MARAL BERENOVA

DISSERTAÇÃO DE MESTRADO INTEGRADO EM MEDICINA DENTÁRIA NA ÁREA DE CIRURGIA ORAL

COMPLICATIONS ASSOCIATED TO INFERIOR ALVEOLAR NERVE BLOCK WITH DIFFERENT ANESTHETICS: A SYSTEMATIC REVIEW

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Trabalho apresentado à Universidade Fernando Pessoa como parte dos requisitos para obtenção do grau de Mestre em Medicina Dentária.

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RESUMO

O Bloqueio do Nervo Alveolar Inferior (IANB), consiste numa das técnicas anestésicas mais utilizadas e tem sido considerada como um padrão de excelência para bloquear a hemimandíbula. Esta técnica é comummente utilizada na prática dentária e cirúrgica oral. O objetivo deste estudo foi analisar os relatórios relacionados com a técnica IANB, combinada com diferentes anestésicos locais. Para identificar os estudos relevantes, foi realizada uma revisão sistemática, em que foi adotado o PRISMA "Preferred Reporting Items for Systematic Reviews and Meta-Analyses", e foram utilizados os critérios de PICO (Problema/Doente/População, Intervenção/Indicador, Comparação, Resultado) para estruturar a questão da investigação. A pesquisa bibliográfica foi realizada através das bases de dados PubMed/Medline, Cochrane Library e Embase, sem qualquer restrição de tempo, e com os filtros: ensaio clínico aleatório prospetivo e ensaio aleatório controlado. Foram escolhidos critérios de inclusão e exclusão para, numa fase inicial, selecionar os artigos apropriados, a partir dos títulos publicados e, em seguida, a leitura abstrata. Após a avaliação de todos os artigos selecionados, os resultados da pesquisa indicaram que não foram observados efeitos colaterais relevantes em nenhum grupo, com quaisquer soluções anestésicas. No entanto, é importante considerar que, um período de seguimento de 1 dia, pode ser demasiado curto para observar complicações posteriores, a evolução ou remissão espontânea das suas sequelas. Desta forma, devemos considerar a necessidade de investigação futura, como ensaios clínicos aleatórios controlados, com amostras grandes e um período de seguimento mais longo, no sentido de confirmar estes resultados.

Palavras-chave: Anestésico, Articaína 4%, Complicações, Bloqueio do Nervo Alveolar Inferior, Lidocaína 2%, Mepivacaína 3%

ABSTRACT

Inferior Alveolar Nerve Block (IANB) is considered as the most widely used anesthetic technique, and it has been considered the gold standard for blocking the hemimandible. This technique is used in everyday dental and oral surgical practice. The aim of this study was to analyze the reports related to IANB technique combined with different local anesthetics. To identify the relevant studies, a systematic review was conducted wherein the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" was adopted, and the Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome (PICO) criteria were used to structure the research question. The literature search was conducted using PubMed/Medline database, Cochrane Library and Embase, without any restriction of time and with prospective randomized clinical trial and randomized controlled trial as filters. Inclusion and exclusion criteria were chosen to initially select the appropriate articles from the published titles and then the abstract reading. After evaluating all selected articles, the results of the research indicate that no relevant side effects were observed in any groups, with any anesthetic solutions, but it is important to consider that a follow-up period of 1 day may be too short to observe later complications, evolution, or spontaneous remission of its eventual sequelae. Therefore, we must consider that future research as randomized controlled clinical trials with large samples and longer follow-up period are required to confirm these findings.

Keywords: Anesthetics; Articaine 4%; Complications; Inferior Alveolar Nerve Block; Lidocaine 2%; Mepivacaine 3%.

SUMMARY

LIST OF ABBREVIATIONS AND ACRONYMS

IANB – *Inferior Alveolar Nerve Block*

MeSH – *Medical Subject Headings*

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

PICO - *Problem/Patient/Population, Intervention/Indicator, Comparison and Outcome*

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1. INTRODUCTION

Traditionally, Inferior Alveolar Nerve Block (IANB) is considered as the most widely used anesthetic technique, and the gold standard for blocking the hemimandible. This technique is used in everyday dental and oral surgical practice. When combined with lingual nerve and long buccal nerve block, it provides adequate anesthesia of a wide anatomical area. This includes all of one side of the mandible teeth and gingivae, body and inferior ramus and anterior two-thirds of the tongue and floor of the mouth (Wilson, 2000; Alamoudi *et al.*, 2016; Sarfaz *et al.*; 2021).

However, the use of this technique was already associated with risks and complications, and the clear mechanism of nerve injury is still discussed. The damage can either be a direct trauma or caused by the neurotoxicity of the local anesthetic solution chosen.

As damage caused by a direct trauma, it can be due to the injection needle causing neural or vascular injury (being the facial nerve the most often affected, when the anesthetic solution is applied inside the parotid gland), hematoma and associated trismus, intravascular injection, mucosa and muscular injury, needle fracture and infection post-injection related to its contamination (Sarfaz *et al.*, 2021, Lustig et Zusman, 1999; Pogrel & Thamby, 2001).

When the damage is caused by the neurotoxicity of the local anesthetic solution, allergic reactions caused by amide local anesthetic may happen, as well as high concentrations of any local anesthetic when it reaches the bloodstream (caused by multiples injections, excessive dose of the anesthetic solution injected or intravascular injection). Also, methemoglobinemia is a reported side effect that may happen when there is an excess of metabolites from the anesthetic solution (Sarfaz *et al.*, 2021; Takasugi *et al*, 2000; Malamed *et al*, 1992).

The selection of an appropriate local anesthetic for a patient includes consideration of several factors as surgical time extension, possibility of self-mutilation in the postoperative period, requirement for hemostasis, potential need for posttreatment pain control and presence of any, relative or absolute, contraindications to the local anesthetic solution selected for administration (Malamed *et al*, 1992).

As adverse events can happen, either caused by trauma or caused by the anesthetic solution, it is important to carefully choose the injection method and the solution, as they are the pillars to a successful and secure procedure.

Thus, the aim of this study was to extract the available data and analyze the reports related to IANB technique combined with different local anesthetics (2% lidocaine with 1:80.000 epinephrine, 2% lidocaine with 1:100.000 epinephrine, 3% plain mepivacaine, 4% plain articaine, 4% articaine with 1:100.000 epinephrine, 4% articaine with 1:200.000 epinephrine and 2% articaine with 1:200.000 epinephrine) in pediatric and adult patients providing valid evidence to compare the results concerning possible complications.

2. MATERIALS AND METHODS

Methodology of review

The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" was adopted for the current review (Moher *et al*, 2009; Shamseer *et al*, 2015).

Formulation of research question and keywords selection

A PICO [patient population (P), intervention (I), comparison (C), and outcomes (O)] approach was used to structure and respond to the research question. It was found that higher precision can be achieved through the use of PICO templates, and the relevance of search results can also be improved (Schardt *et al*, 2007).

PICO criteria for the research question was: "Are there different complications (O) reported by patients (P) who underwent IANB (I) with different anesthetics (C)?". According to this research question, the following keywords, and Medical Subject Headings (MeSH) were used for the search: (complications OR "side-effects" OR "adverse reaction") AND (IANB OR "inferior alveolar nerve block") AND (anesthetics OR "articaine 4%" OR "mepivacaine 3%" OR "lidocaine 2%"). Filters applied: Clinical Trial, Randomized Controlled Trial.

Search strategy

The literature search was performed on PubMed/Medline database, Cochrane Library and Embase. The keywords and MeSH terms were searched individually and combined with Boolean operators (AND, OR, and NOT) to identify the need for this review. There was no systematic review found specifically on this question under the defined criteria, which provided further justification for us to perform this review. The search for the selection of studies was carried out from January 24 to 8 February 2022.

Eligibility criteria

The following selection criteria were applied:

• Population: Patients who underwent IANB.

• Language: Articles published worldwide written in English with full access.

• Timeline: No restrictions.

• Study characteristics: Prospective, randomized clinical trials, or randomized controlled trials were included.

• Outcome: Articles where complications associated to IANB were reported.

• Exclusion criteria: Animal studies, books, case-control, case reports and case series, cross-sectional studies, cohort studies, commentaries and conference papers, gray literature, meta-analysis, policy and guidelines, review articles, and unpublished data.

Study selection process

As a result of the systematic research, 41 articles were identified, 14 from PubMed/Medline, 24 from Cochrane Library and 3 from Embase. After removal of the duplicates (n = 17), preliminary screening of titles and abstracts was performed, and 10 articles were excluded because they did not meet the eligibility criteria. Of these, 14 were assessed in English for full reading. After a complete revision of the entire text, 8 studies were excluded because they did not meet the inclusion criteria for this systematic review. A total of 6 studies met full settings agreement and were selected for analysis and data extraction, in accordance with the recommendations of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)". A flow chart of the study selection process is shown in Fig. 1.

Quality assessment tool

The "Cochrane Risk of Bias Tool for Randomized Controlled Trials" was used to assess the quality of the included studies. If all criteria were met (low for every domain) then the study was labeled as "good." If one criterion was not met (high risk for any domain), then the study was labeled as fair and if two or more criteria were not met (high risk or unclear in more than two domains), then the study was labeled as poor (Page & McKenzie & Higgins, 2018).

3. RESULTS

After retaining articles following scanning of titles, abstracts, and full texts, six studies were successfully identified and included in the systematic review as Study 1, Elbay *et al.*, 2016; Study 2, Kämmerer *et al.*, 2012; Study 3, Youssef *et al.*, 2021; Study 4, Kämmerer *et al.*, 2017; Study 5, Figueiredo *et al.*, 2021; and Study 6, Alamoudi *et al.*, 2016. These studies were categorized as randomized clinical trials. The list and a summary description of all the six studies, including their characteristics viz-a-viz quality analysis, are listed in Table 1, Figs. 2, 3 and 4.

CHARACTERISTICS OF THE INCLUDED STUDIES

The characteristics of the studies included in this review are summarize in Table 1, F. Study 1 compared the behavior of 3% mepivacaine *versus* 2% lidocaine/epinephrine 1:80.000 in computer assisted IANB. Study 2 compared 4% articaine/epinephrine 1:100.000 *versus* 4% articaine (plane) in IANB. Study 3 compared the use of 4% articaine/epinephrine 1:100.000 in intraligamentary anesthesia *versus* IANB. Study 4 compared 2% *versus* 4% articaine/epinephrine 1:200.000 in IANB. Study 5 compared infiltrative anesthesia *versus* IANB 4% articaine/epinephrine 1:100.000. Study 6 compared 2% lidocaine/1:100.000 epinephrine in traditional IANB *versus* computer assisted IANB *versus* computer assisted intraligamentary anesthesia. From a total number of 524 randomized subjects, the 459 that underwent IANB reported 29 complications (Study 1, Study 3 and Study 6), corresponding to 6,32% of all IANB procedures. Study 2, Study 3, Study 4 and Study 6 made telephone calls to assess participants within the first 24 hours. Study 1 reported 2 cases, 1 using 3% mepivacaine and 1 using 2% lidocaine/epinephrine 1:80.000. Study 3 reported 5 cases using 4% articaine/epinephrine 1:100.000, whiles Study 6 reported 22 cases using 2 % lidocaine/epinephrine 1:100.000. (Fig. 3) Pain at the injection site was the most common side effect corresponding to 5,01% (n=23), follow by lip biting with 0,87% (n=4), difficulty during talking with 0,22% (n=1) and pain around the ear with 0,22% (n=1). (Fig. 4) The age range of the participants in the six included studies was from 5 to 80 years. All studies included in this current review were published between 2012 and 2021.

QUALITY ASSESSMENT OF THE INCLUDED STUDIES

The quality assessment of the included studies is expressed in summary, identifying the most relevant elements of the systematization process used by each, and displayed in Fig. 2. The RoB version 2.0 was used to evaluate risk of bias under 5 domains also an overall evaluation of each trial as low or high risk of bias (Sterne *et al*, 2019).

In Study 1, details regarding randomization of allocation are given clearly which makes this study free from allocation bias while no information was given regarding concealment of allocation. Sample size of study, age of participants, study source and gender are given. 3% mepivacaine and 2% lidocaine was used as anesthetic solution. The double blindness of study is mentioned. No information was given on patient/carer awareness regarding type of intervention being sued while practitioners was blinded from it. Thus shows some concerns on biasness due to deviation from intended intervention. Outcomes of all the randomized participants was given and bias from missing outcomes data was low. For the assessment of possible postoperative complications, parents were informed and were advised to call if they observe complication. They were also asked to record the levels (none, mild, moderate) of any complications. As parents are emotionally attached with their child therefore, they can be an over-reporting of the complications and thus making it high risk of bias in the measurement of outcomes. Bias in the selection of the reported results shows some concerns. Thus, overall risk of biasness of study is considered high.

In Study 2, details regarding randomization of allocation are given clearly which makes this study free from allocation bias as allocation was done by online randomization generator while no information given on the concealments of allocation sequence. Sample size of study, age of participants, source of study and gender is given. 4% articaine 1:100.000 epinephrine or 4% articaine without epinephrine was used as anesthetic solution. It was not mentioned in the study whether participants were blinded or not. No information is given regarding awareness of carer. However, it was mentioned that study is double blinded and people delivering intervention were blinded in the study. No information is provided about the deviations thus it has some concerns regarding bias due to deviation from intended intervention. Outcomes of all the randomized participants was given and bias from missing outcomes data was low. No information regarding outcomes measurement is given in the

study and outcomes assessor was blinded. How complications were assessed was not mentioned in this study thus shows some concerns regarding bias in measurement of outcomes. Similarly bias in the selection of the reported results shows some concerns. Thus, overall risk of biasness of study is showing some concerns.

In Study 3, details regarding randomization of allocation are given clearly which makes this study free from allocation bias. Sample size of study, age of participants and gender is given. 4% articaine 1:100.000 epinephrine was used as anesthetic solution. It was not mentioned in the study whether participants were blinded or not. No information is given regarding awareness of carer. However, it was mentioned that study is double blinded and people delivering intervention were blinded in the study. No information is provided about the deviations thus it has some concerns regarding bias due to deviation from intended intervention. Outcomes of all the randomized participants was given and bias from missing outcomes data was low. No information regarding outcomes measurement is given in study and outcomes assessor was blinded. How complications were assessed was not mentioned in study thus shows some concerns regarding bias in measurement of outcomes. Similarly bias in the selection of the reported results was low. Thus, overall risk of biasness of study is showing some concerns.

In Study 4, details regarding randomization of allocation are given clearly which makes this study free from allocation bias. Sample size of study, age of participants and gender is given. 2% articaine and 4% articaine was used as anesthetic solution. It was mentioned in the study that is double blinded clinical trial. Informed consent was obtained from all the eligible participants, but it was not mentioned in the study whether participants were blinded or not. No information is given regarding awareness of carer. However, people delivering intervention were blinded in the study thus bias due to deviation from intended intervention is low. Outcomes of all the randomized participants was given and bias from missing outcomes data was low. No information regarding outcomes measurement is given in study and outcomes assessor was blinded. How complications were assessed was not mentioned in study thus shows some concerns regarding bias in measurement of outcomes. Similarly bias in the selection of the reported results shows some concerns. Thus, overall risk of biasness of study is showing some concerns.

In Study 5, details regarding randomization of allocation are given clearly which makes this study free from allocation bias. Sample size of study, age of participants and gender is given. 4% articaine 1:100,000 epinephrine was used as anesthetic solution. It was mentioned in the study that it is double blinded clinical trial. Informed consent was obtained from all the eligible participants, but it was not mentioned in the study whether participants were blinded or not. No information is given regarding awareness of carer. However, people delivering intervention were blinded in the study thus bias due to deviation from intended intervention shows some concerns. Outcomes of all randomized participants was given and bias from missing outcomes data was low. No information regarding outcomes measurement is given in study and outcomes assessor was blinded. How complications were assessed was not mentioned in study thus shows some concerns regarding bias in measurement of outcomes. Similarly bias in the selection of the reported results shows some concerns. Thus, overall risk of biasness of study is showing some concerns.

In Study 6, details regarding randomization of allocation is given clearly that block randomization technique was applied to assign participants to one of the study groups while no information was given about the concealment of allocation sequence until participants were enrolled and assigned to interventions. Sample size of study, age of participants and gender is given. 2% lidocaine 1:100,000 epinephrine was used as anesthetic solution. It was mentioned in the study that it is double blinded clinical trial. Informed consent was obtained from all the eligible participants, but it was not mentioned in the study whether participants were blinded or not. No information is given regarding awareness of carer. However, people delivering intervention were blinded in the study and no information is provided about the deviations thus bias due to deviation from intended intervention shows some concerns. Outcomes of all the randomized participants was given and bias from missing outcomes data was low. Complications were assessed after 24 hours on phone call. There was a potential risk of information bias and shows high biasness in measurement of the outcomes. Similarly bias in the selection of the reported results shows some concerns. Thus, overall risk of biasness of study is high.

Overall, only 2 trials were evaluated to be at the high risk of bias (33.3%) and 4 trials were evaluated as having some concerns (66.7%). All studies showed low risk of bias for missing outcome data (100%). About five studies showed some concerns regarding randomization process and deviations from intended interventions (83.3%), while only one study showed

low risk of bias for randomization process (16.7%) and one study showed low risk of bias for deviations from intended interventions (16.7%). Of 6 trials, 2 trials showed high risk of bias for measurement of the outcome (33.3%) and 4 studies showed some concerns (66.7%). One study (16.7%) showed low risk of bias due to selection of the reported result and five studies showed some concerns (83.3%). (Fig. 2)

4. DISCUSSION

Inferior alveolar nerve block is the most frequent used technique for achieving local anesthesia for restorative and surgical procedures, especially in mandibular molars (Wilson, 2000). The possibility to anesthetize all teeth in the same mandibular quadrant at once and the gingival mucosa, the body and inferior ramus of the mandible, the anterior two-thirds of the tongue and the floor of the mouth effectively, is the main goal of this technique. Even though is a safe technique, it is not free from complications (Ram & Peretz, 2002; Shabazfar *et al*., 2014).

Totally, 524 patients were studied (151 children and 373 adults) and 7 different anesthetics solutions were included in this systematic review (2% lidocaine with 1:80.000 epinephrine, 2% lidocaine with 1:100.000 epinephrine, 3% plain mepivacaine, 4% plain articaine, 4% articaine with 1:100.000 epinephrine, 4% articaine with 1:200.000 epinephrine and 2% articaine with 1:200.000 epinephrine).

Concerning studies conducted on children's groups, all of them had as an exclusion criteria child who were medically compromised (had allergies to local anesthetics or sulfites, or a history of significant medical conditions) and child who demonstrated uncooperative behavior.

According to Elbay *et al.* (2016), who conducted a study with 60 children ranging in age from 6 to 12, comparing IANB using 2% lidocaine 1:80.000 and 3% plain mepivacaine, none of the patients reported postoperative complications severe enough to require clinical treatment (Elbay *et al.*, 2016).

Regarding about pain, differences in postoperative pain did not vary significantly between the two anesthetics and the two groups observed by Elbay *et al.* (2016), the first one under pulpotomy and the second one under extraction (Elbay *et al*, 2016). In contrast, Alamoudi *et al.* (2016) related a 35,5% of postoperative pain after IANB procedure with 2% lidocaine with 1:100.000 epinephrine (Alamoudi *et al.*, 2016).

In Alamoudi *et al*. (2016) study, after the procedure was performed no complications or side effects were immediately observed. After 24h, all legal guardians of the children were

contacted to record if any postoperative complication was observed. Two patients (6,66%) in the IANB group reported lip biting (Alamoudi *et al.*, 2016).

According to Elbay *et al.* (2016) there were no significant differences in postoperative lip or tongue biting, bleeding, or hematoma between the two groups. Lip biting was experienced only in one patient treated using 2% lidocaine with 1:80.000 epinephrine and one patient treated using 3% plain mepivacaine. In terms of bleeding, no significant difference was observed between the two solutions. None of the patients required any surgical procedure for hemostasis; however, five patients treated using 2% lidocaine with 1:80.000 epinephrine and eight patients treated using plain mepivacaine required a change in sponge to obtain hemostasis. According to all studies with children, no patients in any group reported hematoma, swelling or infection (Elbay *et al*, 2016).

The 2% lidocaine with 1:80.000 epinephrine was expected to have less bleeding compared to 3% plain mepivacaine, given that epinephrine is a vasoconstrictor used to minimize blood loss during surgical procedures, but no differences were observed related to hemostasis with either anesthetic solution (Elbay *et al*, 2016).

Their study found that plain mepivacaine (3% mepivacaine) and 2% lidocaine 1:80.000 epinephrine performed similarly when delivered as IANB anesthesia for primary mandibular molars requiring extraction or pulpotomy, in children. These results are consistent with findings of several other studies who performed similarly in adults (Elbay *et al*, 2016).

Regarding studies conducted on adult groups, besides Kämmerer *et al.* (2012), who had also patients with healthcare conditions (such as hypertension, carcinoma in remission, hepatitis, epilepsy, hypothyroidism, and migraine) into the study group, they all had as an exclusion criteria patient with any systematic disease. The studies selected the patients based on diseases requiring special considerations during their dental treatment or patients with contra-indications for any of the anesthetic solution, besides patients requiring open surgical extractions or teeth with signs of severe acute infection.

Kämmerer *et al.* (2012) research, even with a higher risk group, did not show any adverse reaction reported by the patients or observed by the surgeons during or after the procedure. The article concluded that this finding is in accordance with the known low allergenic and

toxic potential of articaine. However, it must be kept in mind that a follow-up period of 1 day may be too short to observe later complications.

According to Kämmerer *et al.* (2017) study, none of the groups (2% articaine with 1:200.000 epinephrine or 4% articaine with 1:200.000 epinephrine) showed any significant superior side effect, as well as other clinical trials comparing 2% and 4% articaine solutions. Though, in this study, a slightly non-significant better anesthetic effect of the solution with the higher concentration was detected. Additionally, the duration of soft tissue anesthesia was significant shorter when using 2 % articaine, which is in accordance to the results of other researchers. Also, no relevant neurotoxicity was seen in both articaine groups, which the authors reported to be in accordance with several other studies.

As stated by Youssef *et al.* (2021), 5,4% patients reported high scores of pain (>5) during IANB injection, however no sign of detrimental nerve contact or other complications were observed in any patient. Although, five patients in the IANB group reported temporary irritations 24h after the procedure. One case reported difficulty during talking for 1 day after the anesthesia, other three more cases reported pain at the site of injection and one case reported pain around the ear after the injection. Concerning the anesthetic solution, no major transoperative or postoperative complications were observed in all patients underwent 4% articaine with 1:100.000 epinephrine.

When compared both IANB technique and local infiltration, they all proved safe, with no difference in the perception of pain during the injection and no relevant adverse effect, either local complications (local irritation or discomfort) or systemic side effects (palpitations, nausea, vomiting or dizziness). However, a larger volume of anesthetic solution was used in the local infiltration group, which could increase the risk of complications (Figueiredo *et al*, 2021).

5. CONCLUSION

In the current review, we found that substantial percentage of studies had some concerns regarding risk of bias and two studies were evaluated to be at high risk of bias. We found that high risk in trials is mostly because of measurement of the outcome (i.e., assessment method of complications). However, most of the trials showed some concerns regarding randomization process and deviation from the intended intervention. All trials have adequately reported the results and there was no missing data, therefore risk of bias for missing data of the outcome was rated as low in all trials.

In conclusion, the reports related to IANB technique combined with different local anesthetics in pediatric and adult patients comparing the results concerning possible complications have shown that no relevant side effects were observed in any groups, with any anesthetic solutions.

Nonetheless, it is important to be kept in mind that the prevalence of temporarily or even permanent injury of the inferior alveolar nerve block is considered to be very low, but not nonexistent.

Also, it is also relevant to consider that a follow-up period of 1 day may be too short to observe later complications and the fact that most of the studies analyzed had as an exclusion criteria patient with any systematic disease could also be a limitation of this study, both for adults and children.

High quality of trials with low risk of bias are fundamental for recommending local anesthetics. Additionally, future research as randomized controlled clinical trials with large samples are required and encouraged to confirm these findings.

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7. APPENDIX

Table 1. Characteristics of included studies

	Study 1	**Study 2**	**Study 3**	**Study 4**	**Study 5**	**Study 6**
Title	Effects of Two Different Anesthetic Solutions on Injection Pain, Efficacy, and Duration of Soft-Tissue Anesthesia with Inferior Alveolar Nerve Block for Primary Molars	Comparison of 4% articaine with epinephrine (1:100,000) and without epinephrine in inferior alveolar block for tooth extraction: double-blind randomized clinical trial of anesthetic efficacy	RCT on the effectiveness of the intraligamentary anesthesia and inferior alveolar nerve block on pain during dental treatment	Comparison of anesthetic efficacy of 2 and 4 % articaine in inferior alveolar nerve block for tooth extraction—a double-blinded randomized clinical trial	Is it possible to extract lower third molars with infiltration anesthesia techniques using articaine? A double-blind randomized clinical trial	The effectiveness of computerized anesthesia in primary mandibular molar pulpotomy: A randomized controlled trial
Authors, year	Elbay *et al.*, 2016	Kämmerer *et al.*, 2012	Youssef *et al.*, 2021	Kämmerer *et al.,* 2017	Figueiredo *et al.*, 2021	Alamoudi *et al.*, 2016
Study design	Randomized, controlled-crossover, double-blind clinical trial	Clinical prospective, randomized, double-blind study	Randomized, prospective clinical trial	Clinical prospective, randomized, double-blind trial	A randomized, double-blind clinical trial	Controlled, randomized, double-blind clinical trial
Number of patients	60 patients	88 patients	72 patients	95 patients	118 patients	91 patients
Ages	6-12 years	18-80 years	18-50 years	19 – 77 years	18 – 60 years	5-9 years
Gender	Male and female	Male and female	Male and female	Male and female	Male and female	Male and female
Anesthetic solution	3% mepivacaine and 2% lidocaine 1:80.000 epinephrine	4% articaine 1:100.000 epinephrine and 4% articaine without epinephrine	4% articaine 1:100.000 epinephrine	2% articaine 1:200.000 epinephrine and 4% articaine 1:200.000 epinephrine	4% articaine 1:100.000 epinephrine	2% lidocaine 1:100.000 epinephrine
Technique	IANB technique (n=120)	IANB technique (n=88)	IANB technique (n=36)	IANB technique (n=95)	IANB technique (n=59)	IANB technique (n=61)
Time of complications report	No information	24h	24h	24h	No information	24h
Complications	None of the patients reported postoperative complications severe enough to require clinical treatment unless 2 (1,67%) lip biting. No patients in any group reported hematoma, swelling or infection.	Did not show any adverse reaction reported by the patients or observed by the surgeons during or after the procedure.	A total of five (13,89%) patients in the IANB group reported temporary irritations 24h after the procedure. One (2,78%) case of difficulty during talking for 1 day after the anesthesia, 3 (8,33%) pain at the injection site and 1 (2,78%) pain around the ear after the injection.	None of the groups showed any significant superior side effect, as well as other clinical trials comparing 2% and 4% articaine solutions.	No relevant adverse effect, either local complications (local irritation or discomfort) or systemic side effects (palpitations, nausea, vomiting or dizziness).	No complications or side effects were immediately observed. After 24h, 20 (32,79% IANB) patients related pain at the injection site and 2 (3,28%) lip biting.

Conclusions	1. Plain mepivacaine and 2% lidocaine with 1:80,000 epinephrine administered by IANB anesthesia via CCDS were similarly effective for both primary mandibular molar extraction and pulpotomy. 2. Pain during injection was greater with 3% mepivacaine than with 2% lidocaine with 1:80,000 epinephrine, and the duration of anesthesia was shorter with mepivacaine than with lidocaine. 3. Plain mepivacaine and 2% lidocaine with 1:80,000 epinephrine showed similar results in terms of postoperative complications.	Differences between the 2 solutions were seen in terms of time of onset as well as in duration of anesthesia. Four percent articaine solution without epinephrine does not seem to influence the clinical efficacy in terms of several anesthetic properties (need of second injection, injection pain, intra- and postoperative pain). Be-cause the duration of the LA without epinephrine is shorter and postoperative pain is the same, this could add to increased patient comfort after treatment. There-fore, it is possible to successfully use the 4% articaine without epinephrine formulation for dental extractions in the mandible after inferior alveolar nerve block.	ILA has shown to be a safe and reliable method of local an-esthesia for treatment of lower premolars and molars, with a success rate comparable to IANB without complications and temporary irritations. Thus, ILA can be considered as an effective alternative to IANB for routine dental treatment to reduce known side effects of IANB.	The local anesthetic effect of the 4 % articaine solution is not significaly higher than articaine 2% for mandibular tooth extraction.	IANB with additional buccal infiltration is more suitable for achieving adequate analgesia in L3M extractions than the experimental technique (infiltration in the buccal and lingual areas). Moreover, the standard method is safe and provides a shorter onset time and lower initial postoperative pain levels. Additional randomized controlled clinical trials with large samples are required to confirm these findings.	The IANB and the ILA using CCLAD were as effective as the gold standard techniques for anesthetizing mandibular second primary molars during all five steps of pulpotomy and could be used as an alternative technique. During the pulpotomy procedures, the data showed that the ILA using CCLAD provided more anesthesia to the main nerve supply of the tooth; however, a lower amount of anesthesia was used compared to IANB. This difference was not statistically significant. Postoperative pain was more associated with intra-ligamental injection than both IANB anesthesia techniques, but the difference was not statistically significant. Further research is needed to evaluate the anesthesia effectiveness of different techniques using the CCLAD.

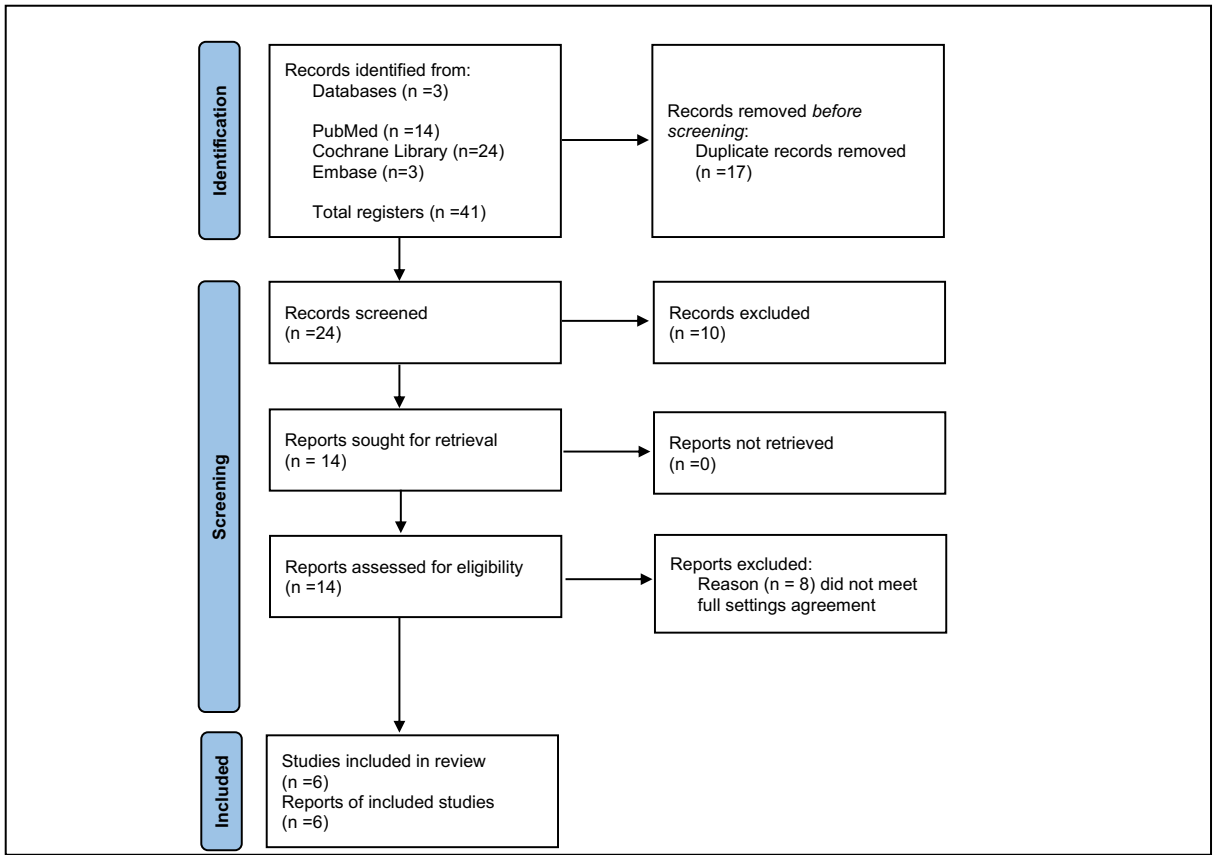

Fig. 1. PRISMA flow protocol representative of the research and literature review process for the selection of studies to be included in the sample of the systematic review.

Fig. 2. Risk assessment of included trials (n=6).

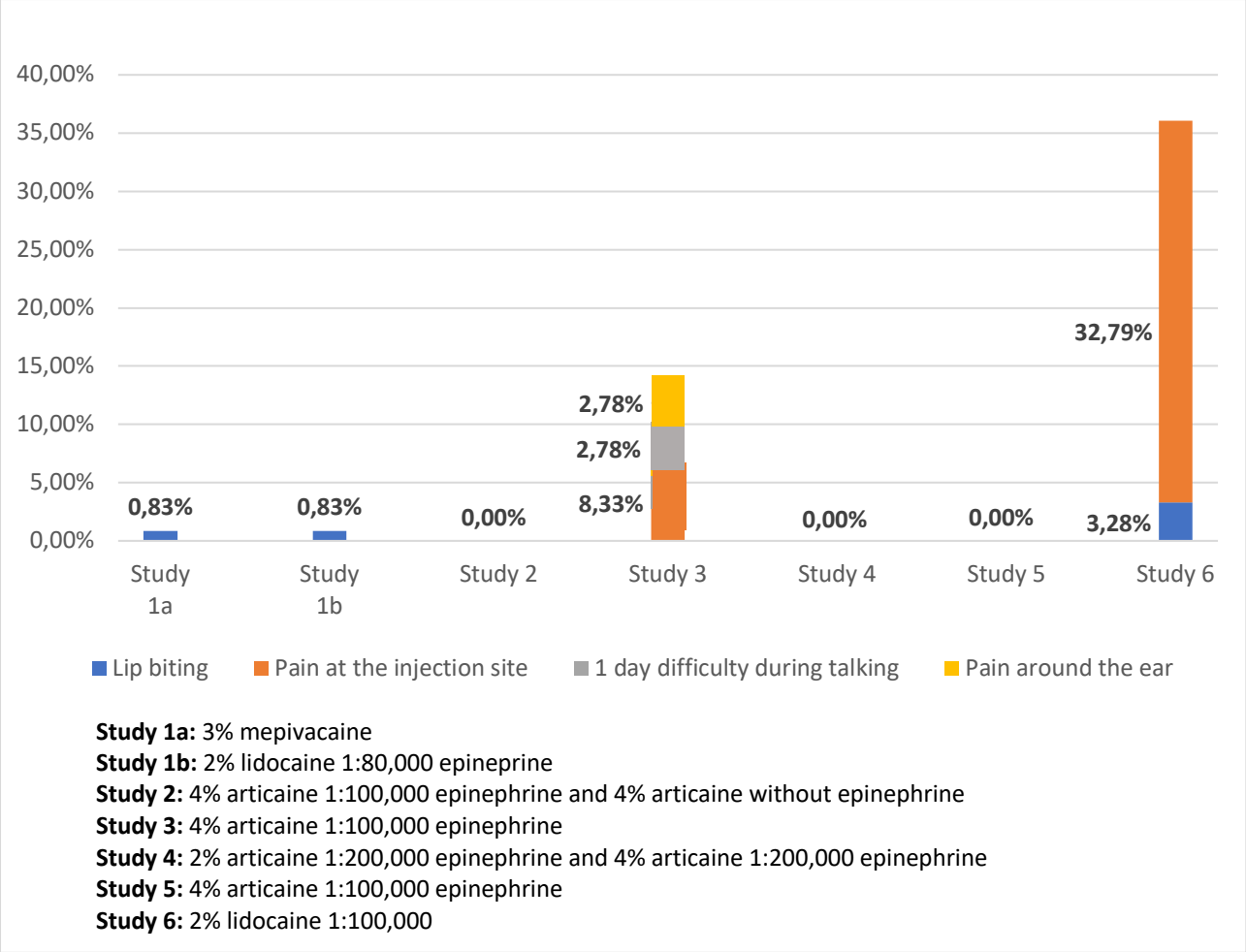

Fig. 3. Studies reporting complications.

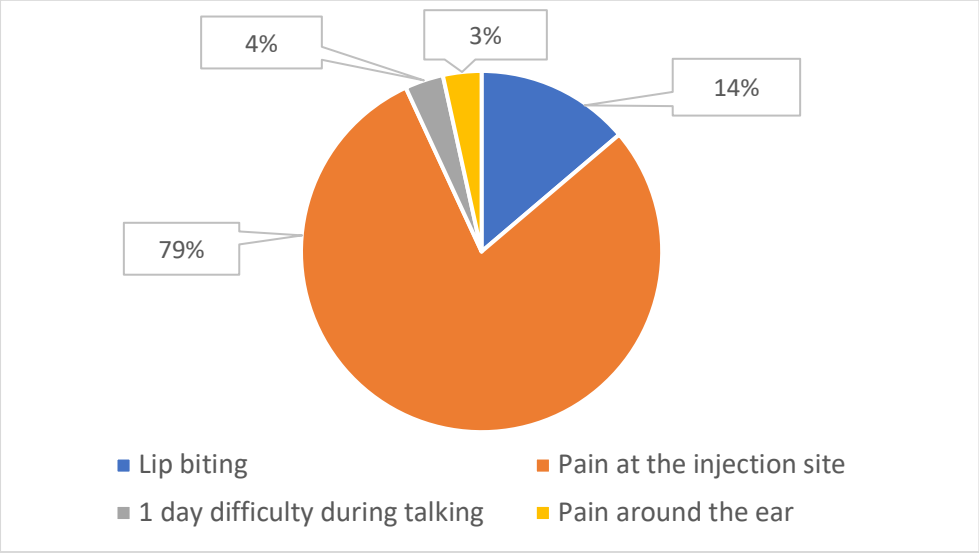

Fig. 4. Complications distribution.