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EFICÁCIA DE MEDICAÇÃO PRÉ-ANESTÉSICA NA TÉCNICA DE BLOQUEIO DO NERVO ALVEOLAR INFERIOR EM PACIENTES COM PULPITE IRREVERSÍVEL EM MOLARES INFERIORES: UMA REVISÃO UMBRELLA.

Porto Alegre
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Orientador: Prof. Dr. Ricardo Abreu da Rosa

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RESUMO

O objetivo desta revisão sistemática *umbrella* foi responder à seguinte questão: “O uso de medicação pré-anestésica aumenta a eficácia anestésica do nervo alveolar inferior em dentes com pulpite irreversível sintomática?”. Esta revisão sistemática seguiu as recomendações dos padrões PRISMA e foi registrada no banco de dados PROSPERO (ID 304361). A busca foi realizada por dois pesquisadores em seis bases de dados eletrônicas. Foram selecionados artigos publicados até agosto de 2021, sem restrição de idioma e sem restrição de ano de publicação. Para tanto, foi realizada uma busca utilizando a combinação de termos MeSH nas seguintes bases de dados eletrônicas: PubMed, Cochrane Library, Web of Science, Scopus, EMBASE e Open Grey. Os critérios de elegibilidade, baseados na estratégia PICOS, foram: (P) humanos adultos com pulpite irreversível em molares inferiores; (I) uso de pré-medicação antes do procedimento anestésico; (C) Técnica anestésica sem o uso de medicação pré-anestésica (O) Avaliar a eficácia anestésica (S) Revisões sistemáticas com e sem meta-análise. Foi realizada a seleção dos estudos, a extração dos dados, a análise de vieses e, a partir disso, descritos os resultados. Doze estudos foram incluídos na análise qualitativa. Apenas em um estudo, a meta-análise não foi realizada. A qualidade metodológica foi avaliada através da ferramenta AMSTAR 2. Os principais achados das revisões sistemáticas foram que anti-inflamatórios não-esteróides tais como: ibuprofeno, oxicam diclofenaco, associação de ibuprofeno com paracetamol e cetorolaco foram eficazes para aumentar o sucesso da técnica de bloqueio do nervo alveolar inferior. Três revisões sistemáticas apresentaram uma qualidade ‘alta’; seis apresentaram uma qualidade ‘moderada’, duas, uma qualidade ‘baixa’; e uma revisão sistemática apresentou uma qualidade "muito baixa". Por meio desta revisão abrangente que reuniu dados de doze revisões sistemáticas, pode-se concluir que a medicação pré-anestésica em casos de pulpite irreversível em molares inferiores aumenta a eficácia da técnica de bloqueio do nervo alveolar inferior.

Palavras Chaves: Endodontia; Pulpite irreversível; Medicação pré-anestésica; Revisão sistemática.

ABSTRACT

The aim of this systematic review was answer the following question: “Does the use of pre-anesthetic medication increase the anesthetic efficacy of the inferior alveolar nerve in teeth with symptomatic irreversible pulpitis?”. This umbrella review followed the PRISMA standard (Preferred Reporting Items for Systematic Review and Meta-analysis) and was record in the PROSPERO database (ID 304361). The search was conducted on the databases by two researchers. Only papers published until August 2021 were selected, with no language restrictions and no restrictions on the year of publication. The search used the combination of MeSH and subject-to-subject terms, and it was performed in the following electronic databases: PubMed, Cochrane Library, Web of Science, Scopus, EMBASE and Open Grey. Eligibility criteria, based on the PICOS strategy, were: (P) human adults with irreversible pulpitis in lower molars; (I) use of premedication before the anesthetic procedure; (C) Anesthetic technique without using pre-anesthetic medication (O) Evaluate anesthetic efficacy (S) Systematic reviews with and without meta-analysis. The selection of studies, the extraction of data and their bias analysis were carried out and, based on that, the results were described. Twelve studies were included in qualitative synthesis. Only in one study, meta-analysis was not performed. The methodological quality was assessed using the AMSTAR 2 tool. The main findings of the systematic reviews were that non-steroidal anti-inflammatory drugs such as ibuprofen, oxicam, diclofenac, association of ibuprofen with paracetamol and ketorolac were effective in increasing the success of the inferior alveolar nerve block anesthetic technique. The AMSTAR 2 overall confidence for the included systematic reviews ranged from very low to high quality. Three systematic reviews presented a ‘high’ quality, six presented a ‘moderate’ quality, two a ‘low’ quality; and one systematic review presented a ‘very low’ quality. This current umbrella review gathered data from twelve systematic reviews and can conclude that premedication in cases of irreversible pulpitis in mandibular molars increases the effectiveness of the inferior alveolar nerve block anesthetic technique.

Keywords: Endodontics; Irreversible Pulpitis; Pre-anesthetic Medication; Systematic Review

SUMÁRIO

1. INTRODUÇÃO

O sucesso da técnica anestésica para manejo da dor durante o tratamento endodôntico é de suma importância para a realização da terapia endodôntica. A técnica de bloqueio do nervo alveolar inferior é comumente utilizada para alcançar a anestesia de dentes molares inferiores.

A inflamação relacionada à polpa radicular em casos de pulpite irreversível sintomática contribui para o insucesso da técnica anestésica. A taxa de falha relacionada ao bloqueio do nervo alveolar inferior em dentes com pulpite irreversível está entre 43% e 83% (REISMAN et al. 1997, NUSSTEIN et al. 1998, KENNEDY et al. 2003, LINDEMANN et al. 2008, ARGUETA-FIGUEROA et al. 2012, FOWLER et al. 2016, AGGARWAL et al. 2017, PULIKKOTIL et al. 2018).

O processo inflamatório presente nas inflamações pulpares é mediado por prostaglandinas (PGs) e subprodutos decorrente das enzimas ciclo-oxigenases (COX). As prostaglandinas atuam sensibilizando as terminações nervosas para as histaminas e bradicininas, que aumentam a permeabilidade vascular através da vasodilatação, resultando no aumento da dor e inflamação (CHAUDARY et al. 2001, STENHOLM et al. 2002, GOODIS et al. 2006, DE GEUS et al. 2018).

O uso de técnicas anestésicas suplementares como a técnica intraligamentar e a técnica infiltrativa auxiliam na eficácia e manejo da dor intra-operatória. A associação de medicações pré-anestésicas através de anti-inflamatórios não-esteroidais tem se mostrado efetivas para alcançar um bloqueio anestésico durante todo tratamento endodôntico (NUSSTEIN et al. 2003, AGGARWAL et al. 2009, KIM et al. 1986, LAPIDUS et al. 2016, TUPYOTA et al. 2017).

Medicamentos anti-inflamatórios não-esteroidais parecem inibir a inflamação e induzir uma analgesia através da inibição de enzimas ciclooxigenases (COX). Essas medicações podem ser uma alternativa viável para alcançar o sucesso da técnica anestésica devido ao custo-benefício e segurança, porém é necessário ter um consenso de qual medicação devemos usar, assim como a dose que deve ser prescrita. (MICHELET et al. 2012, AVELINE et al. 2015, HABIB et al. 1990)

Percebendo a importância do sucesso da técnica anestésica de bloqueio do nervo alveolar inferior em dentes com pulpite irreversível e a variedade de medicações pré-anestésicas para auxiliar no manejo da dor e contribuição para o decorrer do tratamento endodôntico, o objetivo desta revisão *umbrella* é responder a seguinte pergunta: "O uso de medicação pré-anestésica aumenta a eficácia anestésica do nervo alveolar inferior em dentes com pulpite irreversível sintomática?".

2. OBJETIVOS

2.1 Objetivo Geral

Avaliar as evidências científicas disponíveis referentes as diferentes medicações pré-anestésicas usadas previamente à técnica de bloqueio do nervo alveolar inferior em pacientes com pulpite irreversível.

2.2 Objetivos Específicos

Verificar as evidências científicas que tenham analisado diferentes medicações pré-anestésicas e sua influência no sucesso anestésico do nervo alveolar inferior de pacientes com pulpite irreversível em dentes molares inferiores, quanto ao risco de viés e o nível de qualidade de evidência científica encontrada.

3. ARTIGO CIENTÍFICO

Artigo científico formatado de acordo com as normas do periódico International Endodontic Journal (Qualis A1).

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ABSTRACT

The aim of this systematic review was answering the following question: “Does the use of pre-anesthetic medication increase the anesthetic efficacy of the inferior alveolar nerve in teeth with symptomatic irreversible pulpitis?”. This umbrella review followed the PRISMA standard (Preferred Reporting Items for Systematic Review and Meta-analysis) and was record in the PROSPERO database (ID 304361). The search was conducted on the databases by two researchers. Only papers published until August 2021 were selected, with no language restrictions and no restrictions on the year of publication. The search used the combination of MeSH and subject-to-subject terms, and it was performed in the following electronic databases: PubMed, Cochrane Library, Web of Science, Scopus, EMBASE and Open Grey. Eligibility criteria, based on the PICOS strategy, were: (P) human adults with irreversible pulpitis in lower molars; (I) use of premedication before the anesthetic procedure; (C) Anesthetic technique without using pre-anesthetic medication (O) Evaluate anesthetic efficacy (S) Systematic reviews with and without meta-analysis. The selection of studies, the extraction of data and their bias analysis were carried out and, based on that, the results were described. Twelve studies were included in qualitative synthesis. Only in one study, meta-analysis was not performed. The methodological quality was assessed using the AMSTAR 2 tool.The main findings of the systematic reviews were that non-steroidal anti-inflammatory drugs such as ibuprofen, oxicam, diclofenac, association of ibuprofen with paracetamol and ketorolac were effective in increasing the success of the inferior alveolar nerve block anesthetic technique. The AMSTAR 2 overall confidence for the included systematic reviews ranged from very low to high quality. Three systematic reviews presented a ‘high’ quality, six presented a ‘moderate’ quality, two a ‘low’ quality; and one systematic review presented a ‘very low’ quality. This current umbrella review gathered data from twelve systematic reviews and can conclude that premedication in cases of irreversible pulpitis in mandibular molars increases the effectiveness of the inferior alveolar nerve block anesthetic technique.

Keywords: Endodontics; Irreversible Pulpitis; Pre-anesthetic Medication; Systematic Review

Introduction

The success of the anesthetic technique for pain management during endodontic treatment is of paramount importance for the beginning of endodontic therapy. The inferior alveolar nerve block technique is commonly used to achieve pulpal anesthesia of lower molars.

Inflammation related to the pulp tissue in cases of symptomatic irreversible pulpitis contributes to the failure of the anesthetic technique. A failure rate related to inferior alveolar nerve block in teeth with irreversible pulpitis ranges between 43% and 83% (Reisman et al. 1997, Nusstein et al. 1998, Kennedy et al. 2003, Lindemann et al. 2008, Argueta- Figueroa et al. 2012, Fowler et al. 2016, Aggarwal et al. 2017, Pulikkotil et al. 2018).

The inflammatory process is mediated by prostaglandins and products resulting from cyclooxegenases. Prostaglandins act by sensitizing nerve endings to histamines and bradykinins, which increase vascular permeability through vasodilation, causing an increasing of pain and inflammation (Chaudary et al. 2001, Stenholm et al. 2002, Goodis et al. 2006, De Geus et al. 2018).

The use of supplementary anesthetic techniques such as the intraligamentary technique and the infiltrative technique support the effectiveness and management of intraoperative pain. The association of pre-anesthetic medications using non-steroidal anti-inflammatory drugs contributes to achieve an effective anesthetic block during all endodontic treatment (Nusstein et al. 2003, Aggarwal et al. 2009, Kim et al. 1986, Lapidus et al. 2016, Tupyota et al. 2017).

Nonsteroidal anti-inflammatory drugs appear to inhibit inflammation and induce analgesia through the inhibition of cyclooxygenase (COX) enzymes. These medications have been pointed as a viable alternative to achieve the success of the anesthetic technique due to their cost-effectiveness and safety, but it is necessary to have a consensus on which medication should be used, as well as the dose that should be prescribed. (Michelet et al. 2012, Aveline et al. 2015, Habib et al. 1990)

Realizing the importance of the success of the anesthetic technique of inferior alveolar nerve block in mandibular molars with irreversible pulpitis and a variety of medications to manage the patient's pain and contribute to the course of endodontic treatment, the purpose of the review is to answer the following question: “Does the use of pre-anesthetic medication increase the efficacy of the anesthetic technique of inferior alveolar nerve block on teeth with symptomatic irreversible pulpitis?

Materials and Methods

Register

This umbrella review followed the recommendations by the PRISMA standards (Preferred Reporting Items for Systematic Review and Meta-analysis) and were recorded in the PROSPERO database (ID 304361).

Search Strategy

The search were conducted by two researchers (GBS and IAS) on the databases as described on Supplementary File 1. Articles published until August 2021 were selected, with no language restrictions and no restrictions on the year of publication. For this purpose, the most cited descriptors in previous publications referring to this topic were used, combining MeSH (Medical Subject Heading) terms and terms common to the subject. In each database, the following descriptors were combined as presented on Supplementary File 1 as well. The descriptors "AND" and "OR" were applied to combine the terms and establish a search strategy. In addition, a manual search was carried out for relevant publications in the references of the selected articles and, if any relevant article on the subject is found, it was searched in the PubMed database.

Eligibility criteria

Eligibility criteria for the selection of studies was based on the PICOS strategy (PRISMA-P 2015) (Moher et al. 2016, Leong et al. 2020, Pérez-González et al. 2020), as follows:

- Population (P): human adults with irreversible pulpitis in mandibular molars;
- Intervention (I): use of premedication before the anesthetic procedure;
- Control (C): Anesthetic technique without the use of premedication;
- Outcome (O): Assess anesthetic efficacy;
- Study design(S): Systematic reviews with and without meta-analysis

Exclusion criteria

Systematic reviews evaluating the influence of pre-anesthetic medication on anesthetic efficacy in conditions other than symptomatic irreversible pulpitis in mandibular molars or other anesthetic blocks were excluded. Animal studies, histological studies, randomized and non-randomized studies, reviews, letters, opinionated articles, conference abstracts, case reports and in vitro studies were excluded.

Study selection

Two authors (G.B.S. and I.A.S.) were responsible for selecting the studies. Systematic reviews in duplicate were identified to be considered only once. From those eligible for inclusion, titles and abstracts were removed and read. If necessary to determine the inclusion or not of the study, the full text was read and evaluated.

Papers that meet the inclusion criteria were accessed and read in full. The selected studies were checked by both authors and, in case of disagreement, a third and more experienced author (T.W.) were responsible for the decision. The results were registered in an Excel spreadsheet.

Data Extraction

The following information were taken from the studies: name of the author(s), year of publication, country of the first author, name of the journal where it was published, database used, search period, language, performance of meta-analysis, design of included studies, quality assessment instrument and main findings. Again, two authors (G.B.S. and I.A.S.) were responsible for extracting the data. In view of possible disagreements, a third and more experienced author (T.W.) were responsible for the decision. In case of need for additional details or missing information, the researchers contacted, via email, the author(s) of the selected study. The results were registered in an Excel spreadsheet.

Methodological Quality

The methodological quality of the included studies was assessed using the AMSTAR 2 tool (Shea et al. 2017), which consists of 16 items for analysis, with "yes" being assigned if the parameters are in agreement, and "no" in the absence of them. Parameters in which the data have been partially expressed will be assigned as "partial yes". The analysis was done by filling out the "CheckList" of the Amstar 2 tool, which automatically generates, at the end of the review, the "overall" and methodological quality of the selected articles, classifying them as high, moderate, low and very low methodological quality. The identification of the rating overall confidence in the results of the review is subject for sixteen domains of the AMSTAR 2 Checklist items as presented on Figure 3. On these items, there are seven critical domains that classified critical weaknesses on the systematic reviews. These critical domains are: protocol registered before commencement of the review (item 2); adequacy of the literature search (item 4); justification for excluding individual studies (item 7); risk of bias from individual studies being included in the review (item 9); appropriateness of meta-analytical methods (item 11); consideration of risk of bias when interpreting the results of the review (item 13); assessment of presence and likely impact of publication bias (item 15). Using the critical domains and the others twelve domains is it possible to classify the studies as High (no or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest); Moderate (more than one non-critical weakness: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review); Low (one critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest) and Critically Low (more than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies) (SHEA et al. 2017).

Two authors (G.B.S. and I.A.S.) were independently assessed the methodological quality of each study included in the review, and a third author (T.W.) validated the analysis.

Results

Search results

The literature search process used to identify the studies is shown in Figure 1. A total of 144 studies were identified from the searches in the electronic databases, where 63 were excluded for being duplicates. After title and abstract reading, 68 studies were excluded, and 13 were assessed for eligibility. One study was excluded after full-text reading because it was an opinion letter of other published study (Wong Y. 2019). Finally, twelve studies were included in qualitative synthesis.

Characteristics of included reviews

The characteristics of the included studies are presented in Table 1.

The studies were published between 2012 and 2019, in the following journals: Australian Endodontic Journal (n = 2); Biomed Research International (n = 1); Clinical Oral Investigations (n = 1); Journal Dental Anesthesia and Pain Medicine (n = 1); Journal of Endodontics (n = 2); International Endodontic Journal (n = 1); International Journal of Clinical and Experimental Medicine (n = 1); Quintessence International (n= 2); and Open Dentistry Journal (n = 1). The systematic reviews used the following electronic database MEDLINE/PubMed, EBSCO/host, Embase, Cochrane, CINAHL, Chinese Biomedical Literature, Google Scholar, Science Direct, WHO, Web of Science, Scopus, LILACS and Scientific Electronic Library Online, to identify relevant studies in their review. The search was not further supplemented by hand searching only in two studies (Fan et al. 2018, Karapinar-Kazandag et al. 2019) The number of studies included in each systematic review ranged from 4 to 46. Amongst the twelve reviews, eleven conducted a meta-analysis (Chunjie Li *et al.* 2012, Corbella *et al.* 2017, De Geus *et al.* 2018, Fan *et al.* 2018, Nagendrababu *et al.* 2018, Pulikkotil *et al.* 2018, Shirvani *et al.* 2017, Sivaramakrishnan *et al*. 2018, Sivaramakrishnan *et al.* 2019, Tupyota *et al.*

2017, Zanjir *et al.* 2019). To evaluate quality of the included studies, all systematic reviews used Cochrane Risk of Bias Tool. It is the recommended tool to assess the risk of bias in randomized trials and consists in six domains (random sequence generalization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting and other bias). The possible judgment for these domains could be "high risk," "low risk," or "unclear risk" of bias.

Summary of meta-analysis

Three reviews reported statistical heterogeneity among the trials by using the Cochrane Q test (Shirvani *et al.* 2016, Fan *et al.* 2018, De Geus *et al.* 2018); eight studies used I^2 to assess heterogeneity among studies (Fan *et al.* 2018, De Geus *et al.* 2018, Nagendrababu *et al.* 2018, Pulikkotil *et al.* 2018, Tupyota *et al.* 2017, Sivaramakrishnan *et al.* 2019, Sivaramakrishnan *et al.* 2018, Zanjir *et al.* 2019). To determine the relation between premedication and Inferior Alveolar Nerve Block, five reviews used the Mantel–Haenszel with fixed-effects model (Chunjie Li et al. 2012, Corbella *et al.* 2017, Fan et al. 2018, Nagendrababu et al. 2018, Sivaramakrishnan et al. 2018); two studies used Mantel-Haenszel with random effects model (De Geus et al. 2018, Tupyota et al. 2017); two studies used fixed and random-effect inverse variance statistical method (Shirvani et al. 2016, Sivaramakrishnan et al. 2019); one study reported Bayesian random effects model (Zanjir et al. 2019); and one study did not report any test to determine the relations between intervention and outcomes (Pulikkotil et al. 2018) A meta-analysis was not performed in one study (Karapinar-Kazandag et al. 2019)

Methodological quality

The methodological quality assessment of the twelve systematic reviews included in this umbrella review is presented in Figure 2. The AMSTAR 2 overall confidence for the included systematic reviews ranged from very low to high quality. Three systematic reviews presented a 'high' quality (Nagendrababu et al., 2018,

Pulikkotil et al., 2018, Zanjir et al., 2019); six presented a 'moderate' quality (Chunjie Li et al. 2012, Corbella et al., 2017, De Geus et al., 2018, Fan et al., 2018, Shirvani et al., 2017, Tupyota et al., 2017); two a 'low' quality (Sivaramakrishnan et al. 2018. Sivaramakrishnan et al. 2019); and one systematic review presented a 'very low' quality (Karapinar-Kazandag et al. 2019).

Main findings of the systematic reviews

Preemptive oral NSAIDs might have a good effect and are safe in increasing the success rate of inferior alveolar nerve block (IANB) (Chunjie Li *et al.* 2012, Fan *et al.* 2018). Preoperative NSAIDs with or without acetaminophen may increase the efficacy of the IANB (Zanjir *et al.* 2019). The administration of preemptive analgesics can induce superior intraoperative pulp anesthesia for patients with irreversible pulpitis. (Shirvani *et al.* 2017). Ibuprofen and oral premedication with NSAIDs increased the anesthetic success for a better inferior alveolar nerve block (De Geus *et al.* 2018, Nagendrabu *et al.* 2018, Corbella *et al.* 2017, Tupyota *et al.* 2018, Sivaramakrishnan *et al.* 2019). Oral premedication increases the success rate of IANB in teeth with irreversible pulpitis (Pulikkotil *et al.* 2018). Oral ketorolac can be successfully administered as a premedication before conventional inferior alveolar nerve block for endodontic treatment for irreversible pulpitis (Sivaramakrishnan *et al.* 2018).

Discussion

Amongst anesthetic techniques, inferior alveolar nerve block technique in teeth with irreversible pulpitis is the most difficult and failure technique. An error during this technique could compromised or delayed all the endodontic treatment.

The association between pre-medication and the success of inferior alveolar nerve block in teeth with irreversible pulpitis are many. Due to this, this current umbrella review was performed to combine data from the highest level of evidence, systematic reviews, and meta-analyses, to define whether there is an association between pre-medication and the success of the anesthetic technique.

The most acceptable reason to explain the failure of IANB technique on teeth with irreversible pulpitis is the activation of nociceptors by inflammation, which is

mediated by the prostaglandins generated resistant class of voltage-gated channels, which are resistant to local anesthetics and sensitive to prostaglandins. This ensures that the voltage-gated channels could not be blocked by IANB (Chunjie Li et al. 2012).

NSAIDs have been described to relieve pain and improve IANB success in cases of pulpitis (Fan et al. 2018). Studies reported that NSAIDs block the cyclooxygenase (COX) enzymes, which are responsible for the synthesis of inflammationn mediators, such as prostaglandins, that cause pain (Gunaydin & Bilge, 2018). NSAIDs could decrease the inflammatory stage by inciting prostaglandins and interrupting their production (Nagendrababu et al. 2018; Zanjir et al. 2019).

So, it is hypothesized that the use of a medication before the endodontic intervention could help in the efficacy of the anesthetic technique.

This study was performed with a careful methodology, registered in the PROSPERO database. Six electronic databases were searched to provide a solid source of knowledge. Selection criteria was based on the PICOS strategy (PRISMA-P 2015) (Moher et al. 2016, Leong et al. 2020, Pérez-González et al. 2020) to provide a more reliable and accurate data for studies that are associating pre-medication to achieve success on inferior alveolar block anesthetic technique in teeth with irreversible pulpitis.

To evaluate risk of Bias of the individual studies, all systematic reviews included in this study used Cochrane Risk of Bias Tool. This tool is the recommended to assess the risk of bias in randomized trials and consists in six domains (random sequence generalization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting and other bias). The possible judgment for these domains could be “high risk,” “low risk,” or “unclear risk” of bias (Higgins & Altman, 2008). In this current umbrella review, methodological quality assessment of the twelve systematic reviews was appraised using "A measurement Tool to Assess Systematic Reviews” (AMSTAR 2). AMSTAR is

a popular instrument for critically appraising systematic reviews of randomized controlled clinical trials. The revised instrument (AMSTAR 2) retains ten of the original domains, and it presents sixteen items in total (compared with 11 in the original). AMSTAR 2 has simpler response categories than the original AMSTAR, includes a more comprehensive user guide, and has an overall rating based on weaknesses in critical domains (Shea et al. 2017)

Regarding the overall confidence for the included systematic reviews ranged from very low to high quality. Three systematic reviews presented a 'high' quality (Nagendrababu et al., 2018, Pulikkotil et al., 2018, Zanjir et al., 2019); six presented a 'moderate' quality (Chunjie Li et al. 2012, Corbella et al., 2017, De Geus et al., 2018, Fan et al., 2018, Shirvani et al., 2017, Tupyota et al., 2017); two a 'low' quality (Sivaramakrishnan et al. 2018. Sivaramakrishnan et al. 2019); and one systematic review presented a 'very low' quality (Karapinar-Kazandag et al. 2019).

When accessing the main findings, eight studies (Corbella et al. 2017, Chunjie Li et al. 2012; Fan et al. 2018; De Geus et al. 2018 Karapinar-Kazandag et al. 2019; Nagendrababu et al. 2018; Pulikkotil et al. 2018; Zanjir et al. 2019) presented that a premedication using ibuprofen before treatment could increase the efficacy of IANB and could improve the success of inferior alveolar nerve block in patients with irreversible pulpitis. The ibuprofen is a non-selective inhibitor of an enzyme called cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). That enzyme is required for the synthesis of specifics prostaglandins via arachidonic acid pathway. The enzyme COX is needed to convert arachidonic acid to prostaglandin type G2 and next to prostaglandin E2 (an arachidonic acid metabolites which has potent pro-inflammatory and immunomodulatory effects) and others synthesis of prostaglandins. That chain of prostaglandin synthesis could mediate the voltage-gated channels, which are resistant to local anesthetics. When a drug as ibuprofen is used, this cycle is blocked helping in the efficacy of the anesthetic technique (Praveen Rao & Knaus, 2008; Mazaleuskaya et al, 2011).

Five studies (Corbella et al. 2017; Chunjie Li et al. 2012; Fan et al. 2018, Pulikkotil et. 2018; Shirvani et al. 2016;) reported that to maximize the therapeutic

effect, it is recommended to prescribe certain oxicam types of NSAIDs (i.e. meloxicam, and piroxicam). The product of the COXs, prostaglandin type H2 (PGH2), is rapidly converted into other PGs through the activity of various enzymes synthesis. Prostaglandin E2, has a particularly important role in the inflammatory response. It is synthesized by three different enzymes, microsomal PGE2 synthase 1 (mPGES-1), cytosolic PGE2 synthase (cPGES) and microsomal PGE2 synthase 2 (mPGES-2). Studies indicate that has a major route of oxicam synthesis for COX inhibition, as well as recent advances in oxicam medication that mediated mPGES-1 inhibition (Xu et al. 2014).

Five studies (Chunjie Li et al. 2012; Corbella et al. 2017; Fan et al. 2018; Nagendrababu et al. 2018; Shirvani et al. 2016) reported that diclofenac is effective in achieving anesthetic success of IANBs. Diclofenac inhibits the synthesis of prostaglandins pro-inflammatory and nociceptive located at blood and synovial tissue. Diclofenac is described as the most effective inhibitors of prostaglandin E2 (PGE2) production and has been reported to be 3 to 1000 times more powerful compared with other NSAIDs in its ability to inhibit COX activity. (Gan, 2010)

Five studies (Sivaramakrishnan et al. 2019; Tupyota et al. 2017; Zanjir et al. 2019; Pulikkotil et al. 2018; Shirvani et al. 2016) showed results indicating that premedication associating ibuprofen and paracetamol before IANB produced a most successful anesthesia in the mandible and may increase the efficacy of these injections. These analgesics could prevent the establishment of peripheral nociceptor and inhibit the production of inflammatory mediators in the inflammatory process, which is very important and has a significant effect in the improvement of anesthetic success in cases of inflamed pulps (Gould et al. 2004; Averbuch & Katzper, 2000). That combination could be explained by a mechanism of an improved analgesia with an analgesic combination due to one alters the nociceptive sensitivity of the other. For example, after an administration of an NSAID as ibuprofen, an expression of an altered form of COX enzymes probably will occur, this alteration provides a greater sensibility to the Paracetamol. Increasing the sensibility, that mechanism could be described as a synergetic drug interaction (Moore & Hersh, 2013; Simmons et al. 1999)

Six studies (Corbella et al. 2017; Fan et al. 2018; Sivaramakrishnan et al. 2018; Pulikkotil et al 2018; Nagendrababu et al. 2018; Tupyota et al. 2017) presented that oral premedication using ketorolac should be considered before conventional inferior alveolar nerve block for endodontic treatment of irreversible pulpitis. A study used ketorolac mouthrinse to evaluate gingival crevicular fluid (GCF) and PGE2 levels during a 2-week period (Preshaw et al. 1998). So, this study showed that ketorolac influenced the GCF and PGE2 levels, inhibiting the progressive increase in PGE2 concentrations (Preshaw et al. 1998). In addition, some studies have shown that there are some variations in the anesthetic technique that could differ in the anesthetic block of inferior alveolar nerve and the type of anesthetic as his concentration could influence in the achievement of complete anesthesia or success rate in cases of teeth of irreversible pulpitis. More studies using the same study design about type of anesthetic and technique are necessary to complement those findings.

When assessing the limitations of this umbrella review due to flaws in the included studies as for searching on grey literature, so the search was not further supplemented by hand searching in two studies (Fan et al. 2018, Karapinar-Kazandag et al. 2019). Also for a limitation of this study is the fact of only three systematic reviews presented a ‘high’ quality overall rating (Nagendrababu et al., 2018, Pulikkotil et al., 2018, Zanjir et al., 2019). And finally in one study a meta-analysis was not performed (Karapinar-Kazandag et al. 2019).

Conclusion

Through this current umbrella review that gathered data from twelve systematic reviews, it may be concludes that NSAIDs as premedication improve the efficacy of the inferior alveolar nerve block technique in teeth with irreversible pulpitis. Also, is important to think that the best choice between NSAIDs that will be used as premedication is the one that is more secure for each patient and could give the best cost-benefit comprising security, efficacy, and price.

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FIGURES AND TABLES

Figure 1 - Flowchart

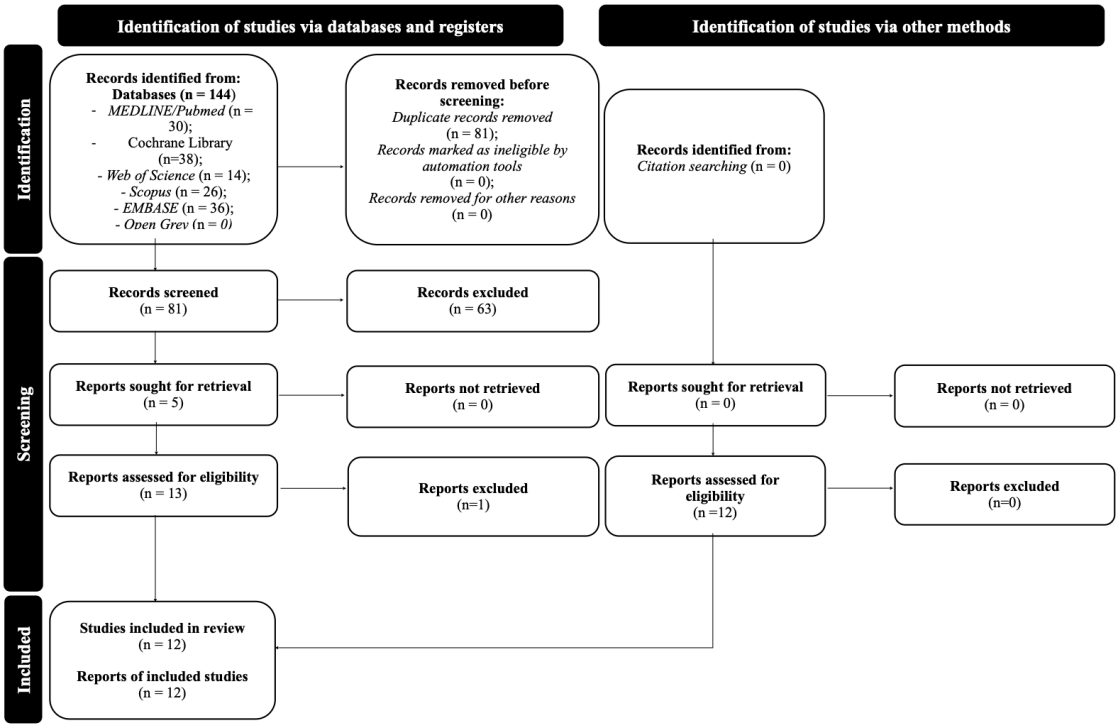
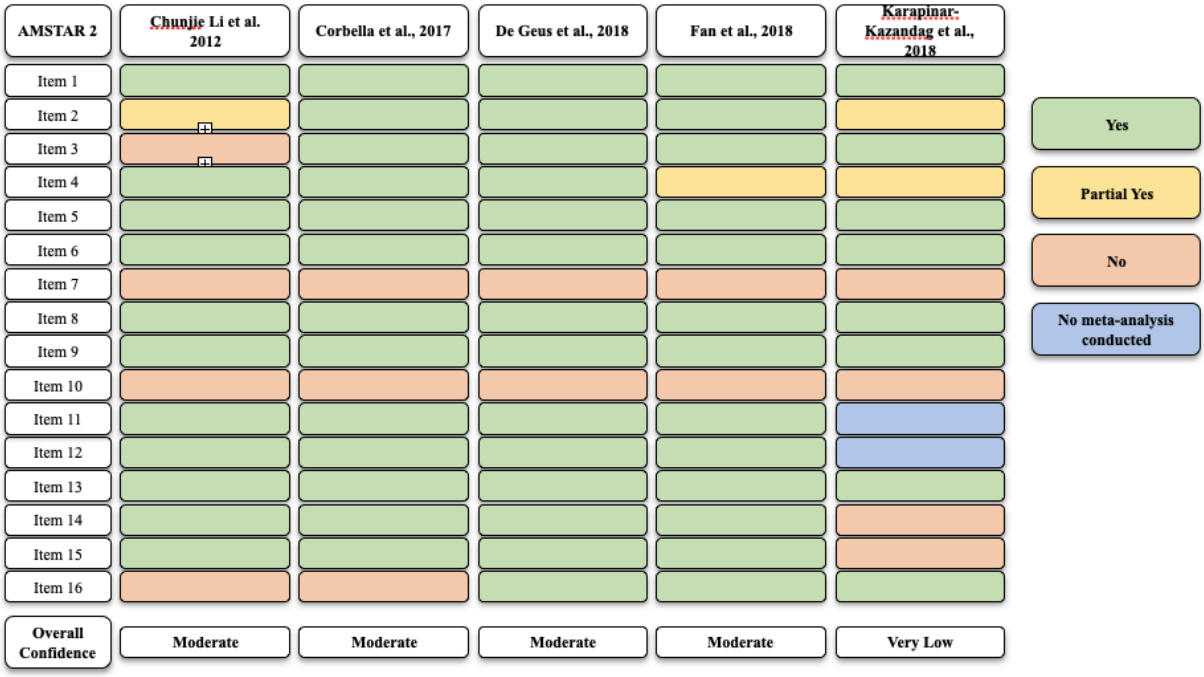
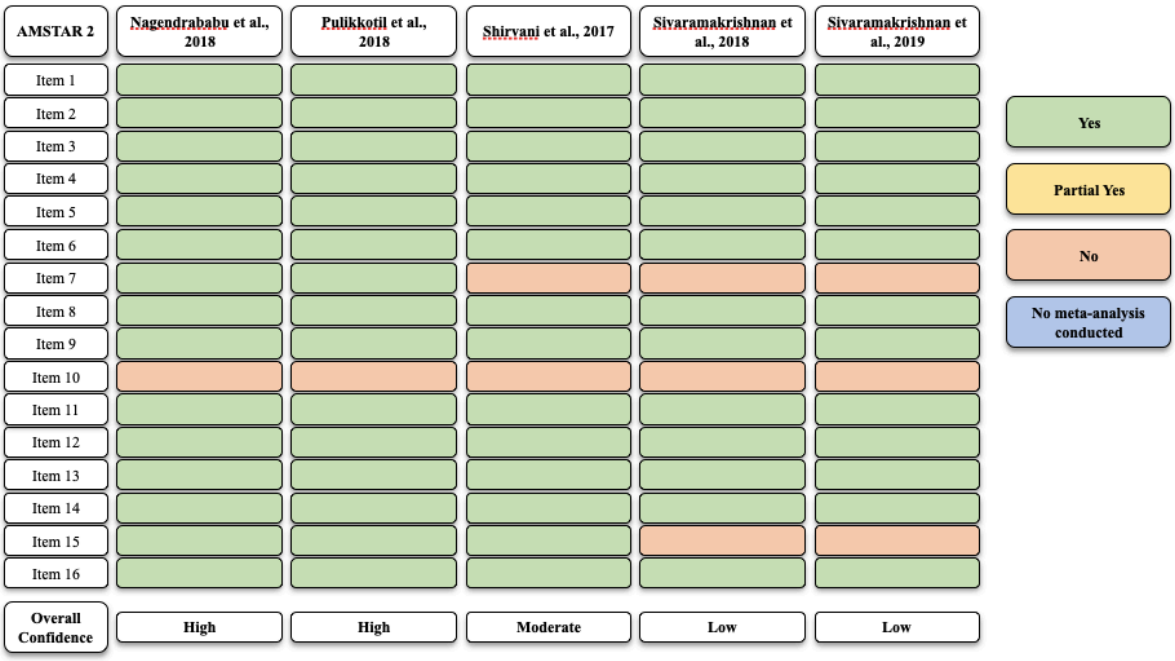


Figure 2 - Amstar 2 Tool for Methodological Quality




AMSTAR 2
Nagendrababu et al., 2018
Pulikkotil et al., 2018
Shirvani et al., 2017
Sivaramakrishnan et al., 2018
Sivaramakrishnan et al., 2019
Item 1
Item 2
Item 3
Item 4
Item 5
Item 6
Item 7
Item 8
Item 9
Item 10
Item 11
Item 12
Item 13
Item 14
Item 15
Item 16
Overall Confidence
High
High
Moderate
Low
Low
Yes
Partial Yes
No
No meta-analysis conducted

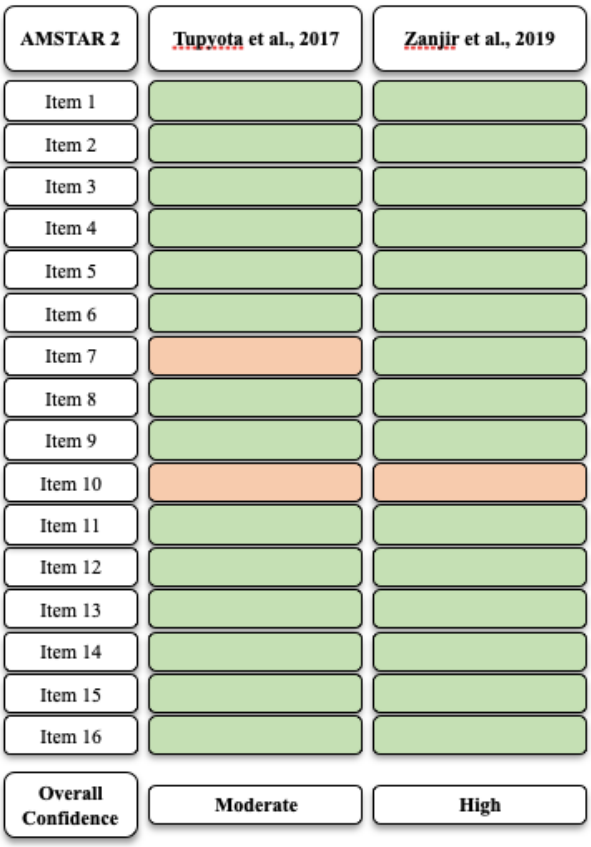

AMSTAR 2
Tupyota et al., 2017
Zanjir et al., 2019
Item 1
Item 2
Item 3
Item 4
Item 5
Item 6
Item 7
Item 8
Item 9
Item 10
Item 11
Item 12
Item 13
Item 14
Item 15
Item 16
Overall Confidence
Moderate
High

Figure 3 - AMSTAR 2 Checklist

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☐ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

- ☐ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☐ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☐ Yes
- ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:
- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:
- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):
- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:
- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

- ☐ Yes
- ☐ Partial Yes
- ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from
- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:
- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☐ No
- ☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:
- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:
- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

- ☐ Yes
- ☐ Partial Yes
- ☐ No
- ☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes
- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

- ☐ Yes
- ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

Table 1 - *Characteristics of included reviews*

Author (s) (Year of publication)	Country of the first author	Name of the journal published	Database researched	Search period	Language	Meta-Analysis Performed	Number of the studies included	Study Design of the included studies	Risk of Bias
Chunjie Li *et al*. 2012	China	Quintessence International	MEDLINE, Cochrane, EMBASE, Chinese BioMedical Literature Database, China National Knowledge Infrastructure	1984 to July 2011	No language restriction	Yes	7	Randomized controlled trials	Cochrane Tool

Corbella *et al*. 2017	Italy	Quintessence International	Eletronic databases: MEDLINE throught PubMed interface, Embase, Cochrane Central Register of Controlled Trials Hand search: Journal of Dentistry, Journal of Dental Research, International Endodontic Journal, Journal of Endodontics, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Oral Surgery Oral Medicine Oral Pathology Oral Radiology, European Journal of Oral Sciences, British Dental Journal, Journal of American Dental Association	Up to April 2016	No language restriction	Yes	38	Randomized controlled clinical trials	Cochrane Tool
De Geus *et al*. 2018	Brazil	Australian Endodontic Journal	Pubmed, Scopus, Web of Science, Lilacsand BBO, Cochrane Library,	From July to November 2017	No language restriction	Yes	10	Randomized clinical trials	Cochrane Tool
Fan *et al*. 2018	China	International Journal of Clinical and Experimental Medicine	PubMed, EMBASE, Cochrane Central Re-gister of Controlled Trials, Chinese BioMedical Literature Database, and WHO International Clinical Trials Registry Platform	Up to October 2017	-	Yes	11	Randomized controlled trials (RCTs)	Cochrane Tool

Karapinar-Kazandag *et al*. 2019	Turkey	BioMed Research International	Cochrane Library database and PubMed	Up to April 2018	Only English	No	35	Randomized clinical trials	Cochrane Tool
Nagendrababu *et al*. 2018	Malaysia	Journal of Endodontics	PubMed, EBSCOhost, and Scopus	Up to September 2017	-	Yes	13	Randomized controlled trials (RCTs)	Cochrane Tool
Pulikkotil *et al*. 2018	Malaysia	International Endodontic Journal	Electronic databases: Medline and Ebscohost - Dentistry & Oral Sciences Source. Trial registries: Cochrane Central Register of Control Trials – CENTRAL, ClinicalTrials.gov.	Up to October 2017	No language restriction	Yes	19	Randomized clinical trials	Cochrane Tool
Shirvani *et al*. 2017	Iran	Clinical Oral Invetigations	Cochrane Databases for Systematic Review, Pub Med, Science Direct, Scopus, and Google Scholar,	Up to March 2015	No language restriction	Yes	16	Randomized placebo-controlled trials	Cochrane Tool
Sivaramakrishnan *et al*. 2018	Fiji	The Open Dentistry Journal	Medline (via PubMed), Cochrane central register of clinical trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE)	Up to May 2016	Only English	Yes	4	Randomized clinical trials	Cochrane Tool
Sivaramakrishnan *et al*. 2019	Bahrain	Journal of Dental Anesthesia and Pain Medicine	Medline (through PubMed), Cochrane CENTRAL, and Google Scholar	Up to April 2017	Only English	Yes	16	Randomized controlled trials	Cochrane Tool

Tupyota *et al*. 2017	Thailand	Australian Endodontic Journal	Eletronic Database:Cochrane Central Register of Controlled Trials, MEDLINE (Pubmed), SCOPUS and MEDLINE (Ovid) Hand Search: Journal of the Endodontic Society of Thailand, Khon Kaen University Dental Journal, Mahidol Dental Journal, Chiang Mai Dental Journal, Journal of the Dental Association of Thailand, Srinakharinwirot University Dental Journal, Chulalongkorn University Dental Journal, North-Eastern Thai Journal of Neuroscience, Thai Journal of Oral and Maxillofacial Surgery, Journal of Orofacial Pain and Songklanagarind Medical Journal.	Eletronic Database:Up to April 2013 Hand Search: From 2003 to 2012	-	Yes	17	Randomised control trials (RCTs)	Cochrane Tool
Zanjir *et al*. 2019	Canada	Journal of Endodontics	MEDLINE, Embase, Cochrane Central, CINAHL, and Scopus	Inception until February 23, 2018,	No language restriction	Yes	46	Randomized controlled trials	Cochrane Tool

Table 2 - Supplementary File 1. Search strategy in each database.

Database	Search strategy	Findings
	#1: Endodontics OR Endodontic OR Root Canal Therapy OR Therapy, Root Canal OR Root Canal Treatment OR Treatment, Root Canal OR Dental Pulp Diseases OR Pulp Diseases, Dental OR Diseases, Dental Pulp OR Pulp Disease, Dental OR Dental Pulp Disease OR Disease, Dental Pulp OR Pulpitis OR Inflammation, Endodontic OR Irreversible Pulpitis OR Pulpitis, Irreversiblev	58.526
	#2: Mandibular Nerve OR Alveolar Nerve, Inferior OR Alveolar Nerve Block OR Nerve Block OR Nerve Blockade OR Anesthesia OR Anesthesia, Dental OR Dental Anesthesia OR Anesthetics, Local OR Anesthetics, Conduction-Blocking OR Conduction-Blocking Anesthetics OR Local Anesthetic OR Anesthetics OR Anesthetic Effect OR Anesthetic Effects OR Anaesthetsia OR Anaesthesia, Dental OR Dental Anaesthesia OR Anaesthetics, Local OR Anaesthetics, Conduction-Blocking OR Conduction-Blocking Anaesthetics OR Local Anaesthetic OR Anaesthetics OR Anaesthetic Effect OR Anaesthetic Effects	767.060

PubMed	#3: Premedication OR Preoperative Care OR Care, Preoperative OR Preoperative Procedure OR Procedure, Preoperative OR Procedures, Preoperative OR Preoperative Procedures OR Preanesthetic Medication OR Analgesia OR Analgesia, Patient-Controlled OR Patient-Controlled Analgesia OR Analgesics OR Analgesic Drugs OR Analgesic OR Analgesic Agents OR Analgesics, Non-Narcotic OR Nonopioid Analgesic OR Nonopioid Analgesics OR Analgesics, Nonnarcotic OR Analgesics, Nonopioid OR Non-opioid Analgesic OR Non-opioid Analgesics OR Analgesics, Opioid OR Opioid Analgesics OR Opioid Analgesic OR Anti-Inflammatory Agents, Non-Steroidal OR NSAID OR Nonsteroidal Anti-Inflammatory Agent OR NSAIDs OR Antiinflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Nonsteroidal OR Non-Steroidal Anti-Inflammatory Agents OR Nonsteroidal Anti-Inflammatory Agents OR Non-Steroidal Anti-Inflammatory Agent OR Anti Inflammatory Agents, Nonsteroidal OR Analgesics, Anti-Inflammatory	4.208.831
	#4: Systematic Review OR Review, Systematic OR Meta-Analysis	321.014
	#1 AND #2 AND #3 AND #4	30
	#1: Endodontics OR Endodontic OR Root Canal Therapy OR Therapy, Root Canal OR Root Canal Treatment OR Treatment, Root Canal OR Dental Pulp Diseases OR Pulp Diseases, Dental OR Diseases, Dental Pulp OR Pulp Disease, Dental OR Dental Pulp Disease OR Disease, Dental Pulp OR Pulpitis OR Inflammation, Endodontic OR Irreversible Pulpitis OR Pulpitis, Irreversible	4.409

Cochrane Library	#2: (Mandibular Nerve OR Alveolar Nerve, Inferior OR Alveolar Nerve Block OR Nerve Block OR Nerve Blockade OR Anesthesia OR Anesthesia, Dental OR Dental Anesthesia OR Anesthetics, Local OR Anesthetics, Conduction-Blocking OR Conduction-Blocking Anesthetics OR Local Anesthetic OR Anesthetics OR Anesthetic Effect OR Anesthetic Effects OR Anaesthetsia OR Anaesthesia, Dental OR Dental Anaesthesia OR Anaesthetics, Local OR Anaesthetics, Conduction-Blocking OR Conduction-Blocking Anaesthetics OR Local Anaesthetic OR Anaesthetics OR Anaesthetic Effect OR Anaesthetic Effects	91.833
	#3: Premedication OR Preoperative Care OR Care, Preoperative OR Preoperative Procedure OR Procedure, Preoperative OR Procedures, Preoperative OR Preoperative Procedures OR Preanesthetic Medication OR Analgesia OR Analgesia, Patient-Controlled OR Patient-Controlled Analgesia OR Analgesics OR Analgesic Drugs OR Analgesic OR Analgesic Agents OR Analgesics, Non-Narcotic OR Nonopioid Analgesic OR Nonopioid Analgesics OR Analgesics, Nonnarcotic OR Analgesics, Nonopioid OR Non-opioid Analgesic OR Non-opioid Analgesics OR Analgesics, Opioid OR Opioid Analgesics OR Opioid Analgesic OR Anti-Inflammatory Agents, Non-Steroidal OR NSAID OR Nonsteroidal Anti-Inflammatory Agent OR NSAIDs OR Antiinflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Nonsteroidal OR Non-Steroidal Anti-Inflammatory Agents OR Nonsteroidal Anti-Inflammatory Agents OR Non-Steroidal Anti-Inflammatory Agent OR Anti Inflammatory Agents, Nonsteroidal OR Analgesics, Anti-Inflammatory	117.721
	#4: Systematic Review OR Review, Systematic OR Meta-Analysis – 42.32	42.324
	#1 AND #2 AND #3 AND #4	38

	#1 (TITLE-ABS-KEY (endodontics) OR TITLE-ABS-KEY (endodontic) OR TITLE-ABS-KEY (root AND canal AND therapy) OR TITLE-ABS-KEY (therapy, AND root AND canal) OR TITLE-ABS-KEY (root AND canal AND treatment) OR TITLE-ABS-KEY (treatment, AND root AND canal) OR TITLE-ABS-KEY (dental AND pulp AND diseases) OR TITLE-ABS-KEY (pulp AND diseases, AND dental) OR TITLE-ABS-KEY (diseases, AND dental AND pulp) OR TITLE-ABS-KEY (pulp AND disease, AND dental) OR TITLE-ABS-KEY (dental AND pulp AND disease) OR TITLE-ABS-KEY (disease, AND dental AND pulp) OR TITLE-ABS-KEY (pulpitis) OR TITLE-ABS-KEY (inflammation, AND endodontic) OR TITLE-ABS-KEY (irreversible AND pulpitis) OR TITLE-ABS-KEY (pulpitis, AND irreversible)	56.209

Scopus	#2 (TITLE-ABS-KEY (mandibular AND nerve) OR TITLE-ABS-KEY (alveolar AND nerve, AND inferior) OR TITLE-ABS-KEY (alveolar AND nerve AND block) OR TITLE-ABS-KEY (nerve AND block) OR TITLE-ABS-KEY (nerve AND blockade) OR TITLE-ABS-KEY (anesthesia) OR TITLE-ABS-KEY (anesthesia, AND dental) OR TITLE-ABS-KEY (dental AND anesthesia) OR TITLE-ABS-KEY (anesthetics, AND local) OR TITLE-ABS-KEY (anesthetics, AND conduction-blocking) OR TITLE-ABS-KEY (conduction-blocking AND anesthetics) OR TITLE-ABS-KEY (local AND anesthetic) OR TITLE-ABS-KEY (anesthetics) OR TITLE-ABS-KEY (anesthetic AND effect) OR TITLE-ABS-KEY (anesthetic AND effects) OR TITLE-ABS-KEY (anaesthetsia) OR TITLE-ABS-KEY (anaesthesia, AND dental) OR TITLE-ABS-KEY (dental AND anaesthesia) OR TITLE-ABS-KEY (anaesthetics, AND local) OR TITLE-ABS-KEY (anaesthetics, AND conduction-blocking) OR TITLE-ABS-KEY (conduction-blocking AND anaesthetics) OR TITLE-ABS-KEY (local AND anaesthetic) OR TITLE-ABS-KEY (anaesthetics) OR TITLE-ABS-KEY (anaesthetic AND effect) OR TITLE-ABS-KEY (anaesthetic AND effects)	577.029

#3 (TITLE-ABS-KEY (premedication) OR TITLE-ABS-KEY (preoperative AND care) OR TITLE-ABS-KEY (care, AND preoperative) OR TITLE-ABS-KEY (preoperative AND procedure) OR TITLE-ABS-KEY (procedure, AND preoperative) OR TITLE-ABS-KEY (procedures, AND preoperative) OR TITLE-ABS-KEY (preoperative AND procedures) OR TITLE-ABS-KEY (preanesthetic AND medication) OR TITLE-ABS-KEY (analgesia) OR TITLE-ABS-KEY (analgesia, AND patient-controlled) OR TITLE-ABS-KEY (patient-controlled AND analgesia) OR TITLE-ABS-KEY (analgesics) OR TITLE-ABS-KEY (analgesic AND drugs) OR TITLE-ABS-KEY (analgesic) OR TITLE-ABS-KEY (analgesic AND agents) OR TITLE-ABS-KEY (analgesics, AND non-narcotic) OR TITLE-ABS-KEY (nonopioid AND analgesic) OR TITLE-ABS-KEY (nonopioid AND analgesics) OR TITLE-ABS-KEY (analgesics, AND nonnarcotic) OR TITLE-ABS-KEY (analgesics, AND nonopioid) OR TITLE-ABS-KEY (non-opioid AND analgesic) OR TITLE-ABS-KEY (non-opioid AND analgesics) OR TITLE-ABS-KEY (analgesics, AND opioid) OR TITLE-ABS-KEY (opioid AND analgesics) OR TITLE-ABS-KEY (opioid AND analgesic) OR TITLE-ABS-KEY (anti-inflammatory AND agents, AND non-steroidal) OR TITLE-ABS-KEY (nsaid) OR TITLE-ABS-KEY (nonsteroidal AND anti-inflammatory AND agent) OR TITLE-ABS-KEY (nsaids) OR TITLE-ABS-KEY (antiinflammatory AND agents, AND non AND steroidal) OR TITLE-ABS-KEY (antiinflammatory AND agents, AND nonsteroidal) OR TITLE-ABS-KEY (non-steroidal AND anti-inflammatory AND agents) OR TITLE-ABS-KEY (nonsteroidal AND anti-inflammatory AND agents) OR TITLE-ABS-KEY (non-steroidal AND anti-inflammatory AND agent) OR TITLE-ABS-KEY (anti AND inflammatory AND agents, AND nonsteroidal) OR TITLE-ABS-KEY (analgesics, AND anti-inflammatory)	648.073

	#4 (TITLE-ABS-KEY (systematic AND review) OR TITLE-ABS-KEY (review, AND systematic) OR TITLE-ABS-KEY (meta-analysis)	543.181
	#1 AND #2 AND #3 AND #4	26
	#1: TS= (Endodontics) OR TS= (Endodontic) OR TS= (Root Canal Therapy) OR TS= (Therapy, Root Canal) OR TS= (Root Canal Treatment) OR TS= (Treatment, Root Canal) OR TS= (Dental Pulp Diseases) OR TS= (Pulp Diseases, Dental) OR TS= (Diseases, Dental Pulp) OR TS= (Pulp Disease, Dental) OR TS= (Dental Pulp Disease) OR TS= (Disease, Dental Pulp) OR TS= (Pulpitis) OR TS= (Inflammation, Endodontic) OR TS= (Irreversible Pulpitis) OR TS= (Pulpitis, Irreversible)	20.563
	#2: TS= (Mandibular Nerve) OR TS= (Alveolar Nerve, Inferior) OR TS= (Alveolar Nerve Block) OR TS= (Nerve Block) OR TS= (Nerve Blockade) OR TS= (Anesthesia) OR TS= (Anesthesia, Dental) OR TS= (Dental Anesthesia) OR TS= (Anesthetics, Local) OR TS= (Anesthetics, Conduction-Blocking) OR TS= (Conduction-Blocking Anesthetics) OR TS= (Local Anesthetic) OR TS= (Anesthetics) OR TS= (Anesthetic Effect) OR TS= (Anesthetic Effects) OR TS= (Anaesthetsia) OR TS= (Anaesthesia, Dental) OR TS= (Dental Anaesthesia) OR TS= (Anaesthetics, Local) OR TS= (Anaesthetics, Conduction-Blocking) OR TS= (Conduction-Blocking Anaesthetics) OR TS= (Local Anaesthetic) OR TS= (Anaesthetics) OR TS= (Anaesthetic Effect) OR TS= (Anaesthetic Effects	258.608

Web of Science (All Databases)	#3: TS= (Premedication) OR TS= (Preoperative Care) OR TS= (Care, Preoperative) OR TS= (Preoperative Procedure) OR TS= (Procedure, Preoperative) OR TS= (Procedures, Preoperative) OR TS= (Preanesthetic Medication) OR TS= (Analgesia) OR TS= (Analgesia, Patient-Controlled) OR TS= (Patient-Controlled Analgesia) OR TS= (Analgesics) OR TS= (Analgesic Drugs) OR TS= (Analgesic) OR TS= (Analgesic Agents) OR TS= (Analgesics, Non-Narcotic) OR TS= (Nonopioid Analgesic) OR TS= (Nonopioid Analgesics) OR TS= (Analgesics, Nonnarcotic) OR TS= (Analgesics, Nonopioid) OR TS= (Non-opioid Analgesic) OR TS= (Non-opioid Analgesics) OR TS= (Analgesics, Opioid) OR TS= (Opioid Analgesics) OR TS= (Opioid Analgesic) OR TS= (Anti-Inflammatory Agents, Non-Steroidal) OR TS= (NSAID) OR TS= (Nonsteroidal Anti-Inflammatory Agent) OR TS= (NSAIDs) OR TS= (Antiinflammatory Agents, Non Steroidal) OR TS= (Antiinflammatory Agents, Nonsteroidal) OR TS= (Non-Steroidal Anti-Inflammatory Agents) OR TS= (Nonsteroidal Anti-Inflammatory Agents) OR TS= (Non-Steroidal Anti-Inflammatory Agent) OR TS= (Anti Inflammatory Agents, Nonsteroidal) OR TS= (Analgesics, Anti-Inflammatory	231.929
	#4 TS= (Systematic Review) OR TS= (Review, Systematic) OR TS= (Meta-Analysis)	401.029
	#1 AND #2 AND #3 AND #4	14

	#1: endodontics OR endodontic OR (root AND canal AND therapy) OR (therapy, AND root AND canal) OR (root AND canal AND treatment) OR (treatment, AND root AND canal) OR (dental AND pulp AND diseases) OR (pulp AND diseases, AND dental) OR (diseases, AND dental AND pulp) OR (pulp AND disease, AND dental) OR (dental AND pulp AND disease) OR (disease, AND dental AND pulp) OR pulpitis OR (inflammation, AND endodontic) OR (irreversible AND pulpitis) OR (pulpitis, AND irreversible)	66.115
	#2: mandibular AND nerve OR (alveolar AND nerve, AND inferior) OR (alveolar AND nerve AND block) OR (nerve AND block) OR (nerve AND blockade) OR anesthesia OR (anesthesia, AND dental) OR (dental AND anesthesia) OR (anesthetics, AND local) OR (anesthetics, AND 'conduction blocking') OR ('conduction blocking' AND anesthetics) OR (local AND anesthetic) OR anesthetics OR (anesthetic AND effect) OR (anesthetic AND effects) OR anaesthetsia OR (anaesthesia, AND dental) OR (dental AND anaesthesia) OR (anaesthetics, AND local) OR (anaesthetics, AND 'conduction blocking') OR ('conduction blocking' AND anaesthetics) OR (local AND anaesthetic) OR anaesthetics OR (anaesthetic AND effect) OR (anaesthetic AND effects)	622.313

EMBASE	#3: premedication OR (preoperative AND care) OR (care, AND preoperative) OR (preoperative AND procedure) OR (procedure, AND preoperative) OR (procedures, AND preoperative) OR (preoperative AND procedures) OR (preanesthetic AND medication) OR analgesia OR (analgesia, AND 'patient controlled') OR ('patient controlled' AND analgesia) OR analgesics OR (analgesic AND drugs) OR analgesic OR (analgesic AND agents) OR (analgesics, AND 'non narcotic') OR (nonopioid AND analgesic) OR (nonopioid AND analgesics) OR (analgesics, AND nonnarcotic) OR (analgesics, AND nonopioid) OR ('non opioid' AND analgesic) OR ('non opioid' AND analgesics) OR (analgesics, AND opioid) OR (opioid AND analgesics) OR (opioid AND analgesic) OR ('anti inflammatory' AND agents, AND 'non steroidal') OR nsaid OR (nonsteroidal AND 'anti inflammatory' AND agent) OR nsaids OR (antiinflammatory AND agents, AND non AND steroidal) OR (antiinflammatory AND agents, AND nonsteroidal) OR ('non steroidal' AND 'anti inflammatory' AND agents) OR (nonsteroidal AND 'anti inflammatory' AND agents) OR ('non steroidal' AND 'anti inflammatory' AND agent) OR (anti AND inflammatory AND agents, AND nonsteroidal) OR (analgesics, AND 'anti inflammatory')	646.244
	#4: systematic AND review OR (review, AND systematic) OR 'meta analysis'	577.383
	#1 AND #2 AND #3 AND #4	36

	#1: endodontics OR endodontic OR (root AND canal AND therapy) OR (therapy, AND root AND canal) OR (root AND canal AND treatment) OR (treatment, AND root AND canal) OR (dental AND pulp AND diseases) OR (pulp AND diseases, AND dental) OR (diseases, AND dental AND pulp) OR (pulp AND disease, AND dental) OR (dental AND pulp AND disease) OR (disease, AND dental AND pulp) OR pulpitis OR (inflammation, AND endodontic) OR (irreversible AND pulpitis) OR (pulpitis, AND irreversible)	17
Open	#2: Mandibular Nerve OR Alveolar Nerve, Inferior OR Alveolar Nerve Block OR Nerve Block OR Nerve Blockade OR Anesthesia OR Anesthesia, Dental OR Dental Anesthesia OR Anesthetics, Local OR Anesthetics, Conduction-Blocking OR Conduction-Blocking Anesthetics OR Local Anesthetic OR Anesthetics OR Anesthetic Effect OR Anesthetic Effects OR Anaesthetsia OR Anaesthesia, Dental OR Dental Anaesthesia OR Anaesthetics, Local OR Anaesthetics, Conduction-Blocking OR Conduction-Blocking Anaesthetics OR Local Anaesthetic OR Anaesthetics OR Anaesthetic Effect OR Anaesthetic Effects	17.445

Grey	#3: Premedication OR Preoperative Care OR Care, Preoperative OR Preoperative Procedure OR Procedure, Preoperative OR Procedures, Preoperative OR Preoperative Procedures OR Preanesthetic Medication OR Analgesia OR Analgesia, Patient-Controlled OR Patient-Controlled Analgesia OR Analgesics OR Analgesic Drugs OR Analgesic OR Analgesic Agents OR Analgesics, Non-Narcotic OR Nonopioid Analgesic OR Nonopioid Analgesics OR Analgesics, Nonnarcotic OR Analgesics, Nonopioid OR Non-opioid Analgesic OR Non-opioid Analgesics OR Analgesics, Opioid OR Opioid Analgesics OR Opioid Analgesic OR Anti-Inflammatory Agents, Non-Steroidal OR NSAID OR Nonsteroidal Anti-Inflammatory Agent OR NSAIDs OR Antiinflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Nonsteroidal OR Non-Steroidal Anti-Inflammatory Agents OR Nonsteroidal Anti-Inflammatory Agents OR Non-Steroidal Anti-Inflammatory Agent OR Anti Inflammatory Agents, Nonsteroidal OR Analgesics, Anti-Inflammatory	13.159
	#4: Systematic Review OR Review, Systematic OR Meta-Analysis	2.769
	#1 AND #2 AND #3 AND #4	0

4. CONSIDERAÇÕES FINAIS

Diante de todas as medicações que foram discutidas nessa revisão *umbrella*, vale enfatizar também que alguns estudos mostram que existem algumas variações na técnica anestésica que podem diferir no sucesso do bloqueio do nervo alveolar inferior e o tipo de anestésico da mesma forma, pois sua concentração pode influenciar na obtenção de uma anestesia completa ou na taxa de sucesso em casos de dentes de pulpite irreversível. Mais estudos usando o mesmo desenho de estudo abordando o tipo de anestésico e técnica são necessários para complementar esses achados.

Além disso, é importante pensar que a melhor escolha entre os AINEs que serão utilizados como pré-medicação é aquela que for mais segura para cada paciente e poderá apresentar o melhor custo-benefício compreendendo segurança, eficácia e preço.

5. CONCLUSÃO

Por meio desta revisão umbrella que reuniu dados de doze revisões sistemáticas, salvo às suas limitações, o fato de apenas três revisões sistemáticas apresentarem uma classificação geral de qualidade 'alta' e em um estudo, não foi realizada uma meta-análise, este estudo reuniu dados do maior grau de evidência científica presente na literatura. Diante disso, pode-se concluir que os AINEs são eficazes para uso como pré-medicação para obter sucesso e aumentar a eficácia da técnica de bloqueio do nervo alveolar inferior em dentes com pulpite irreversível.

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