anti-hyperalgesic effects two to four times the dose when compared to gabapentin [23,24].

Recently, the multimodal analgesia approach has been supposed to be more effective than the traditional approach in post-operative pain treatment. Adding pregabalin to the analgesic approach in multimodal postoperative pain management increases the analgesic effect [4,5].

As a result, the addition of Pregabalin was associated with low VAS scores when compared to the control group. And the need of rescue

analgesia and opioid consumption seems to be less in those cases who received Pregabalin.

Studies have shown that postoperative pain was the most frequently encountered condition after orthognathic surgery. Pre-operative treatment for acute pain can be able to control or prevent post-operative pain.

In the literature 75-150mg of Pregabalin was used in reducing post-operative pain and its effectiveness was discussed. In both of the studies they have concluded that there was a significant reduction in post-operative pain following orthognathic surgery.

There are some limitations to this study, which includes, the number of patients involved in these studies were less. All patients in the studies were treated surgically in one institution. Only Post-operative pain was evaluated using the VAS scale, whether a single dose of pregabalin actually affected chronic pain should also be considered. Only a single dose of 150mg of Pregabalin was used preoperatively but not maintained postoperatively.

#### 4.1 Interpretation of Results

In a study conducted by Ahiskalioglu A et al in 2015, a total sample size of 40 with each one

group consisting of 20 patients. One group was given 150 mg of Pregabalin one hour before anaesthesia and one group was given an oral placebo. In pregabalin group, after undergoing orthognathic surgery, VAS was significantly low in first 24 hours and the analgesic requirement was less. The VAS score was 2.6-3.3 in Pregabalin group and 4.7-5.2 in control group.

In the study conducted by Cillo, Jr et al in 2014, a total number of 12 patients having Obstructive sleep apnea with each group consisting of 6 patients, one group was given 150mg of pregabalin and another group received placebo. There was significant reduction in VAS scale and opioid consumption  $4.3 \pm 3.5$  in pregabalin group and  $5.5 \pm 5.0$  in control group.

## 5. SUMMARY

The aim of this systematic review is to assess the efficacy of preemptive analgesia with pregabalin on postoperative pain in orthognathic surgery. There were 2 randomised controlled trails included in this systematic review. Both of the studies have used single dose of 150mg of pregabalin and evaluated post-operative pain in the first 24 hours. In these studies only less number of patients were evaluated. So more studies to be done in future. Thus in this systematic review we conclude that, a single dose of pregabalin is effective in reducing post-operative pain following orthognathic surgery.

## 6. CONCLUSION

In this systematic review we have concluded that, on average, a single dose of pregabalin was shown to decrease post-operative pain. More studies have to be done to evaluate the efficacy of the drug.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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