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Complications associated to inferior alveolar nerve block with different anesthetics in pediatric patients: a systematic review

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como parte dos requisitos para obtenção do grau de

Mestre em Medicina Dentária

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Iana Dier-Belozerova

RESUMO

O Bloqueio do Nervo Alveolar Inferior (IANB) é considerado como a técnica anestésica mais difundida para o tratamento de molares decíduos na prática odontológica pediátrica, mas pode evocar ansiedade e comportamento negativo induzido pela dor. O objetivo desta revisão é analisar os relatórios relacionados com a técnica de IANB combinada com diferentes anestésicos locais. Para identificar os estudos relevantes, foi realizada uma revisão sistemática sem restrição de tempo. Dos 46 artigos identificados, um total de 6 estudos obteve concordância total. Este estudo envolveu 384 crianças com idades entre os 4 e os 16 anos. As complicações foram distribuídas entre dor no local da injeção, lesões nos tecidos moles e sensação de sensibilidade dentária. Os resultados da investigação sugerem que não foram observados efeitos secundários significativos em nenhum dos grupos, independentemente das soluções anestésicas. Por conseguinte, é importante que são necessários estudos futuros, nomeadamente ensaios clínicos controlados e aleatórios, para validar estes resultados.

Palavras-chave: anestésico; articaína 4%; complicações; bloqueio do nervo alveolar inferior; lidocaína 2%; mepivacaína 3%; lignocaine 2%; pacientes pediatricas

ABSTRACT

Inferior Alveolar Nerve Block (IANB) is considered as the most widespread anesthetic technique for treatment of primary molars in pediatric dental practice but it can immediately evoke anxiety and pain-induced negative behavior. The objective of this systematic review is to analyze the reports related to IANB technique combined with different local anesthetics. To identify the relevant studies, a systematic review was conducted without any time restrictions. From 46 articles identified, a total of 6 studies met full settings agreement. This study involved 384 children aged between 4 and 16. The complications reported were distributed between pain at the injection site, soft tissue lesions and tender tooth sensation.Research findings suggest that there were no significant side effects observed in any groups, regardless of the anesthetic solutions used. Therefore, it is important to acknowledge that future studies, particularly randomized controlled clinical trials are necessary to validate these results.

Keywords: anesthetics; articaine 4%; complications; inferior alveolar nerve block; lidocaine 2%; mepivacaine 3%; lignocaine 2%; pediatric patients

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To my parents, who have always supported me since the very beginning when I decided to enter my first dental school and become the third generation of dentists in our family.

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To all the teachers for transmitting their knowledge

SUMMARY

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LIST OF ABBREVIATIONS AND ACRONYMS

®	Registered
BI	Buccal Infiltration
CCDS	Computer-Controlled Delivery System
CCLAD	Computer-Controlled Local Anesthetic Delivery System
HP-VAS	Heft-Parker Visual Analog Scale
IANB	Inferior Alveolar Nerve Block
MeSH	Medical Subject Headings
ml	Mililiter
mm	Milimeter
PICO	Problem/Patient/Population, Intervention/Indicator, Comparison and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SEM	Sound, Eye, and Motor
STA	Single Tooth Anesthesia
VAS	Visual Analog Scale
Vs	Versus
WBFPRS	Wong-Baker Faces Pain Rating Scale

I. INTRODUCTION

Control of pain during dental treatment is an essential aspect of modern dentistry. Many adults have developed a strong aversion to dental treatment as a result of negative childhood experiences. Local anesthesia is a tried and tested approach for relieving pain during dental procedures (Davis, 2011; Jain *et al.,* 2021; Saxena *et al.,* 2021).

Injection pain, inadequate or incomplete anaesthesia/analgesia and soft-tissue injury are among the complications of local anaesthesia in pediatric dental care. Considering that pain is a major etiological factor in the development of both dental anxiety and dental behaviour-management problems, research in the areas of pain prevention and management during dental treatment is of great importance, particularly for pediatric dentistry (Zarbock *et al.,* 2000).

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, inferior ramus and anterior two-thirds of the tongue and floor of the mouth (Abdel-Galil, 2008; Alamoudi *et al.,* 2016; Shabazfar *et al.,* 2012; Sarfaraz *et al.,* 2021). The ability to anesthetize all molars, premolars, and canines on the side of the injection makes it possible to treat multiple teeth in the same quadrant at one appointment (Ram & Peretz, 2002).

The conventional inferior alveolar nerve block technique is the most commonly used approach. Recognition of the following anatomical landmarks is imperative: the coronoid process, coronoid notch, anterior and posterior margin of the mandibular ramus, and the sigmoid notch. Other significant landmarks are the coronoid notch and the pterygomandibular raphe formed by the buccinator and superior constrictor muscles; the preferred location of needle entry is between these 2 structures. The syringe barrel is placed over the premolars opposite the side of the injection. The insertion point is an imaginary line starting at the deepest part of the pterygomandibular raphe and continuing to the coronoid notch. The exact location of the entry point is one-fourth the distance

towards the raphe above the occlusal level of mandibular teeth. The needle is inserted after locating the target area until bony resistance is felt. The depth of penetration is between 19 and 25 mm. After that, the needle is withdrawn gently and slowly. When the needle can be inserted more than 25 mm, it may be posterior to the posterior border of the mandible. If the bone is touched prematurely, it suggests an anterior position of the needle. (Suazo-Galdames *et al.*, 2008).

However, IANB also includes some disadvantages, especially for pediatric patients. As soft-tissue anaesthesia lasts significantly longer than pulpal anaesthesia, dental patients who receive local anaesthetic during treatment usually leave the dental office with residual soft-tissue numbness, and many children cannot cope with this problem. Therefore, soft-tissue injury caused by inadvertently biting or chewing tissue following inferior alveolar nerve injection occurs more frequently in pediatric patients than in adults. The problem of soft-tissue injury following local anaesthesia may be resolved by selecting a local anesthetic solution with an appropriate duration for the length of the treatment procedure (Malamed, 2004).

Application of local anaesthetics with shorter durations reduces the risk of lip and cheek biting; moreover, long acting local anaesthetics are not recommended either for children or physically or mentally disabled patients, as the prolonged effect increases the risk of soft-tissue injury (Malamed, 2004).

The history of using the inferior alveolar nerve block (IANB) in pediatric dentistry is a narrative of adaptation, innovation, and ongoing improvement in pediatric dental anaesthesia. The IANB, a cornerstone technique in dental anaesthesia, has played a vital role in providing pain control for children undergoing dental procedures, despite it is not unique challenge associated with pediatric patients. Historically, the use of local anaesthesia in pediatric dentistry faced several obstacle due to children's heightened anxiety, fear of needles, and limited cooperation during dental treatment. Early attempts at utilizing nerve blocks in children were met with scepticism and caution due to concerns about safety, efficacy, and potential adverse effects. However, a dental anaesthesia techniques advanced and our understanding of pediatric pain management evolved, clinicians began to explore the feasibility and utility of the IANB in pediatric patients. Through meticulous research and clinical experience, pediatric dentists developed modified approaches to the IANB tailored specifically to the anatomical and

physiological characteristics of children. One of the key challenges in administering the IANB to pediatric patients is achieving adequate anaesthesia while minimizing discomfort and anxiety. Pediatric dentists employ various strategies to address these challenges, including the use of topical anaesthetics, distraction techniques, and child-friendly language to alleviate fear and anxiety associated with the procedure. Today, the IANB remains a valuable tool in pediatric dentistry, providing reliable anaesthesia for a wide range of dental treatments, including restorative work, extractions, and pulp therapy. While newer techniques and adjunctive measures continue to emerge, the IANB continues to serve as a primary choice for achieving profound anaesthesia in pediatric patients, reflecting its enduring importance in pediatric dental practice (Khalil, 2014).

Nevertheless the use of IANB 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 (Sarfaraz *et al.,* 2021). 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 (Sarfaraz *et al.,* 2021; Takasugi *et al.,* 2000).

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).

The correct technique of local anesthetic administration has been valued as an important consideration in pediatric patient behaviour guidance (Davis, 2011). Clinical studies have found failure with IANB between 44% and 81% of the time (Corbett *et al.,* 2008).

Painless dentistry plays a vital role in the management of dental pain in children, with continued focus on local anaesthesia. From cocaine (1884), procaine (1904), to lidocaine (1948), dentistry has been at the forefront in providing patients with less painful treatment. Lidocaine hydrochloride is considered the "gold standard," for its widespread efficacy and safety, against which other local anesthetic agents are compared (Khanna *et al.*, 2021).

Disposable cartridges, traditional methods of infiltration, or nerve block treatments with a dental syringe needle are used in the majority of local anesthetic treatments in pediatric dentistry. Alternative methods, on the other hand, are available such as computer-controlled local anesthetic distribution, periodontal injection techniques, needleless systems, and intraseptal or intrapulpal injection are among them (Daneswari *et al.*, 2021). Despite the fact that local anaesthetics have a long history of efficacy and safety, they all can also trigger substantial toxicity (Baroni, Franz-Montan & Cogo, 2013).

Taking into consideration the existence of side effects, it is essential for dentist to be proficient in injection technique, carefully choose the injection method and the anesthetic solution as it is fundamental for the successful and secure procedure.

Thus, the aim of this study was to allocate the available data elements 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% articaine with 1:100.000 epinephrine) in pediatric patients providing reliable data to compare the results concerning possible complications.

II. MATERIALS ANS METHODS

1. Metodology 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).

2. Formulation of research question and keywords selection

The research question was approached using the PICO framework, which stands for Patient Population (P), Intervention (I), Comparison (C), and Outcomes (O). This method was utilized to organize and address the research question. It was determined that employing PICO templates enhances higher precision and increases the relevance of search results (Schardt *et al.*, 2007).

PICO criteria for the research question was: "Are there different complications reported by pediatric patients who underwent IANB with different anesthetics?".

1. Population (P) = Pediatric patients

2. Intervention (I) = IANB

3. Comparison (C) = Different anesthetics

4. Outcome (O) = Different complications

According to this research question, the following keywords, and Medical Subject Headings (MeSH) were used for the search: (complications OR "side-effect" OR "adverse reaction") AND (IANB OR "inferior alveolar nerve block") AND (anesthetics OR "articaine 4%" OR "mepivacaine 3%" OR "lidocaine 2%" OR "lignocaine 2%"). Filters applied- Study design: Clinical Trial, Randomized Controlled Trial, Crossover Trial.

3. Search strategy

The research involved exploration of the PubMed/Medline database, Cochrane Library, and Embase. Keywords and MeSH terms were meticulously examined both separately and in combinations using Boolean operators (AND, OR, and NOT) to meet the specific criteria of this review. No systematic review was found specifically on this question under the specific criteria, which prove further necessity to carry out this review. The search for the selection of studies was carried out from February 17 to 19 March 2023.

4. Eligibility criteria

The following selection criteria were chosen:

• Population: Pediatric patients who underwent IANB.

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

• Timeline: No restrictions.

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

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

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

5. Study selection process

Following a systematic research, a total of 46 articles were meticulously identified, with 17 sourced from PubMed/Medline, 25 from the Cochrane Library, and 4 from Embase. In the process of refining the dataset, duplicates were systematically removed, resulting in the exclusion of 19 redundant articles (n= 19). Subsequently, a comprehensive screening of titles and abstracts was conducted, leading to the exclusion of 13 articles

that failed to align with the predefined eligibility criteria. Out of the remaining 14 articles, which were meticulously scrutinized in English, a detailed examination revealed that 8 studies did not meet the stringent criteria set forth for inclusion in this systematic review. As a result, these studies were conscientiously excluded from further analysis. In total 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.

6. Quality assessment tool

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).

III. RESULTS

A total of 46 studies were initially identified through search strategy. Total 19 duplicate articles were removed. Following a thorough evaluation of titles, abstracts, and full texts, 6 studies were successfully identified and included in the systematic review as Study 1 (Elbay *et al.,* 2016), Study 2 (Arrow, 2012), Study 3 (Jain *et al.,* 2021), Study 4 (Daneswari *et al.,* 2021), Study 5 (Khanna *et al.,* 2021) and Study 6 (Alamoudi *et al.,* 2016). Among them, five studies were categorized as randomized clinical trials and one as crossover trial. This study involved 384 children aged between 4 and 16. The complications reported were distributed between pain at the injection site 56%, soft tissue lesions 42% and tender tooth sensation. 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.

1. Characteristics of the included studies

The characteristics of the studies included in this review are summarize in Table 1.

In the first study, a comparison was made between 2% lidocaine with 1:80.000 epinephrine and 3% mepivacaine without epinephrine in computer-assisted inferior alveolar nerve blocks (IANB). The second study evaluated the effectiveness of 4% articaine with 1:100.000 epinephrine and 2% lidocaine with 1:80.000 epinephrine in IANB and buccal infiltration (BI). The third study contrasted 4% articaine with 1:100.000 epinephrine in BI with 2% lidocaine with 1:80.000 epinephrine in IANB for extracting primary mandibular molars. The fourth study focused on comparing articaine with 1:100.000 epinephrine in BI with 2% lidocaine with 1:80.000 epinephrine in IANB for pediatric pulp therapy. In the fifth study, the efficacy of 4% articaine with 1:100.000 epinephrine for BI was compared with 2% lidocaine with 1:80.000 epinephrine for IANB in children. Finally, the sixth study investigated the effectiveness of 2% lidocaine with 1:100.000 epinephrine in traditional IANB, computer-assisted IANB, and computer-assisted intraligamentary anesthesia.

Study 1 involved 60 children undergoing pediatric dental procedures. The purpose of the study was to compare the efficacy, injection pain, duration of soft tissue anaesthesia, and postoperative complications of two different anaesthetics (2% lidocaine with 1:80.000 epinephrine and 3% plain mepivacaine) in pediatric patients in inferior alveolar nerve block (IANB) administered by a computer-controlled delivery system (CCDS)- new technique aimed at reducing injection pain and anxiety during intraoral injection that is considered as alternatives to the conventional syringe. CCDSs have a number of reported advantages, including application of a more comfortable injection, even in tissues with low elasticity, a more sensitive, tactile, and ergonomic handpiece and a non-threatening design that resembles a pen, making it particularly useful in pediatric patients who are afraid of conventional needles. In the study were included patients who required similar procedures (extraction or pulpotomy) bilaterally on primary molars with similar operative difficulties and demonstrated positive or definitely positive behaviour during pretreatment behavioural assessment. Patients with allergies to local anaesthetics or sulfites, a history of significant medical conditions or dental treatment, or a site of active pathosis in the area of injection were excluded, as well as those taking any medication that might affect anesthetic assessment. The mean age of children undergoing pulpotomy was 7.5±0.8 years and children undergoing extraction was 9.93±1.3 years. There were 16 girls and 14 boys in the pulpotomy group; 19 girls and 11 boys in the extraction group. The study was conducted using a randomized, controlled, crossover, double-blind study design. Patients were divided into two groups according to the treatment procedures (Group I: Pulpotomy Group; Group II: Extraction Group) and two subgroups according to anesthetic solutions (2% lidocaine with 1:80.000 epinephrine or 3% plain mepivacaine). A CCDS was used to deliver 3% mepivacaine to 1 primary tooth and 2% lidocaine to the contralateral tooth with an IANB technique. In total, 120 operative procedures (60 pulpotomies, 60 extractions) were performed and 120 injections (60 with lidocaine 1:80.000 and 60 with plain mepivacaine) were carried out. The “tell-show-do” technique was used for all patients. Severity of pain and efficacy of anaesthesia were evaluated using the Face, Legs, Activity, Cry, Consolability Scale, and comfort and side effects were assessed using a questionnaire. Patients receiving 2% lidocaine experienced less pain during injection compared to those receiving 3% mepivacaine. No significant differences in pain during treatments or postoperative complications between the two anesthetics were found. Mean durations of anesthesia were 139.68 minutes for mepivacaine and 149.10 minutes for lidocaine. Regarding 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. A few instances of lip biting and the need for a change of sponge for hemostasis were noted, but these were not significantly difference between groups. Study 1 concluded that plain mepivacaine and 2% lidocaine with 1:80,000 epinephrine administered by IANB anaesthesia via CCDS were similarly effective for both primary mandibular molar extraction and pulpotomy. Also pain during injection was greater with 3% mepivacaine than with 2% lidocaine with 1:80,000 epinephrine, and the duration of anaesthesia was shorter with mepivacaine than with lidocaine. Plain mepivacaine and 2% lidocaine with 1:80,000 epinephrine showed similar results in terms of postoperative complications.

Study 2 compared the efficacy of articaine 4% with 1:100.000 adrenaline and lidocaine 2% with 1:80.000 adrenaline, delivered either through an inferior alveolar nerve block (IANB) or buccal infiltration (BI) for routine restorative procedures in mandibular posterior teeth among children. The study used a parallel group and split-mouth randomized controlled design and the target population was the school children. Fifty-seven children were recruited into the study for restorative procedures on mandibular posterior teeth. Exclusion criteria were children requiring restorative care on teeth affected with enamel hypomineralization. The mean age in both groups of 4% articaine and 2% lidocaine was same (12,4 years). Participants were allocated to LA technique (IANB or BI) and then to LA type (lidocaine or articaine) using a two-stage computer generated random permuted block design. Analgesia success was 100% in IANB and 67% in BI. There was no significant difference in analgesia success between 4% articaine and 2% lidocaine for BI was observed. Higher success and less painful treatment were associated with IANB. Participants with unsuccessful LA were more likely to report moderate/severe pain. Postoperative complications included 1 lip-bite with BI/lidocaine, 1 cheek-bite with IANB/lidocaine, 1 pain at injection site with BI/articaine, 1 tender tooth with IANB/articaine, and 4 episodes of aching jaw. Study 2 concluded that while the findings suggest a higher proportion of LA success with BI using articaine than lidocaine, the difference was not statistically significant and neither agent can be recommended for routine clinical use via BI in restoring posterior mandibular teeth among children. The findings of no difference in the report of pain from LA administration with IANB and BI while producing a significantly higher success with IANB suggests that continued use of

IANB for restorative treatment in mandibular posterior teeth among children, using either lidocaine or articaine, is clinically acceptable.

Study 3 was conducted to evaluate and compare the anesthetic efficacy of 4% articaine buccal infiltration with 2% lignocaine inferior alveolar nerve block (IANB) for primary mandibular molar extractions. The study was a prospective, split mouth, randomized controlled trial. It includes bilateral symmetrical carious primary mandibular molar (n = 92) extractions in 46 healthy children. The mean age of children was 7,86 years. The exclusion criteria were: history of allergy to local anesthetic agent, teeth with dentoalveolar abscess and evident infection near the injection site as this might affect anesthetic efficacy of the agent used. There were 29 male and 17 female patients. Each child was subjected to two different anesthetic agents. Extraction was performed on one side using 4% of articaine buccal infiltration and on the contralateral side using 2% lignocaine IANB in two subsequent appointments. Washout period between the two appointments was at least 1 week. Anesthetic efficacy was assessed on the basis of pain experienced and behaviour depicted by the child. Pain was scored using Wong Baker Faces Pain Rating Scale and Modified Behaviour Pain Scale. The mean value of pain experienced in the form of cry during injection was reported to be more for 2% lignocaine IANB (1.76) as compared to 4% articaine buccal infiltration (1.30), which was statistically significant (P = 0.024). Comparison of behaviour depicted showed no statistically significant difference between the groups. Adverse event recordings were done 24 hours postoperatively by a phone call. Accidental lip injury was observed in four patients from the 2% lidocaine IANB group and two patients from the 4% articaine group. No other major adverse effects were observed in both groups. Study 3 concluded that BI with 4% articaine was found to be equally efficacious to IANB with 2% lidocaine for extraction of primary mandibular molars in terms of pain perception and behavior observed. In addition pain perceived in the form of cry during injection was seen to be statistically lower in buccal infiltration with 4% articaine as compared to IANB with 2% lidocaine. Also no major adverse events were reported in both the groups at 24 hours follow-up phone call. Therefore, buccal infiltration using 4% articaine can be considered as an alternative to 2% lidocaine IANB for primary mandibular molar extraction procedures. Further clinical trials with more sample size are recommended.

Study 4 aimed to assess the efficacy of buccal infiltration with articaine in achieving anaesthesia for pulp therapy in primary mandibular second molars as compared with inferior alveolar nerve block (IANB) with lidocaine. Study is comprised of 30 patients with an indication of pulp therapy in at least two primary mandibular second molars. The mean age of the children was 5,41 ± 1,40 years. There were 17 females and 13 males. This study used a crossover design, in which patients were randomly assigned to receive nerve block with lidocaine on the first appointment and buccal infiltration with articaine on the second appointment spaced one week apart. On the first appointment, patients were randomly assigned to receive IANB with 1.8 ml of 2% lignocaine hydrochloride and 1:80.000 adrenaline solution and buccal infiltration with 0.8 ml of 4% articaine hydrochloride and 1:100.000 epinephrine on the second appointment. The pain scores and sound, eye, and motor (SEM) scores were recorded by two researchers. Pain-related behavior scores were higher for IANB compared to BI. Facial image and Heft-Parker Visual Analog Scale (HP-VAS) scores were higher in the 2% lidocaine IANB group, indicating more pain and discomfort. No significant side effects were identified with 4% articaine except for prolonged soft tissue anesthesia, which lasted 2–4 hours. 6 patients (20% of the children (4–8-year-olds)) suffered soft tissue injuries. Study 4 concluded that with the growing use of novel delivery systems like single tooth analgesia, a buccal infiltration with articaine offers a viable alternative with minimal discomfort, allowing practitioners to avoid using IANB in children. To ensure the safety of children, more studies with a larger sample size are recommended.

Study 5 compared and evaluated the clinical efficacy, hemodynamic changes and postoperative complications of 2% lidocaine with epinephrine 1:80,000 using IANB and 4% articaine with epinephrine 1:100,000 using buccal infiltration in mandibular primary molars. Participants were randomly distributed to receive either 4% articaine using infiltration anaesthesia or 2% lidocaine using inferior alveolar nerve block on each side of the mandibular arch, in two different appointments, after a one week interval. This in vivo, randomized, split-mouth study included 100 children for dental procedures in primary mandibular molars. Healthy children aged 6 to 8 years, who required bilateral anaesthesia for different dental procedures in primary mandibular molars, were recruited. The mean age of the children was 7.05 ± 0.77 years. There were 66 boys and 34 girls. Pulp sensitivity was determined by the dental operator using an electric pulp tester (Digitest Pulp Vitality Tester, Parkell) on the occlusal surface of the primary mandibular

molar twice before the injection to establish a baseline reading. The subjective assessment of pain during administration of local anaesthetics was carried out using two different validated pain rating scales, the visual analog scale (VAS) and the Wong-Baker Faces pain rating scale (WBFPRS). The heart rate and oxygen saturation levels were measured using pulse oximetry (Life-line fingertip pulse oximeter, Lifeshield Healthcare) before, during, and after administering the local anesthetic solutions. The postoperative assessment and reporting of adverse events were based on the subjective evaluation gathered through a follow-up within 24 hours of dental procedures. The patient/parent was asked specific questions related to the postoperative pain, any prolonged numbness, soft tissue injuries, and need for further medications. Pain scores were lower for articaine infiltration compared to lidocaine block ($p < 0.05$). Shorter onset of action was observed with articaine ($p < 0.05$). Statistically significant differences between groups were noted with regard to heart rate ($P < 0.05$). Oxygen saturation levels did not show significant differences ($P > 0.05$). Few postoperative complications as pain at 2 patients, soft tissue injuries at 3 patients and need for re-anesthesia at 6 patients were noted with no significant differences between the two anesthetics. Study 5 concluded 4% articaine administered in the form of infiltration analgesia can offer profound anesthesia, as 2% lidocaine does when administered using IANB among pediatric dental patients. Thus, articaine infiltration can serve as a potential alternative to lidocaine nerve block because of better diffusion and higher potency than lidocaine.

In **Study 6** the purpose was to compare the anaesthesia effectiveness of traditional IANB, IANB using a computer-controlled local anesthetic delivery system (CCLAD) and intraligamental anaesthesia (ILA) using CCLAD in pulpotomy of the primary mandibular second molars. CCLAD technique is combined with dynamic pressure-sensing technology and it is specifically engineered for dental applications. The study involved 91healthy children for primary mandibular second molar pulpotomy. The exclusion criteria were children who were medically compromised and children who were uncooperative. Specific mean or median age was not provided, but age ranged between 5 and 9 years. There were 39 boys (42.9%) and 52 girls (57.1%). Patients were randomly assigned to one of three groups. Group A underwent the traditional IANB, which was performed according to the standard technique. Group B underwent IANB using a computer-regulated device performed with the STA system. Group C underwent ILA using CCLAD performed with the STA system using STA mode. Effectiveness of the

anaesthesia during different steps of pulpotomy was evaluated by using the SEM scale. The effectiveness of anaesthesia in 10 patients was evaluated twice: the first time during the procedure and the second time after 24 hours using a video tape. For all five pulpotomy steps, the anaesthesia effectiveness was similar among the three anaesthesia techniques. Anaesthesia effectiveness was not significantly different (based on SEM scores) between the three groups during clamp application, drilling of the tooth, entering the pulp, pulp extirpation, and removal of the clamp . The parent was contacted by phone the day after the child received the anaesthesia to check the child's postoperative pain and postoperative lip biting. Intraligamental anesthesia was associated with the highest percentage (46.7%) of postoperative pain, but the difference was not statistically significant. No complications or side effects were immediately observed. After 24 hours only two patients in the IANB group anesthetized by CCLAD showed lip biting, and this difference was also not statistically significant compared to the other groups. Also 20 patients related pain at the injection site. Study 6 concluded that 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 anaesthesia to the main nerve supply of the tooth. However, a lower amount of anaesthesia was used compared to IANB. This difference was not statistically significant. Postoperative pain was more associated with intra-ligamental injection than both IANB anaesthesia techniques, but the difference was not statistically significant. Further research is needed to evaluate the anesthesia effectiveness of different techniques using the CCLAD.

2. Quality assessment of the included studies

The quality assessment of the included studies is represented in a form of summary, which delineates the most relevant elements of the systematization process utilized in each trial. This summary serves as a meticulous evaluation, delving into the complexity of study methodology to discern its robustness and reliability (Fig.2). To evaluate the biasness, risk the RoP version 2.0 was used, 5 evaluation criteria were taken in account to evaluate final general risk as low or high (Sterne *et al.*, 2019).

Study 1. In the study conducted by Elbay *et al*. (2016), a thorough analysis was provided concerning the detailed process of participant selection, which involved a systematic randomization method facilitated by a sophisticated computerized system designed to allocate anesthetic solutions to each patient. However, while the method of participant selection was clearly delineated, the study failed to offer detailed insights into the concealment of allocation, a critical aspect in evaluating the potential for bias within the randomization procedure. This lack of transparency raises concerns regarding the integrity of the randomization process and underscores the need for further clarification in future research endeavors. Moreover, the study's experimental design was meticulously crafted as a double-blind trial, aimed at minimizing potential biases. Both the healthcare provider administering the treatment and the evaluator assessing the outcomes were deliberately kept unaware of the specific type of local anesthetic being administered. This effective blinding mechanism was achieved by entrusting a dental assistant with the task of preparing the anesthetic solutions without disclosing their identities. However, the study failed to explicitly address whether parents or caregivers were similarly kept uninformed about the intervention, introducing a degree of uncertainty regarding potential deviations from the planned interventions and their impact on bias assessment. This ambiguity categorizes the study's blinding approach under the classification of "Some concerns." Furthermore, the study's treatment of missing outcome data was not explicitly elucidated, leaving room for interpretation regarding the completeness of the data analysis. While it appears that the study initially accounted for all randomized participants, the absence of explicit mention regarding missing outcome data necessitates further scrutiny to ascertain the potential risk of bias stemming from such omissions. Additionally, the study highlighted the potential for bias in outcome measurement, particularly concerning parental reporting of postoperative complications influenced by emotional factors. The inherent emotional attachment of parents to their children's well-being may lead to an overestimation of adverse effects or complications, thereby introducing bias into the data analysis. This reliance on parental reports for postoperative complications underscores a "high risk" of bias in outcome measurement, emphasizing the need for cautious interpretation of the study findings. Finally, the study's comprehensive reporting encompassed all anticipated outcomes, including the efficacy of anesthesia, pain experienced during injection, and any postoperative complications. This thorough attention to detail in reporting signifies a low risk of bias in result selection and dissemination. However, ongoing efforts to improve transparency in participant

allocation concealment, address missing outcome data, and reduce biases resulting from parental reporting are imperative for ensuring the robustness and reliability of future research in this domain.

Study 2. The study conducted by Arrow (2012) exemplified a thorough approach to participant allocation through a well-defined randomization process. Utilizing a two-stage computer-generated random permuted block design, the study ensured an equitable distribution of participants across treatment groups, thereby minimizing the risk of bias in allocation. This comprehensive randomization methodology serves as a cornerstone in establishing the study's credibility and reliability. Additionally, the study was structured as a double-blind experiment, underscoring its commitment to reducing potential biases in intervention delivery. By withholding information regarding the specific anesthetic agent administered, the study aimed to minimize the influence of subjective biases. However, while the healthcare provider, dental chair assistant, patient, and parent were kept unaware of the specific agent, they were not blinded to the local anesthesia (LA) technique employed. This partial blinding approach raises concerns regarding the accurate evaluation of procedural efficacy and pain levels experienced by participants. Consequently, the study encounters "some concerns" regarding the risk of bias stemming from this deviation from complete blinding protocols. Further, scrupulous documentation of participant flow throughout the trial underscores the study's commitment to transparency and rigor. A clear account of all participants included in the study mitigates concerns regarding bias from missing outcome data, affirming the study's methodological robustness. However, the reliance on parental reporting for post-anesthetic events and post-operative pain assessments introduces a notable risk of bias. Parent’s subjective perceptions may inadvertently influence reported outcomes, potentially skewing the study's findings. Consequently, the risk of bias in outcome measurement due to parental involvement is considered "high," necessitating cautious interpretation of study results. Despite these potential biases, the study diligently reported all anticipated outcomes, including the success of analgesia, pain assessments during analgesia administration, and postoperative complications. This thorough reporting of results signifies the study's commitment to transparency and completeness, thereby alleviating concerns regarding bias in outcome selection. Overall, while acknowledging the inherent limitations and potential biases, the study's comprehensive methodology and meticulous reporting contribute to its credibility and reliability in informing clinical practice and future

research endeavors.

Study 3. Jain *et al.* (2021) in their study, undertook a randomized controlled trial distinguished by a unique approach to participant allocation. Employing sequentially numbered opaque, sealed envelopes, the study thoroughly allocated participants to their respective groups, thereby ensuring a robust randomization process with minimal risk of bias. This methodological precision underscores the study's commitment to scientific rigor and reliability. The study was meticulously designed as a double-blind trial, aiming to reduce potential biases in data interpretation. Both participants and the data analyst were deliberately kept unaware of the interventions administered, minimizing the risk of bias in outcome assessment. However, the operator was not blinded, primarily due to the distinct techniques employed in delivering local anesthesia. This deviation from complete blinding protocols raises concerns regarding the potential impact on bias, particularly concerning the evaluation of intervention effectiveness. While efforts were made to minimize bias, this partial blinding approach necessitates cautious interpretation of the study's findings and underscores the need for further methodological refinement in future research endeavors. Furthermore, the study demonstrated a assiduous approach to data collection and reporting. Comprehensive documentation of all participants and systematic recording of adverse effects postoperatively exemplify the study's commitment to transparency and completeness. This meticulous approach suggests a low risk of bias from missing outcome data, enhancing the study's methodological robustness. However, the reliance on parental reporting for assessing adverse events introduces a notable risk of bias in outcome measurement. Parents' subjective perceptions and personal biases may inadvertently influence reported outcomes, potentially skewing the study's findings. Consequently, the risk of bias in outcome measurement due to parental involvement is considered "high," necessitating careful consideration of these factors in data interpretation and analysis. In spite of these potential biases, the study demonstrated thoroughness in reporting all anticipated outcomes, including assessments of pain, behavior, and adverse events. This comprehensive reporting approach suggests that the study did not selectively report outcomes based on favorable results, thereby minimizing the risk of bias in outcome selection. Overall, while acknowledging the inherent limitations and potential biases, the study's rigorous methodology and transparent reporting contribute to its credibility and reliability in informing clinical practice and guiding future research in the field.

Study 4. Daneswari *et al.* (2021) in their study adopted a crossover design, although certain critical aspects, such as details regarding randomization, were left ambiguous. The lack of explicit information regarding participant randomization and allocation concealment adds complexity to the assessment of the study's overall validity and reliability. While the research acknowledged the impracticality of implementing blinding due to the distinct and easily recognizable nature of the injection procedures utilized, the absence of blinding in studies evaluating pain introduces significant risks of bias. Blinding is crucial in mitigating subjective influences on participant's perception of pain and observer's evaluations. Thus, the absence of blinding in this study raises concerns, particularly concerning the assessment of pain and responses to the procedures, categorizing the risk as "High." Nevertheless, the study appears to have thoroughly reported outcomes for all participants, indicating effective data collection practices and minimizing the risk of bias due to missing outcome data. However, this study involved self-assessment of post-surgical experiences by young children, with an average age of 5.41 years. The young age of participants introduces a notable likelihood of subjective bias in their self-reports, as their ability to accurately and consistently communicate their pain or discomfort is questionable. Consequently, the risk of bias in outcome measurement for this study is deemed "High," highlighting the need for careful consideration of these factors in data interpretation and analysis. Regarding the reporting of outcomes, the study demonstrated a low risk of bias. There were no indications of selective reporting, suggesting that the study comprehensively reported its findings and did not exclude any crucial data. However, further clarity on randomization details and considerations for mitigating subjective bias in pain assessment would enhance the study's methodological robustness and strengthen confidence in its findings.

Study 5. Khanna *et al*. (2021) in their study employed a randomized split-mouth design, utilizing systematic allocation of interventions, yet failed to provide information regarding the concealment of allocation. The absence of such critical details introduces uncertainty in evaluating the risk of bias stemming from the randomization process, as the lack of clarity typically leads to a judgment of “Some concerns” for risk associated with randomization. Furthermore, the study did not mention whether participants were blinded, leaving a significant gap in understanding the potential for bias. Specifically, there is no particular mention of blinding procedures for outcome assessors or participants, which could introduce bias, particularly in studies involving subjective

assessments such as pain evaluation. Without details on whether assessors or participants were blinded to the intervention they received, it is appropriate to categorize the risk of bias due to blinding as "high risk." Additionally, the study did not report any instances of participants dropping out or missing data, suggesting a low risk of bias due to missing outcome data. However, the postoperative assessment and reporting of adverse events relied heavily on subjective evaluations gathered through follow-ups conducted within 24 hours of dental procedures. This assessment involved asking patients/parents specific questions related to postoperative pain, prolonged numbness, soft tissue injuries, and the need for further medications. Given that this approach relies on subjective evaluations by patients or parents, which can introduce personal biases and perceptions into the reporting, the risk of bias in outcome measurement is considered high. Despite these potential biases, the study reported comprehensive results, including efficacy, hemodynamic changes, and postoperative complications, with a low risk of bias in the selection of reported results. However, further transparency regarding allocation concealment, blinding procedures, and consideration of subjective biases in outcome measurement would enhance the study's methodological robustness and increase confidence in its findings.

Study 6. Alamoudi *et al.* (2016) in their work meticulously outlined the process of block randomization for allocating participants to different groups, ensuring a robust methodological approach. The primary investigator took stringent measures to conceal allocation, while a second investigator, who was unaware of the anesthesia technique, assessed its effectiveness. This meticulous methodological approach suggests a low risk of bias stemming from the randomization process, underscoring the study's methodological rigor. Furthermore, the study maintained a double-blind design, with both the primary investigator and the evaluator blinded to the anesthesia technique used, further minimizing the potential for bias in outcome assessment. However, despite the rigorous blinding procedures for investigators, it remains unclear whether participants or their caregivers were similarly blinded, raising some concerns about potential bias related to the implementation of the intended intervention. The lack of clarity on this aspect introduces uncertainties regarding the validity of participant-reported outcomes, highlighting the need for further clarification in future studies. Nevertheless, the study reported outcomes for all randomized participants, indicating a thorough approach to data collection and thereby minimizing the risk of bias due to missing outcome data.

Postoperative complications, particularly pain and lip biting due to numbness caused by anesthesia, were diligently evaluated through phone calls to parents 24 hours after the procedure. However, this reliance on parental reporting for assessing postoperative complications introduces the possibility of subjective bias. Parent's assessments may be influenced by their own perceptions and concerns, potentially leading to over-reporting or under-reporting of symptoms, thereby significantly elevating the risk of information bias and bias in outcome measurement. Regardless of potential biases, the study appears to have comprehensively covered all expected outcomes, including the effectiveness of anesthesia during various stages of pulpotomy and postoperative complications. This thorough reporting of results indicates a low risk of bias in the selection of reported outcomes, further affirming the study's methodological rigor and reliability. However, future studies could benefit from addressing the uncertainties regarding blinding procedures for participants and caregivers to enhance the overall validity and reliability of findings.

3. Overall quality of the included studies

In summarizing the findings across the six studies, it is apparent that the quality varies significantly, with a nuanced assessment revealing both strengths and areas of concern. Out of the total studies analyzed, four studies were found to have some concerns, while two studies were categorized as high risk, indicating a notable variability in research methodology and rigor. Approximately 50% of the studies effectively managed the randomization process, demonstrating adequate control over participant allocation. However, the remaining 50% exhibited concerns primarily due to a lack of transparency in allocation concealment, highlighting the need for greater clarity and adherence to established protocols in future research endeavors.

A common issue observed across the studies is the partial or complete lack of blinding, which significantly contributes to concerns or high risk in deviations from intended interventions. This lack of blinding introduces the potential for bias, particularly in subjective assessments such as pain evaluation. Therefore, future studies should prioritize implementing robust blinding procedures to enhance the reliability and validity of study outcomes.

Despite these concerns, all studies generally scored well in terms of managing missing outcome data, indicating thorough and complete data collection practices. However, the measurement of outcomes emerged as a significant area of concern across all studies, with 100% exhibiting a high risk of bias due to reliance on subjective reports by parents or young children. This reliance introduces inherent biases, potentially skewing the interpretation of study findings and underscoring the need for objective measurement tools and standardized assessment protocols.

On a positive note, all studies reported a low risk in the selection of reported results, suggesting comprehensive and unbiased reporting practices. This transparency in reporting is commendable and contributes to the overall trustworthiness of study findings.

In conclusion, while there are strengths in certain domains such as outcome data management and reporting of results, significant concerns persist in areas like deviation from intended intervention and outcome measurement. This mixed picture underscores the importance of addressing potential biases comprehensively in clinical research and emphasizes the need for methodological rigor and transparency in study design and execution. Only through meticulous attention to research methodology can the integrity and reliability of study findings be ensured, ultimately advancing evidence-based practice in healthcare.

IV. DISCUSSION

Ironically, local anaesthetic is both the salvation and the bane of modern dentistry. Injection seems to be the procedure that causes the most psychological stress in children and adults constituting one of the most significant challenges in providing dental care. Though it allows for nearly painless treatment, but it is also linked to a lot of anxiety and misunderstandings among young patients (Ram & Peretz, 2001).

Disposable cartridges, traditional methods of infiltration, or nerve block treatments with a dental syringe needle are used in the majority of local anesthetic treatments in pediatric dentistry, as documented so far. However, alternative methods are available, such as computer-controlled local anesthetic distribution, periodontal injection techniques, needleless systems, as well as intraseptal or intrapulpal injection are used in dental practice for tailoring anaesthesia to individual patient’s needs potentially reducing discomfort and anxiety.

Over the past century, there is perhaps no greater contribution to the practice of clinical dentistry than the development and application of local anaesthesia. Local anaesthetics have made significant advancements in dentistry and have fundamentally transformed patient attitude of dental treatments. The history of advancements in local anaesthetics in dentistry is a testament to the continuous pursuit of improving patient comfort and pain management during dental procedures. Over the centuries, the development and refinement of local anaesthetics have transformed dental practice, revolutionizing the way dentists approach pain control and anaesthesia delivery. The use of local anaesthetics in dentistry dates back to ancient times, with early civilizations employing natural substances such as opium, mandrake root, and coca leaves to alleviate pain during dental procedures. However, it was only in the 19th century that significant advancements in local anaesthesia began to emerge. One of the key milestones in the history of local anaesthetics in dentistry was the discovery of cocaine's anesthetic properties by Austrian ophthalmologist Carl Koller in 1884. Koller's groundbreaking research demonstrated that cocaine could be used to produce localized anaesthesia, leading to its widespread adoption in dental and medical practice. However, the use of cocaine as a local anesthetic was short-lived due to its addictive properties and potential for toxicity. In response,

researchers began searching for safer and more effective alternatives, leading to the development of synthetic local anaesthetics. In 1905, German chemist Alfred Einhorn synthesized procaine, commonly known by its trade name Novocain. Procaine quickly gained popularity as a local anesthetic due to its efficacy, safety profile, and relatively low cost. Novocain became the go-to anesthetic for dental procedures for much of the 20th century, significantly improving patient comfort and enabling more extensive and complex dental treatments. Throughout the 20th century, further advancements in local anaesthetics continued to emerge, with the development of newer agents such as lidocaine, mepivacaine, and articaine. These newer agents offered improved potency, faster onset of action and longer duration of anaesthesia compared to procaine, further enhancing the precision and effectiveness of dental anaesthesia. Overall, the history of advancements in local anaesthetics in dentistry reflects a continuous journey of innovation and improvement aimed at providing safer, more effective, and more comfortable pain management solutions for dental patients. As technology and research continue to evolve, the future of local anaesthesia in dentistry holds exciting possibilities for further enhancing patient care and improving treatment outcomes (Decloux & Ouanounou, 2020).

However, there is still a need for the development of painless procedures, especially in pediatric dental practice. To take advantage of all of the local anesthetic devices and techniques available for dental operations, knowledge of the agent being used, the neuroanatomy involved and doctor’s skills are essentials. Even though local anaesthetics have a long history of efficacy and safety, complications related to local anaesthesia such as persistent paraesthesia and numbness due to nerve trauma and local hematoma formation, triggered by the injury and bleeding of the vascular tissue, and trismus in the pterygomandibular area, by intramuscular injection and needle fracture, can occur. Likewise, if a large volume of the local anesthetic is administered or an inadvertent intravascular injection has taken place, the patient may manifest a systemic toxic response to the local anesthetic used. This may involve minimal to moderate symptoms, but in some cases, it can result in central nervous system and cardiovascular collapse. Therefore, more effective approaches, with need for fewer technical repetitions and less reinforcement, contribute to a lower risk of injury of important anatomical structures. Identifying the nature of the complications associated with the use of different local anaesthetics and their limitations is a crucial strategy to ensure high efficacy and low risk

in anesthetic procedures, especially in children.

In our systematic review we have examined the clinical approach with both use of traditional and alternative (a computer-controlled delivery system (CCDS)) methods of infiltration in pediatric dental practice.

Computer-controlled local anesthetic delivery systems (CCDS) represent one of the resources that have progressed the most in recent years, but their efficacy and applicability in pediatric dentistry is still the subject of certain controversies The history of computer-controlled delivery systems (CCDS) in dentistry marks a significant evolution in dental practice, particularly in the administration of local anaesthesia. The development of CCDS can be traced back to the late 20th century when advancements in computer technology began to intersect with dental innovation. In the 1980s and 1990s, early prototypes of computer-controlled anaesthesia delivery systems emerged, aiming to improve the precision and comfort of local anesthetic injections. These initial systems utilized basic computer programming to regulate the flow and rate of anaesthesia administration, offering dentists greater control over dosage and injection speed. As computer technology continued to advance into the 21st century, so did the sophistication of CCDS in dentistry. By the early 2000s, more advanced CCDS models began to integrate features such as real-time feedback mechanisms, digital dosage calculation, and customizable injection profiles tailored to individual patient needs. One of the notable milestones in the history of CCDS in dentistry occurred with the introduction of The Wand by Milestone Scientific in 1997. The Wand® represented a significant leap forward in anaesthesia delivery technology, featuring a pen-like design and computer-controlled injection system that offered precise, virtually painless injections. The Wand® quickly gained popularity among dental professionals and patients alike, paving the way for further innovations in CCDS. Throughout the 2000s and into the present day, CCDS systems have continued to evolve, with manufacturers introducing new features such as ergonomic designs, touchscreen interfaces, and integration with digital imaging technologies. These advancements have not only improved the patient experience by minimizing discomfort and anxiety associated with injections but have also enhanced the precision and efficacy of anaesthesia delivery, ultimately leading to better clinical outcomes. Today, CCDS systems have become increasingly commonplace in dental practices worldwide, representing a standard of care in modern dentistry. With ongoing advancements in technology and continued innovation in dental anaesthesia delivery, the

future of CCDS holds the promise of further improving patient comfort, safety, and overall dental care quality (Castelo *et al.*, 2022).

Totally, 384 pediatric patients were studied, and four 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% articaine with 1:100.000 adrenaline). The analyzed studies from IANB combined report complication rates for 2% lidocaine 1:80.000 epinephrine of 5,86 % for soft tissue injuries and 8,2% for pain. Furthermore, for 2% lidocaine 1:100.000 epinephrine, 3,28% of soft tissue injuries and 32,79% of pain were mentioned. On the other hand, 3% mepivacaine was associated to 1,67% of soft tissue injuries and, 4% articaine 1:100.000 epinephrine to 10% of tender tooth. The differences expressed in the results for lidocaine 1:80.000 and 1:100.000 epinephrine may be the result of methodological differences regarding the anesthetic deposition device and the complication measurement node. As for the complications associated with the use of 3%mepivacaine, the low number of occurrences is in line with others concerning different anesthetics administered by a computer-controlled delivery system in the same study. Despite the small sample of procedures using 4% articaine 1:100.000 epinephrine, in which no reference is made to pain or soft tissue injury, suggests a high potential for safe and effective use, despite the fact that one study reported cases of tender tooth which is less likely to be associated with the anesthetic itself and are more likely to be associated with the procedure performed.

For all studies the inclusion criteria were cooperative behavior for dental treatment, no history of allergy or contraindications to any of the components in the local anesthetic solution, no evidence of soft tissue infection／inflammation near site of injection. From other side the exclusion criteria were children who were medically compromised, uncooperative, who had history of allergy to local anesthetic agent, infection evident near the injection site as this might affect anesthetic efficacy of the agent used.

In relation to perception of pain during injection, according to Elbay *et al.* (2016) the pain was greater with 3% plain mepivacaine than with the 2% lidocaine 1:80.000 with the vasoconstrictor epinephrine, which appears to conflict with other studies (Oikarinen, Ylipaavalniemi & Evers, 1975; Kramp, Eleazer & Scheetz, 1999) that report less pain with plain anaesthetic solutions, possibly because of their higher pH levels that varies for 3% plain mepivacaine between 4,5 to 6.0 instead of 3.5 to 5.5 for 2% lidocaine 1:80.000

epinephrine. The pH levels of anesthetic solutions used in dentistry typically vary depending on the specific formulation and brand. However, they are generally adjusted to be close to the physiological pH of human tissues that ranges between 7,35 and 7,45 to minimize irritation and discomfort upon injection. The pH of dental anesthetic solutions typically ranges from around 3 to 5.5. This acidity helps in the stability and efficacy of the solution while also minimizing the risk of tissue damage upon administration.

In another study by Alamoudi *et al*. (2016), a substantial difference (35.5%) of postoperative pain after IANB procedure with 2% lidocaine with 1:100.000 epinephrine was observed. Moreover, the findings of Khanna *et al*. (2021) regarding the onset of action and pain scores associated with articaine versus lidocaine emphasize the importance of continual assessment and adaptation of anesthetic choices in pediatric dentistry. We should also mention that the injection site is an important factor for injection pain perception as for example in palatal-anterior superior alveolar injection the non-elastic nature of palatal tissue can have a role in more high level of pain during injection. In the study of Daneswari *et al.* (2021) the pain related score concerning pain of injection with 2% lidocaine 1:80.000 in IANB technique demonstrates eye squeezing at 73% children, 46% hand movement, 13% torso movement, 20% leg movement and 20% of children crying.

The studies highlight how different anesthetic techniques, such as IANB versus BI, can elicit varied responses in pediatric patients. This is particularly evident in studies that examine patient comfort levels and pain perception, such as study of Arrow (2012) and study of Daneswari *et al.* (2021). These findings identified the need for clinicians to not only consider the technical aspects of anesthetic administration but also the patient's psychological and physiological response as it plays a crucial role in determining the overall success of dental treatment and the patient's experience. Understanding and effectively managing these responses are essential for providing safe, comfortable, and successful dental care for children. Pediatric patients may experience fear, anxiety, and apprehension related to dental procedures and the administration of local anaesthesia. This fear can stem from various factors, including previous negative experiences, fear of needles, unfamiliarity with the dental environment, and sensory sensitivities. To address psychological responses, pediatric dentists employ various strategies to create a supportive and comforting environment for children. These may include: communication, distraction techniques, positive reinforcement, parental involvement. In communication

pediatric dentists use child-friendly language and explanations to help children understand the procedure and alleviate fears. Distraction techniques such as playing music, watching cartoons, or using interactive toys can help divert the child's attention away from the procedure and reduce anxiety. Offering praise and rewards for cooperative behaviour can help reinforce positive associations with dental visits and local anaesthesia administration. Having a parent or caregiver present during the procedure can provide reassurance and emotional support for the child. The physiological response to local anaesthesia in pediatric patients involves various bodily reactions triggered by the administration of the anesthetic agent. These responses can include pain perception even if local anaesthesia aims to block pain sensation during dental procedures. Pediatric patients may still experience discomfort or mild pain during injection or dental treatment, particularly if they are anxious or sensitive to sensory stimuli. Some children may also experience a vasovagal response, characterized by symptoms such as dizziness, nausea, sweating, and fainting in response to stress or anxiety associated with dental treatment. Anxiety and fear can lead to increases in heart rate and blood pressure in pediatric patients undergoing dental procedures, potentially affecting their physiological responses to local anaesthesia.

Regarding postoperative pain there was no significant difference between the two groups of pulpotomy and extraction and two subgroups according to anaesthetic solutions (2% lidocaine with 1:80,000 epinephrine or 3% plain mepivacaine) observed by Elbay *et al.* (2016). In contrast, Alamoudi *et al.* (2016) reported a substantial difference (35,5%) of postoperative pain after IANB procedure with 2% lidocaine with 1:100.000 epinephrine. In all studies we can observe that the most frequent complication was associated with soft tissue injuries as lip biting and cheek biting. This aspect, emphasized in study of Jain *et al*. (2021) and study of Alamoudi *et al*. (2016), serves as a reminder of the clinician's responsibility to educate caregivers about potential post-treatment complications and the importance of follow-up care. Further research should include long-term follow-up of patients to assess any delayed side effects or complications, providing a more comprehensive view of the safety profile of these anaesthetics.

The findings from these studies advocate for a more patient-centric approach in pediatric dentistry. This involves not only selecting the most effective anesthetic but also considering factors like patient comfort, anxiety levels, and potential for postoperative complications.

Regarding the duration of anesthesia, in the study of Elbay *et al.* (2016) it was 139.68 minutes for 3% plain mepivacaine and 149.10 minutes for 2% lidocaine 1.80000. This is in concordance of most studies (Malamed, Tavana & Falkel, 1995; Liu *et al.*, 1995; Caldas *et al.*, 2015) which revealed the extension of duration of anaesthesia with the use of epinephrine as a vasoconstrictor. Epinephrine works by constricting blood vessels at the site of injection, which slows down the absorption of the local anesthetic into the bloodstream. This results in a prolonged duration of action for the anesthetic, as it remains localized to the target area for a longer period of time. The vasoconstrictive effect of epinephrine reduces blood flow to the injection site, limiting the systemic absorption of the anesthetic agent. Consequently, the systemic levels of the anesthetic remain lower for a longer duration, reducing the risk of systemic toxicity and allowing for a more prolonged and effective anaesthesia. However, mean duration of anaesthesia was less than expected. It can be due to 2 reasons: information on duration of anaesthesia was obtained by parents, who may not provide reliable information, and the disappearance of insensitivity of soft tissues might not have been similarly determined by all participants.

Concerning postoperative bleeding after tooth extraction, in the study of Elbay *et al.* (2016) was expected that 2% lidocaine with epinephrine will have less bleeding in comparison with 3% plain mepivacaine as epinephrine have an effect of blood loss reduction during surgical treatment. As the result of the study the need of sponge changing in patients underwent IANB anesthesia with 3% plain mepivacaine was greater than in patients who underwent IANB anesthesia with 2% lidocaine with epinephrine. But the difference between the two datas was not statistically significant, it may be because of limited subject number

In contrast of expectations in the study of Elbay *et al.* (2016) was found that the aesthetic solution had no effect on postoperative complications. In all studies we can observe that the most frequent complication was associated with soft tissue injuries as lip biting and cheek biting that can be due to the nature of IANB and its technique, which is often challenging in pediatric patients during the procedure and children's ability to cope with post-operative unusual sensations. To help children cope with post-operative sensations after IANB, pediatric dentists can employ various strategies as providing age-appropriate explanations to children and their parents about the expected sensations following IANB administration that can help to alleviate anxiety. This may include informing patients about temporary numbness, tingling, or discomfort that may occur as the anaesthesia

wears off. Also care givers can offer reassurance and encouragement to children during and after the procedure that will help alleviate fears and build confidence in their ability to cope with post-operative sensations. Pediatric dentists can reassure children that the unusual sensations are temporary and normal. No less important is to create a supportive environment in the dental office that can help children feel more comfortable and relaxed during and after the procedure. Pediatric dentists and staff can offer emotional support and encouragement to children and their parents throughout the post-operative recovery period. It is essential for pediatric dentists to communicate openly with children and their parents, address any concerns or questions they may have, and provide ongoing support and guidance to help children cope effectively with post-operative sensations after IANB administration. By employing these strategies, pediatric dentists can help ensure a positive and comfortable experience for children undergoing dental procedures involving local anaesthesia.

In four studies performed by Arrow (2012), Jain *et al.* (2021), Daneswari *et al.* (2021) and Khanna *et al.* (2021) was analysed the efficacity of buccal infiltration with 4% articaine comparing with IANB technique with 2% lidocaine taking in account the bone thickness in pediatric patients. The goal was to establish if BI with 4% articaine would be eligible as an effective alternative to IANB as it is known to have lowest level of patient discomfort compared with other techniques. In turn, Arrow (2012) in his study concluded that there was higher success and less painful treatment with IANB technique which is in conflict with the results of other studies (Jain *et al.*, 2021; Daneswari *et al*., 2021; Khanna *et al*., 2021) who state that BI with 4% articaine can be used as an effective alternative to 2% lidocaine IANB. It is important to mention that the study of Arrow (2012) was examined efficacy of anaesthesia during restorative procedures while in Jain *et al*. (2021) and Daneswari *et al.* (2021) studies were carried out extraction and pulp therapy respectively. This fact in our opinion can influence the difference in obtained results.

The only study that used not only visual scales (like faces Pain scale in the study of Arrow (2012) or Wong-Baker facial rating scale in Jain *et al.* (2021)) who are based only on visible signs of pain perception or discomfort is the study of Khanna *et al.* (2021) who took in account also cardiovascular parameters, which included pulse rate and oxygen saturation levels. Measurements were carried out with the help of a pulse oximeter that can provide valuable insights into the physiological responses of children to pain and stress. Oximeters are medical devices commonly used to measure oxygen saturation and

pulse rate non-invasively, making them ideal tools for assessing the impact of pain and anxiety on a child's cardiovascular system during dental procedures. They are also used as safety monitoring devices during dental procedures, allowing clinicians to promptly detect and respond to any signs of respiratory distress or cardiovascular compromise in pediatric patients. During the study the mean pulse rate increased more after administration of lidocaine when given as IANB than with articaine as buccal infiltration, the difference can be attributed to the additional adrenaline in the lidocaine group (Khanna *et al.,* 2021). Adrenaline increases the mean pulse rate by stimulating beta-adrenergic receptors in the heart, enhancing the SA node's firing rate, shortening the cardiac action potential, increasing sympathetic nervous system activity, and inducing vasodilation of peripheral blood vessels. These effects collectively lead to a faster heart rate and an elevated mean pulse rate.

As stated by Khanna *et al.* (2021) articaine has shorter onset of action with higher anesthetic success. During their study they also used an electric pulp tester that can give more reliable information about the efficacy and onset of anaesthesia. It is commonly used to assess the vitality of teeth by measuring the nerve response to electrical stimulation. While traditional electric pulp testers have been primarily utilized for diagnostic purposes, advancements in technology have led to the development of more sophisticated electric pulp testers capable of providing reliable information about the efficacy and onset of anaesthesia during dental procedures The measurements were conducted after injection every 2 minutes during 30 minutes. In the end of the study was determined that the number of episodes of no sensation to maximal stimulation in primary molars over the period was greater with earlier onset with 4% articaine than 2% lidocaine.

Elbay *et al.* (2016) in his study state that the pulp entering step and the pulp extirpation step were significantly more painful (based on the SEM scale), compared to rubber dam application and removal. Similar findings were found with the effectiveness of IANB using CCLAD and ILA using CCLAD. These results were supported by Alamoudi *et al.* (2016), who concluded that the highest mean SEM scores were recorded on entering the pulp and on pulp extirpation, whereas during clamp removal the SEM mean score was very low when using the traditional infiltration method or the CCLAD method.

The IANB and the ILA using CCLAD were as effective as the gold standard techniques for anesthetizing mandibular molars during pulpotomy and could be used as an alternative

technique. Postoperative pain was more associated with intra- ligamental injection than both IANB anaesthesia techniques, but the difference was not statistically significant. Further research is needed in order to evaluate the anaesthesia effectiveness of different techniques using the CCLAD (Alamoudi *et al.*, 2016).

Regarding the anaesthetic solution, according to Khanna *et al.* (2021), articaine was considered the safest local anesthetic as it has minimal toxicity, fast elimination and can be useful during treatment of children with coagulation disorders. Articaine is a local anesthetic solution, which was earlier synthesized by Rusching in 1969 as articaine (Jones & Dean, 2015). Molecular structure of articaine reveals an amide as well as an ester group. This combination allows its metabolization by both liver microsomal enzymes and plasma esterases. A thiophene ring present in place of aromatic ring in articaine increases lipid solubility of the solution as well as its potency (one and a half times greater than that of lidocaine). Nevertheless it is important to mention that pediatric patients with coagulation disorders, such as hemophilia or von Willebrand disease, are at increased risk of bleeding following invasive dental procedures, including local anesthetic injections and it is crucial to obtain a detailed medical history and consult with the child's hematologist or pediatrician to assess the risk-benefit ratio and develop a tailored management plan. Additionally, pediatric dentists may consider adjunctive measures to enhance hemostasis and minimize bleeding risk, such as the application of topical hemostatic agents or the use of local vasoconstrictors in conjunction with articaine to reduce blood flow at the injection site

The quality assessment of the included studies highlights a mixed picture in terms of methodological robustness. Key issues identified across the studies include concerns regarding blinding procedures, potential biases in outcome measurements, and the clarity of randomization processes. While some studies (Arrow, 2012; Jain *et al.*, 2021) demonstrated strong randomization methods, others (Daneswari *et al.*, 2021; Khanna *et al.*, 2021) lacked clear information about the randomization process and blinding procedures. The concerns regarding potential biases in the allocation of participants and the assessment of outcomes underscore the importance of implementing more rigorous methodologies in future studies. Enhancing randomization and blinding techniques is paramount to mitigating biases and ensuring the reliability and validity of study findings. To achieve this, future research endeavors should prioritize comprehensive detailing of allocation concealment methods, providing transparency in participant assignment

procedures. Furthermore, it is imperative to implement robust blinding protocols that encompass all stakeholders involved in the study, including participants, caregivers, and evaluators. By ensuring that all parties are blinded to the intervention received, the risk of bias can be minimized, enhancing the integrity and credibility of study outcomes. Overall, fostering methodological rigor and transparency in study design is essential to advance the quality and reliability of research in the field, thereby facilitating more informed clinical decision-making and improving patient care outcomes.

A consistent issue across the studies was the reliance on subjective parental reports or young children's self-assessment for postoperative complications and pain evaluation. Parental perceptions of their child's pain or discomfort may be influenced by their own experiences, biases, or cultural beliefs, leading to variability in reporting. They may interpret their child's behaviour differently, leading to discrepancies in the reporting of pain or discomfort levels. Also parents may have difficulty accurately recalling specific details about their child's postoperative experience, particularly if there is a delay between the dental procedure and reporting. This reliance introduces a high risk of bias due to subjective interpretations and emotional influences, as seen in studies such as Study 1 by Elbay *et al.* (2016) and Study 4 by Daneswari *et al*. (2021). Hence, there is a clear need for more objective measures in assessing postoperative outcomes, moving away from reliance on subjective reports. This could involve the use of standardized pain scales or clinical evaluations by unbiased observers.

Most studies were thorough in reporting their findings, which indicates a low risk of bias in the selection of reported results. This thorough reporting is crucial for a comprehensive understanding of the study's findings and their implications.

In our work we have came to similar results that other researchers who conducted a systematic review at the same thematic of adult's and children's trials who concluded that the reports related to IANB technique combined with different local anaesthetics in pediatric and adult patients comparing the results concerning possible complications have shown that no relevant side effects in any groups, with any anesthetic solutions. At the same time, it is also relevant to consider that a follow-up period of one day may be too short to observe later complications and the fact that most of the studies analysed had as an exclusion criteria patient with any systematic disease could also be a limitation of this study, both for adults and children. 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 non-existent (Berenova, 2022).

This systematic review offers several strengths, including its comprehensive coverage of a range of studies, which provides a broad overview of different anesthetic techniques and solutions in pediatric dentistry. This breadth ensures a well-rounded understanding of the subject. The methodological rigor, marked by detailed quality assessments of the included studies, lends credibility to the findings, while the focus specifically on pediatric patients addresses a critical and challenging area in dental practice. The diversity of anesthetic techniques reviewed, from traditional methods to advanced options like computer-controlled local anesthetic delivery systems, offers a better understanding of available options in pediatric dental care. Additionally, the review's consideration of psychological factors such as dental anxiety in children highlights its holistic approach to patient care.

However, the review is not without limitations. The variability in study designs, sample sizes, and methodologies among the included studies might affect the comparability and generalizability of the findings. Many studies relied on subjective measures such as parental reports for assessing pain and postoperative effects, potentially introducing biases. Most studies had short follow-up periods, which may not capture delayed postoperative complications or long-term effects adequately. The limited demographic representation in some studies potentially restricts the applicability of the findings to broader populations.

V. CONCLUSION

In conclusion, the included studies in the present systematic review indicate that no relevant side effect were observed in the Inferior Alveolar Nerve Block (IANB) technique suggesting that 2% lidocaine with 1:80.000/1:100.000 epinephrine, 3% plain mepivacaine and 4% articaine with 1:100.000 epinephrine are safe and effective in pediatric patients.

In contrast of adult's studies, the studies conducted in pediatric patients can represent more difficulties and less reliable results assessment as pain associated reactions involve multiple factors and self-reporting of pain or discomfort is not easy to achieve, furthermore in many cases it is unreliable in pediatric patients.

Also we should note that in only one study (Arrow, 2012) the follow-up period was more than one week, all other studies had only one day follow-up period that can be insufficient to establish late post-operative complications. The fact that information about post-operative complications was obtained by parents, who may not provide reliable and objective information as parents are emotionally attached to their children therefore they can over-report the complications that could also influence the final trial results.

Today, the IANB remains a valuable tool in pediatric dentistry, providing reliable anesthesia for a wide range of dental treatments, including restorative work, extractions, and pulp therapy. While newer techniques and adjunctive measures continue to emerge, the IANB continues to serve as a primary choice for achieving profound anesthesia in pediatric patients, reflecting its enduring importance in pediatric dental practice.

However, it is important to remember, especially at these ages, that episodes of complications associated with IANB are considered to be few but not nonexistent and Buccal Infiltration (BI) of 4% articaine with 1:100.000 epinephrine should be taken into account as an alternative.

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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	A comparison of articaine 4% and lignocaine 2% in block and infiltration analgesia in children	Comparative evaluation of anesthetic efficacy of 4% articaine infiltration versus 2% lignocaine inferior alveolar nerve block for extraction of primary mandibular molars.	Assessing the Pain Reaction of Children and Evaluation of Efficacy of Buccal Infiltration with Articaine and Inferior Alveolar Nerve Block with Lignocaine for Pulp Therapy in Primary Mandibular Second Molars	An in vivo, randomized, controlled comparative evaluation of efficacy, hemodynamic changes, and postoperative complications of 4% articaine using buccal infiltration and 2% lidocaine using inferior alveolar nerve block in mandibular primary molars of children aged 6 to 8 years	The effectiveness of computerized anesthesia in primary mandibular molar pulpotomy: A randomized controlled trial
Authors, year	Elbay *et al.*, 2016	Arrow, 2012	Jain *et al.*, 2022	Daneswari *etal.*, 2021	Khanna *et al.*, 2021	Alamoudi *et al.*, 2016
Study design	Randomized, controlled-crossover, double-blind clinical trial	Split-mouth randomized controlled trial	A prospective, split-mouth, randomized controlled trial	A crossover trial	Randomized, split-mouth trial	Controlled, randomized, double-blind clinical trial
Number of patients	60 patients	57 patients	46 patients	30 patients	100 patients	91 patients

Age	6-12 years	5,9-16,9 years	5-10 years	4 – 8 years	6 – 8 years	5-9 years
Gender	Male and female	Male and female	Male and female	Male andfemale	Male andfemale	Male and female
Anesthetic solution	3% mepivacaine and 2% lidocaine 1:80.000 epinephrine	4% articaine with 1:100 000 adrenaline and 2% lidocaine with 1:80 000 adrenaline	4% articaine with 1:100 000 adrenaline and 2% lidocaine with 1:80 000 adrenaline	2% lidocaine with 1:80.000 adrenaline and 4% articaine with 1:100.000 epinephrine	2% lidocaine with 1:80.000 adrenaline and 4% articaine with 1:100.000 epinephrine	2% lidocaine 1:100.000 epinephrine
Technique	IANB technique(n=120)	IANB technique(n=29)	IANB technique(n=46)	IANB technique (n=30)	IANB technique (n=100)	IANB technique (n=61)
Time of complication report	No information	2-, 4-, 24-hours and one week after local anaesthetic administration	24h	No information	24h	24h
Complications	None of the patients reportedpostoperative complications severe enough torequire clinical treatment unless 2 (1,67%) lip biting. No patients inany group reported hematoma, swelling or infection.	1 cheek-bite (3,5%), 1 tender tooth (3,5%), 2 episodes of aching (6,9%)	Accidental lip injury was seen in around 4 patients of lidocaine IANB group and in 2 patients of articaine group. No other major adverse effects were observed in both groups	No side effects were identified with articaine except for the prolonged soft tissue anesthetic that lasted for up to 2–4 hours, 6 (20%) patients suffered soft tissue injuries	Postoperative complications:Pain-2 patients (2%), Soft tissue injuries -3 patients (3%), Need for re-anesthesia -6 patients (6%)	No complications or side effects were 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	While the findings suggest a higher proportion of LA success with BI using articaine than lidocaine, the difference was not statistically significant and neither agent can be recommended for routine clinical use via BI in restoring posterior mandibular teeth among children. The findings of no difference in the report of pain from LA administration with IANB and BI while producing a significantly higher success with IANB suggests that continued use of IANB for restorative treatment in mandibular posterior teeth among children, using either lidocaine or articaine, is clinically acceptable.	1. Buccal infiltration with 4% articaine was found to be equally efficacious to IANB with 2% lidocaine for extraction of primary mandibular molars in terms of pain perception and behavior observed 2. Pain perceived in the form of cry during injection was seen to be statistically lower in buccal infiltration with 4% articaine as compared to IANB with 2% lidocaine 3. No major adverse events were reported in both the groups at 24 h follow-up phone call. Therefore, buccal infiltration using 4% articaine can be considered as an alternative to 2% lidocaine IANB for primary mandibular molar extraction procedures. Further clinical trials with more sample size are recommended	With the growing use of novel delivery systems like single tooth analgesia, a buccal infiltration with articaine offers a viable alternative with minimal discomfort, allowing practitioners to avoid using IANB in children.8 To ensure the safety of children, more studies with a larger sample size are recommended.	4% articaine administered in the form of infiltration analgesia can offer profound anesthesia, as 2% lidocaine does when administered using IANB among pediatric dental patients. Thus, articaine infiltration can serve as a potential alternative to lidocaine nerve block because of better diffusion and higher potency than lidocaine.	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.

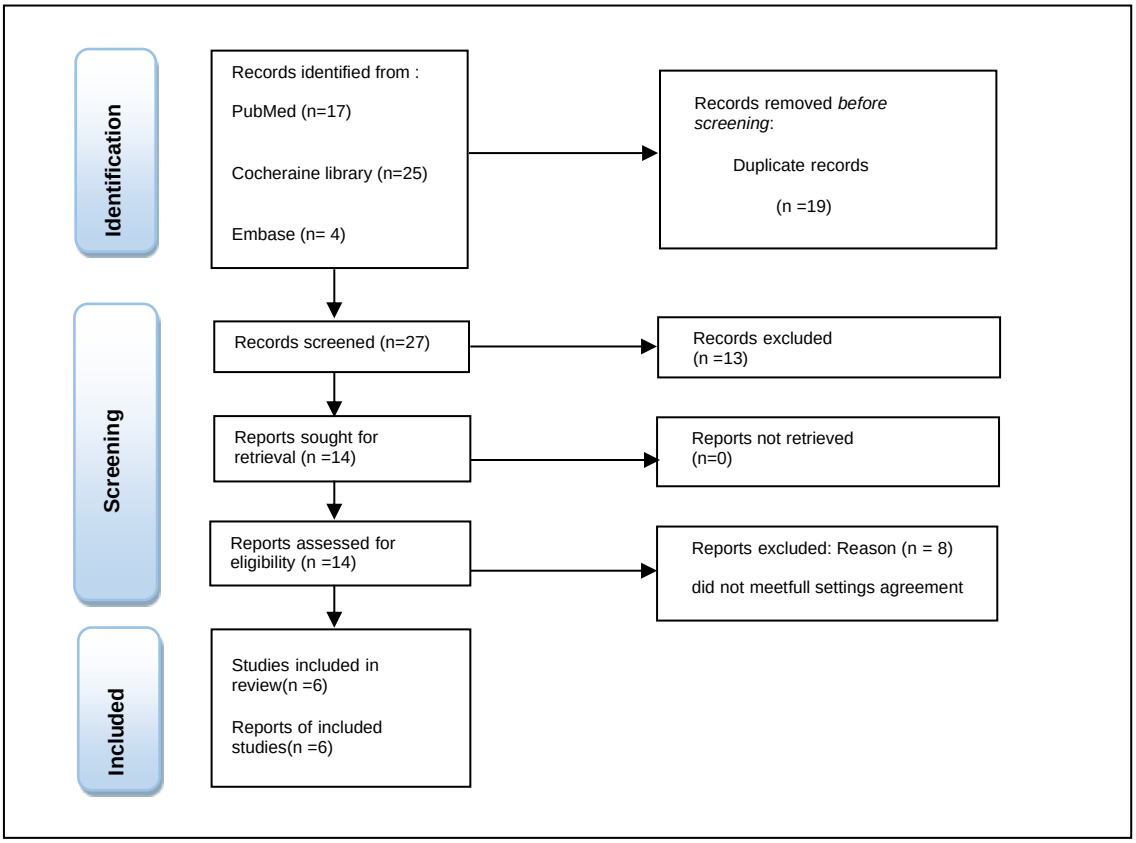

Fig. 1. PRISMA flow protocol representative of the research and literature review process for the selection of studies to be included in the sample of the systematic review.

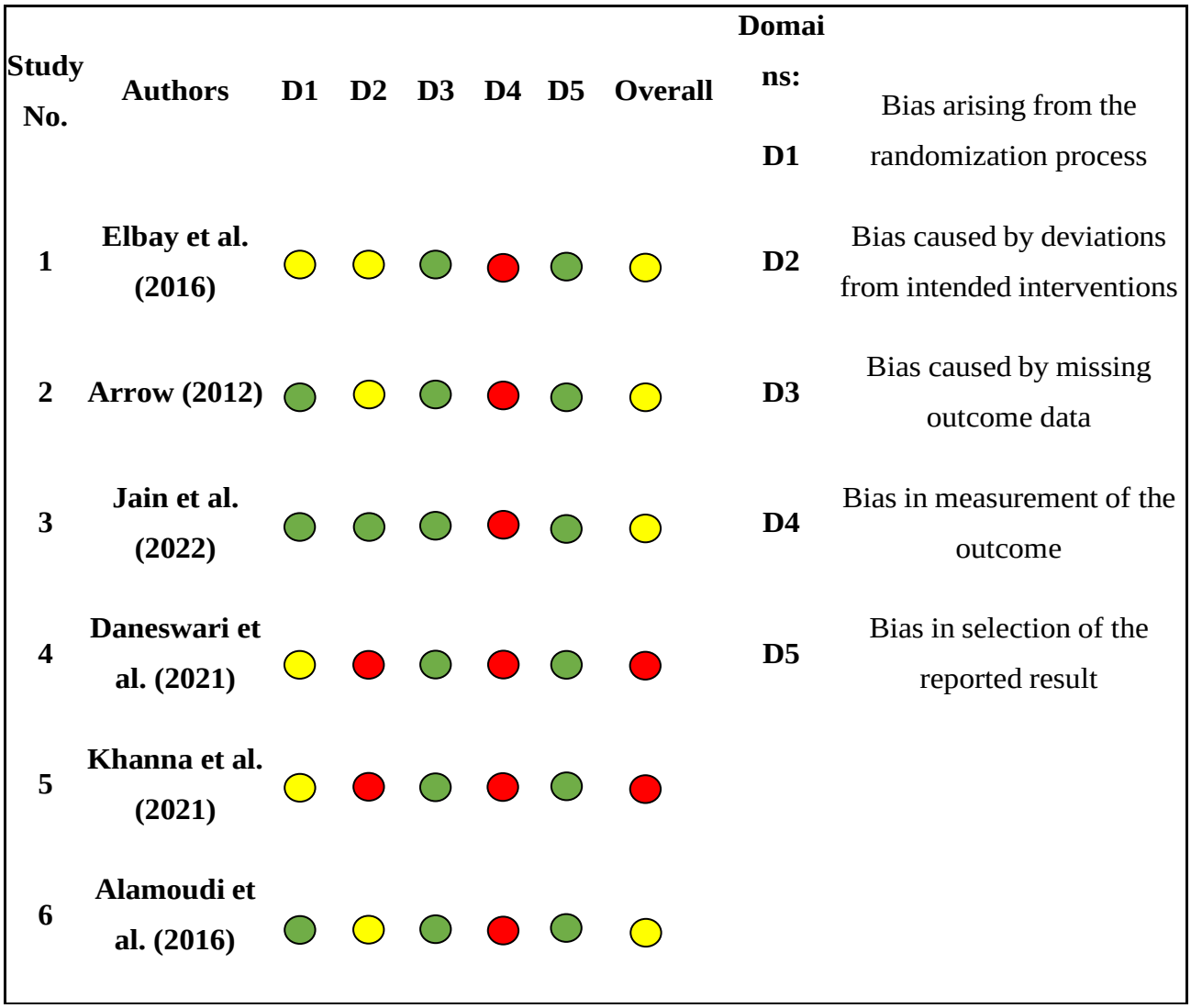

Fig. 2. Risk assessment of included trials (n=6)

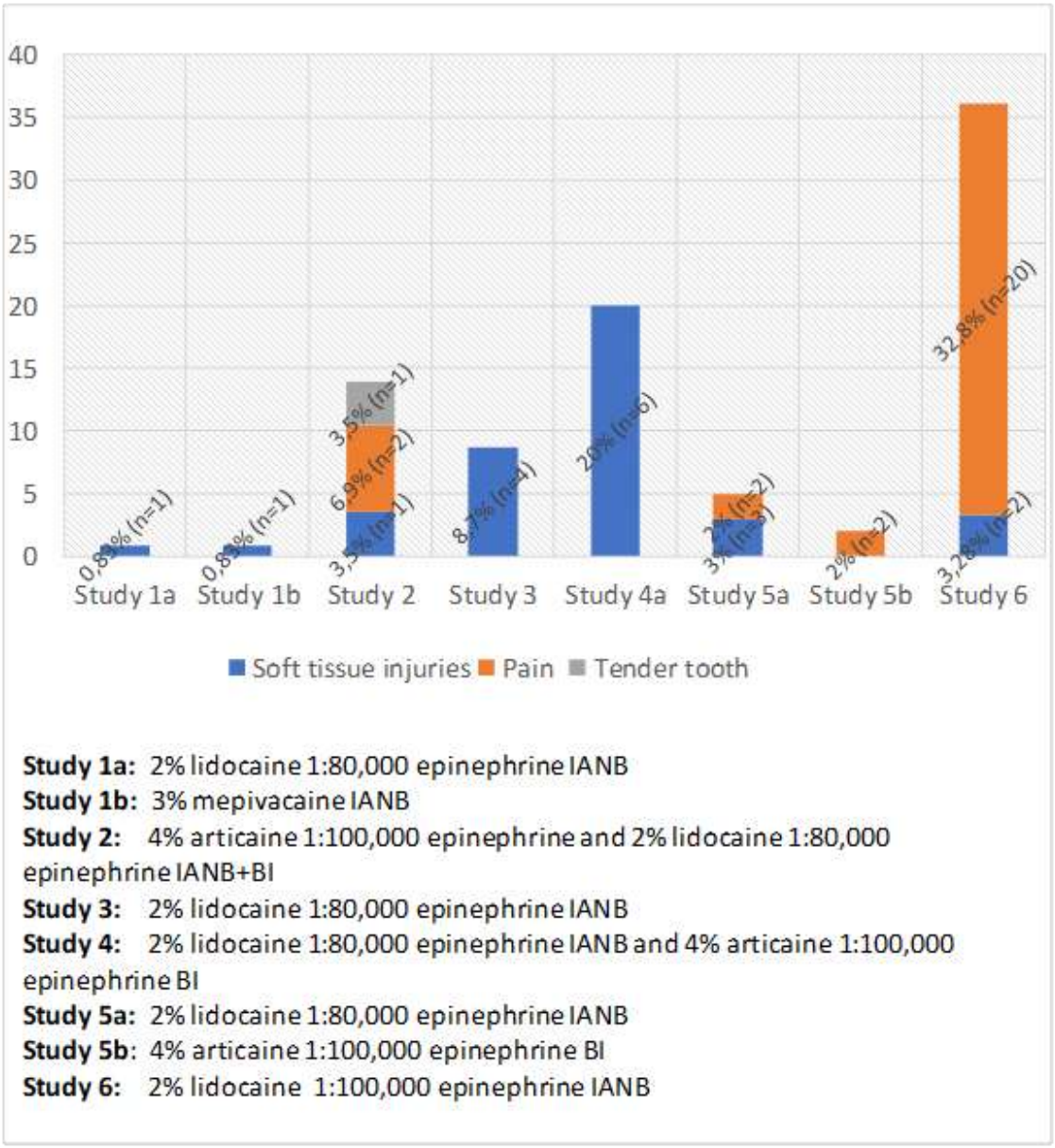

Fig. 3. Studies reporting complications

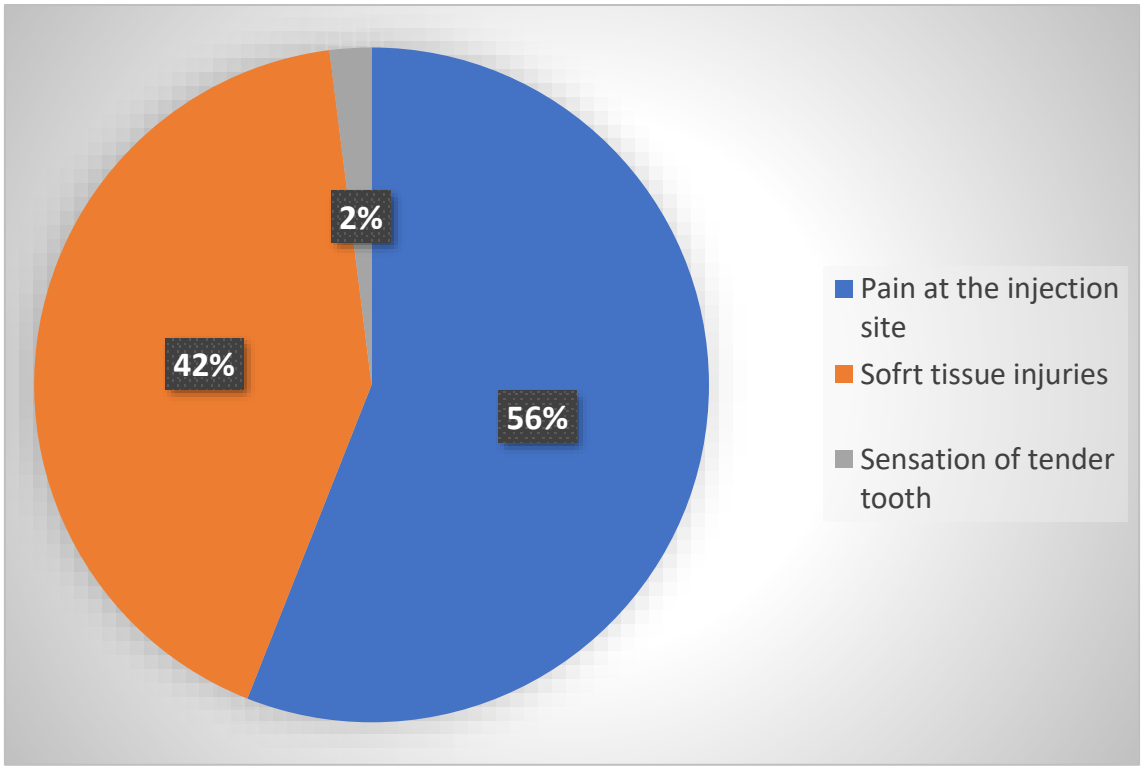

Fig. 4. Complications distribution.