Research, Society and Development, v. 9, n. 9, e968997979, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i9.7979

A combinação de corticosteroides mais AINEs melhora a analgesia preemptiva após cirurgia de terceiros molares? Uma revisão sistemática e meta-análise

Is the combination of corticosteroids plus NSAIDs improve the preemptive analgesia after third molars surgery? A systematic review and meta-analysis

¿La combinación de corticoesteroides más antiinflamatorios no esteroideos mejora la analgesia preventiva después de la cirugía del tercer molar? Una revisión sistemática y un metanálisis

Received: 08/29/2020 | Reviewed: 09/09/2020 | Accept: 09/14/2020 | Published: 09/14/2020

Gustavo Antonio Correa Momesso
ORCID: https://orcid.org/0000-0003-4529-683X
São Paulo State University, Brasil
E-mail: gustavomomesso@gmail.com
Cleidiel Aparecido Araújo Lemos
ORCID: https://orcid.org/0000-0001-8273-489X
São Paulo State University, Brasil
E-mail: cleidiel@gmail.com
Valthierre Nunes de Lima
ORCID: https://orcid.org/0000-0001-7673-4439
São Paulo State University, Brasil
E-mail: valthierre@gmail.com
Leonardo Alan Delanora
ORCID: https://orcid.org/0000-0002-3002-4420
São Paulo State University, Brasil
E-mail: leonardoaland@gmail.com
Joel Ferreira Santiago-Júnior
ORCID: https://orcid.org/0000-0003-1735-2224
Sacred Heart University, Brasil
E-mail: jf.santiagojunior@gmail.com
Leonardo Perez Faverani
ORCID: https://orcid.org/0000-0003-2249-3048
São Paulo State University, Brasil

E:mail: leonardo.faverani@unesp.br

Eduardo Piza Pellizzer

ORCID: https://orcid.org/0000-0003-0670-5004

São Paulo State University, Brasil

E-mail: ed.pl@foa.unesp.br

Resumo

Este estudo teve como objetivo realizar uma revisão sistemática e metanálise para avaliar a ação preemptiva da combinação de corticosteroides e antiinflamatórios não esteroidais (AINEs) ou ambos os fármacos isoladamente após cirurgia de terceiros molares. Foi realizada uma busca nas bases de dados PubMed / MEDLINE, Scopus e Cochrane, segundo os critérios PRISMA, sem restrição de tempo até março de 2020. A dor pós-operatória foi avaliada, qualitativamente, por meio da escala visual analógica (EVA) e do número de analgésicos de resgate (NRA). O edema e o trismo foram avaliados de forma qualitativa por meio de medidas lineares. Além disso, foi realizada uma meta-análise da dor pós-operatória (EVA). Foram encontrados 103 artigos, dos quais quatro artigos foram selecionados de acordo com os critérios de inclusão e exclusão. Foram avaliados 208 pacientes e a combinação de corticosteroides e AINEs apresentou ótimo comportamento na ação preemptiva após cirurgia de terceiros molares para todos os parâmetros avaliados quando comparados aos dois fármacos isoladamente. Meta-análise sobre a VAS mostrou que a combinação de drogas reduziu significativamente a dor pós-operatória quando comparada aos AINEs isoladamente (P <0,05). Concluiu-se que a combinação de AINEs e corticosteroides melhorou a dor pós-operatória, o edema e o trismo após a cirurgia dos terceiros molares.

Palavras-chave: Terceiros molares; Dor; Corticosteróides; Inflamação; Mediadores da inflamação; Anti-inflamatórios; Anti-inflamatórios não esteroides.

Abstract

This study aimed to perform a systematic review and meta-analysis to evaluate the preemptive action of the combination of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) or both drugs singly after third molars surgery. It was performed a search on the PubMed/MEDLINE, Scopus, and Cochrane databases, according to the PRISMA criteria, with no time restrictions up to March 2020. The postoperative pain was evaluated, qualitatively, through the visual analogue scale (VAS) and the number of rescue analgesics (NRA). The edema and trismus were evaluated in a qualitative way through linear measures.

Besides that, a meta-analysis of the post-operative pain (VAS) was performed. It was found 103 articles, which four articles were selected according to the inclusion and exclusion criteria. A total of 208 patients was evaluated and the combination of corticosteroids and NSAIDs showed great behavior in the preemptive action after third molars surgery for all the parameters evaluated when compared to both drugs singly. Meta-analysis about the VAS showed that the combination of drugs reduced significantly the postoperative pain when compared to the NSAIDs singly (P<0.05). It was concluded that the combination of NSAIDs and corticosteroids improved postoperative pain, edema, and trismus after third molars surgery.

Keywords: Molar third; Pain; Adrenal cortex hormones; Inflammation; Inflammation mediators; Anti-inflammatory agents; Anti-inflammatory non-steroidal.

Resumen

Este estudio tuvo como objetivo realizar una revisión sistemática y un metanálisis para evaluar la acción preventiva de la combinación de corticosteroides y antiinflamatorios no esteroideos (AINE) o ambos fármacos solos después de la cirugía de terceros molares. Se realizó una búsqueda en las bases de datos PubMed / MEDLINE, Scopus y Cochrane, según los criterios PRISMA, sin restricción de tiempo hasta marzo de 2020. Se evaluó el dolor postoperatorio, cualitativamente, mediante la escala visual analógica (EVA) y del número de analgésicos de rescate (ANR). El edema y el trismo se evaluaron cualitativamente mediante medidas lineales. Además, se realizó un metanálisis de dolor postoperatorio (EVA). Se encontraron 103 artículos, de los cuales se seleccionaron cuatro artículos según los criterios de inclusión y exclusión. Se evaluaron 208 pacientes y la combinación de corticosteroides y AINE mostró un excelente comportamiento en la acción preventiva después de la cirugía de terceros molares para todos los parámetros evaluados en comparación con los dos fármacos solos. El metanálisis en VAS mostró que la combinación de fármacos redujo significativamente el dolor posoperatorio en comparación con los AINE solos (P <0,05). Se concluyó que la combinación de AINE y corticosteroides mejoró el dolor postoperatorio, el edema y el trismo después de la cirugía de terceros molares.

Palabras clave: Tercer molar; Dolor; Corticoesteroides; Inflamación; Mediadores de inflamación; Antiinflamatorios; Antiinflamatorios no esteroideos.

1. Introduction

It is still a challenge for oral surgeons to control the pain, edema, and trismus in the postoperative period after third-molar surgery. The patient may have decreased quality and ability to perform some physiological and social activities (Aznar-Arasa, Harutunian, Figueiredo, Valmaseda-Castellón & Gay-Escoda, 2012; Costa et al., 2015). Thus, drugs have been administered prior to this surgical procedure to minimize inflammatory complications (Bamgbose et al., 2005; Ong, Seymour, Chen, & Ho, 2004).

Corticosteroids are widely used in preemptive administration for third molar removal to decrease the production of inflammatory mediators (Bamgbose et al., 2005). Laureano-Filho (Laureano Filho, Maurette, Allais, Cotinho, & Fernandes, 2008) and Alcântara et al (Alcântara, Falci, Oliveira-Ferreira, Santos, & Pinheiro, 2014) concluded that an 8 mg dose of dexamethasone administered in the preemptive period showed better control of postoperative edema and trismus after third-molar surgery. It seems corticosteroids alone were unable to decrease pain or suppress prostaglandins, an important inflammatory cytokine related to pain (Dionne, Gordon, Rowan, Kent, & Brahim, 2003).

For this reason, several clinical studies have investigated the coadministration of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) and the isolated use of NSAIDs as a preemptive action to improve the quality of life of surgical patients (Aznar-Arasa et al., 2012; Costa et al., 2015; Bamgbose et al., 2005; Ong et al., 2004; Dionne et al., 2003)

Therefore, this systematic review and meta-analysis was aimed at establishing a clinical consensus about the preemptive administration of corticosteroids and NSAIDs in the postoperative third-molar surgery for pain, edema, and trismus.

2. Methodology

This systematic review was made according to the PRISMA statement and by following models proposed in the literature. (Pereira A.S. et al., 2018) The articles were selected by two authors.

Eligibility Criteria

The selected studies for this review met the criteria established by the PICO index: (1) **Population**: patients who underwent third-molar surgery; (2) **intervention**: patients who used only corticosteroids or NSAIDs for preemptive analgesia; (3) **comparison**: patients who used both corticosteroids and NSAIDs for preemptive analgesia; and (4) **outcome**: comparison of pain, edema, trismus, and total number of rescue analgesics (TNRA).

Information Sources

Relevant studies published only in the English language were searched in the PubMed/MEDLINE, Embase, and Scopus databases, with no time restrictions up to March 2020.

Search

The search terms were as follows: "*Third molar AND edema OR third molar AND trismus OR third molar AND swelling AND third molar AND glucocorticoids AND Third molar AND NSAIDs*." The search was performed on the PubMed/MEDLINE, Embase, and Scopus databases. Furthermore, a manual search was performed on the main journals of the field: the *International Journal of Oral and Maxillofacial Surgery*; the *Journal of Oral and Maxillofacial Surgery*; the *British Journal of Oral and Maxillofacial Surgery*; and the *Journal of Cranio-Maxillo-Facial Surgery and Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*.

Study Selection

Inclusion criteria: relevant clinical trials that involved more than five patients, had been published in the English language, and involved patients who had underdone third-molar surgery and received at least glucocorticoids and NSAIDs.

Exclusion criteria: animal studies, systematic reviews and clinical studies involving less than six patients, were not published in the English language, involved no patients who underwent third-molar surgery, studies that used glucocorticoids or NSAID as a postoperative protocol or involved patients who did not use glucocorticoids or NSAIDs.

Data Collection

The authors who selected the articles were subjected to the interexaminer (kappa) tests which were performed to evaluate the titles and abstracts, and the articles were interpreted by means of a complete reading, resulting in concordance values of k = .90 for the PubMed/MEDLINE database and k = 1 for the Scopus and Embase databases. After analyzing the titles and abstracts, we considered 4 articles for inclusion.

Data Items

The following data were identified in each article: first author, level of evidence, number of patients, mean age, study type, drugs used, original drug doses, and method of drug delivery.

Risk of Bias in Individual Studies

The studies were classified according to their level of evidence, as proposed by the National Health and Medical Research Council (NHMRC) (Coleman et al., 2015), to show their quality and grades in terms of recommendations. This classification established the levels of evidence according to the type of research question, taking into account the intervention, diagnostic accuracy, prognosis, etiology, and screening intervention. The hierarchy of the studies was classified into scores (I; II; III-1; III-2; III-3; IV).

Summary Measures

A comparative analysis was conducted regarding the preemptive use of corticosteroids alone and versus both corticosteroids and NSAIDs in third-molar surgeries to discover which therapy is best regarding postoperative pain, edema, and trismus.

Bias Risk in the Meta-analysis

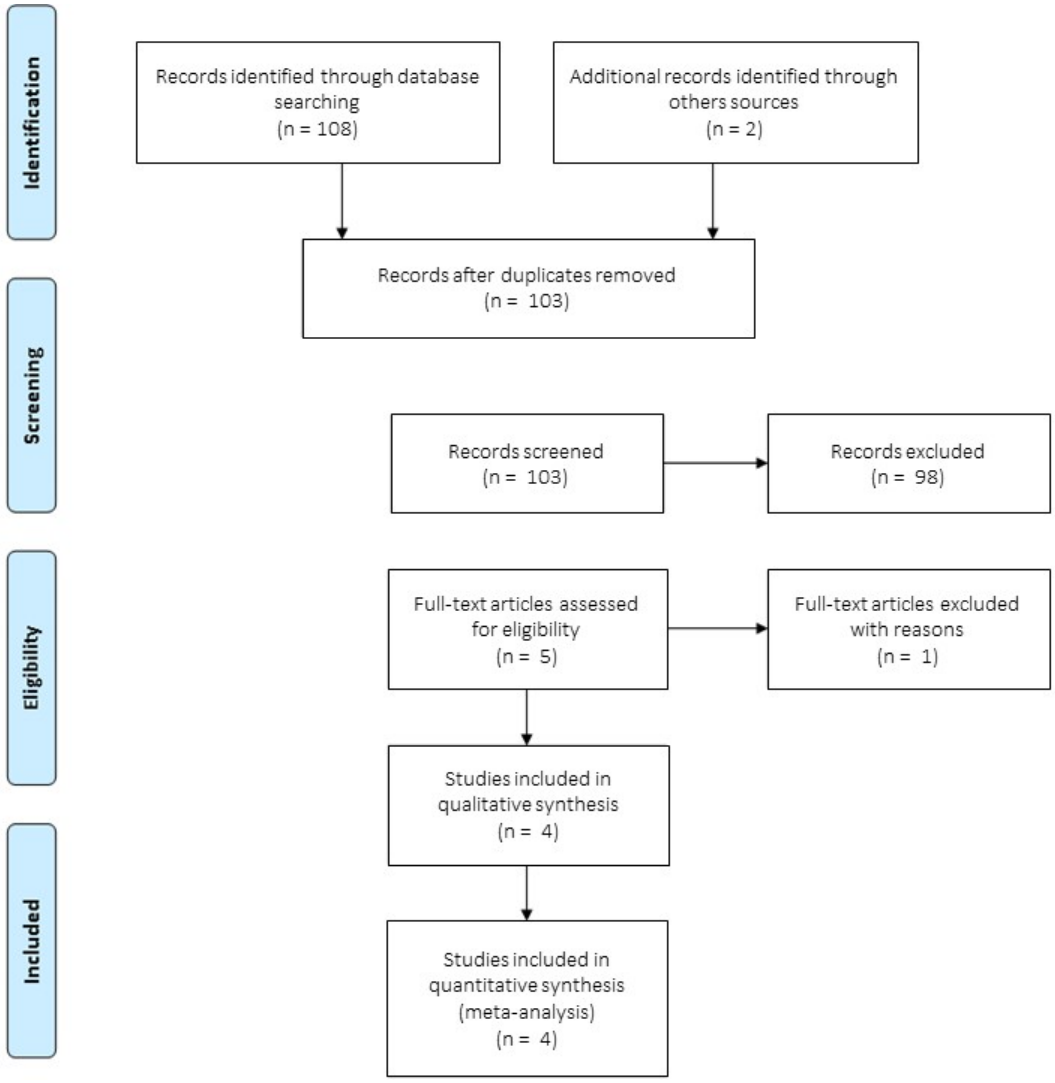
A fixed-effect model was used when there was no statistically significant difference, and a random-effects model was adopted when there was a statistically significant difference, which is a higher indication of heterogeneity between studies. The heterogeneity was

significant for $P < .1$, and it was evaluated using the method Q (x^2). The value of I^2 was also measured to analyze the heterogeneity variation. I^2 was considered above 75 (0-100), indicating relevant heterogeneity (Annibali et al., 2012; Atieh, Ibrahim, & Atieh, 2010; Higgins, & Thompson, 2002).

3. Results

After the search, 108 articles were found, including 26 from PubMed/MEDLINE, 3 from Scopus, and 79 from Embase. Two articles were found through manual search of the main journals of the field. Duplicates of the databases have been removed, resulting in 103 articles in total. Five articles were selected after the evaluation of titles and abstracts regarding the inclusion and exclusion criteria and after elimination of the duplicate references. One study was excluded because it did not meet the inclusion criteria after the entire text was read. Thus, 4 articles were selected for the qualitative and quantitative analyses (Figure 1).

Figure 1. Flow diagram of the study selection for the systematic review.



Resource: Own authorship

In Figure 1, it is possible to see the flowchart corresponding to the entire article selection and exclusion process that comprised the present literature review.

Study Characteristics

All of the studies are randomized clinical trials published between 2005 and 2017. The studies evaluated 208 total patients, and their mean age was about 24 years old. The groups were divided into patients who received only preoperative corticosteroids, NSAIDs only, or both corticosteroids and NSAIDs. Thus, 101 patients used preoperative corticosteroids plus NSAIDs, 78 patients used preoperative NSAIDs only, and 29 patients used preoperative corticosteroids only. The only exception regarding the time of steroid delivery was in the

study by Moore (Moore, Brar, Smiga, & Costello, 2005), who administered the steroid immediately after the start of the surgery. This study was considered in this review because the author described the treatment as a preemptive therapy. The drugs and doses was variable among the studies. All the authors used dexamethasone as steroids, however the dose varied between 8 mg and 10 mg. The NSAIDs used varied among all of the studies. The method of delivery varied between via oral (VO) and intravenous (IV) (Tables 1 and 2).

Table 1. Characteristics of included studies.

	Type of studies	Type of blinding	Number of patients	Level of evidence	Mean age (yr)	Groups	Original drugs	Original dose (mg)	Method of delivery	Time of steroid delivery	Outcomes
Barbalho, 2017 [13]	RCT Split-mouth	Triple blind	40	II	23.4	A - Steroid + NSAID B - Steroid	Dexamethasone and Nimesulide	Dexamethasone: 8mg Nimesulide: 100mg	VO	Pre-op	Pain, edema, trismus and TNRA
Bauer, 2013 [14]	Randomized clinical trial	Double blind	47	II	22	A- Steroid + NSAID B - NSAID	Dexamethasone and Ibuprofen	Dexamethasone: 8mg Ibuprofen: 600mg	VO	Pre-op	Pain and TNRA
Moore, 2005 [12]	Randomized clinical trial	Double blind	21	II	22.8	A - Steroid + NSAID B - NSAID C - Steroid	Dexamethasone and Rofecoxib	Dexamethasone: 10mg Rofecoxib: 50mg	IV/VO	Intra-op/pre-op	Pain and trismus
Bamgbose, 2005 [3]	Randomized clinical trial	Double blind	100	II	27.9	A - Steroid +NSAID B - NSAID	Dexamethasone and Diclofenac	Dexamethasone: 8mg/4mg Diclofenac: 50mg	IV/VO	Pre-op/ pos-op	Pain, edema and trismus

Resource: Own authorship

In Table 1, it is possible to see the characteristics of the selected studies, such as type of study, blinding, number of patients, average age, level of evidence, type of medication, dosage, route of administration and evaluated parameters.

Table 2. Groups and posology.

	Pre-op	Intra-op	Pos-op	Control group	Group 1	Group 2	Group 3
Barbalho, 2017 [13]	Dexamethasone: 8mg Nimesulide: 100mg	-	-	No	Dexamethasone 8mg + Nimesulide 100mg VO 1h pre-op	Dexamethasone 8mg 1 hour pre-op	-
Bauer, 2013 [14]	Dexamethasone: 8mg Ibuprofen: 600mg	-	-	Yes	Dexamethasone 8mg + Ibuprofen 600mg VO 1h pre-op	Ibuprofen 600mg VO 1 hour pre-op	-
Moore, 2005 [12]	Rofecoxib 50mg	Dexamethasone 10 mg	-	Yes	Dexamethasone 10mg IV intra-op + Rofecoxib 50mg VO pre-op	Dexamethasone 10mg IV intra-op	Rofecoxib 50mg VO pre-op
Bamgbose, 2005 [3]	Dexamethasone: 8mg Diclofenac: 50mg	-	Dexamethasone: 4mg Diclofenac: 50mg	No	Dexamethasone 8mg IV pre-op + Diclofenac 50mg VO pre-op	Diclofenac 50mg VO pre-op	-

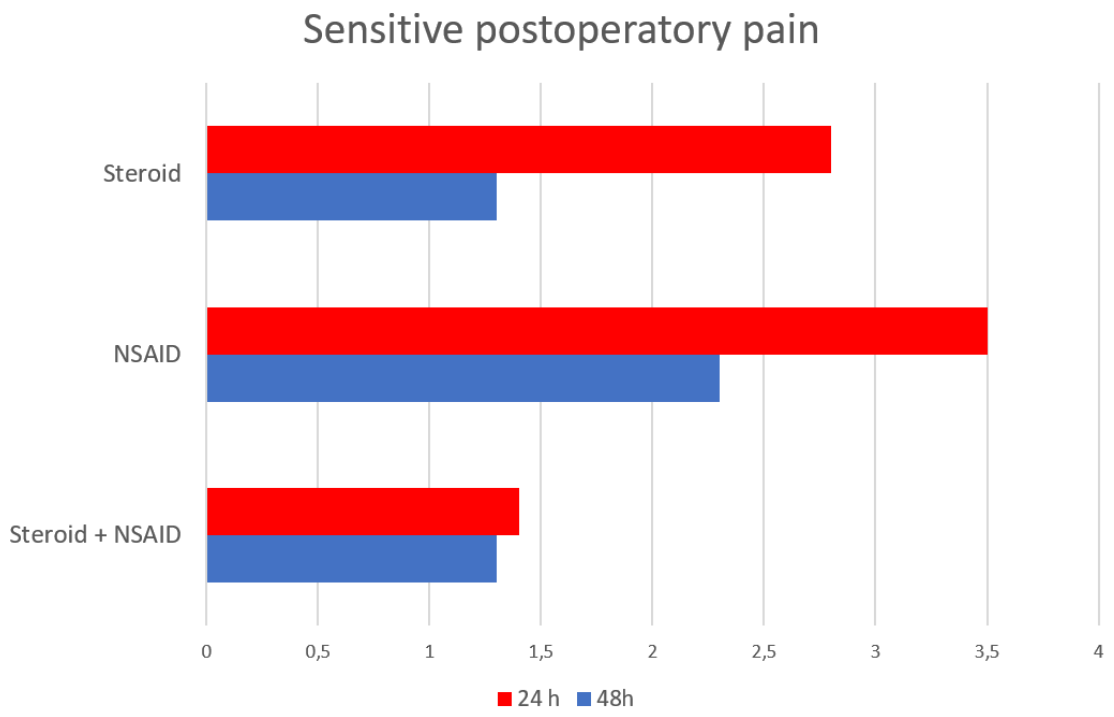
Resource: Own authorship

In Table 2, it is possible to see the division of groups by each selected work, dosage of the drugs and their periods of administration.

Sensitive Postoperative Pain

Three studies evaluated sensitive postoperative pain with the visual analogue scale (VAS) (Moore et al., 2005; Barbalho et al., 2017; Bauer et al., 2013). Only 1 author used the 4-point CRS scale (Bamgbose et al., 2005). Moreover, the postoperatory period evaluated varied among the authors. A postoperatory period of 24 hour or 48 hours was common to all studies. The group that received a combination of steroids plus NSAIDs showed a great decrease in postoperative pain during both periods compared with both of the other groups. There was no apparent difference in the reduction of postoperative pain between steroids-only and NSAIDs-only groups, despite the steroids-only group seeming to have decreased postoperative pain after 24 hours compared with the NSAIDs-only group (Figure 2 and Table 3).

Figure 2. Graph with the qualitative results regarding postoperative pain (VAS).



Resource: Own authorship

In Figure 2 it is possible to see the graph with the qualitative results regarding postoperative pain (VAS) showing the superiority of the combination of NSAIDs and corticosteroids in the preemptive analgesia compared to both drugs singly.

Table 3. Average of sensitive post-operatory pain (VAS).

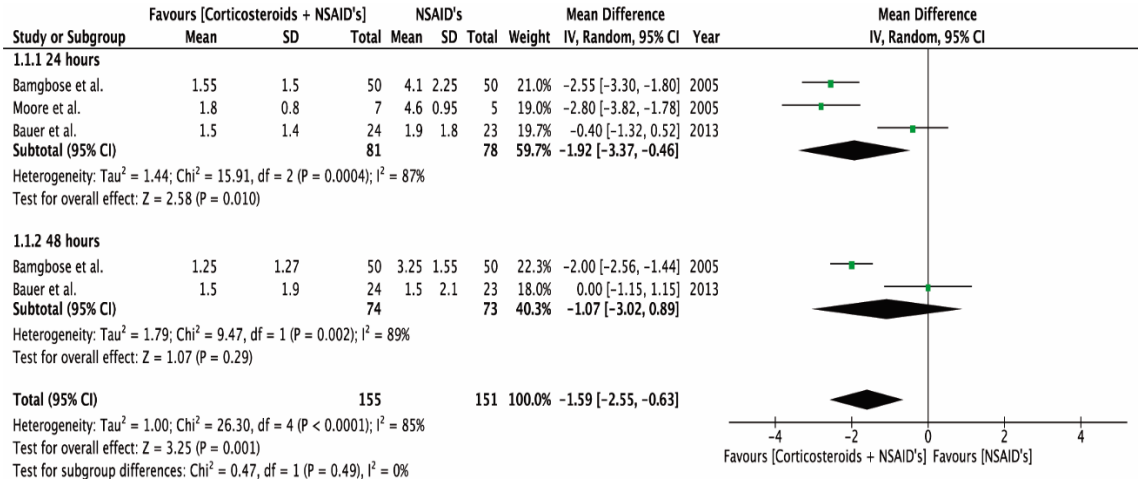
		24 HOURS			48 HOURS		
	Type of analysis	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**
Barbalho, 2017 [13]	VAS	1.12 (0.93)	-	0.87 (0.91)	1.37 (1.37)	-	1.30 (1.52)
Bauer, 2013 [14]	VAS	1.5 (1.4)	1.9 (1.8)		1.5 (1.9)	1.5 (2.1)	
Moore, 2005 [12]	VAS	1.8 (0.8)	4.6 (0.95)	4.9 (0.7)	-	-	-
Bamgbose, 2005 [3]	Four-point CRS	1.55 (1.5)	4.1 (2.25)		1.25 (1.27)	3.25 (1,55)	

Resource: Own authorship

Table 3 shows the different levels of postoperative pain sensitivity measured by different studies for the groups of NSAIDs associated with corticosteroids, and isolated corticosteroids, twenty-four, and forty-eight hours after the procedure.

Furthermore, this parameter was also evaluated by meta-analysis and, when the data about both periods (24 hours and 48 hours) were analyzed together, showed a significant decrease of postoperative pain for combination of preoperatively steroids plus NSAIDs compared to either therapy alone ($P < .001$). Also, when the combination of drugs was compared to steroids alone, the reduction of postoperative pain was more evident after 24 hours ($P < .001$) than after 48 hours ($P = .83$) (Figures 3 and 4).

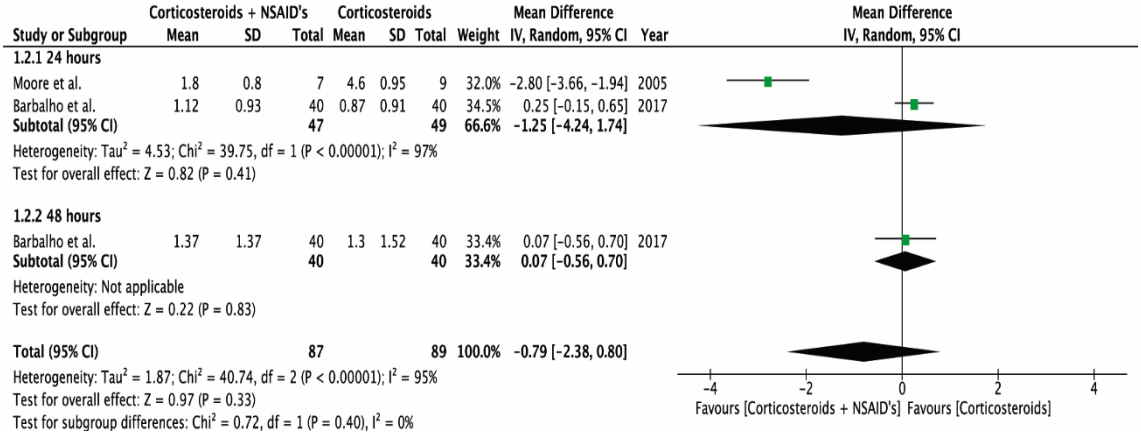
Figure 3. Forest plot of the pain parameter (VAS) comparing Corticosteroids + NSAIDs vs NSAIDs groups.



Resource: Own authorship

In Figure 3, it is possible to see in the forest plot graph of the meta-analysis the comparison made between NSAIDs and corticosteroids in combination and the NSAIDs alone, for the pain parameter.

Figure 4. Forest plot of the pain parameter (VAS) comparing Corticosteroids + NSAIDs vs Corticosteroids groups.



Resource: Own authorship

In Figure 4, it is possible to see in the forest plot graph of the meta-analysis the comparison made between NSAIDs and corticosteroids in combination and isolated corticosteroids, for the pain parameter.

Edema

Only two studies evaluated postoperatory edema (Bamgbose et al., 2005; Barbalho et al., 2017). Although the methods used to measure the edema were different, both studies showed lower values of edema for patients who received both steroids and NSAIDs compared with either drug in isolation (Table 4). This parameter was not evaluated by meta-analysis because only 2 authors evaluated this outcome and due the lack of homogeneity between them in how edema was measured.

Table 4. Average of postoperative edema (mm).

		24 HOURS			48 HOURS		
	Type of analysis	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**
Barbalho, 2017 [13]	Average of between each pre-op and post-op points values (mm)	1.76 (1.86)	-	4.34 (1.80)	5.22 (2.23)	-	5.80 (2.18)
Bauer, 2013 [14]	-	-	-	-	-	-	-
Moore, 2005 [12]	-	-	-	-	-	-	-
Bamgbose, 2005 [3]	Average of each point measurement (mm)	309 (16)	317 (16)	-	310 (15.8)	320 (15)	-

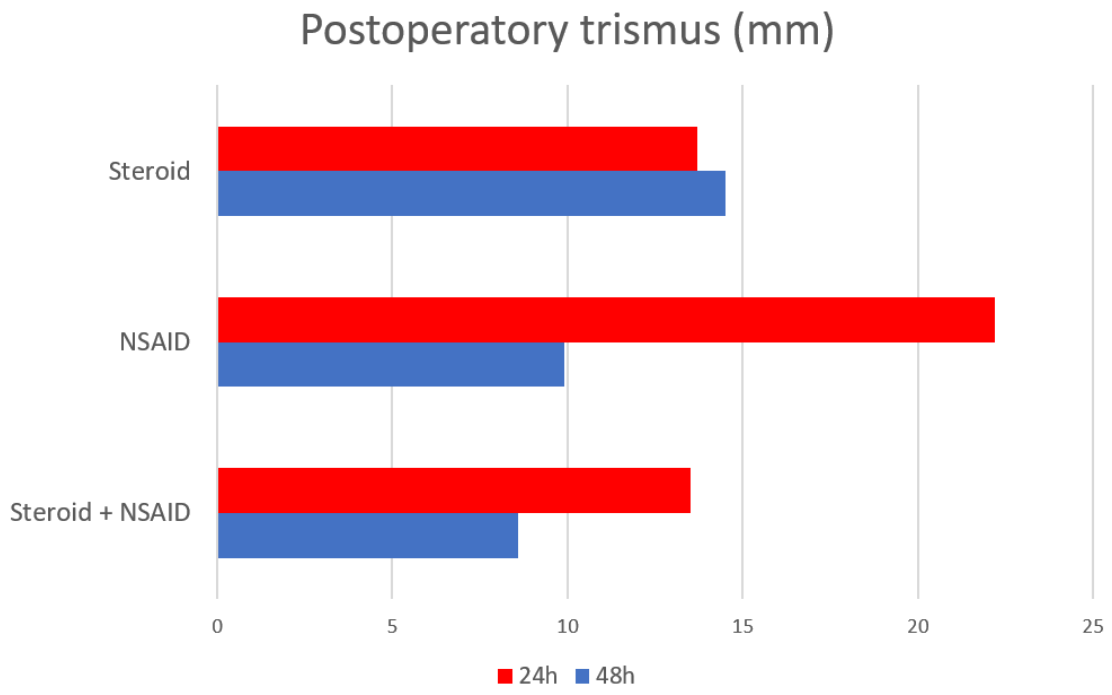
Resource: Own authorship

Table 4 shows the edema levels measured by different studies for the NSAID groups associated with corticosteroids, isolated NSAIDs, and isolated corticosteroids, twenty-four, and forty-eight hours after the procedure.

Trismus

Trismus also was not evaluated in the meta-analysis due to the lack of homogeneity regarding how trismus was measured and because the studies that measured trismus differed in the drug therapy used, which might lead to great bias in this analysis. Only one study (Bauer et al., 2013) did not evaluate postoperatory trismus. In the qualitative analysis, trismus showed a discrete reduction with the combination of drugs compared to the isolated drugs. At 24 hours postoperation, trismus decreased in patients who received a combination of drugs as well as steroids alone. At 48 hours postoperation, the combination of drugs showed more similar results with NSAIDs alone (Figure 5 and Table 5).

Figure 5. Graph with the qualitative results regarding postoperative trismus showing the behavior of the combination of corticosteroids plus NSAIDs, and both drugs singly**.**



Resource: Own authorship

In Figure 5 we can notice the graph with the qualitative results regarding postoperative trismus showing a greater behavior of the combination of corticosteroids plus NSAIDs than both drugs singly**.**

Table 5. Average of reduction post-operatory trismus (MM).

		24 HOURS			48 HOURS		
	Type of analysis	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**	**Corticosteroids + NSAID's**	**NSAID's**	**Corticosteroids**
Barbalho, 2017 [13]	Difference between pre-op and post-op	14.7	-	14.8	14.5	-	14.5
Bauer, 2013 [14]	-	-	-	-	-	-	-
Moore, 2005 [12]	Difference between pre-op and post-op	12.4	22.2	12.6	11	16.8	13.6
Bamgbose, 2005 [3]	Difference between pre-op and post-op	-	-	-	0.31	3.19	-

Resource: Own authorship

Table 5 shows the values for the parameter trismus for the NSAID groups associated with corticosteroids, isolated NSAIDs, and isolated corticosteroids, measured by the different studies twenty-four and forty-eight hours after the procedure.

Total Number of Rescue Analgesic

Total number of rescue analgesic (TNRA) was not evaluated in the meta-analysis, because only 2 authors observed the total number of rescue analgesics taken by the patients of each group (Barbalho et al., 2017; Bauer et al., 2013). Furthermore, the authors employed different techniques to analyze this parameter, and 1 author compared the combination of corticosteroids and NSAIDs to corticosteroids alone while another author compared the combination with NSAIDs only. Thus, the number of rescue analgesics taken was lower for groups that received a combination of corticosteroids and NSAIDs compared with both isolated therapies, both at 72 hours and 7 days postoperation (Table 6).

Table 6. Average of total number of rescue analgesics (TNRA).

	Time of evaluation	Corticosteroids + NSAID's	NSAID's	Corticosteroids
Barbalho, 2017 [13]	7 days post-op	2.02 (0.25)	-	3.02 (0.28)
Bauer, 2013 [14]	72 hours post-op	14	22	-
Moore, 2005 [12]	-	-	-	-
Bamgbose, 2005 [3]	-	-	-	-

Resource: Own authorship

Table 6 shows the values of the parameter amount of rescue analgesics used for the groups of NSAIDs associated with corticosteroids, isolated NSAIDs and isolated corticosteroids, measured by different studies at a given postoperative time.

Bias Risk in the Individual Studies

All of the selected studies were randomized clinical trials, presenting scores in level II based on the NCHMR scale, which represents low bias for this review.

4. Discussion

Postoperative pain is one the greatest concerns among patients and surgeons after third-molar extractions. Thus, postoperative pain evaluation is a study model extensively used to create drug clinical protocols that minimize the pain symptoms after dental surgeries (Mojsa et al., 2017; Barden, Edwards, McQuay, & Andrew Moore, 2004; Brignardello-Petersen, 2017) Corticosteroids are the most widely used drugs for preemptive analgesia in surgical practice, and several clinical trials have showed their effectiveness in reducing postoperative pain, edema, and trismus (Antunes, Avelar, Martins Neto, Frota, & Dias, 2011; Darawade, Kumar, Mehta, Sharma, & Reddy, 2014; Paiva-Oliveira et al., 2016; Simone, Jorge, Horliana, Canaval, & Tortamano, 2013). However, recent studies have shown that the combination of corticosteroids and NSAIDs may improve the postoperative symptoms after

third-molar surgeries, mainly the acute pain in the first hours (Bamgbose et al., 2005; Moore et al., 2005; Barbalho et al., 2017; Bauer et al., 2013).

Although corticosteroids are well-known to reduce postoperative edema and trismus in third-molar surgeries, they seem to have no great effects on postoperative pain (Laureano Filho et al., 2008). Laureano Filho et al (Laureano Filho et al., 2008) showed that a preemptive oral dose of 8 mg of dexamethasone 1 hour before a third-molar surgery decreased postoperative edema and trismus but not pain symptoms when compared with a preoperative 4 mg dose by IV. Furthermore, authors who compared the effects of preoperative dexamethasone and ketorolac showed better results for the steroid, mainly regarding the limitation of mouth opening, and similar values for postoperative pain and analgesic consumption (Paiva-Oliveira et al., 2016).

Two authors evaluated postoperative edema, but one study compared the combination of NSAIDs and corticosteroids to corticosteroids alone and the other compared the combination of both drugs to NSAIDs alone. Despite the lack of pattern between the studies, this current review shows lower postoperative edema values for the combination of steroids and NSAIDs compared to both drugs alone, at both 24 hours and 48 hours. Besides that, the combination of drugs also showed great improvement regarding postoperative trismus, mainly at 48 hours after surgery.

Furthermore, the combination of both corticosteroids and NSAIDs showed better results for pain. All studies used the visual analogue scale (VAS) to evaluate sensitive postoperative pain, except for 1, which used the 4-point CRS analysis. A proportion calculation was conducted on the quantitative data. The preoperative combination of steroids and NSAIDs showed greater results in sensitive postoperative pain compared to both drugs alone, mainly at 24 hours postoperation, which is when the worst acute pain occurred. At 48 hours postoperation, the data were similar between the combination of drugs and corticosteroids alone but even lower. These data underwent meta-analysis and showed significant differences favoring the combination of drugs compared to NSAIDs alone, along with greater results for the combination compared to corticosteroids alone.

Two authors also evaluated the TNRA, but one author evaluated the average at 72 hours postoperation and the other the average at 7 days postoperation. Moreover, one study evaluated the combination of drugs compared to corticosteroids alone and the other one compared the combination of drugs to NSAIDs alone. Despite the lack of pattern, both studies showed lower postoperative analgesic consumption for the combination of steroids and

NSAIDs compared to both isolated therapies, with greater difference for NSAIDs alone, which corroborates with the results about sensitive postoperative pain.

Despite corticosteroids acting at the start of the inflammatory chain to inhibit phospholipase A2 and, consequently, the 2 cyclooxygenase enzymes, cytokines, and pain mediators, it seems that these drugs have no significant effect in inhibiting prostaglandin E2 (Sisk, & Bonnington, 1985). For Dionne et al (Dionne et al., 2003), this occurs because in humans, corticosteroids are related with the suppression of COX-1 associated with TxB2 in one cell type and shows little effect on COX-1-mediated production of PGE2 in other cell types. Furthermore, corticosteroids inhibit the release of beta-endorphins by the anterior pituitary, which is known for its endogenous analgesic effect (Troullos, Hargreaves, Butler, & Dionne, 1990). This data might explain why corticosteroids alone showed no significant reduction in postoperative pain, mainly in the first hours, which is the most acute phase of the postoperative period.

Indeed, NSAIDs alone showed the worst values for postoperative trismus, edema, and pain. Besides that, patients who took only preoperatively NSAIDs showed the highest consumption of rescue analgesics in the postoperative period. This probably occurred because NSAIDs act only on the COX enzymes, after phospholipase A2 has already been released (Cashman, 1996). This is the reason why these drugs are not used for preemptive analgesia. However, when associated with corticosteroids, NSAIDs seems to compensate for the lack of analgesic effects of these drugs, as explained above, besides increase the anti-inflammatory potential. Furthermore, the fact that corticosteroids are superior in reducing postoperative edema and trismus compared to NSAIDs might contribute to decreasing postoperative pain.

This current study has several limitations, which can be an incentive for authors to perform other clinical trials and create a pattern in the evaluation data, such as by comparing a test group (NSAIDs + corticosteroids) with both drugs alone, in addition to employing the same type of analysis, which will increase the relevance of the results. This is an important subject but is still very controversial. Postoperative pain is the major concern among patients who undergo third-molar extraction; thus, searching for therapies that will decrease pain symptoms after surgery will have a great clinical impact on surgical practice.

Thus, corticosteroids remain a great choice for preemptive analgesia in third-molar surgeries when compared to NSAIDs. However, the preoperatively combination of both drugs improves the postoperative symptoms, mainly the first hours of acute pain.

5. Conclusion

Through the analysis of the systematic review and meta-analysis, it was noted that the combination of NSAIDs with corticosteroids showed a significant reduction in postoperative pain, compared to the two isolated therapies, also being effective in reducing postoperative edema and trismus. In addition, the total number of rescue analgesics was lower for patients who received the drug combination. This article highlights the importance of this theme and reaffirms the need for more investigative clinical studies that compare these classes of anti-inflammatories, in combination or isolated, in the preemption model.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Alcântara, C. E., Falci, S. G., Oliveira-Ferreira, F., Santos, C. R., & Pinheiro, M. L. (2014). Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split-mouth randomized triple-blind clinical trial. International journal of oral and maxillofacial surgery, 43(1), 93–98.

Annibali, S., Bignozzi, I., Cristalli, M. P., Graziani, F., La Monaca, G., & Polimeni, A. (2012). Peri-implant marginal bone level: a systematic review and meta-analysis of studies comparing platform switching versus conventionally restored implants. Journal of clinical periodontology, 39(11), 1097–1113.

Antunes, A. A., Avelar, R. L., Martins Neto, E. C., Frota, R., & Dias, E. (2011). Effect of two routes of administration of dexamethasone on pain, edema, and trismus in impacted lower third molar surgery. Oral and maxillofacial surgery, 15(4), 217–223.

Atieh, M. A., Ibrahim, H. M., & Atieh, A. H. (2010). Platform switching for marginal bone preservation around dental implants: a systematic review and meta-analysis. Journal of periodontology, 81(10), 1350–1366.

Aznar-Arasa, L., Harutunian, K., Figueiredo, R., Valmaseda-Castellón, E., & Gay-Escoda, C. (2012). Effect of preoperative ibuprofen on pain and swelling after lower third molar removal: a randomized controlled trial. International Journal Of Oral And Maxillofacial Surgery, 41(8), 1005-1009.

Bamgbose, B., Akinwande, J., Adeyemo, W., Ladeinde, A., Arotiba, G., & Ogunlewe, M. (2005). Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. Head & Face Medicine, 1(1).

Barbalho, J. C., Vasconcellos, R. J., de Morais, H. H., Santos, L. A., Almeida, R. A., Rêbelo, H. L., Lucena, E. E., & de Araújo, S. Q. (2017). Effects of co-administered dexamethasone and nimesulide on pain, swelling, and trismus following third molar surgery: a randomized, triple-blind, controlled clinical trial. International journal of oral and maxillofacial surgery, 46(2), 236–242.

Barden, J., Edwards, J. E., McQuay, H. J., & Andrew Moore, R. (2004). Pain and analgesic response after third molar extraction and other postsurgical pain. Pain, 107(1-2), 86–90.

Bauer, H. C., Duarte, F. L., Horliana, A. C., Tortamano, I. P., Perez, F. E., Simone, J. L., & Jorge, W. A. (2013). Assessment of preemptive analgesia with ibuprofen coadministered or not with dexamethasone in third molar surgery: a randomized double-blind controlled clinical trial. Oral and maxillofacial surgery, 17(3), 165–171.

Brignardello-Petersen R. (2017). Submucosal dexamethasone reduces pain, swelling, and trismus after impacted third-molar extraction. Journal of the American Dental Association (1939), 148(5), e64.

Cashman J. N. (1996). The mechanisms of action of NSAIDs in analgesia. Drugs, 52 Suppl 5, 13–23.

Coleman, K., Norris, S., Weston, A., Grimmer-Sommers, K., Hillier, S., & Merlin, T. (2015). HMRC additional levels of evidence and grades for recommendations for developers of

guidelines. NHMRC. Retrieved from http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/stage_2_consultation_levels_and_grades.pdf.

Costa, F., Soares, E., Esses, D., Silva, P., Bezerra, T., & Scarparo, H. et al. (2015). A split-mouth, randomized, triple-blind, placebo-controlled study to analyze the pre-emptive effect of etoricoxib 120mg on inflammatory events following removal of unerupted mandibular third molars. International Journal Of Oral And Maxillofacial Surgery, 44(9), 1166-1174.

Darawade, D. A., Kumar, S., Mehta, R., Sharma, A. R., & Reddy, G. S. (2014). In search of a better option: dexamethasone versus methylprednisolone in third molar impaction surgery. Journal of international oral health : JIOH, 6(6), 14–17.

Dionne, R. A., Gordon, S. M., Rowan, J., Kent, A., & Brahim, J. S. (2003). Dexamethasone suppresses peripheral prostanoid levels without analgesia in a clinical model of acute inflammation. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, 61(9), 997–1003.

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. Statistics in medicine, 21(11), 1539–1558.

Laureano Filho, J. R., Maurette, P. E., Allais, M., Cotinho, M., & Fernandes, C. (2008). Clinical comparative study of the effectiveness of two dosages of Dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. Medicina oral, patologia oral y cirugia bucal, 13(2), E129–E132.

Mojsa, I. M., Stypulkowska, J., Novak, P., Lipczynski, K., Szczeklik, K., & Zaleska, M. (2017). Pre-emptive analgesic effect of lornoxicam in mandibular third molar surgery: a prospective, randomized, double-blind clinical trial. International journal of oral and maxillofacial surgery, 46(5), 614–620.

Moore, P. A., Brar, P., Smiga, E. R., & Costello, B. J. (2005). Preemptive rofecoxib and dexamethasone for prevention of pain and trismus following third molar surgery *. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics, 99(2), E1–E7.

Ong, K., Seymour, R., Chen, F., & Ho, V. (2004). Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. International Journal Of Oral And Maxillofacial Surgery, 33(8), 771-776.

Paiva-Oliveira, J. G., Bastos, P. R., Cury Pontes, E. R., da Silva, J. C., Delgado, J. A., & Oshiro-Filho, N. T. (2016). Comparison of the anti-inflammatory effect of dexamethasone and ketorolac in the extractions of third molars. Oral and maxillofacial surgery, 20(2), 123–133.

Pereira, A.S.; Shitsuka, D.M.; Parreira, F.J. & Shitsuka, R. (2018). Metodologia da pesquisa científica. Editora UAB/NTE/UFSM, Santa Maria/RS. Retrieved from <https://repositorio.ufsm.br/bitstream/handle/1/15824/Lic_Computacao_Metodologia-Pesquisa-Cientifica.pdf?sequence=1>.

Simone, J. L., Jorge, W. A., Horliana, A. C., Canaval, T. G., & Tortamano, I. P. (2013). Comparative analysis of preemptive analgesic effect of dexamethasone and diclofenac following third molar surgery. Brazilian oral research, 27(3), 266–271.

Sisk, A. L., & Bonnington, G. J. (1985). Evaluation of methylprednisolone and flurbiprofen for inhibition of the postoperative inflammatory response. Oral surgery, oral medicine, and oral pathology, 60(2), 137–145.

Troullos, E. S., Hargreaves, K. M., Butler, D. P., & Dionne, R. A. (1990). Comparison of nonsteroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, with methylprednisolone and placebo for acute pain, swelling, and trismus. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons, 48(9), 945–952.

Porcentagem de contribuição de cada autor no manuscrito

Gustavo Antonio Correa Momesso – 16%

Cleidiel Aparecido Araújo Lemos – 14%

Valthierre Nunes de Lima – 14%

Leonardo Alan Delanora – 14%

Joel Ferreira Santiago-Júnior – 14%

Leonardo Perez Faverani – 14%

Eduardo Piza Pellizzer – 14%