



**CATÓLICA**  
**FACULDADE DE MEDICINA DENTÁRIA**

---

VISEU

**THE USE OF METHYLPREDNISOLONE AFTER  
THIRD MOLAR SURGERY. A SYSTEMATIC  
REVIEW.**

Dissertação apresentada à Universidade Católica Portuguesa  
para obtenção do grau de Mestre em Medicina Dentária

Por:

Hélio Tomás Lourenço Libório

Viseu, 2024





**CATÓLICA**  
FACULDADE DE MEDICINA DENTÁRIA

---

VISEU

# **THE USE OF METHYLPREDNISOLONE AFTER THIRD MOLAR SURGERY. A SYSTEMATIC REVIEW.**

Dissertação apresentada à Universidade Católica Portuguesa  
para obtenção do grau de Mestre em Medicina Dentária

Por:

Hélio Tomás Lourenço Libório

Orientador: Bruno Leitão de Almeida

Coorientador: Tiago Gonçalves Ferreira Borges

Viseu, 2024



## Membros do Júri das Provas Públicas

**Presidente:** Professora Dra. Helena Salgado

**Arguente:** Professora Dra. Patrícia Fonseca

**Orientador:** Professor Dr. Bruno Leitão de Almeida

Data das provas públicas: 13/09/2024

Validação e confirmação pelos serviços escolares:

\_\_\_\_\_

\_\_\_ / \_\_\_ / \_\_\_

## **QUOTE**

**“Success is not final, failure is not fatal: it is the courage to continue that counts.” - Winston Churchill**



# **Acknowledgment**

**Aos meu pais,**

**Agradeço profundamente pelo apoio inabalável e pela presença constante ao longo desta jornada. O seu encorajamento e força foram fundamentais para que eu alcançasse este marco. Cada gesto e sacrifício feito em prol do meu sucesso não passaram despercebidos.**

**Ao meu orientador,**

**Expresso minha sincera gratidão pela sua orientação perspicaz e disponibilidade contínua. O seu apoio e conselhos foram cruciais para o desenvolvimento deste trabalho. Agradeço por partilhar o seu conhecimento e experiência.**



# Abstract

**Background:** Extraction of impacted third molars is a common procedure in dentistry, but the post-operative period can be uncomfortable. Methylprednisolone has emerged as a possible solution to improve outcomes. This systematic review seeks to evaluate its efficacy and safety, providing clear guidelines for oral health professionals and helping to optimize clinical practice and the patient experience.

**Materials and Methods:** This study adopted a PICO approach to search for articles related to the use of methylprednisolone in third molar extraction. Two databases were used (Medline/PubMed and Scopus). The search included articles published in the last 10 years, with the language restriction to English. The analysis of the articles followed the PRISMA principles, with pre-defined inclusion and exclusion criteria.

**Results:** Of the 158 articles identified, 149 were excluded due to duplication or not meeting the inclusion criteria. Nine articles were analyzed and five were selected for meta-analysis. In the methylprednisolone vs. control studies, there was no significant heterogeneity for pain at 24 hours ( $p=0.15$ ,  $I^2=47\%$ ) and 7 days ( $p=0.15$ ,  $I^2=47\%$ ), with non-significant effects ( $p=0.85$ ). In the inter-incisal reduction, there was homogeneity at 48 hours ( $p=0.96$ ,  $I^2=0\%$ ) and 7 days ( $p=0.37$ ,  $I^2=0\%$ ), with a greater reduction in the methylprednisolone group ( $p<0.01$  and  $p<0.05$ , respectively). Dexamethasone proved to be more effective than methylprednisolone in inter-incisal reduction at 48 hours and 7 days.

**Conclusion:** While recognizing variations in efficacy, methylprednisolone shows benefits after surgery for impacted third molars. Dexamethasone was more effective in inter-incisal reduction. A personalized approach is essential to optimize results and ensure patient well-being.

Keywords:

Third molar, impacted teeth, Methylprednisolone, Corticosteroids, Oral Surgery



# Resumo

**Introdução:** A extração de terceiros molares impactados é procedimento comum na medicina dentária, porém o pós-operatório pode ser desconfortável. A metilprednisolona surge como uma possível solução para melhorar os resultados. Esta revisão sistemática busca avaliar a sua eficácia e segurança, fornecendo orientações claras para os profissionais de saúde oral e contribuindo para otimizar a prática clínica e a experiência do paciente.

**Materiais e Método:** Este estudo adotou uma abordagem PICO na busca por artigos relacionados ao uso de metilprednisolona na extração de terceiros molares. Utilizaram-se duas bases de dados (Medline/PubMed e Scopus). A busca incluiu artigos publicados nos últimos 10 anos, com a restrição de idioma para inglês. A análise dos artigos seguiu os princípios PRISMA, com critérios de inclusão e exclusão pré-definidos.

**Resultados:** Dos 158 artigos identificados, 149 foram excluídos por duplicação ou não atenderem aos critérios de inclusão. Analisaram-se nove artigos, sendo cinco selecionados para meta-análise. Nos estudos de metilprednisolona vs. controlo, não houve heterogeneidade significativa para a dor às 24 horas ( $p=0.15$ ,  $I^2=47\%$ ) e 7 dias ( $p=0.15$ ,  $I^2=47\%$ ), com efeitos não significativos ( $p=0.85$ ). Na redução inter-incisal, houve homogeneidade às 48 horas ( $p=0.96$ ,  $I^2=0\%$ ) e 7 dias ( $p=0.37$ ,  $I^2=0\%$ ), com maior redução no grupo da metilprednisolona ( $p<0.01$  e  $p<0.05$ , respetivamente). A dexametasona mostrou-se mais eficaz que a metilprednisolona na redução inter-incisal aos 48 horas e 7 dias.

**Conclusão:** Embora reconhecendo variações na eficácia, a metilprednisolona demonstra benefícios após a cirurgia de terceiros molares impactados. A dexametasona foi mais eficaz na redução inter-incisal. Uma abordagem personalizada é essencial para otimizar os resultados e garantir o bem-estar do paciente.

**Palavras-chave:** Terceiro molar, Dentes inclusos, Metilprednisolona, Corticosteroides, Cirurgia Oral



# INDEX

<b>1.INTRODUCTION</b> .....	<b>- 1 -</b>
I.1 Framing the subject.....	- 3 -
I.2. Third molars and extraction indications .....	- 4 -
I.2.1. Third molar classification.....	- 5 -
1.2.1.1. Winter´s Classification .....	- 5 -
1.2.1.2. Pell & Gregory´s Classification .....	- 6 -
I.3. Postoperative complications of third molar surgery .....	- 8 -
I.4 Postoperative care and control.....	- 9 -
I.4.1 Role of NSAIDs in dentistry.....	- 10 -
I.4.2 Corticosteroids .....	- 11 -
I.4.2.1 Corticosteroids in Oral Surgery .....	- 13 -
I.4.2.2 Methylprednisolone.....	- 13 -
I.5. Objectives .....	- 14 -
<b>2.MATERIALS AND METHODS</b> .....	<b>- 17 -</b>
II.1. Study and recording protocol:.....	- 19 -
II.2. PICO question .....	- 19 -
II.3. Eligibility Criteria.....	- 20 -
II.4. Source of information and search strategy .....	- 21 -
II.5. Quality assessment .....	- 22 -
II.6. Statistical Analysis.....	- 22 -
<b>3.RESULTS</b> .....	<b>- 27 -</b>
III.1. Study selection, PRISMA.....	Erro! Marcador não definido.
III.2. Data extraction and outcome variables ...	Erro! Marcador não definido.
III.3 Characteristics of interventions .....	- 29 -
III.3.1. Methylprednisolone vs Control/ Placebo group .....	- 29 -
III.3.1.1. Trismus / Inter-incisal reduction.....	- 30 -
III.3.1.2. Pain.....	- 30 -
III.3.1.3. Swelling.....	- 30 -
III.3.2. Methylprednisolone vs Various Routes of Administration.....	- 31 -
III.3.3. Methylprednisolone vs Dexamethasone .....	- 31 -
III.3.3.1. Trismus / Inter-incisal reduction.....	- 31 -
III.3.3.2. Pain.....	- 32 -
III.3.3.3. Swelling.....	- 32 -

III.4. Study characteristics .....	- 33 -
III.5 Quality Assessment .....	- 36 -
III.6 Statistical Analysis.....	- 39 -
III.6.1 Methylprednisolone .....	- 39 -
III.6.1.1 Inter-incisal reduction .....	- 39 -
III.6.1.2. Swelling.....	- 41 -
III.6.2 Methylprednisolone vs Dexamethasone .....	- 41 -
III.6.2.1. Pain.....	- 41 -
III.7 Meta-analysis.....	- 42 -
III.7.1. Methylprednisolone VS Control Group.....	- 42 -
III.7.2. Methylprednisolone vs Dexamethasone.....	- 43 -
<b>4. DISCUSSION .....</b>	<b>- 47 -</b>
IV. Discussion.....	- 49 -
Statistical Analysis .....	- 49 -
Variability between studies.....	- 49 -
Methylprednisolone .....	- 49 -
Methylprednisolone vs Dexamethasone .....	- 51 -
Meta-analysis .....	- 52 -
Methylprednisolone vs Control Group .....	- 53 -
Methylprednisolone vs Dexamethasone .....	- 53 -
<b>5. CONCLUSION .....</b>	<b>- 57 -</b>
V. Conclusion .....	- 59 -
V.1. Methylprednisolone vs Dexamethasone .....	- 59 -
V.2. Methylprednisolone .....	- 59 -
<b>6. BIBLIOGRAPHY.....</b>	<b>- 61 -</b>
VI. Bibliography.....	- 63 -



# Tables and Figure Index



<b>Figure 1-</b> Angular variations of third molars according to Winter. (Adapted from Andersson et al.) .....	- 6 -
<b>Figure 2-</b> Pell–Gregory depth (A, B, C) and ramus impaction (1, 2, 3) groups on CBCT panoramic reconstructions.....	- 7 -
<b>Figure 3-</b> Flowchart following PRISMA guidelines.3 .....	- 24 -
<b>Figure 4 -</b> Meta-analysis results for pain (24h)4 .....	- 42 -
<b>Figure 5 -</b> Meta-analysis results for pain (7 days)5.....	- 43 -
<b>Figure 6 -</b> Meta-analysis results for inter-incisal reduction (48h)6 .....	- 43 -
<b>Figure 7 -</b> Meta-analysis results for inter-incisal reduction (7 days)7 .....	- 44 -
<b>Figure 8 -</b> Meta-analysis results for pain (24h)8 .....	- 44 -

<b>Table 1.</b> The duration of action and anti-inflammatory potency of glucocorticoids.(Adapted from Ngeow WC et al.)(31).....	- 12 -
<b>Table 2:</b> Articles .....	- 29 -
<b>Table 3:</b> Demographic Information (Part 1 of 2): .....	- 33 -
<b>Table 4:</b> Demographic Information (Part 2 of 2) .....	- 34 -
<b>Table 5:</b> Outcomes evaluation .....	- 35 -
<b>Table 6:</b> Overall Risk of bias assessment using The Cochrane Risk of Bias 2 (RoB2) tool (1).....	- 37 -
<b>Table 7:</b> Overall Risk of bias assessment using The Cochrane Risk of Bias 2 (RoB 2) tool (2).....	- 38 -
<b>Table 8 -</b> Overview of studies.....	- 39 -
<b>Table 9 -</b> Summary of studies on inter-incisal reduction.....	- 40 -
<b>Table 10 -</b> Summary of studies on inter-incisal reduction (methylprednisolone with a single group) .....	- 40 -
<b>Table 11 -</b> Summary of studies on edema (Tragus-Commissure) .....	- 41 -
<b>Table 12 -</b> Summary of studies on edema (Canthus-Gnathion) .....	- 41 -
<b>Table 13-</b> Overview of pain studies .....	- 42 -

## **List of abbreviations and acronyms**

**NSAIDs:** Non-steroidal anti-inflammatory

**PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses

**PICO:** Population, Intervention, Comparison, Outcome

**RCT:** Randomized Controlled Trial

**CCT:** controlled clinical trial

**VAS:** Visual analog scale

**DNA-** Data Not Available

**MMO-** Maximum mouth opening

**Preop.** - preoperatively



# 1. INTRODUCTION



# I. Introduction

## **I.1 Framing the subject**

The extraction of third molars is complex and requires a significant amount of time from the professional carrying it out. Due to the high vascularization of the region where these teeth are located, it is common for the surgical procedure to be followed by post-operative sequelae, such as edema, pain and trismus, which appear immediately after surgery (1–4).

During the first half of the 20th century, extractions were not routine, safe, or clinically predictable procedures, especially before the availability of antibiotics. At the time, surgeries were often followed by serious post-operative complications, often leading to postponement until the patient presented symptoms or pathologies related to the tooth in question. However, the second half of the 20th century witnessed great advances in third molar surgery, due to improvements in cutting instruments, anesthesia techniques and the emergence of new therapeutic agents. The use of auxiliary diagnostic radiographic examinations, such as panoramic dental radiographs, also contributed to these advances (4).

Pain following the extraction of these teeth is common and serves as a representative model of post-operative pain, often being used in the evaluation of analgesic drugs(4–6). Among the drugs most used to reduce post-operative pain are non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. While NSAIDs inhibit the synthesis of prostaglandins and thromboxane's, reducing the action of these mediators on nerve endings, corticosteroids have an effective anti-inflammatory action, although their regular use is controversial due to possible adverse effects (2,4,6).

NSAIDs have been extensively tested for their efficacy in controlling post-operative sequelae, showing favorable results such as a reduction in edema and pain. In addition, studies indicate that the preoperative administration of NSAIDs can reduce the postoperative need for analgesics, especially opiates, which can cause undesirable side effects. On the other hand, corticosteroids, despite their possible adverse effects, have been reported as effective in reducing typical post-

operative sequelae such as edema, pain and trismus, exerting their action at each stage of the inflammatory process (4,6).

This framing of the subject serves as a basis for more specific investigations into the use of methylprednisolone in third molar extraction, highlighting the importance of analyzing the efficacy and possible adverse effects of this drug in this surgical context (4).

## **I.2. Third molars and extraction indications**

The extraction of third molars is a common procedure in the field of oral surgery. As a result, there has been a great discussion about technical execution and associated care(7,8).

Frequent surgical management is due to the occurrence of complications or diseases related to wisdom teeth. However, there are situations in which there are no symptoms or signs but present associated pathology. Evidence-based decisions are paramount to make decisions about the procedure to follow (8–10).

Usually, the main indication for extraction is related to associated pathology. In the case of asymptomatic third molars, without pathology, one can monitor the patient as a result of risk-benefit ratio evaluation(8).

Based on scientific evidence, third molars that are impacted or erupted should be extracted in the presence of signs and/or symptoms such as: pain, tooth decay, changes in the periodontal health of adjacent teeth or infections.

Orthodontics, prosthetic and orthognathic surgery can also indicate the extractions.

Frequent indications for extractions are (4):

- Presence of apical periodontitis.
- Resorption observed in the third molar or adjacent teeth.
- Orthodontic considerations (such as preparation for orthognathic surgery).
- Periodontal disease with pockets  $\geq$  5mm starting in the distal area of the second molar.

-Recurrence or severity of pericoronitis.

-Identification of cysts or tumors related to the third molar.

-Caries that cannot be restored in the third molar or caries in the second molar that could be treated with restoration after extraction of the third molar.

-Presence of a third molar on a jaw fracture line.

In addition to the indications for extraction, we also need to know what the contraindications are. Although sometimes a tooth may be recommended for extraction, certain factors may prevent the procedure from being carried out. There are important considerations to be made regarding systemic contraindications, both absolute and relative, which can influence the decision to go ahead with extraction. Absolute systemic contraindications for any extraction procedure include conditions such as uncontrolled diabetes, leukemia, uncontrolled heart disease, kidney failure and severe liver complications such as cirrhosis (4).

On the other hand, relative systemic contraindications that should be taken into consideration are controlled diabetes, controlled hypertension, patients on corticosteroid therapy, coagulation problems, pregnancy, active infections and patients undergoing recent radiotherapy (4,8).

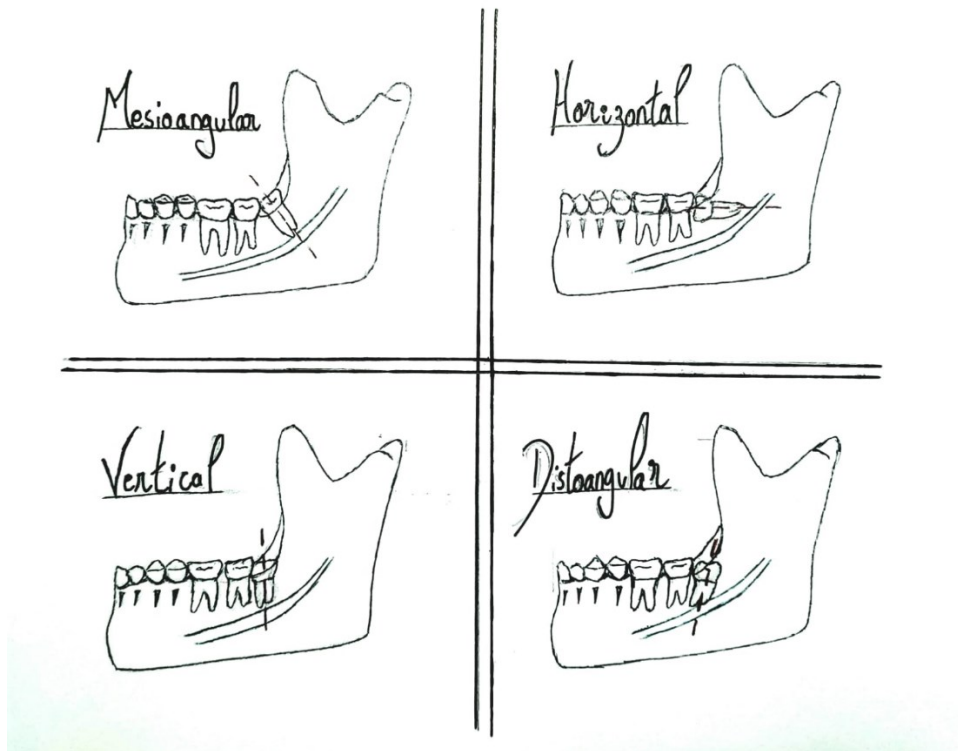
### **1.2.1. Third molar classification**

The classification of third molars has been a widely studied topic in dental literature, with various approaches developed over the years. The contributions of classic authors such as Winter, Tetsch and Wagner, Pell and Gregory, and Asanami and Kasazaki are fundamental to understanding the different categorization methods (11).

#### **1.2.1.1. Winter's Classification**

The Winter classification is the most used because it has the simplest classification method. This classification is based on the angulation of the impacted third molar, considering the angle formed between the long axis of the second and third molar. (1-vertical impaction/2-mesioangular impaction/3-

distoangular impaction/4-horizontal impaction/5-oral-lingual impaction/6-inverted impaction/7-other orientation) (4).



**Figure 1.** Angular variations of third molars according to Winter(4). (Adapted from Andersson *et al.*)<sup>1</sup>

### **1.2.1.2. Pell & Gregory's Classification**

According to the Pell & Gregory classification, third molars can be categorized into level A, B or C, depending on their depth in relation to the occlusal plane, and class I, II or III based on the available space to the mandibular ramus.

Regarding the occlusal plane:

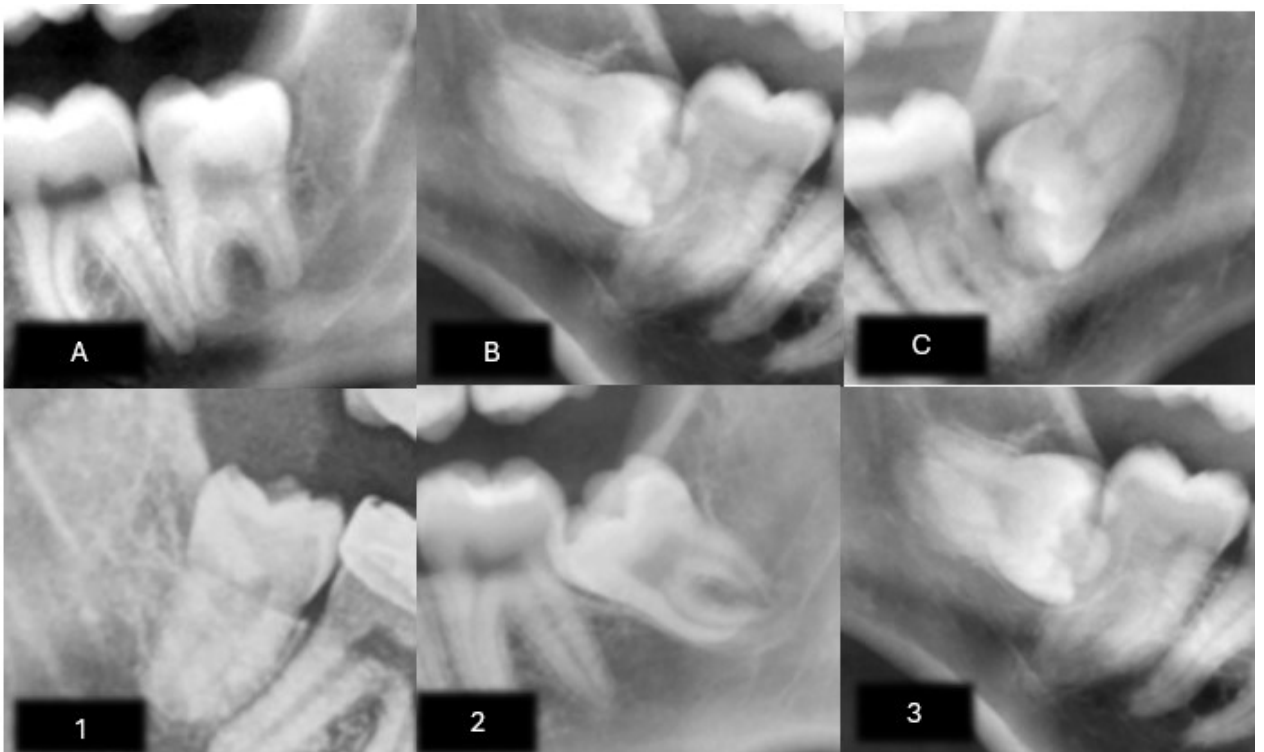
- A: The surface of the lower third molar is at or above the occlusal plane.
- B: The surface of the lower third molar lies between the neck of the second molar and the occlusal plane.
- C: The occlusal surface of the lower third molar is below the second molar.

Regarding the position in relation to the anterior margin of the mandibular ramus:

- Class 1: Distance between the distal surface of the second molar and the margin of the mandibular ramus is greater than the anteroposterior dimension of the crown of the lower third molar.

- Class 2: Distance between the distal surface of the second molar and the anterior margin of the mandibular ramus is less than the anteroposterior dimension of the crown of the lower third molar.

- Class 3: Complete absence of space between the anterior margin of the ramus of the mandible and the distal surface of the lower third molar.



**Figure 2.** Pell–Gregory depth (A, B, C) and ramus impaction (1, 2, 3) groups on CBCT panoramic reconstructions(12).

2

These classifications of impacted lower third molars allow us to determine the degree of impaction of the tooth and thus define and understand the degree of difficulty of the procedure (11,12).

### **I.3. Postoperative complications of third molar surgery**

Extracting a tooth is an invasive procedure and we need to provide to our patients the best pre-, intra-, and post-operative cares. Pain, trismus, and swelling are the most common post-operative complications in this type of surgery. We have different ways of approaching these situations depending on the type of surgery and patient (13).

Pain, one of the post-operative complications, is relative, as it depends on the perception of patient. The degree of pain, since there is no precise method for characterizing it, depends on each individual's tolerance threshold. As such, it will be influenced by various factors such as gender, age, the difficulty of the surgery and even the level of anxiety. Post-operative pain is associated with changes in the central and peripheral nervous systems due to the trauma caused by the surgery. This trauma leads to the release of the enzyme cyclooxygenase-2 (COX-2), which activates prostaglandins responsible for synthesizing peripheral nociceptors that cause inflammatory symptoms (4,14).

Pain is the post-operative complication that can have the biggest impact on the patient's life and therefore requires a great deal of attention. We should inform the patient that the pain will initially be stronger, peaking within the first 24 hours and will usually resolve within a maximum of 3 to 4 days. If this pain continues, it could be a sign of another complication (4,15–17).

As for trismus, this is defined by the limitation of maximum mouth opening. This becomes one of the most limiting post-operative sequelae reported by patients (4).

This complication results from the edema, as it causes compression of the nerve structures. It is usually most intense in the first 24 hours after surgery and has an average reduction in mouth opening of around 24%. As a rule, positive results can be seen after 7 days (1,4).

On the topic of edema, it is a consequence of damaged body tissue, regardless of the cause, which will have a physiological response through inflammation. Edema occurs due to an increase in osmotic pressure, transudation of fluids along the vessels to the injured area, changes in capillary permeability and local lymphatic obstruction (4,18).

This is a sequel that will have an impact on the patient's oral function, comfort, and appearance. Among the published studies on this issue, the duration of edema is most consistent between day 2 and 3. However, there are surgeries that are more complex than others and sometimes unwanted situations may occur. This may involve cases such as alveolitis, infections, tuberosity fractures in the case of the upper arch, jaw fractures, injuries to the inferior alveolar nerve in the case of the lower arch (19,20).

Some situations can only be defined later. Such as cases of alveolitis, which is defined by the presence of pain with the need for treatment between 2 and 5 days after surgery. In the case of paresthesia, it is defined as any change after surgery that involves sensitivity related to innervations associated with the trigeminal nerve. In case of infection, this is defined as the presence of purulent secretion in the place where the procedure/extraction was performed or painful induration (13,21).

These complications are also associated with factors such as: the degree of impaction; the patient's age and health status; the surgeon's experience; smoking habits; the use of contraceptives and the technique used (21).

Therefore, you must have good planning and a good forecast to solve the case in the best way, whether or not there are complications that were not expected (13,18,21).

#### **I.4 Postoperative care and control**

As already mentioned, third molar extraction causes a physiological inflammatory response in our body. The inflammatory response, focusing more on the sensation of pain during the period after surgery, can cause immense fear and anxiety in patients. In order for them to have a good quality of life in their daily lives, it is essential to use anti-inflammatory drugs to help control the most recurrent post-operative sequelae (4).

Non-steroidal anti-inflammatory (NSAIDs) drugs are the group of drugs most regularly used and prescribed by dentists when there is a dental intervention that requires symptom control. Nowadays, and especially for surgeries with a higher

degree of complexity and a predictably more complicated post-operative period, corticosteroids are beginning to be seen as an effective option for controlling post-operative symptoms (4,22,23).

#### **I.4.1 Role of NSAIDs in dentistry**

NSAIDs represent a diverse class of analgesics widely used around the world due to their anti-inflammatory, analgesic and antipyretic properties. Although NSAIDs offer considerable therapeutic benefits, such as pain relief and reduced inflammation, their use is limited by potential serious adverse effects, including peptic ulcers, digestive hemorrhages, and kidney failure. It is therefore crucial to carefully consider the indications and contraindications before prescribing these drugs to patients (4,24).

NSAIDs can be classified based on their therapeutic anatomy (ATC) or mechanism of action, especially considering cyclooxygenase (COX) inhibition. These drugs are often used as first-line analgesics for mild to moderate pain and can be combined with opioids for severe pain, potentiating their analgesic effects, especially in the inflammatory component of pain. It is important to emphasize that NSAIDs inhibit prostaglandin synthesis and are therefore indicated not only for the treatment of acute pain, but also for the prevention of post-operative pain. Several clinical studies have demonstrated the efficacy of NSAIDs in reducing post-operative pain and reducing the need for opioids during the recovery period (4).

In addition, NSAIDs are often prescribed for other painful conditions, such as headaches, migraines, myalgia, neuralgia, and dysmenorrhea. However, their most common use is associated with rheumatological diseases, including rheumatoid arthritis, gout, and arthrosis. A prominent example of an NSAID is ibuprofen, considered the prototype of the group. This drug has a potent peripheral analgesic and anti-inflammatory action, reversibly inhibiting COX-1 and COX-2 in a balanced manner. Its efficacy in controlling post-operative dental pain has been widely evaluated due to the combination of analgesic and anti-inflammatory effects (4,24).

In summary, NSAIDs play a significant role in dental practice, providing effective relief from pain and inflammation in a variety of clinical conditions. However, it is essential to consider their indications, contraindications, adverse effects, and drug interactions to ensure the safe and effective use of these drugs in clinical dental practice (4).

### **I.4.2 Corticosteroids**

Corticosteroids tend to be prescribed for a variety of conditions due to the fact that they are a type of medicine with a wide range of effects on the human body. They are synthetic analogues of natural steroid hormones that are produced by the adrenal cortex, their function and objective being to reduce inflammation by suppressing the immune system (25,26).

Corticosteroids act through lower layer glucocorticoids and upper layer mineralocorticoid receptors. This type of receptors is abundantly distributed throughout our brain, with the highest concentration of them in the hypothalamus, pituitary, and hippocampus region. It is also believed that glucocorticoids suppress myelin content in the brain, impair serotonin biosynthesis and provide norepinephrine uptake in the brain. With their more frequent use in medicine, healthcare professionals who work with this type of drugs must be familiar with their restrictions, toxicities, formulas, monitoring parameters and know how to best advise you. This can lead to problems such as depression, anxiety, insomnias, delirium, psychosis, thus having unwanted behavioral and cognitive effects (27,28).

In terms of absorption, corticosteroids are immediately absorbed from the gastrointestinal tract, where they vigorously bind to proteins, undergoing hepatic metabolism and renal excretion. These types of drugs are available in several ways: oral, intramuscular, intravenous, intra-articular, topical and aerosols for inhalation (27,29).

Corticosteroids are classified according to the duration of their action. *Short-acting* contain cortisone and cortisol (hydrocortisone), with an action time of less than 12 hours and an anti-inflammatory potency of 1. *Intermediate acting* has an action time of between 12 and 36 hours. These contain prednisone and

prednisolone with an anti-inflammatory potency of 4, 6-methylprednisolone and triamcinolone, both with an anti-inflammatory potency of 5 are examples of such drugs. Betamethasone and dexamethasone are *Long-acting* glucocorticoids, with a time of action greater than 36 hours and potency of anti-inflammatory character of 25 hours (30).

As described below in Table 1, to obtain a similar effect of 10 mg of prednisolone, it is necessary to prescribe 40 mg of hydrocortisone (cortisol), 50 mg of cortisone, 8 mg of methylprednisolone or 1.5 mg of betamethasone / dexamethasone. These doses are 2x the equivalent of what is physiologically generated by the adrenal cortex in an average individual during a normal day (31).

**Table 1.** *The duration of action and anti-inflammatory potency of glucocorticoids. (Adapted from Ngeow WC et al.) (31).*

Glucocorticoids	Anti-inflammatory potency	Duration of action	Equivalent dose
Cortisol	1	Short(<12h)	20
Cortisone	0.8		25
Prednisolone	4	Intermediate(12-36h)	5
Prednisone	4		5
Triamcinolone	5		4
6-Methyl prednisolone	5	Long(>36h)	4
Dexamethasone	25		0.75
Betamethasone	25		0.75

Corticosteroids reduce inflammation by preventing phospholipase A2 (this is the first enzyme involved in the conversion of phospholipids into arachidonic acid), thus blocking the synthesis of other products such as leukotrienes, prostaglandins and production that is related to thromboxane A2. Therefore, corticosteroids basically stop the formation of these end products, which are potent inflammatory mediators and cause the symptoms and signs described above (31,32).

### **I.4.2.1 Corticosteroids in Oral Surgery**

The use of corticosteroids in oral surgery has been recurrently practiced in the postoperative period. It has been reported to have an effective impact in relation to pain, trismus and flare-ups (31).

Corticosteroids, recognized for their anti-inflammatory efficacy, play a fundamental role in modulating the immune response and attenuating inflammatory reactions. This property makes them valuable agents in oral surgery, especially in the surgical removal of third molars, where inflammation plays a major role in post-operative discomfort. Unlike traditional analgesics and anti-inflammatories, which often relieve symptoms temporarily, corticosteroids act in a comprehensive manner, interfering with the inflammatory processes at deeper levels. This not only provides longer-lasting relief, but also reduces the need for multiple pharmacological agents, minimizing potential associated side effects (30,31,33).

Methylprednisolone, betamethasone, and dexamethasone are the corticosteroids most often used after impacted third molars surgery to decrease the initial inflammatory response. These can be administered by injection into the surgical area or systemically (30).

### **I.4.2.2 Methylprednisolone**

Methylprednisolone, which is a variant of prednisolone, is a synthetic corticosteroid, methylated at carbon 6 of the ring. On a par with dexamethasone, these two are possibly the most used corticosteroids in oral surgery, due to their minimal mineral corticoid action and excellent anti-inflammatory action. Methylprednisolone has good characteristics, considering that its biological half-life is around 18-36 hours (4,34).

In addition, methylprednisolone is indicated for endocrine diseases (e.g. adrenocortical insufficiency), non-endocrine diseases (e.g. dermatological, ophthalmic, respiratory, rheumatic, hematological, gastrointestinal and neoplastic diseases) and is also used to control severe allergic conditions and edematous states (induction of diuresis) (4).

As for its pharmacokinetics, methylprednisolone is independent of the route of administration and occurs in a linear way. If taken orally, the absolute bioavailability of methylprednisolone is high, between 82% and 89%. It is metabolized in the liver and is important to note that in the case of renal insufficiency it is not necessary to make dose adjustments. This is because methylprednisolone is haemodialysable. It is metabolized in the liver, mainly via the CYP3A4 enzyme pathway. It is important to note that in the case of renal insufficiency it is not necessary to make dose adjustments (4,34).

In terms of contraindications, methylprednisolone is absolutely contraindicated in patients with systemic fungal infections, or with hypersensitivity to any type of compound found in the drug (4).

There are, of course, adverse effects, which are typical of systemic corticosteroids, and not just methylprednisolone. Musculoskeletal, dermatological, metabolic, neurological, endocrine, ophthalmic, and even immune systemic disorders have been described after its use (34).

Regarding the dosage, mode, and route of administration of methylprednisolone; its dosage requirements vary and must be individualized for each situation, based on the disease and the response that the patient is going to have. Doses, can range from 4 to 48mg a day, depending on the situation. If after what is considered a reasonable period of use of this drug no significant response is seen, administration should be discontinued, and a new appropriate therapy instituted. If the drug has been used for a long period of time, the withdrawal must be gradual and not radical (4,35).

## **I.5. Objectives**

To evaluate the use of methylprednisolone in the postoperative period of impacted third molars, in relation to its efficacy in postoperative pain and edema, dosage regimens, forms of administration and adverse effects by using the PRISMA methodology. In addition, we also sought to analyze the impact of methylprednisolone after the extraction of impacted teeth compared to its non-use or the use of other drugs from the same pharmacotherapeutic group, according to the PICO question.





## **2. MATERIALS AND METHODS**



## **II. Materials and Methods**

### **II.1. Study and recording protocol:**

Type of study: Systematic review

The protocol observed in this systematic review was according to the PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (36).

This revision was registered in PROSPERO under the number: CRD42024512561.

### **II.2. PICO question**

PICO (Population/Intervention/Comparison/Outcome) study design was stipulated as model to formulate the clinical question:

What is the impact of methylprednisolone after the extraction of impacted teeth compared to its non-use or the use of other medications from the same pharmacotherapeutic group?

1.P(problem/population)

- Patients who underwent extraction of impacted teeth

2.I(intervention)

- Administration of methylprednisolone during the extraction of impacted teeth

3.C(Comparison/Control)

- Administration of other drugs from the same pharmacological group or no administration of drugs

#### 4.O(Objective/Result)

- Reduction of postoperative pain.
- Postoperative edema.
- Other complications of inflammatory origin
- Trismus
- Need for parallel analgesia
- Quality of life after extraction

### **II.3. Eligibility Criteria**

#### INCLUSION

- RCT's/CCT's less than 10 years old.
- Clinical studies in humans.
- Human studies with a minimum of 10 patients.
- RCT's (Randomized controlled trials) published in English.
- RCTs that contain the use of methylprednisolone in the postoperative period of extraction of impacted teeth in a control group

#### EXCLUSION

- *In vitro* studies.
- Reported cases.
- Case series.

## **II.4. Source of information and search strategy**

Two independent investigators (1 and 2) performed a digital search using Google and Safari search engines in the following electronic databases: Medline/PubMed and Scopus to find articles about methylprednisolone and that were related to the extraction of third molars.

A PICO approach was adopted in the search strategy. The search included articles published in the last 10 years. The search was limited to English-language articles as a specific eligibility criterion.

### PubMed/Medline:

(methylprednisolone) OR (corticosteroids) OR (steroids) AND ((third molar) OR (impacted teeth) OR (impacted tooth))

### Filters:

-RCT/CCT/SR-studies.

-10 years studies.

-Human studies.

-English studies.

### Scopus:

(methylprednisolone) OR (corticosteroids) OR (steroids) AND ((third molar) OR (impacted teeth) OR (impacted tooth))

## Filters:

- Limited to dentistry/limited article, review, final, English, all open access and 2013-2023

## **II.5. Quality assessment**

The quality of the study was independently assessed by two reviewers. The risk of RCT's bias was evaluated by using a revised Cochrane risk-of-bias tool for randomized trials (RoB2) (37). The domain of the tool (RoB2) was randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported outcomes.

## **II.6. Statistical Analysis**

The random effects model was used to analyze the variables, as it is the most recommended for generalizing results. It assumes that the effect of interest is not the same for all studies and considers that the studies under analysis form a random sample from a hypothetical population of studies. Heterogeneity is analyzed using Cochran's Q test and Higgins' I<sup>2</sup> statistic; the existence of heterogeneity is the manifestation of differences between studies in relation to the estimation of effects.

The method used to measure the effect was standardized mean differences. Effect measurement is at the heart of meta-analysis (38). It allows us to measure the effect of treatment or the impact of an intervention and can quantify the difference between two variables or the difference between two groups (39). The method used, difference in means, is used above all when the units of measurement are different from study to study, because by dividing the difference in means of each study by its standard deviation, a comparable measure is obtained between studies (39).

All statistical analyses were carried out using Review Manager 5.4 software.

In the analysis of variables where it was not possible to apply meta-analysis, a comparative analysis of the results of the studies was used.

## **II.7. Study selection, PRISMA**

Two independent investigators (1 and 2) conducted a digital search using Google and Safari search engines across the electronic databases Medline/PubMed and Scopus to identify articles discussing methylprednisolone in relation to the extraction of third molars. The search strategy followed a PICO approach and included articles published within the last 10 years, with a specific criterion limiting inclusion to English-language articles.

The search queries identified a total of 158 abstracts from 2 different databases and from hand searching.

A total of 149 articles were then excluded because they were duplicates and/or did not meet the predefined inclusion criteria. These were excluded after evaluation their title and abstract.

A total of 9 articles were selected for full text analysis.

After this analysis, it was found that these articles met the inclusion criteria and provided useful information for the project.

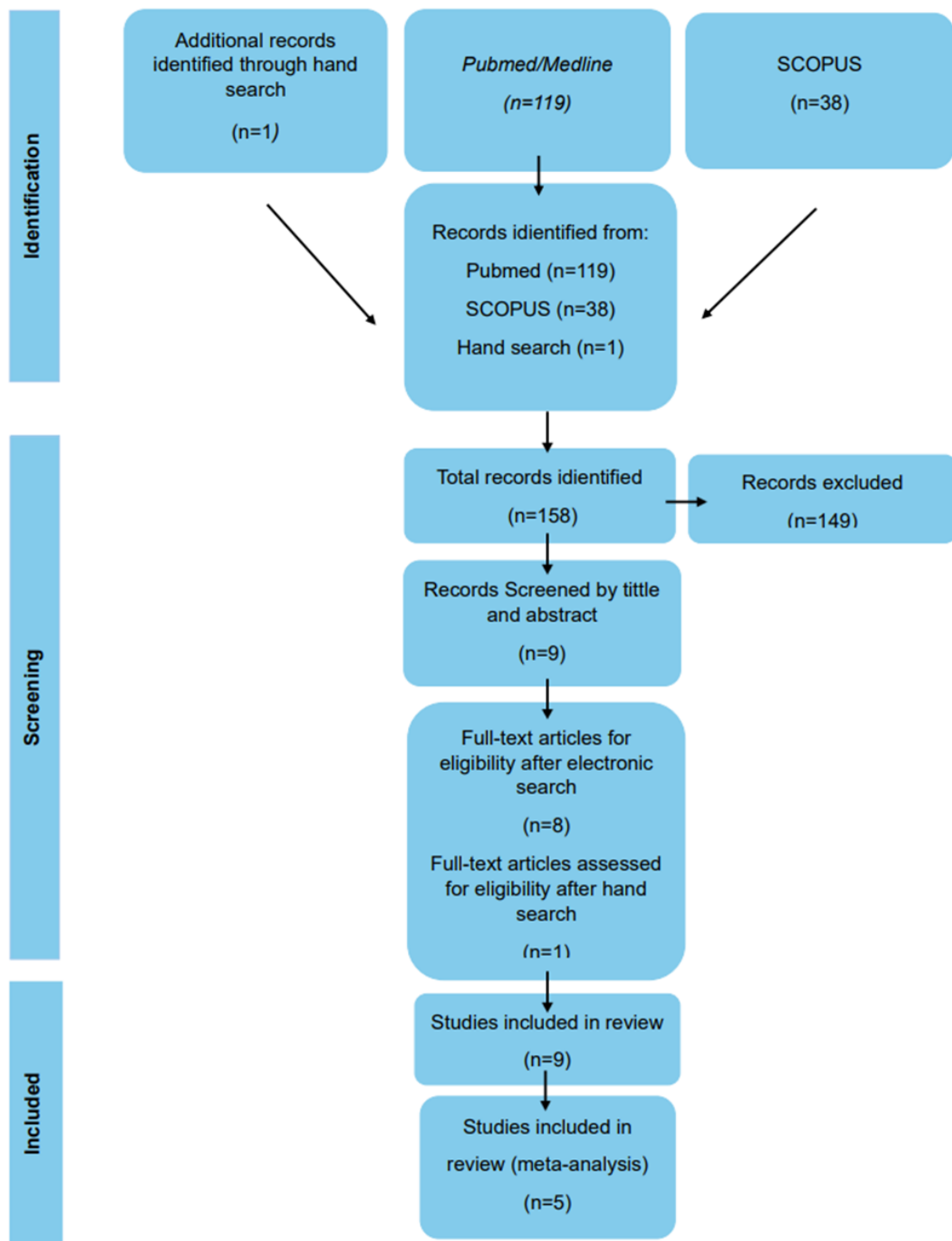


Figure 3: Flowchart following PRISMA guidelines.

## **II.8. Data extraction and outcome variables**

Two reviewers (1 and 2) independently extracted the data from the selected articles that met the inclusion criteria. Data was extracted based on the general characteristics of the study, characteristics of the population, methods of assessing postoperative surgical parameters.

Any discrepancies were resolved through discussion and collaboration. The data was collected in pre-defined tables:

- General information: study design, year of publication, number of patients and patient information.
- Information related to post-surgical assessment methods
- Main Outcomes: Method of swelling evaluation, Method of maximum mouth opening evaluation, Method of pain evaluation:
  - Method of swelling evaluation - assessed by measurements between various points (Tragus–commissure line and Canthus–gnathion line).
  - Method of maximum mouth opening evaluation- assessed in terms of its reduction, i.e. the measurement between upper and lower incisors before and after surgery.
  - Method of pain evaluation- assessed using the results of Visual analog scale (VAS), on a scale of 0-10.



### **3. RESULTS**



### III. Results

*Table 2: Articles*

AUTHOR	Year	Type of study	Title
Alcântara et Al.	2013	RCT	Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split-mouth randomized triple-blind clinical trial
Daniel Lim et Al.	2017	RCT	A comparative study on the efficacy of submucosal injection of dexamethasone versus methylprednisolone in reducing post operative sequelae following third molar surgery
Chug et Al.	2017	RCT	Submucosal injection of dexamethasone and methylprednisolone for the control of postoperative sequelae after third molar surgery: randomized controlled trial
Srivastava et Al.	2020	RCT	Comparison of Preemptive Effect of Dexamethasone and Methylprednisolone After Third Molar Surgery: A Split Mouth Randomized Triple-Blind Clinical Trial
Koçer et Al.	2014	RCT	Effect of the route of administration of methylprednisolone on oedema and trismus in impacted lower third molar surgery
Madhi Gholami et Al.	2021	RCT	What Are the Effects of Methylprednisolone Injection Into the Masseter and Gluteal Muscle on Pain, Edema and Trismus After Impacted Lower Third Molar Surgery? A Randomized Clinical Trial
Dattatraya A Darawade et Al.	2014	RCT	In Search of a Better Option: Dexamethasone Versus Methylprednisolone in Third Molar Impaction Surgery
M-K Larsen et Al.	2021	RCT	Efficacy of methylprednisolone on pain, trismus and quality of life following surgical removal of mandibular third molars: a double-blind, split-mouth, randomised controlled trial
Loganathan Selvaraj et Al.	2013	RCT	Comparison of Efficacy of Methylprednisolone Injection into Masseter Muscle Versus Gluteal Muscle for Surgical Removal of Impacted Lower Third Molar

#### III.1 Characteristics of interventions

##### III.1.1. Methylprednisolone vs Control/ Placebo group

5 studies (Koçer *et al.* (2014), M-K Larsen *et al.* (2021), Madhi Gholami *et al.* (2021), Daniel Lim *et al.* (2017), Chug *et al.* (2017)) compare methylprednisolone and the control/placebo group in the postoperative period of impacted third molars.

#### **III.1.1.1. Trismus / Inter-incisal reduction**

The assessment of postoperative trismus in the studies by Koçer *et al.* (2014), **M-K Larsen *et al.* (2021)**, **Madhi Gholami *et al.* (2021)**, **Daniel Lim *et al.* (2017)** and **Chug *et al.* (2017)** was a key aspect of the analysis carried out. The researchers examined the patients' range of mouth opening after impacted third molar extraction surgery, noting any restriction in mandibular movement. This objective assessment allowed a comprehensive understanding of postoperative trismus in each treatment group, highlighting possible differences between those who received methylprednisolone and the control/placebo group.

#### **III.1.1.2. Pain**

The assessment of postoperative pain in the studies by **M-K Larsen *et al.* (2021)**, **Madhi Gholami *et al.* (2021)**, **Daniel Lim *et al.* (2017)** and **Chug *et al.* (2017)** was a key part of the analysis carried out. The intensity and duration of pain reported by patients following the extraction of impacted third molars was examined using standardized pain assessment scales. This analysis allowed for a more in-depth understanding of the effects of methylprednisolone on post-operative pain relief compared to the control/placebo group. By considering these results, it is possible to identify any additional benefit provided by methylprednisolone in pain control, thus contributing to the development of more effective approaches to postoperative pain management.

#### **III.1.1.3. Swelling**

The analysis of postoperative swelling in the studies by **Koçer *et al.* (2014)**, **Madhi Gholami *et al.* (2021)**, **Daniel Lim *et al.* (2017)** and **Chug *et al.* (2017)** played a significant role in the research carried out. The levels of facial swelling in patients undergoing impacted third molar extraction were examined, noting any noticeable increase in the soft tissues around the surgical region. This assessment provided a comprehensive understanding of the effects of methylprednisolone in reducing postoperative edema compared to the control/placebo group.

### **III.1.2. Methylprednisolone vs Various Routes of Administration**

Three studies (**Koçer et al. (2014)**, **Madhi Gholami et al. (2021)** and **Loganathan Selvaraj et al. (2013)**) compared different routes of administration of methylprednisolone in the postoperative period after extraction of impacted third molars. Koçer et al. (2014) evaluated the oral, intravenous and masseter routes. Madhi Gholami et al. (2021) investigated the gluteal and masseter routes. Loganathan Selvaraj et al. (2013) administered the medication in the gluteal and masseter regions. This comprehensive analysis of these studies aims to investigate the relative efficacy of methylprednisolone administered by different routes, offering valuable insights for clinical practice by identifying the most effective route of administration to optimize the control of postoperative pain, edema, and trismus.

### **III.1.3. Methylprednisolone vs Dexamethasone**

5 studies (**Alcantara et al. (2013)**, **Daniel Lim et al. (2017)**, **Chug et al. (2017)**, **Dattatraya A Darawade et al. (2014)**, **Loganathan Selvaraj et al. (2013)**) compare methylprednisolone and dexamethasone in the postoperative period of impacted third molars.

#### **III.1.3.1. Trismus / Inter-incisal reduction**

The assessment of postoperative trismus in the studies by **Alcantara et al. (2013)**, **Daniel Lim et al. (2017)**, **Chug et al. (2017)**, **Dattatraya A Darawade et al. (2014)** and **Loganathan Selvaraj et al. (2013)** consisted mainly of measurements of mouth opening amplitude. These measurements were carried out using standardized assessment instruments, recording the distance between anatomical reference points in the mandible and maxilla. This assessment method allowed for a quantitative analysis of trismus, providing objective data on the extent of mouth opening limitation following impacted third molar extraction surgery. By considering these results, it is possible to obtain a more precise and detailed understanding of the impact of the surgical procedure on trismus and,

consequently, to evaluate the effectiveness of therapeutic interventions, such as the use of methylprednisolone and dexamethasone, in mitigating this adverse effect.

### **III.1.3.2. Pain**

The assessment of postoperative pain in the studies by **Alcantara *et al.* (2013)**, **Daniel Lim *et al.* (2017)**, **Chug *et al.* (2017)**, **Dattatraya A Darawade *et al.* (2014)** and **Loganathan Selvaraj *et al.* (2013)** was carried out exclusively using the Visual Analog Scale (VAS).

### **III.1.3.3. Swelling**

The assessment of postoperative edema in the studies by **Alcantara *et al.* (2013)**, **Daniel Lim *et al.* (2017)**, **Chug *et al.* (2017)**, **Dattatraya A Darawade *et al.* (2014)** and **Loganathan Selvaraj *et al.* (2013)** was considered as part of the analysis. The patients' facial edema after impacted third molar extraction surgery was examined, noting the presence and magnitude of the edema. This assessment provided an understanding of the extent of postoperative edema and its impact on patient recovery.

## III.2. Study characteristics

**Table 3: Demographic Information (Part 1 of 2)**

<b>AUTHOR</b>	<b>Year</b>	<b>Type of study</b>	<b>N° of Patients</b>	<b>Gender</b>	<b>Mean Age</b>
<b>Alcântara et al.</b>	2013	RCT	18	3M/12F	20.3 ±1.25
<b>Daniel Lim et al.</b>	2017	RCT	65	11M/49F Group 1: 3M/17F Group 2: 0M/20F Group 3: 8M/12F	Mean: 25±4 Group 1: 24.2 Group 2: 25.2 Group 3: 25.8
<b>Chug et al.</b>	2017	RCT	60	38M/22F	29.7
<b>Srivastava et al.</b>	2020	RCT	20	7M/13F	26.7
<b>Koçer et al.</b>	2014	RCT	44	18M/26F	29.6
<b>Madhi Gholami et al.</b>	2021	RCT	60	29M/31F Group 1: 8M/12F Group 2: 13M/7F Group 3: 8M/12F	Mean: 27.55 Group 1: 27.55 Group 2: 27.25 Group 3: 25.7
<b>Dattatraya A Darawade et al.</b>	2014	RCT	25	DNA	25.9±6
<b>M-K Larsen et al.</b>	2021	RCT	52	16M/36F	27±6
<b>Loganathan Selvaraj et al.</b>	2013	RCT	10	6M/4F	27±6

DNA- Data Not Available

**4Table 4: Demographic Information (Part 2 of 2)**

<b>AUTHOR</b>	<b>Follow Up</b>	<b>Surgeries</b>	<b>Dosage of administration</b>	<b>Drug administration route</b>
<b>Alcântara et al.</b>	24h/48h/72h/7days	32	Group 1: 8mg Dexamethasone Group 2: 40mg Methylprednisolone	Group 1: Oral Group 2: Oral
<b>Daniel Lim et al.</b>	24h/48h/72h/(5/7)days	65	Group 1: Control Group 2: 4mg Dexamethasone Group 3: 40mg Methylprednisolone	Group 1: Control Group 2: Masseter muscle Group 3: Masseter muscle
<b>Chug et al.</b>	48h/7days	60	Group 1: saline solution Group 2: 8mg Dexamethasone Group 3: 40mg Methylprednisolone	Group 1: Placebo Group 2: Submucosal Group 3: Submucosal
<b>Srivastava et al.</b>	24h/48h/72h/(4/5/7) days	40	Group 1: 40mg Methylprednisolone Group 2: 8mg Dexamethasone	Group 1: Masseter muscle Group 2: Masseter muscle
<b>Koçer et al.</b>	48h/7days	44	Group 1: Control Group 2: 20mg Methylprednisolone Group 3: 20mg Methylprednisolone Group 4: 20mg Methylprednisolone	Group 1: Control Group 2: Masseter muscle Group 3: Oral Group 4: Intravenous
<b>Madhi Gholami et al.</b>	24h/(5/7)days	60	Group 1: 40mg Methylprednisolone Group 2: 40mg Methylprednisolone Group 3: Control	Group 1: Masseter muscle Group 2: Gluteal muscle Group 3: Control
<b>Dattatraya A Darawade et al.</b>	24h/48h/72h/7days	50	Group 1: 8mg Dexamethasone Group 2: 40mg Methylprednisolone	Group 1: Oral Group 2: Oral
<b>M-K Larsen et al.</b>	24h/72h/7days/ 1 month	104	Group 1: 20mg Methylprednisolone Group 2: 30mg Methylprednisolone Group 3: 40mg Methylprednisolone Group 4: Saline solution	Group 1: Masseter muscle Group 2: Masseter muscle Group 3: Masseter muscle Group 4: Placebo
<b>Loganathan Selvaraj et al.</b>	48h/7days	20	Group 1: 40mg Methylprednisolone Group 2: 40mg Methylprednisolone	Group 1: Masseter muscle Group 2: Gluteal muscle

**Table 5: Outcomes evaluation**

<b>AUTHOR</b>	<b>Method of Swelling Evaluation</b>	<b>Method of Maximum Mouth Opening Evaluation (MMO)</b>	<b>Method of Pain Evaluation</b>
<b>Alcântara et al.</b>	Sum of the three measurements (corner of the eye/angle of the mandible-tragus/corner of the mouth-tragus/pogonion)	Reduction in MMO from baseline value	VAS score (0-10)
<b>Daniel Lim et al.</b>	Sum of 2 lines-corner of the eye to angle and tragus to corner of mouth. Measure as % change in baseline value. Reported in graphical data only	Maximum interincisal distance between pre-operative and post-operative days	VAS score (0-10)
<b>Chug et al.</b>	Sum of 2 lines-corner of the eye to angle and tragus to corner of mouth. Measure as mean change in base value in mm.	Reduction in MMO from baseline value	VAS score (0-10)
<b>Srivastava et al.</b>	Lines Tragus-Comissure +Gonion-external canthus + gonion-comissure	MMO	VAS score (0-10)
<b>Koçer et al.</b>	Lines Canthus–gnathion line; tragus–commissure line; tragus–pogonion	The distance between the upper and lower incisal borders of the central incisors was measured using a digital calliper	DNA
<b>Madhi Gholami et al.</b>	Measured by ultrasound imaging	Maximum interincisal distance between pre-operative and post-operative days	VAS score (0-10)
<b>Dattatraya A Darawade et al.</b>	Tape measuring method described by Ustun et al.	Measure of the distance between the right upper and lower central incisors with the help of a caliper	VAS score (0-10)
<b>M-K Larsen et al.</b>	DNA	Maximum interincisal distance between pre-operative and post-operative days	VAS score (0-100)
<b>Loganathan Selvaraj et al.</b>	Distance between tragus-lip commissure, gonion-lip commissure and gonion-external canthus of the eye using surgical silk thread	Measured with Caprovich callipers	VAS score (0-100)

MMO- Maximum mouth opening/ DNA- Data Not Available

### **III.3 Quality Assessment**

The risk of bias RCTs was evaluated by using a revised Cochrane risk-of-bias tool for randomized trials (RoB2) (37).

The domain of the tool (RoB2) was randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported outcomes.

**Table 6: Overall Risk of bias assessment using The Cochrane Risk of Bias 2 (RoB2) tool (1).**

References	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Alcântara <i>et al.</i>	-	-	-	-	*	-
Daniel Lim <i>et al.</i>	-	*	*	*	*	*
Chugh <i>et al.</i>	-	+	-	-	*	-
Srivastava <i>et al.</i>	*	-	-	-	*	-
Koçer <i>et al.</i>	-	*	*	-	*	*
Mahdi Gholami <i>et al.</i>	-	+	-	-	-	-
Dattatraya A Darawade <i>et al.</i>	*	-	-	*	*	*
M-K Larsen <i>et al.</i>	-	-	-	-	*	-
Loganathan Selvaraj <i>et al.</i>	*	+	*	*	*	*

Green (-) indicates that the study implemented robust measures, minimizing the risk of bias in the respective domain (Low risk).

Yellow (\*) suggest a lack of clear information or details in the study, making it difficult to determinate the risk of bias (Uncertain).

Red (+) indicates that the study has significant limitations or flaws in design or execution, increasing the risk of bias (High risk)

**Table 7:** Overall Risk of bias assessment using The Cochrane Risk of Bias 2 (RoB 2) tool (2).

## THE PERCENTUALS

Randomization process		
66.67%	33.33%	0%
Deviations from the intendend interventions		
44.44%	22.22%	33.33%
Missing outcome data		
66.67%	33.33%	0%
Measurement of the outcome		
66.67%	33.33%	0%
Selection of the reported result		
11,10%	88,89%	0%
Overall		
55.56%	44.44%	0%

### III.4 Statistical Analysis

Table 8 shows a summary of the studies used in this work. There is a great deal of variability in sample size, with one study having a sample of 10 patients and another with 65 patients, giving a mean value of  $39.33 \pm 21.18$  patients per study, which confirms the high variability as the standard deviation is high. Except for the studies by Chug *et al.* (2017) and Loganathan Selvaraj *et al.* (2013), female patients prevailed. The average age of the patients is relatively close between the studies, except for the Alcantara *et al.* (2013) study, which has the lowest average value, 20.3, and the Koçer *et al.* (2014) study, which has the highest average value, 29.6. Regarding the number of surgeries reported in the studies, this varies between a minimum of 20 and a maximum of 104, translating into an average value of 52.78 surgeries per study with a standard deviation of 24.06 surgeries, which reveals a disparity in the number of surgeries analyzed in the studies.

Table 8 - Overview of studies

Author	Type of study	N°of patients	Gender		Mean age	surgeries
			M	F		
Alcantara <i>et al.</i> (2013)	RCT	18	3	12	$20.3 \pm 1.25$	32
Daniel Lim <i>et al.</i> (2017)	RCT	65	11	49	$25 \pm 4$	65
Chug <i>et al.</i> (2017)	RCT	60	38	22	29.7	60
Srivastava <i>et al.</i> (2020)	RCT	20	7	13	26.7	40
Koçer <i>et al.</i> (2014)	RCT	44	18	26	29.6	44
Madhi Gholami <i>et al.</i> (2021)	RCT	60	29	31	27.55	60
Dattatraya A Darawade <i>et al.</i> (2014)	RCT	25			$25.9 \pm 6$	50
M-K Larsen <i>et al.</i> (2021)	RCT	52	16	36	$27 \pm 6$	104
Loganathan Selvaraj <i>et al.</i> (2013)	RCT	10	6	4	$27 \pm 6$	20

#### III.4.1 Methylprednisolone

##### III.6.1.1 Inter-incisal reduction

Table 9 shows a summary of the studies that reported results on inter-incisal reduction using methylprednisolone and compared it with the control group.

Koçer and Chug's results show that the experimental group has less reduction and that it decreases over time. On the other hand, in the 7-day results of Chug *et al.* and Madhi *et al.*, the average reduction is higher in the experimental group.

**Table 9 - Summary of studies on inter-incisal reduction**

Author	Administration route	Dose(mg)	Control(mm)			Methylprednisolone(mm)		
			Average (48h)	Average (7d)	n	Average (48h)	Average (7d)	n
Koçer <i>et al.</i> (a)	Oral	20	17.5	11.1	11	13.3	5.1	11
Koçer <i>et al.</i> (b)	I.V.	20	17.5	11.1	11	8	1.7	11
Koçer <i>et al.</i> (c)	Muscular(masseter)	20	17.5	11.1	11	7.7	1.6	11
Chugh <i>et al.</i>	Submucosal	40	7.2±4.54	1.4±2.45	17	5.5±4.73	1.7±3.09	23
Madhi <i>et al.</i> (a)	Muscular(masseter)	40	DNA	3.55	20	DNA	8	20
Madhi <i>et al.</i> (b)	Muscular (gluteal)	40	DNA	3.55	20	DNA	6.33	20

On the other hand, table 10 shows a summary of the studies that reported results on inter-incisal reduction using methylprednisolone and using a single group.

**Table 10 - Summary of studies on inter-incisal reduction (methylprednisolone with a single group)**

Author	Administration route	Dose(mg)	Methylprednisolone(mm)		
			Average (24h)	Average (48h)	Average (7d)
Selvaraj <i>et al.</i> (a)	Muscular(masseter)	40	DNA	10.8	4.7
Selvaraj <i>et al.</i> (b)	Muscular (gluteal)	40	DNA	11.1	3.3
Alcantara <i>et al.</i>	Oral	40	16.27±8.13	19.97±7.88	6.47±4.32
Lim <i>et al.</i>	Submucosal	40	8	7	2
Srisvastava <i>et al.</i>	Muscular(masseter)	40	DNA	15.85	7.15
Darawade <i>et al.</i>	Oral	40	14.64±7.30	17.97±7.09	5.82±3.88

### III.4.1.2. Swelling

Tables 11 and 12 show the results for Tragus-Comissure and Canthus-Gnathion edema, respectively, reported in Koçer's studies. For Tragus-Comissure, the experimental group has lower average values than the control group in all three studies and that in both groups the results decrease over time. For Canthus-Gnathion, the experimental group shows higher results on average than the control group in all three studies, and in both groups the results decrease over time.

**Table 11 - Summary of studies on edema (Tragus-Commissure)**

Author	Administration route	Dose (mg)	Control(mm)				Methylprednisolone(mm)			
			Preop.	Average (48h)	Average (7d)	n	Preop.	Average (48h)	Average (7d)	n
Koçer <i>et al.</i> (a)	Oral	20	114	126.4	120.6	11	114	123.0	117.5	11
Koçer <i>et al.</i> (b)	I.V.	20	114	126.4	120.6	11	116.6	122.4	117.3	11
Koçer <i>et al.</i> (c)	Muscular (masseter)	20	114	126.4	120.6	11	111.2	114.6	111.6	11

**Preop.** - preoperatively

**Table 12 - Summary of studies on edema (Canthus-Gnathion)**

Author	Administration route	Dose (mg)	Control(mm)				Methylprednisolone(mm)			
			Preop.	Average (48h)	Average (7d)	n	Preop.	Average (48h)	Average (7d)	n
Koçer <i>et al.</i> (a)	Oral	20	92	98.3	95.1	11	99,6	103.6	100.5	11
Koçer <i>et al.</i> (b)	I.V.	20	92	98.3	95.1	11	109.6	112.8	110.3	11
Koçer <i>et al.</i> (c)	Muscular (masseter)	20	92	98.3	95.1	11	101.9	102.9	101.9	11

**Preop.** – preoperatively

## III.4.2 Methylprednisolone vs Dexamethasone

### III.4.2.1. Pain

Pain was recorded in four of the studies analyzed (Table 13), where the results were compared between the Methylprednisolone group and the Dexamethasone

group. In the Alcantara *et al.* study, pain increased over time in both groups; in the Srivastava *et al.* and Darawade *et al.* studies, it decreased in the methylprednisolone group and remained the same in the dexamethasone group over time.

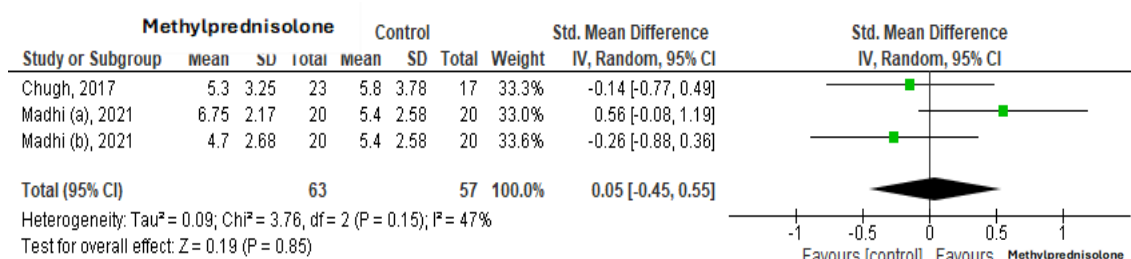
**Table 13-** Overview of pain studies

Author	Administration route	Dose(mg)	Methylprednisolone(mm)			Dexamethasone(mm)		
			Average (24h)	Average (48h)	n	Average (24h)	Average (48h)	n
Alcantara <i>et al.</i>	Oral	40	2	4	16	1	2	16
Srivastava <i>et al.</i>	Muscular (masseter)	40	7±6.60	6±6.05	10	7±6.80	7±6.45	10
Chugh <i>et al.</i>	Submucosal	40	5.3±3.25	DNA	23	3.5±3.13	DNA	20
Darawade. <i>et al.</i>	Oral	40	2,5	1,5	25	1,5	1,5	25

### III.5 Meta-analysis

#### III.5.1. Methylprednisolone VS Control Group

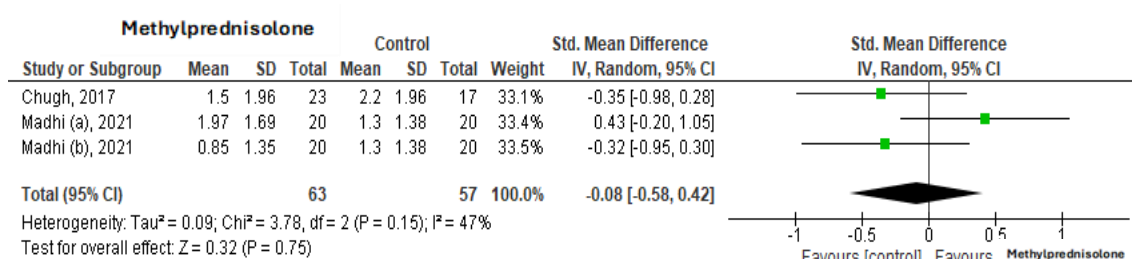
##### Pain (24h)



**Figure 4 -** Meta-analysis results for pain (24h)

Considering the results of figure 4, Cochran's Q (p=0.15>0.05) and I<sup>2</sup>=47%, it was concluded that heterogeneity was not significant between studies regarding pain at 24 hours. The forest plot shows that the effect of the meta-analysis 0.05 (95%CI [-0.45;0.55]) is not statistically significant (p=0.85).

## Pain (7 days)

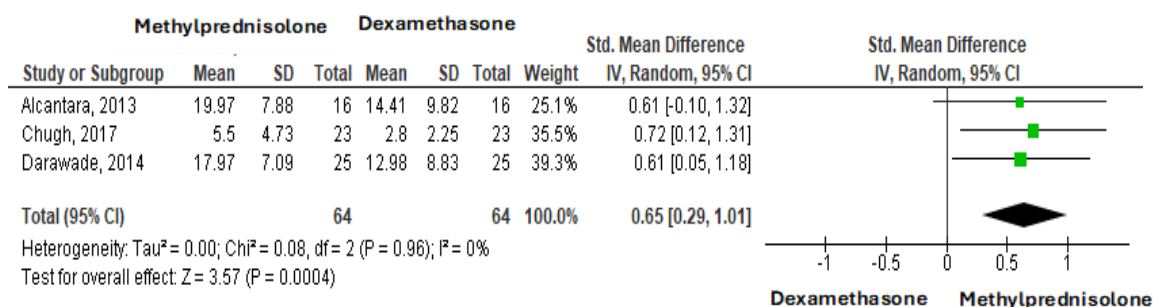


**Figure 5 - Meta-analysis results for pain (7 days)**

Considering the results of figure 5, Cochran's Q ( $p=0.15>0.05$ ) and  $I^2=47\%$ , it was concluded that the heterogeneity was not significant between studies regarding pain at 7 days. The forest plot shows that the effect of the meta-analysis  $-0.08$  (95%CI  $[-0.58;0.42]$ ) is not statistically significant ( $p=0.85$ ).

### III.5.2. Methylprednisolone vs Dexamethasone

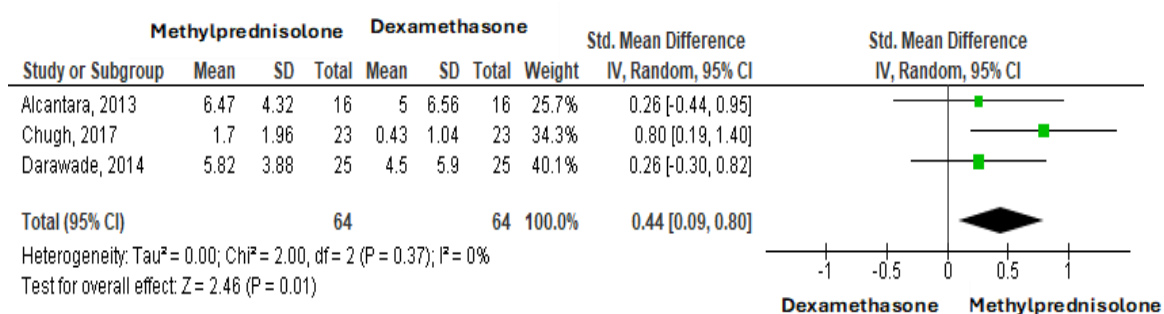
#### Inter-incisal reduction (48h)



**Figure 6 - Meta-analysis results for inter-incisal reduction (48h)**

Figure 6 shows the results for inter-incisal reduction at 48 hours. Given the results in figure 6, Cochran's Q ( $p=0.96>0.05$ ) and  $I^2=0\%$ , it was concluded that there was homogeneity between studies about inter-incisal reduction at 48 hours. Looking at the forest plot, in the studies under analysis the greatest reduction occurs in the methylprednisolone group and the effect of the meta-analysis  $0.65$  (95%CI  $[0.29;1.01]$ ) is statistically significant ( $p<0.01$ )

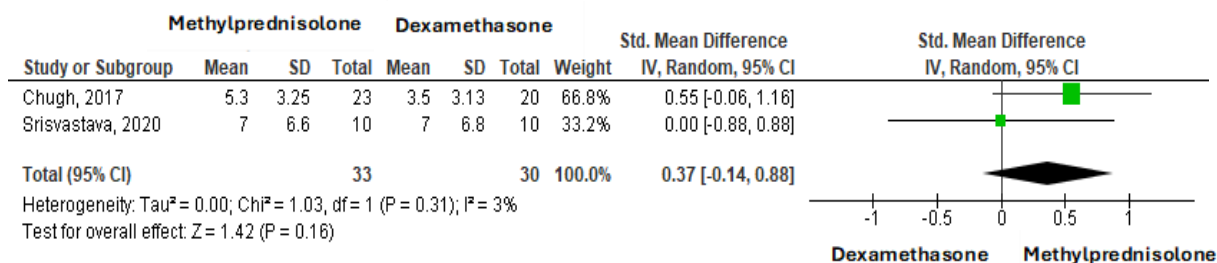
### Inter-incisal reduction (7 days)



**Figure 7** - Meta-analysis results for inter-incisal reduction (7 days)

Figure 7 shows the results for inter-incisal reduction at 7 days. Given the results in figure 7, Cochran's Q ( $p=0.37>0.05$ ) and  $I^2=0\%$ , it was concluded that there was homogeneity between studies about inter-incisal reduction at 7 days. Looking at the forest plot in the studies under analysis the greatest reduction occurs in the methylprednisolone group and the effect of the meta-analysis 0.44 (95%CI [0.09;0.80]) is statistically significant ( $p<0.05$ ).

### Pain (24h)



**Figure 8** - Meta-analysis results for pain (24h)

Considering the results of figure 8, Cochran's Q ( $p=0.31>0.05$ ) and  $I^2=3\%$ , it was concluded that the heterogeneity was not significant between studies about pain at 24 hours. A look at the forest plot shows that the effect of the meta-analysis 0.37 (95%CI [-0.14;0.88]) is not statistically significant ( $p=0.16$ ).





## 4. DISCUSSION



## **IV. Discussion**

The aim of this systematic review and meta-analysis was to assess the effect of methylprednisolone in patients undergoing third molar surgery, with a specific focus on post-operative trismus, pain, and edema. This analysis was carried out considering the predefined criteria, grouping together all available randomized controlled trials (RCTs) that investigated the use of methylprednisolone in comparison with a control group, as well as in comparison with dexamethasone.

## **Statistical Analysis**

### **Variability between studies**

The statistical analysis was conducted using the random effects model, which is appropriate for generalizing results and considering the variability between studies. This model allowed for a more in-depth understanding of the heterogeneity present in the studies analyzed. The statistical analysis revealed high variability in sample sizes and patient characteristics between the studies (Table 8).

### **Methylprednisolone Interincisal reduction**

In the study by Koçer *et al.* (2014), various routes of methylprednisolone administration were investigated, including oral, intravenous, and muscular administration (specifically in the masseteric region). It should be noted that in this study they used around half the sample that the other authors considered. The results showed the effectiveness of the corticosteroid in reducing interincisal reduction after oral surgery, with muscle administration, especially in the masseter, standing out as the most effective (Table 9). When the results were compared between the groups treated with methylprednisolone, it was found that although there was a reduction in the case of the Chugh *et al.* study, it did not show better results than the control group. In the case of the other article, Madhi *et al.* showed better results in the control group, although only after 7 days (Table 9) (40).

The choice of the muscular route for administering methylprednisolone in the masseteric region is supported by additional studies highlighting its effectiveness in reducing post-operative trismus. Buyukkurt *et al.* demonstrated that the local administration of corticosteroids provides a significant reduction in these symptoms following the removal of third molars. In addition, Markiewicz *et al.* carried out a meta-analysis which indicated greater efficacy of corticosteroids administered via the submucosal route in the management of post-operative complications, due to the greater concentration of the drug at the surgical site and less systemic dispersion (41,42). In addition, the meta-analysis carried out by Markiewicz *et al.* revealed that patients who received perioperative treatment with corticosteroids, such as methylprednisolone, experienced a significant reduction in trismus. Specifically, the study found that subjects treated with corticosteroids were able to open their mouths 4.1 mm more than controls 1 to 3 days after surgery ( $P < .001$ ), and 2.7 mm more than controls 4 to 7 days after surgery ( $P = .005$ ). These results highlight the effectiveness of corticosteroids in improving mandibular mobility after surgery, corroborating part of our observation that the administration of methylprednisolone, particularly through the muscle in the masseteric region, can significantly reduce mandibular mobility in the postoperative period. On the other hand, this lack of efficacy was also observed in the other articles compared, which may have been due to factors such as differences in the surgical techniques used, variations in the time the corticosteroid was administered, as well as the heterogeneity of the patient samples studied (42).

## **Edema**

Analysis of the edema in the area between the tragus and the labial commissure revealed an improvement with the use of methylprednisolone, with administration in the masseter muscle being the most effective (Table 11). When analyzing the edema between the corner of the eye and the gnathion, there was also an improvement in the group treated with methylprednisolone. Here, the masseteric route managed to achieve the same values as the initial result, thus showing the most positive effects (Table 12). Compared to the control group, where there was also a reduction in both measurements, the improvement was not as noticeable

as with the use of methylprednisolone, especially through the muscular pathway in the masseter. Although there was an improvement with the use of methylprednisolone, there could have been factors influencing a less positive result, due to the complex mechanisms of action of corticosteroids, which can affect fluid retention and the distribution of fluids in the body in different and individualized ways. However, in this case, the use of corticosteroids, particularly methylprednisolone, led to a tendency for the edema to regress, with good results achieved via the masseteric route, which is in line with published studies that report the benefit of using corticosteroids (40). The meta-analysis carried out by Markiewicz *et al.* revealed that the perioperative administration of corticosteroids, such as methylprednisolone, results in a statistically significant reduction in postoperative oedema in both the early (1-3 days) and late (4-7 days) phases after third molar removal surgery. The average reduction in oedema was 0.6 mm in the first few days and 0.5 mm in subsequent days, thus corroborating the results obtained in this study. This suggests that methylprednisolone is effective in reducing post-operative oedema, providing better recovery and higher patient comfort (42).

### **Methylprednisolone vs Dexamethasone**

#### **Pain**

Pain is a multifaceted phenomenon whose perception can vary significantly between individuals and different clinical contexts. In the Alcantara *et al.* studies, an increase in pain was observed over time in both treatment groups, which can be attributed to various factors, including individual sensitivity to pain, the patient's inflammatory response and the characteristics of the surgery. On the other hand, in the studies by Srivastava *et al.* and Darawade *et al.* there was a reduction in pain in the group treated with methylprednisolone, while in the group treated with dexamethasone pain remained low and constant in both evaluation periods. These discrepancies highlight the complexity of the perception of postoperative pain and the influence of various factors (such as the patient's psychological state, pre-existing conditions, genetic predispositions, and the effectiveness of pain management strategies can all play a role in how pain is experienced and reported) on its development and management (17,23,27).

## **Meta-analysis**

The meta-analysis was only carried out for specific parameters due to limitations found in the available literature, mainly the lack of essential information and the absence of standard deviations. The careful selection of parameters was based on the availability and comparability of data, guaranteeing the robustness and validity of the results obtained.

One of the main reasons for restricting the parameters was the frequent absence of crucial values in many of the articles reviewed. Several studies did not report complete measurements, and many did not include standard deviations, which made it impossible to include these studies in the meta-analysis. Meta-analysis requires a minimum set of statistical data to make valid comparisons, and the absence of this essential information made it impossible to include several articles.

In addition, the divergence in the measures used between the different studies represented a significant challenge. For example, when assessing trismus, we opted to use the inter-incisal reduction measure, based on the fact that most of the available articles employed this specific method, providing greater consistency and comparability between studies. However, when trying to convert data from articles that measured maximum mouth opening to the inter-incisal reduction measure, we often lost the value of the standard deviation, making it impossible to accurately calculate this crucial statistic for the meta-analysis.

Similarly, in the assessment of edema, there was significant variability in the measurement methods used between the different studies. This methodological heterogeneity, together with the lack of reported standard deviations, made it difficult to harmonize the data, limiting the possibility of carrying out a comprehensive and comparative meta-analysis.

Therefore, the decision to carry out the meta-analysis only for certain parameters was based on the need to ensure the integrity and accuracy of the statistical analyses. The choice of parameters was based on the availability of complete

and consistent data, as well as the presence of the necessary standard deviations.

### **Methylprednisolone vs Control Group**

#### **Pain (24h and 7 days)**

The meta-analysis of pain in the first 24 hours and at 7 days in the control group did not reveal a significant effect of methylprednisolone (Figures 4 and 5). For example, the effect of the meta-analysis was 0.05 (95% CI [-0.45; 0.55]) after 24 hours and -0.08 (95% CI [-0.58; 0.42]) at 7 days, with p-values of 0.85 in both cases. This suggests that methylprednisolone may not be more effective than the control in reducing pain at these time intervals. However, it is important to consider that post-operative pain is a subjective experience and can be influenced by various factors (such as the type of surgery performed, the patient's psychological state, the presence of pre-existing conditions, the quality of pain management and the level of social support.) (4,17). Subgroup analyses may provide additional insights into the efficacy of methylprednisolone in different populations and surgical contexts (40). Another study, notably Markiewicz *et al.* also found no significant differences in pain between the groups treated with methylprednisolone and the control groups at 24 hours and 7 days after surgery. These results highlight the need to consider postoperative pain as a multifaceted experience, influenced by a variety of factors, and the importance of more detailed analyses to fully understand the effects of methylprednisolone on postoperative pain management.

### **Methylprednisolone vs Dexamethasone**

#### **Interincisal reduction (48h and 7 days)**

The results of the meta-analysis revealed significant homogeneity between the studies on interincisal reduction both 48 hours and 7 days after surgery, when methylprednisolone and dexamethasone were compared (Figures 6 and 7). In both periods, the group treated with dexamethasone showed less interincisal reduction compared to the group receiving methylprednisolone. For example, the meta-analysis effect was 0.65 (95% CI [0.29; 1.01]) after 48 hours, indicating a

more significant reduction in the methylprednisolone-treated group, with a p-value of <0.01. Similarly, at 7 days, the meta-analysis effect was 0.44 (95% CI [0.09; 0.80]), also indicating a more significant reduction in the methylprednisolone-treated group, with a p-value of <0.05.

The results of this meta-analysis are in line with the evidence presented in the study by Amiya Agrawal *et al.*, reinforcing the efficacy of corticosteroids. There was a significant reduction in inter-incisal reduction both 48 hours and 7 days after surgery when methylprednisolone and dexamethasone were compared. This consistency strengthens the evidence of the positive potential of corticosteroids in mitigating postoperative trismus, providing additional support for their efficacy in promoting a more comfortable and effective recovery after third molar surgery (43).

#### **Pain (24h)**

The meta-analysis of pain after 24 hours did not show a significant effect, suggesting that the differences between methylprednisolone and dexamethasone may not be substantial in this period (Figure 8). For example, the effect of the meta-analysis was 0.37 (95% CI [-0.14; 0.88]), with a p-value of 0.16. This highlights the complexity of post-operative pain, which is influenced by different factors such as surgical trauma and the individual inflammatory response. Variability in pain administration and measurement methods between studies may also have contributed to these results.





## **5. CONCLUSION**



## **V. Conclusion**

### **V.1. Methylprednisolone vs Dexamethasone**

The comparative analysis between methylprednisolone and dexamethasone, based on meta-analysis data, indicates a higher value in inter-incisal measurement in the groups treated with methylprednisolone compared to those treated with dexamethasone, both at 48 hours and 7 days after third molar surgery. These results suggest that dexamethasone may be preferable in minimizing post-operative trismus, highlighting its potential superiority over methylprednisolone in this specific clinical context.

On average, the reduction in jaw opening was approximately 0.65 millimeters for methylprednisolone and 0.44 millimeters for dexamethasone after 48 hours, and 0.44 millimeters for methylprednisolone after 7 days.

### **V.2. Methylprednisolone**

A positive trend was observed edema reduction of patients treated with methylprednisolone via masseter muscle.

Regarding pain, best route of administration, adverse effects and patient post-operative comfort no significant difference was observed, or no comparable data was available.



## 6. BIBLIOGRAPHY



## **VI. Bibliography**

1. McGrath C, Comfort MB, Lo ECM, Luo Y. Changes in life quality following third molar surgery - The immediate postoperative period. *Br Dent J*. 2003;194(5):265–8
2. López Carriches C, Martínez-González JM, Rodríguez MD. Eficacia analgésica de diclofenaco versus metilprednisolona en el control del dolor postoperatorio tras la cirugía del tercer molar inferior. *Med Oral Patol Oral Cir Bucal*. 2005;10(5):432–9.
3. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO. Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. *Head Face Med*. 2005;1:1-6.
4. Torcato J. Estudo comparativo do efeito da metilprednisolona e ibuprofeno na redução das complicações pós operatórias após exodontia de terceiros molares inferiores retidos. [Master thesis], Universidade Católica Portuguesa; 2013
5. Ordulu M, Aktas I, Yalcin S, Azak AN, Evlioğlu G, Disçi R, et al. Comparative study of the effect of tube drainage versus methylprednisolone after third molar surgery. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*. 2006;101(6):96–100.
6. Esen E, Taşar F, Akhan O. Determination of the anti-inflammatory effects of methylprednisolone on the sequelae of third molar surgery. *J Oral Maxillofac Surg*. 1999;57(10):1201–6.
7. Guillaumet-Claire MA, Juiz-Camps AM, Gay-Escoda C. Prevalence of intraoperative and postoperative iatrogenic mandibular fractures after lower third molar extraction: A systematic review. *J Clin Exp Dent*. 2022;14(1):85–94.
8. Peñarrocha-Diago M, Camps-Font O, Sánchez-Torres A, Figueiredo R, Sánchez-Garcés MA, Gay-Escoda C. Indications of the extraction of

- symptomatic impacted third molars. A systematic review. *J Clin Exp Dent.* - 63 - 2021;13(3):e278–86.
9. Li Z-B, Qu H-L, Zhou L-N, Tian B-M, Chen F-M. Influence of non-impacted third molars on pathologies of adjacent second molars: a retrospective study. *J Periodontol.* 2017;88(5):450–6.
  10. Morey-Vargas OL, Zeballos-Palacios C, Gionfriddo MR, Montori VM. The hierarchy of evidence. *Netw meta-analysis Evid Synth with Mix Treat Comp.* 2014;3–19.
  11. Demirel O, Akbulut A. Evaluation of the relationship between gonial angle and impacted mandibular third molar teeth. *Anat Sci Int.* 2020;95(1):134–42.
  12. Jaroń A, Trybek G. The pattern of mandibular third molar impaction and assessment of surgery difficulty: A retrospective study of radiographs in east baltic population. *Int J Environ Res Public Health.* 2021;18(11).
  13. Od O, Ra A, Uk O. Management of inflammatory complications in third molar surgery: A review of the literature. *Afr Health Sci.* 2011;11(3):530– 7.
  14. Marques J, Pié-Sánchez J, Figueiredo R, Valmaseda-Castellón E, Gay-Escoda C. Effect of the local administration of betamethasone on pain, swelling and trismus after impacted lower third molar extraction. A randomized, triple blinded, controlled trial. *Med Oral Patol Oral Cir Bucal.* 2014;19(1).
  15. Aznar-Arasa L, Harutunian K, Figueiredo R, Valmaseda-Castellón E, Gay-Escoda C. Effect of preoperative ibuprofen on pain and swelling after lower third molar removal: A randomized controlled trial. *Int J Oral Maxillofac Surg.* 2012;41(8):1005–9.
  16. Lago-Méndez L, Diniz-Freitas M, Senra-Rivera C, Gude-Sampedro F, Gándara Rey JM, García-García A. Relationships between surgical difficulty and postoperative pain in lower third molar extractions. *J Oral Maxillofac Surg.* 2007;65(5):979–83.
  17. Khorshidi R, Maghsood K, Ayda P, Saadat P, Khiavi G. Pain control

- following impacted third molar surgery with bupivacaine irrigation of tooth socket: a prospective study. *J Dent Res Dent Clin Dent Prospect.* 2010;4(4):105–9.
18. Cho H, Lynham AJ, Hsu E. Postoperative interventions to reduce inflammatory complications after third molar surgery: review of the current evidence. *Aust Dent J.* 2017;62(4):412–9.
  19. Renton T. Oral surgery: Part 4. Minimising and managing nerve injuries and other complications. *Br Dent J.* 2013;215(8):393–9.
  20. Ali AS, Benton JA, Yates JM. Risk of inferior alveolar nerve injury with coronectomy vs surgical extraction of mandibular third molars—A comparison of two techniques and review of the literature. *J Oral Rehabil.* 2018;45(3):250–7.
  21. Ahmed A, Mohamed F, Hattab K. Surgical extraction of impacted mandibular third molars: postoperative complications and their risk factors. *Jamahiriya Med J.* 2009;9(4):272–5.
  22. Aloy-Prósper A, Pellicer-Chover H, Balaguer-Martínez J, Llamas-Monteagudo O, Peñarrocha-Diago M. Patient compliance to postoperative instructions after third molar surgery comparing traditional verbally and written form versus the effect of a postoperative phone call follow-up a: A randomized clinical study. *J Clin Exp Dent.* 2020;12(10):e909–15.
  23. Davies AN, Brailsford S, Beighton D. Corticosteroids and oral candidosis [1]. *Palliat Med.* 2001;15(6):521.
  24. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochemical pharmacology*, 2020, 180: 114147
  25. Prado CE, Crowe SF. Corticosteroids and cognition: A meta-analysis. *Neuropsychol Rev.* 2019;29(3):288–312.
  26. Judd LL, Schettler PJ, Brown ES, Wolkowitz OM, Sternberg EM, Bender BG, et al. Adverse consequences of glucocorticoid medication: Psychological, cognitive, and behavioral effects. *Am J Psychiatry.* - 65 -

- 2014;171(10):1045–51.
27. Kapugi M, Cunningham K. Corticosteroids. *Orthop Nurs*. 2019;38(5):336–9.
  28. Belanoff JK, Gross K, Yager A, Schatzberg AF. Corticosteroids and cognition. *J Psychiatr Res*. 2001;35(3):127–45.
  29. Madsbad S, Bjerregaard B, Henriksen JH, Juhl E, Kehlet H. Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis. *Gut*. 1980;21(1):52–6.
  30. Larsen MK, Kofod T, Christiansen A-E, Starch-Jensen T. Different dosages of corticosteroid and routes of administration in mandibular third molar surgery: a systematic review. *J Oral Maxillofac Res*. 2018;9(2):1–20.
  31. Ngeow WC, Lim D. Do Corticosteroids still have a role in the management of third molar surgery? Vol. 33, *Advances in Therapy*. Springer Healthcare; 2016. 1105–1139 p.
  32. Sugragan C, Sirintawat N, Kiattavornchareon S, Khoo LK, KC K, Wongsirichat N. Do corticosteroids reduce postoperative pain following third molar intervention? *J Dent Anesth Pain Med*. 2020;20(5):281.
  33. Sanghavi J, Aditya A. Applications of corticosteroids in dentistry. *J Dent Allied Sci*. 2015;4(1):19.
  34. Micó-Llorens JM, Satorres-Nieto M, Gargallo-Albiol J, Arnabat-Domínguez J, Berini-Aytés L, Gay-Escoda C. Efficacy of methylprednisolone in controlling complications after impacted lower third molar surgical extraction. *Eur J Clin Pharmacol*. 2006;62(9):693–8.
  35. Acham S, Klampfl A, Truschnegg A, Kirmeier R, Sandner-Kiesling A, Jakse N. Beneficial effect of methylprednisolone after mandibular third molar surgery: A randomized, double-blind, placebo-controlled split-mouth trial. *Clin Oral Investig*. 2013;17(7):1693–700.
  36. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for - 66 - reporting systematic reviews. *BMJ*. 2021;372.

37. Methods c. Risk of Bias 2 (RoB 2) tool [Available from: <https://methods.cochrane.org/risk-bias-2>].
38. Borenstein M, Hedges L, Rothstein H. Meta-Analysis Fixed effect vs . random effects. Test [Internet]. 2007;162. Available from: [www.meta-analysis.com](http://www.meta-analysis.com)
39. Evrenoglou T, Metelli S, Chaimani A. Introduction to meta-analysis. Principles and Practice of Clinical Trials. 2022. 2179–2195 p.
40. Koçer G, Yuce E, Tuzuner Oncul A, Dereci O, Koskan O. Effect of the route of administration of methylprednisolone on oedema and trismus in impacted lower third molar surgery. *Int J Oral Maxillofac Surg*. 2014;43(5):639–43.
41. Buyukkurt MC, Gungormus M, Kaya O. The effect of a single dose prednisolone with and without diclofenac on pain, trismus, and swelling after removal of mandibular third molars. *J Oral Maxillofac Surg*. 2006;64(12):1761–6.
42. Markiewicz MR, Brady MF, Ding EL, Dodson TB. Corticosteroids reduce postoperative morbidity after third molar surgery: A systematic review and meta-analysis. *J Oral Maxillofac Surg*. 2008;66(9):1881–94.
43. Yadav R, Verma U, Tiwari R, Article O. Heterogeneous conceptualization of etiopathogenesis: Oral pyogenic granuloma. *Natl J Maxillofac Surg*. 2019;10(1):3–7.



## Annex A: PROSPERO registration

- ID: CRD42024512561
- Title: The use of methylprednisolone after third molar surgery: A Systematic Review
- Status: Registered
- Last Edit: 03/05/2024

ID	Title	Status	Last edited
CRD42024512561	THE USE OF METHYLPREDNISOLONE AFTER THIRD MOLAR SURGERY. A SYSTEMATIC REVIEW	Registered	03/05/2024  