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The effect of articaine and lidocaine on pain perception and behavior when used among pediatric patients: systematic review

BOSTON UNIVERSITY

HENRY M. GOLDMAN SCHOOL OF DENTAL MEDICINE

THESIS

THE EFFECT OF ARTICAINE AND LIDOCAINE ON PAIN PERCEPTION AND BEHAVIOR WHEN USED AMONG PEDIATRIC PATIENTS: SYSTEMATIC REVIEW

by

NOOR MOHAMAD SALEEM AL SHALTONI

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Approved by:

First Reader

Jayapriyaa Shanmugham, BDS, MPH, DrPH, CAGS DPH
Director of Research and Clinical Associate Professor
Department of Pediatric Dentistry

Second Reader

Dolrudee Jumlongras, DDS
Clinical Associate Professor
Department of Pediatric Dentistry

Third Reader

Patricia Castillo, DMD
Clinical Instructor
Department of Pediatric Dentistry

DEDICATION

To my parents, Mohamad and Taghreed, who always been a constant source of inspiration. Thank you for believing in me and encouraging me to chase my dreams.

To my siblings, who have patiently and lovingly supported me through this journey, thank you.

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NOOR MOHAMAD SALEEM AL SHALTONI

Boston University, Henry M. Goldman School of Dental Medicine, 2024

Major Professor: Jayapriyaa Shanmugham, BDS, MPH, DrPH
Director of Research and Clinical Associate Professor
Department of Pediatric Dentistry

ABSTRACT

Systematic reviews comparing the anesthetic efficacy of articaine and lidocaine for dental procedures in pediatric patients have been previously published in 2018 and 2020. However, none of them compared the effect of articaine and lidocaine on pain perception and child’s behavior during dental treatment. Moreover, several new randomized clinical trials (RCTs) have been published recently. Hence, the goal of this project was to conduct an updated systematic review to evaluate the evidence available on the effects of articaine on pain perception and behavior when used as a single buccal infiltration in maxilla or mandible among children.

The search strategy was formulated according to the PICO methodology following the guidelines outlined by the PRISMA and Cochrane Handbook for Systematic Reviews of Intervention studies. RCTs published between the years 2000 –

2022 were searched in electronic databases, such as PubMed, Cochrane CENTRAL Register of Controlled Trials, EMBASE, and Web of Science. Initial search revealed 20819 articles, from which 270 articles were screened for inclusion. Finally, 24 articles were eligible to be included in this review. Results from self-reported pain perception and behavior scales following different dental procedures in pediatric patients were evaluated among the selected studies.

Although there was a clear variability in the statistical significance of the results, it was evident that articaine is useful in better management of pediatric patients during dental procedures.

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LIST OF ABBREVIATIONS

BI ……………………………………………………………………Buccal Infiltration

CHEOPS ………………………………Children's Hospital of Eastern Ontario Pain Scale

FPS-R …………………………………………………………Faces Pain Scale – Revised

FLACC ………………………………………..Face, Legs, Activity, Cry, Consolability

FIS …………………………………………………………………..Facial Image Score

FBRS ………………………………………………………Frankl Behavior Rating Scale

HP-VAS …………………………………………...Heft Parker-Visual Analog Scale

IANB ………………………………………………………Inferior Alveolar Nerve Block

LA ……………………………………………………………………..Local Anesthesia

MBPS ………………………………………………………Modified Behavior Pain Scale

MeSH ……………………………………………………..Medical Subject Headings

PPPM ………………………………………………..Parents' Postoperative Pain Measure

PRISMA …………Preferred Reporting Items for Systematic Reviews and Meta-analyses

PICO ……………………………………Population, Intervention, Comparison, Outcome

RCTs …………………………………………………..... Randomized Controlled Trials

SEM ……………………………………………………………………Sound, Eye, Motor

VAS ………………………………………………………………. Visual Analog Scale

WBFPS ………………………………………………. Wong Baker FACES Pain Scale

INTRODUCTION

Pain is considered an unpleasant sensory and emotional experience associated with actual or potential tissue damage. [1] For pediatric patients, apprehension and anxiety can be brought on by many factors, including local anesthesia injection, which often may be necessary during a dental visit. An unpleasant treatment experience can negatively influence the child’s behavior toward subsequent dental treatments. [2] Less traumatic techniques in achieving local anesthesia among children would be helpful while treating them, such as computer-controlled local anesthetic delivery, periodontal injection techniques, needleless systems and intra-septal or intra-pulpal injections. [3] Therefore, understanding which local anesthetics can lower pain perception and improve children's behavior is essential.

Lidocaine remains the gold standard local anesthetic agent of choice in dental practices. [3] However, with the introduction of articaine in 1976, it became more prevalent in pediatric dental offices. [4] Articaine is a short-acting amide local anesthetic that contains an ester group in its structure, resulting in quicker metabolism and faster onset of action. [5] Moreover, articaine has a higher lipid solubility and diffusion into the nerve cell membranes, providing effective pulpal and palatal anesthesia with a single buccal infiltration. [3]

The efficacy of articaine and lidocaine in pediatric patients has been studied recently through several randomized clinical trials. They compared the two agents in different dental procedures, such as restorative treatments, pulp therapy or extraction, and using several administration techniques, for instance single buccal infiltration, combined buccal and palatal infiltration and inferior alveolar nerve block (IANB). Palatal injections and IANB are known to be the most painful injections. It has been shown that a single buccal infiltration with 4% articaine solution caused a significant difference in anesthetic solution concentration in the palatal bone and mucosal tissues, implying that articaine was successfully able to spread to the palatal region without actual palatal injection. (6) Likewise, articaine infiltration technique can be used as an alternative to IANB for the extraction (7) and restorative treatments (8) of primary mandibular molars. Therefore, achieving palatal anesthesia without injecting directly into palatal tissue and using buccal infiltration rather than IANB gives a significant advantage over lidocaine, as it reduces the number of necessary injections for pediatric patients, thus reducing anxiety. (9) The results of these studies concluded that articaine provided better pain control in pediatric patients. (3)

Systematic reviews comparing the anesthetic efficacy of articaine and lidocaine for dental procedures in pediatric patients have been previously published in 2018 and 2020. (3,10,11) However, none of them compared the effect of articaine and lidocaine on pain perception and child's behavior during dental treatment. Moreover, during an initial electronic database search that was conducted, it revealed that since the publication of the previous reviews, several new randomized clinical trials (RCTs) have been published and added to the literature. Hence, the goal of this project is to conduct an updated systematic review using the below hypothesis:

$\mathbf{H_0}$ = There is no difference in the effects of articaine and lidocaine local anesthetic agents on pain perception and behavior of pediatric patients.

$\mathbf{H_A}$ = There is a difference in the effects of articaine and lidocaine local anesthetic agents on pain perception and behavior of pediatric patients.

Aims and objectives:

- Conduct a comprehensive systematic review to evaluate the evidence available on the effects of articaine on pain perception and behavior when used as a single buccal infiltration on primary and permanent teeth whether on the maxillary or mandibular arches in pediatric patients from 0 to 15 years old.
- Assess the differences in the onset of action, duration of action and adverse events associated with articaine and lidocaine in pediatric patients.

LITERATURE REVIEW

Local anesthesia

Definition:

Local anesthesia is the numbness of a small area of the body temporarily as a result of the administration of special drugs called local anesthetics. Local anesthetics have been used in dentistry since the 19th Century. They have been applied to reduce and eliminate pain associated with various dental procedures. (12) Onset of action, duration of action and the potency of the local anesthetic agent depend on specific pharmacological properties. The pKa is defined as the pH at which the ionized and unionized forms of the drug exist in equal amounts and it affects the onset of action. Duration of action is affected by the agent's protein binding whereas the potency is dependent on lipid solubility. (13) Since 90% of the nerve cell membrane is comprised of lipid, increased lipid solubility of a drug results in a rapid diffusion into the nerve and inactivation of sodium channels. (14)

Mechanism of action (See Figure. 1)**:**

Once administered local anesthetic molecules bind to sodium channels on the nerve fibers leading to their inactivation reversibly. Sodium ions influx is required for the depolarization of nerve cell membranes and the propagation of impulses through the nerve. By inactivating the sodium channels, Local anesthetics are able to inhibit the action potentials in nerve fibers and blocking the transmission of pain impulses. (13) Subsequently, the loss of sensation in that area.

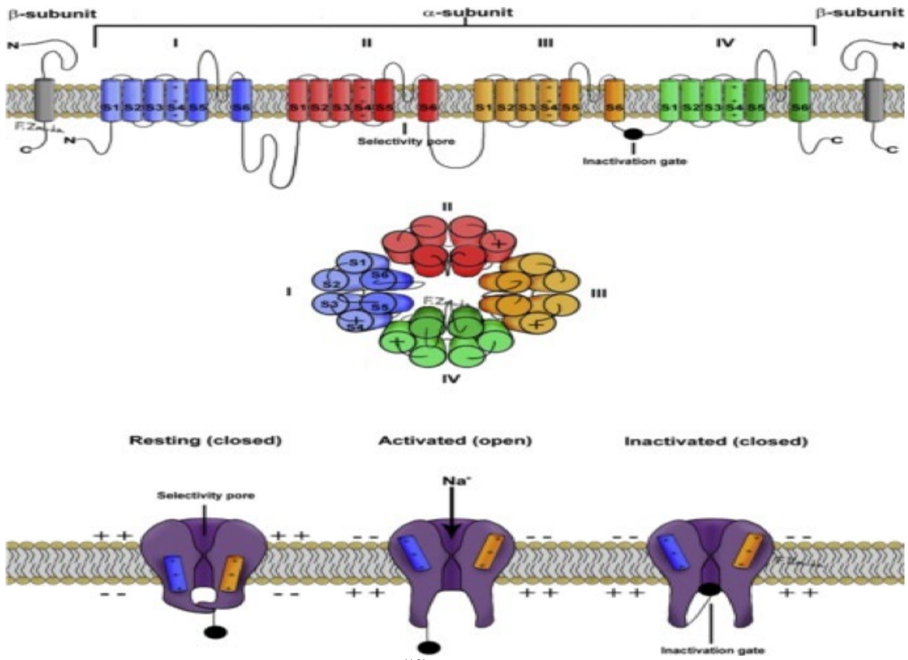

Figure 1: LA mechanism of action [13]

Classification:

Local anesthetics are composed of three parts: aromatic group which is lipophilic, intermediate chain and amine group which are hydrophilic. The aromatic ring provides lipid solubility to the local anesthetic agent. Lipid solubility affects the anesthetic diffusion in the nervous membrane which is related to the potency of the agent. [15]

Based on the link between the intermediate chain and the aromatic group, there are two main types of local anesthetics; amides and esters. Amides local anesthetics, such as lidocaine, mepivacaine and bupivacaine have an amide link, whereas esters local anesthetics, such as tetracaine and procaine have an ester link. Both classes differ in several aspects most prominently metabolism. Amides are metabolized in the liver where they undergo hydroxylation, amide hydrolysis and N-dealkylation. However, esters are metabolized rapidly in plasma by pseudocholinesterase to para-aminobenzoic acid (PABA). PABA is responsible for the allergic reactions that occurs with the esters local anesthetics. [13]

Lidocaine:

The Swedish pharmaceutical company "Astra" introduced lidocaine to the market in the year 1949 as the first non-ester local anesthetic (Figure. 2). [16] Lidocaine, also known as Xylocaine, is an amide local anesthetic that is considered the gold standard agent used in dentistry in both adult and pediatric patients. It has a rapid onset, moderate duration of action, high efficacy, reduced allergic reactions and minimal toxicity. [18] The average duration of action when using 2% lidocaine with epinephrine to administer maxillary infiltration is 60 min for pulp tissue and 170 min for soft tissue compared with 85 min for pulp tissue and 190 min for soft tissue in mandibular block. [19] Lidocaine has a half-life of 90 minutes. [20]

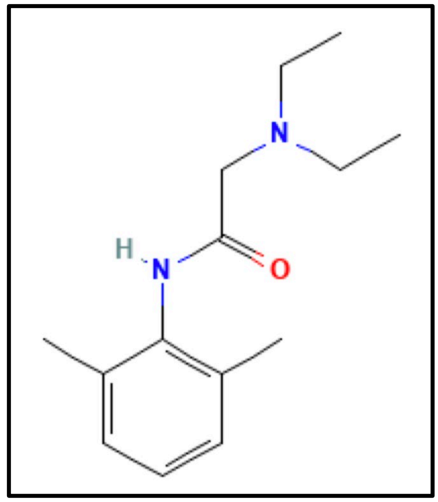

Figure 2: Lidocaine chemistry [17]

Articaine:

Articaine was formerly known as carticaine when it was first prepared by Rusching and his colleagues in 1969. Since its discovery it had progressively spread worldwide entering Canada in 1983, the United Kingdom in 1998 and Australia in 2005. [21] However, it was initially approved by the FDA in 2000 and being available in the United States in October 2010. [22] Articaine was the first, and is still the only, local anesthetic agent developed particularly to be used in dentistry. [21]

Articaine is categorized as an amide local anesthetic because of the link between its intermediate chain and the aromatic group. All local anesthetic agents contain benzene as their aromatic ring, while articaine has a thiophene ring (Figure. 3). The thiophene ring contains an ester side chain rendering articaine having both amides and esters properties. It significantly increases articaine's lipid solubility and diffusion into tissues. [24] Moreover, the ester side chain is metabolized in the plasma quickly via pseudocholinesterase. Therefore, articaine has a short half-life that ranges from 20 to 40 minutes that reduces the risk of systemic toxicity. This is beneficial if multiple injections are required. [20]

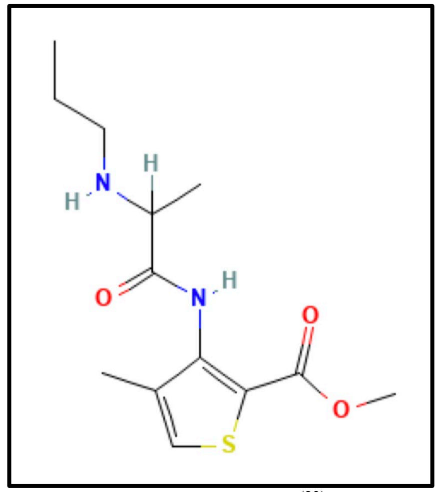

Figure 3: Articaine chemistry [23]

It has been reported that Articaine has a faster time of onset in children as compared to adults. [25] Following a nerve block with articaine, the mean time of anesthesia onset is 168 ± 131 seconds in children, whereas 170 ± 131 seconds in adults. Moreover, the mean onset time in infiltration is 85 ± 60 seconds in children, but 119 ± 84 seconds in adults. [26]

Local anesthesia in pediatric patients:

Pain has been defined by The International Association for the Study of Pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". It is clearly a dynamic and subjective experience that alerts children about possible threats and encourages avoidance, to protect themselves from whichever additional injury. Children are usually able to learn effective methods to deal with everyday pain.

However, untreated negative experiences may have a significant physiological and psychological impact. [27] Most commonly dental visits are a fearful event in a child's life. To gain a child's cooperation during a dental treatment, pediatric dentists are required to establish a trustful relationship with their pediatric patients. It has been shown in the literature that children's level of fear before or during any dental treatment increases their pain perception. Consequently, leading to nervousness, anxiety, and apprehension for any upcoming treatments. [28] Expectedly, children's strongest fear is associated with injections. [27]

To control the pain associated with dental procedures as a result of local anesthesia, there are several factors to be considered. For instance, type of the local anesthetic agent used, accuracy of the injection, pH of the tissues injected, bone density at the site of the injection, nerve anatomy as well as the patient's stress level. [29] The administration of local anesthesia in pediatric patients is a major challenge.

Behavior management is an essential tool to ensure a successful dental visit for a child. There is a constant exploration to come up with different ways to avoid the painful event of the injection and to change that feeling into a more pleasant one. There are different pharmacological and non-pharmacological methods described to allow for a better management of pediatric patients' behavior in any dental setting. The non-pharmacological methods are widely preferred to be used in pediatric patients and the include Tell Show Do, desensitization, and hypnosis. [30] Moreover, pre-cooling of the injection site, the use computerized delivery systems, applying pressure during injection, and distraction are becoming more popular to reduce pain and discomfort of pediatric patients during local anesthesia injection. [31]

Inferior alveolar nerve block (IANB) and palatal injections are known to be least favorable to children and the most painful. Failure to achieve a profound pulpal anesthesia with IANB has been reported to be around 10%, which demands the use of additional intra-pulpal injection. [32] Moreover, Palatal injections are extremely painful due to the tight binding of the palatal mucosa to its underlying periosteum and its copious nervous supply. [33] The evidence available shows that multiple injections in pediatric patients can be a serious source of anxiety and consequently a negative behavior of the child. [32] Therefore, it has been shown through several randomized clinical trials that articaine would provide an advantage over lidocaine via eliminating the need for palatal injection. Moreover, articaine has 1.5 times anesthetic potency than that of lidocaine. [34]

After dental treatment, children still feel numbness of the lips, tongue, and soft tissues. Self-induced lesions of lips, tongue, cheek and soft tissues may occur due to this loss of sensation. [35]

Pain perception scales:

There are three acceptable approaches established to assess pain in infants and children, and they are self-report scales, observational or behavioral scales and physiologic parameters, such as blood pressure and heart rate. [36]

However, due to the subjective nature of the self-report scales and the fact that they are strongly influenced by the level of cognitive development of the pediatric patient, pain evaluation in children is very challenging. [37] Nonetheless, younger children pain evaluation is chiefly based on the observation of their behavior. [38] Therefore, multidimensional observational scales have been developed to assess and quantify pain intensity in infants and children who are unable to understand and provide self-report. There are over then 40 scales reported in the literature. [39]

Using a valid and reliable pain assessment tool to accurately assess pain in pediatric dentistry is crucial to adequately manage pain which is the key for a successful treatment. [27] Based on the scale used, the prevalence of dental fear and anxiety in children and adolescents has been assessed to be between 10% and 30% respectively. [37]

Pain perception assessment in pediatric patients during the administration of local anesthesia depends significantly on the assessing person and the treated child. Thus, caution should be taken when interpreting the patient's pain perception by dental practitioners and researchers. [37]

Types of scales:

- **Subjective (self-report) Scales:**

1) Wong-Baker FACES Pain Scale (WBFPS):

The Wong-Baker Faces Pain Scale uses illustrations of different facial expressions demonstrating a range of pain intensity. [40] It has been comprehensively studied and confirmed to be reliable and valid in children aged 3 to 18 years. [41]

WBFS is composed of six faces given a score from 0 to 5, with 0 being no pain and 5 is the most painful. There is a short verbal description for each face that ranges from "no hurt" to "hurts worst" (Figure. 4). It a self-assessment tool which is not intended to be used by a third person to assess the patient's pain. Also, patients should get well familiarized to the scale to be able to choose the figure that best demonstrates the physical pain they are going through. (42)

Figure 4: Wong-Baker FACES Pain Scale (WBFPS) (42)

2) Faces Pain Scale - Revised (FPS-R):

The Faces Pain Scale - Revised is a self-report tool used to assess the pain intensity in children older than 4 years old. FPS-R was adjusted from the Faces Pain Scale to be able to score pain perception in a 0 to 10 metric (Figure. 5). (43) Unlike WBFPS, The Faces Pain Scale - Revised has a neutral face without smiles and tears to represent pain. (40)

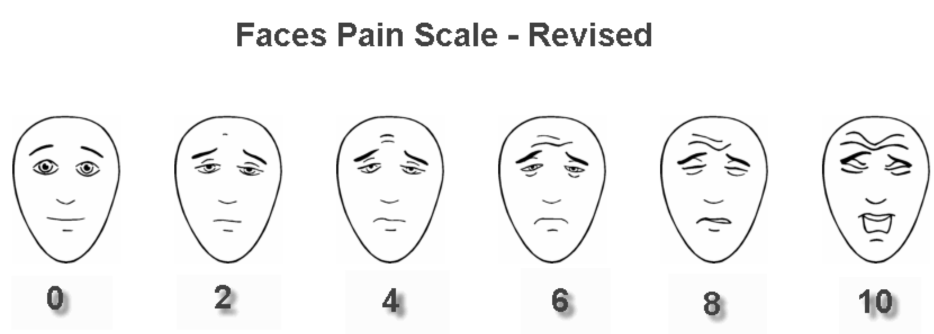

Figure 5: Faces Pain Scale - Revised (FPS-R) (43)

3) The Visual Analog Scale (VAS):

The Visual Analog Scale is a common measure used to quantify pain severity. It can be used as a self-report or as an observational tool. It consists of a 100 mm scale from 0 to 10, with 0 represents "no pain" and 10 represents "worst pain" (Figure. 6). When compared to other scales, VAS is more sensitive and easier to use. It has been validated for the use in adults and children over the age of 8 years. (44)

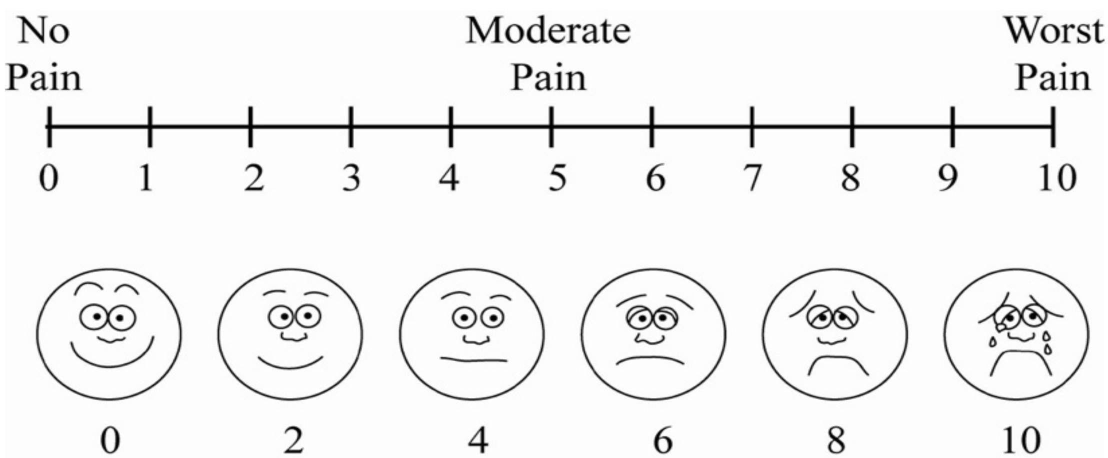

Figure 6: The Visual Analog Scale (VAS) (44)

4) Heft-Parker Visual Analog Score (HP-VAS):

The Heft-Parker Visual Analog Score is similar to the VAS, except that it is a 170 mm score consisting of several descriptions that help in the interpretation of the data (Figure. 7). (45)

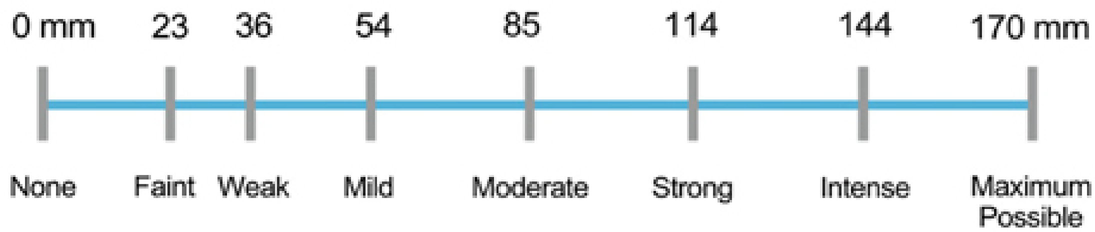

Figure 7: Heft-Parker Visual Analog Score (HP-VAS) [45]

5) Facial Image Score (FIS):

The Facial Image Score is a valid scale to measure dental anxiety in young children in different clinical settings. [46] It contains a row of five faces numbered from 5 to 1 and symbolizing a range from “very unhappy” to “very happy” (Figure. 8). [47]

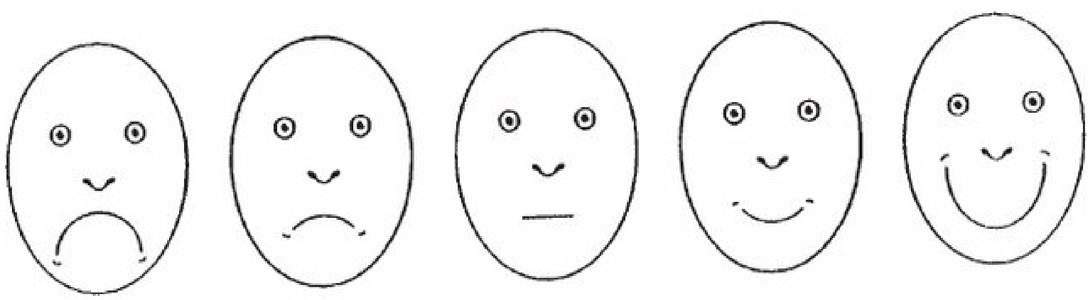

Figure 8: Facial Image Score (FIS) [47]

6) Parents’ post-operative pain measure (PPPM):

The Parents’ Postoperative Pain Measure is a scale used to assess children's postoperative pain at home. It consists of 15 items behavioral checklist based on non-verbal pain signs children show following surgery, such as complaining more than usual or holding the sore part of their body. [48]

- **Behavioral scales:**

1) Face, Legs, Activity, Cry, Consolability (FLACC):

Face, Legs, Activity, Cry, Consolability scale is categorized into five groups. Each category is given a score from 0 to 2. After that, summing up all the categories would give a score that ranges from 0 to 10 (Figure. 9). It has been proved in the literature that FLACC scale has good inter-examiner reliability and is a valid measure to assess pain in infants and children up to 7 years of age. [38]

The FLACC scale

	Scoring		
Categories	*0*	*1*	*2*
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

Each of the five categories (F) Face, (L) Legs, (A) Activity, (C) Cry, (C) Consolability is scored from 0 to 2, which results in a total score between 0 and 10. Printed with permission © 2002, The Regents of the University of Michigan.

Figure 9: Face, Legs, Activity, Cry, Consolability (FLACC) [38]

2) Children's Hospital of Eastern Ontario Pain Scale (CHEOPS):

The CHEOPS is a reliable behavioral and observational scale. It is used to evaluate postoperative pain in children. It consists of six behavioral components which provide a score that ranges from 4 to 13. This scale is scored in time intervals. The child's behavior is observed for 5 seconds followed by 25 seconds for recording the score (Figure. 10). CHEOPS is an effective tool to monitor the efficiency of interventions that aim to reduce pain and discomfort. [49]

Item	Behaviour	Score
Cry	No cry	1
	Moaning	2
	Crying	2
	Screaming	3
Facial expression	Composed	1
	Grimace	2
	Smiling	0
Verbal	None	1
	Other complaints	1
	Pain complaints	2
	Both complaints	2
	Positive	0
Torso	Neutral	1
	Shifting	2
	Tense	2
	Shivering	2
	Upright	2
	Restrained	2
Touch	Not touching	1
	Reach	2
	Touch	2
	Grab	2
	Restrained	2
Legs	Neutral	1
	Squirming/kicking	2
	Drawn up/tensed	2
	Standing	2
	Restrained	2

Figure 10: Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) [50]

3) Modified Behavior Pain Scale (MBPS):

The Modified Behavioral Pain Scale (MBPS) by Taddio and her colleagues is a modified version of the Children's Hospital Eastern Ontario Pain Scale (CHEOPS). It was developed to provide a clinically appropriate pain severity measurement for infants.

Modified Behavioral Pain Scale (MBPS)

Observed behavior	Score (0–10)	Operational definitions
Facial expression		
Definite positive expression	0	smiling
Neutral expression	1	
Slightly negative expression: for example, grimace	2	brow bulge, naso-labial furrow
Definite negative expression: that is, furrowed brows, eyes closed tightly	3	brow bulge, naso-labial furrow, eyes closed tight, open lips; with or without reddened face
Cry		
Laughing or giggling	0	
Not crying	1	
Moaning, quiet vocalizing, gentle or whimpering cry	2	
Full lunged cry or sobbing	3	
Full lunged cry, more than baseline cry	4	to be scored only if infant crying during baseline
Movements		
Usual movements/activity, or resting/relaxed	0	
Partial movement or attempt to avoid pain by withdrawing the limb where puncture is done	2	squirming, arching, limb tensing/clenching
Agitation with complex movements involving the head, torso, or the other limbs, or rigidity	3	generalized limb and/or body movements, or rigidity

Figure 11: Modified Behavior Pain Scale (MBPS) [51]

The MBPS includes 3 suggestive behaviors of pain in infants which are facial expression, cry and body movements. The role of facial expression for pain evaluation is well supported in the literature. Likewise, latency to cry and cry duration are considered indicators of pain in infants and young children. Moreover, these cry characteristics are featured in various observational scales. Lastly, certain body movement patterns have been linked to painful stimuli in infants and children. Each of the 3 behaviors included in the MBPS is evaluated and scored independently, then added collectively to create a pain intensity score that ranges from 0 to 10 (Figure. 11). [39]

4) Sound, Eye, Motor Scale (SEM):

The Sound, Eye, Motor Scale is an observational assessment tool measuring the intensity of pain perception in patients. It evaluates the child’s body reaction in response to pain. It records any verbal expressions of discomfort and the reactions of the patient’s eyes and body movements (Figure. 12). [52]

Parameter	*Comfort 1*	*Mild discomfort 2*	*Moderate discomfort 3*	*Severe discomfort 4*
Sound	No sound	Non-specific sound	Verbal complaint, louder sound	Verbal complaint, shouting, crying
Eye	No sign	Dilated eyes without tears (anxiety sign)	Tears, sudden eye movements	Crying, tears covering the face
Motor	Relaxed body and hand status	Muscular contraction, contraction of hands	Sudden body and hand movements	Hand movement for defence, turning the head to opposite side

Figure 12: Sound, Eye, Motor Scale (SEM) [52]

5) Frankl Behavior Rating Scale (FBRS):

Frankl Behavior Rating Scale was created in 1962. It is one of the most commonly used behavior assessment scales in pediatric dental research and in daily clinical practice. It is a reliable tool for behavior rating of children in dental setting. FBRS consists of four behavior categories based on the child's attitude during dental treatment (Figure. 13). The categories range from definitely positive to definitely negative. Dental professionals can apply this scale any time during treatment. [36]

Rating	Attitude	Definition
1 (--)	Definitely negative	Refusal of treatment, crying forcefully, fearful or any other overt evidence of extreme negativism.
2 (-)	Negative	Reluctant to accept treatment, uncooperative, some evidence of negative attitude but not pronounced, i.e. sullen, withdrawn.
3 (+)	Positive	Acceptance of treatment; at times curious, willingness to comply with the dentist, at times with reservation but patient follows the dentist's directions cooperatively.
4 (++)	Definitely positive	Good rapport with the dentist, interested in the dental procedures, laughing and enjoying the situation.

Figure 6: Frankl Behavior Rating Scale (FBRS) [53]

As mentioned, pain can be assessed subjectively that could be influenced by several factors, for instance, age of the child, gender, anxiety status, presence of prior pain, and past dental experiences. [54] Therefore, a comprehensive assessment is required to evaluate pain perceived among children during dental procedures.

METHODOLOGY

To conduct this systematic review the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [55] and Cochrane Handbook for Systematic Reviews of Intervention studies were followed. Only a qualitative data analysis was carried out.

The search strategy was formulated according to the PICO methodology (Population, Intervention, Comparison or Control and Outcome) to emphasize the following research question "How would single buccal infiltration of articaine versus lidocaine maxillary buccal/palatal infiltrations or mandibular IANB affect pain perception and behavior in children during dental procedures?". (See Table. 1)

Table 1: PICO Question

How would single buccal infiltration of articaine versus lidocaine maxillary buccal/palatal infiltrations or mandibular IANB affect pain perception and behavior in children during dental procedures?	
Population	**Children** aged 0 - 18 years, undergoing dental procedures that require the **administration of local anesthesia**.
Intervention	2% or 4% **Articaine** Buccal infiltration to **Maxillary/ Mandibular** arch.
Comparison	2% **Lidocaine Buccal/Palatal infiltrations** to Maxillary arch or **IANB** to Mandibular arch.
Outcome	Primary outcome: Child's **pain perception and behavior** during dental procedures. Secondary outcomes: **Onset** of action, **duration** of action and **adverse effects**.

Inclusion criteria:

To include an article in the review, it had to follow certain inclusion criteria:

- The study design included in the review was clinical trials involving human subjects. There were no restrictions on the type of the clinical trial.
- Clinical trials conducted between the year 2000 and 2022.
- Articles that were in English language and in full texts.
- The population of the study was pediatric patients (age 0 – 18 years) undergoing any dental procedure that requires the use of local anesthesia.
- Studies that included different dental treatments such as, restorative treatment, pulp therapy or extractions done on either of the arches, maxilla, mandible or both.
- Studies that compared the anesthetic effect of articaine as a single injection versus lidocaine using different types of anesthesia techniques (buccal infiltration or inferior alveolar nerve block).
- Studies that assessed the anesthetic efficacy using subjective or objective evaluation of pain. Assessment by pain perception scales, behavior scales and hemodynamic parameters.

Exclusion criteria:

- Any study type other than clinical trials. For instance, case reports, case series, systematic reviews, in vitro studies and letters to the editor.
- Clinical trials done on adults.

- Studies conducted on cadavers or animals.
- Trials comparing articaine to other anesthetic agents than lidocaine.
- Trials out of the assigned interval 2000 – 2022.

Search strategy:

To identify the included studies, electronic databases were searched thoroughly using specific keywords (See Appendix. 1) related to the PICO question and Medical Subject Headings (MeSH) terms coupled with Boolean operators (OR, AND). A comprehensive and frequent search for new publications was conducted up to June 29th, 2022. Databases used were PubMed, Cochrane CENTRAL Register of Controlled Trials, EMBASE and web of science. Manual searching of the references of the included studies and previous systematic reviews was performed. Full search strategy for each database is described in Appendix. 1. The results from each database were imported into "Zotero" software, for initial screening.

Data collection and analysis:

- **Selection of studies:**

After the removal of duplicate articles, one review author screened all titles and abstracts of publications to assess their eligibility. Any publication that clearly did not meet the inclusion criteria was excluded at this stage. Full-text articles of potentially relevant studies were retrieved. Each full-text study was assessed in depth and analyzed according to the established inclusion and exclusion criteria.

- **Data extraction:**

One review author independently extracted the following data from the included articles: title of the article, author, publication year, location of the study, journal of publication, sample size, age range, gender, study design, randomization, blinding, intervention, comparison, presence of control group, time frame and visits, teeth included and the procedure done, waiting time prior to the initiation of the treatment, outcome variable, outcome measurements and scales, findings. The data were analyzed and recorded using Excel spreadsheet.

- **Assessments of the risk of bias:**

The Cochrane Collaboration tool for randomized controlled trials was used to assess the risk of bias in the included studies. It is a domain-based evaluation to critically assess each study. The risk of bias assessment was conducted based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Other bias domain was considered "high risk" if the study was not blinded, as risk of outcome ascertainment bias or assessment bias are higher.

After reviewing the article, each domain was evaluated to be "high", "unclear" or "low" risk of bias. If one or more domains were assessed as high risk, the overall risk of bias of that study would be high. Likewise, if all the 7 domains were assessed as low risk, the overall risk of bias of that study would be low. Furthermore, if one or more domains were assessed as unclear risk, the study was considered to be of a moderate risk. Risk of bias summary and graph were formulated using RevMan 5.4 software.

- **Outcome measurements and scales:**

The primary outcome measure studied in this systematic review was pediatric patients' pain perception and behavior scores reported through self-report scales or observational scales. Any validated subjective or objective pain scale used in a trial was satisfactory for inclusion into the review. Moreover, the physiological parameters recorded in the studies were analyzed. The outcomes were recorded to compare both local anesthetic agents' effect on the attitude of children during dental treatments.

In addition, we analyzed onset and duration of action of each local anesthetic agent and the adverse events associated with their administration in pediatric patients as the secondary outcome measures.

RESULTS

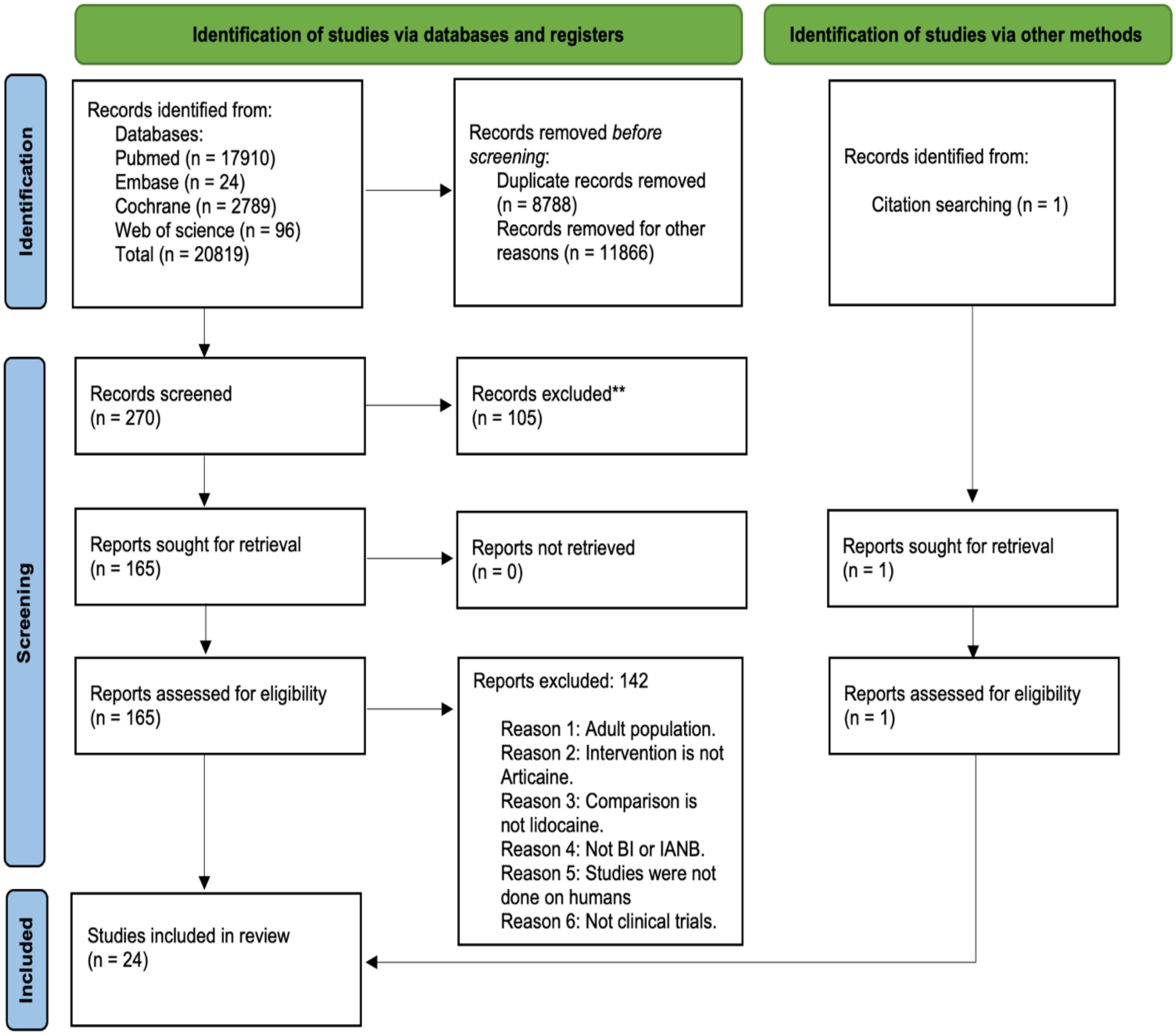

Figure 74: PRISMA Flow chart describing the process of identifying the included studies

Literature search:

The search strategy initially yielded a total of 20,819 articles from all databases. After the removal of duplicates and unrelated articles to this study, a total of 270 articles were extracted and screened for inclusion in the review. Of the 270 articles, 105 were excluded as articaine and lidocaine were studied in the medical field rather than in the dental field, and 165 articles were retrieved. Citation searching yielded an additional article, thus resulting in 166 articles. Finally, 142 articles were excluded due to the following reasons: the population studied was adults, intervention was not articaine, comparison was not lidocaine, anesthetic technique was not buccal Infiltration or inferior alveolar nerve block, studies were not done on humans and study type was not a clinical trial, resulting in 24 articles that were eligible for inclusion in this systematic review. The PRISMA flowchart summarizing the selection process is presented in Figure 14.

Characteristics of the included studies:

There was a total of 24 studies were included in the final review. The studies were categorized according to the arch treated during the trial; 5 studies were conducted on primary teeth in the maxillary arch (Zahra Bahrololoomi, et al.,[31] Manisha Nair, et al.,[9] Kolli, et al.,[56] Mittal, et al.,[57] Jaikaria, et al.[58]), 13 studies were conducted on primary teeth in the mandibular arch (Zahra Bahrololoomi, et al.,[7] Sara Ghadimi, et al.,[59] Velagala Daneswari, et al.,[60] Fatma AL Zahrani, et al.,[61] Jain, et al.,[62] Arali, et al.,[63] Alinejhad, et al.,[64] Chopra, et al.,[32] Afsal, et al.,[65] Daneshvar, et al.,[66] Hamid Elheeny,[67] Khanna, et al.,[68] Zhang, et al.[8]), 4 studies on primary teeth in both arches (Rathi, et al.,[69] Ram, et al.,[35] Massignan, et al.,[70] Malamed, et al.[26]) and 2 studies included permanent teeth in pediatric patients in mandibular arch (P Arrow, [71] Jorgenson, et al.[72]). See Table. 2, Table. 3, Table. 4 and Table. 5.

Table 2: Characteristics of the included studies (Maxilla):

Title	**Articaine use does not routinely eliminate the need for palatal injections for primary maxillary molar extractions: a randomized cross-over clinical trial.** [31]	**Comparing the efficiency of 2% lidocaine and 4% articaine as a local anesthetic agent in children.** [9]	**The Effectiveness of Articaine and Lidocaine Single Buccal Infiltration versus Conventional Buccal and Palatal Injection Using Lidocaine during Primary Maxillary Molar Extraction: A Randomized Control Trial.** [56]	**Comparison of Anesthetic Efficacy of Articaine and Lidocaine During Primary Maxillary Molar Extractions in Children.** [57]	**Comparative evaluation of the efficacy of 4% articaine and 2% lidocaine in children during the primary maxillary molar extractions.** [58]
Author	Zahra Bahrololoomi, et al.	Nair, et al.	Kolli, et al.	Mittal, et al.	Jaikaria, et al.
Publication Year	2021	2018	2017	2015	2017
Location	Iran	India	India	India	India
Journal	Oral and Maxillofacial Surgery	Asian Journal of Pharmaceutical and Clinical Research	Anesthesia Essays and Researches	Pediatric dentistry	Indian Journal of Oral Health and Research
Sample Size	30	45	90	102	102
Age Range	6 - 9 years	6 - 9 years	6 - 14 years	5 - 12 years	5 - 12 years
Gender	Females: 15. Males: 13.	Not Specified.	Females: 45. Males: 45.	Females: 68. Males: 36.	Females: 46. Males: 61.
Study Design	**Crossover design** randomized controlled trial.	Randomized clinical trial.	Randomized Control Trial.	Randomized clinical trial.	Randomized clinical trial.
Randomization	Yes.	Yes.	Yes.	Yes.	Yes.
Blinding	Double-blind.	Not Blinded.	Triple-blind.	Triple-blind.	Triple-blind.

Intervention	Single buccal infiltration of 4% articaine.	Group C: 4% articaine injected buccally.	Group B: 4% articaine injected buccally.	4% articaine was used for single buccal infiltration.	4% articaine was used for single buccal infiltration.
Comparison	Buccal and palatal injections of 2% lidocaine.	Group A: 2% lidocaine injected buccally and palatally. Group B: 2% lidocaine injected buccally.	Group A: 2% lidocaine injected buccally and palatally. Group C: 2% lidocaine injected buccally.	Buccal and palatal infiltrations using 2% lidocaine.	Buccal and palatal infiltrations using 2% lidocaine.
Presence of control group.	NO control group. The same patient served as the control and the intervention.	Yes	Yes	Yes	Yes
Time frame and visits	2 visits.	1 visit.	1 visit.	1 visit.	1 visit.
Teeth included / Procedure	Primary maxillary molars / Extraction	Primary maxillary molars / Extraction	Primary maxillary molars / Extraction	Primary maxillary molars / Extraction	Primary maxillary molars / Extraction
Waiting time	10 minutes.	10 minutes.	5 minutes.	5 minutes.	5 minutes.
Outcome Variable	Anesthesia depth.	Anesthetic efficacy was evaluated by the assessment of pain perception.	Assessment of pain perception.	Anesthetic effectiveness was evaluated by the assessment of pain perception.	Assessment of pain perception.

Outcome measurements and scales	1) Subjective assessment of pain: WBFPS. 2) Objective evaluation of pain: FLACC. 3) Physiological parameters: Blood pressure and pulse rate.	Subjective assessment of pain: VAS.	1) Physiological indicators: Pulse rate. 2) subjective evaluation: FPS-R. 3) objective evaluation: FLACC.	1) Subjective evaluation: WBFPS. 2) Objective evaluation: MBPS. 3) Physiological indicators: Heart rate and blood pressure.	1) Subjective evaluation: WBFPS. 2) Objective evaluation: FLACC. 3) Physiological indicators: Heart rate and blood pressure.

Findings	1) WBFPS: The mean values 2.36 in the lidocaine group and 1.43 in the articaine group. There was statistically significant difference. 2) FLACC: The mean values 1.18 in the lidocaine group and 1.39 in the articaine group. No statistically significant difference. 3) Pulse rate: No significant difference. - Before injection: * Lidocaine group: 89.50 ± 12.048. * Articaine group: 89.54 ± 10.330. - Post-extraction: * Lidocaine group: 99.93 ± 11.972. * Articaine group: 98.39 ± 11.458. 4) Blood Pressure: No statistically significant difference. - Before injection: * Lidocaine group: mean systolic 103.11 ± 14.642, mean diastolic	Articaine group had significantly lower pain scores when compared to the lidocaine group.	1) Heart rate: No statistically significant difference. 2) FPS-R and FLACC scores were higher in the lignocaine group, compared to the articaine group. It was a statistically significant difference.	1) FPS: The mean values were higher in the lidocaine group (1.88±1.688) than the articaine group (1.31±1.13), No statistically significant difference. 2) MBPS: different results depends on the part of the scale. 3) Heart rate: No statistically significant difference. * Lidocaine group: Stage 1: 94.23±14.64. Stage 2: 99.51±14.86. Stage 3: 105.92±14.322. * Articane group: Stage 1: 97.13±14.65. Stage 2: 100.64±13.11. Stage 3: 105.13±16.197. 4) Blood pressure: No statistically significant	3 min before injection (Stage 1), during injection (Stage 2), and 3 min after extraction (Stage 3) were recorded. 1) WBFPS: mean values in lidocaine group 2.200 ± 2.148. mean values in articaine group 1.400 ± 1.29. Not statistically significant. 2) FLACC: values among the groups were not statistically significant. 3) Heart rate and blood pressure: No statistically significant difference between the two group.

	71.86 ± 11.594. * Articaine group: mean systolic 101.46 ± 14.185, mean diastolic 68.14 ± 8.822. - Post-extraction: * Lidocaine group: mean systolic 115.86 ± 16.852, mean diastolic 78.86 ± 16.429. * Articaine group: mean systolic 111.82 ± 13.974, mean diastolic 76.32 ± 10.335.			difference. Mean Systolic: * Lidocaine group: Stage 1: 106.5±8.449. Stage 2: 107.06±8.120. Stage 3: 110.27±13.08. * Articane group: Stage 1: 108.29±7.910. Stage 2: 109.67±7.0157. Stage 3: 110.57±10.12. Mean Diastolic: * Lidocaine group: Stage 1: 65.08±6.967. Stage 2: 64.88± 5.731. Stage 3: 64.67 ± 6.94. * Articane group: Stage 1: 64.56±5.177. Stage 2: 64.52±4.128. Stage 3: 64.48±5.919.	

Table 3: Characteristics of the included studies (Mandible):

Title	**Anesthetic efficacy of single buccal infiltration of 4% articaine compared to routine inferior alveolar nerve block with 2% lidocaine during bilateral extraction of mandibular primary molars: a randomized controlled trial.** [7]	**Efficacy of articaine infiltration versus lidocaine inferior alveolar nerve block for pulpotomy in mandibular primary second molars: A randomized clinical trial.** [59]	**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.** [60]	**Anaesthetic efficacy of 4% articaine and 2% lidocaine for extraction and pulpotomy of mandibular primary molars: an equivalence parallel prospective randomized controlled trial.** [61]	**Comparative evaluation of anesthetic efficacy of 4% articaine infiltration versus 2% lignocaine inferior alveolar nerve block for extraction of primary mandibular molars: A prospective, split-mouth, randomized controlled trial.** [62]
Author	Zahra Bahrololoomi, et al.	Sara Ghadimi, et al.	Velagala Daneswari, et al.	Alzahrani, et al.	Jain, et al.
Publication Year	2021	2018	2021	2018	2022
Location	Iran	Iran	India	UK	India
Journal	Journal of Dental Anesthesia and Pain Medicine.	Journal of Dental Research, Dental Clinics, Dental Prospects.	International Journal of Clinical Pediatric Dentistry	International Journal of Pediatric Dentistry	Journal of Indian Society of Pedodontics and Preventive Dentistry
Sample Size	30	23	30	98	46
Age Range	6 - 9 years	5 - 8 years	4 - 8 years	5 - 9 years	5 - 10 years
Gender	Females: 12. Males: 16.	Females: 10. Males: 13.	Females: 17. Males: 13.	Females: 45. Males: 53.	Females: 17. Males: 29.

Study Design	**Crossover design** randomized controlled trial.	**Crossover design** randomized clinical trial	**Crossover design** randomized controlled trial.	Parallel prospective randomized controlled study.	**Split-mouth** randomized controlled trial.
Randomization	Yes.	Yes.	Yes.	Yes.	Yes.
Blinding	Single-blind.	Double-blind.	Not Blinded.	Single-blind.	Double-blind.
Intervention	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI	4% articaine BI with Intrapapillary infiltration.	4% articaine Buccal infiltration.
Comparison	2% lidocaine with 1:100,000 epinephrine IANB.	2% lidocaine with 1:80,000 epinephrine as IANB	2% Lidocaine with 1:80,000 epinephrine as IANB	2% Lidocaine IANB with long buccal.	2% Lidocaine IANB.
Presence of control group.	NO control group. The same patient served as the control and the intervention.	NO control group. The same patient served as the control and the intervention.	NO control group. The same patient served as the control and the intervention.	Yes	NO control group. The same patient served as the control and the intervention.
Time frame and visits	2 visits / 2 weeks apart.	2 visits / at least 1 week apart.	2 visits / 1 week apart.	1 visit.	2 visits / at least 1 week apart.

Teeth included / Procedure	Primary mandibular molars / Extraction	Primary mandibular molars / Pulpotomy	Primary mandibular second molar / Pulp therapy	Primary mandibular molars / Pulpotomy and Extraction	Primary mandibular molars / Extraction
Waiting time	1) 10 minutes after articaine infiltration. 2) 15 minutes after lidocaine block.	N/A	N/A	N/A	N/A
Outcome Variable	Anesthetic efficacy was evaluated by the assessment of pain perception.	Assessment of pain perception and behavior.	Assessment of pain perception.	Successful completion of the treatment determined by pain perception.	1) Anesthetic efficacy based on pain perception and behavior. 2) Adverse events.

Outcome measurements and scales	1) Subjective evaluation: WBFPS. 2) Objective evaluation: FLACC. 3) Physiologic parameters: blood pressure and pulse rate.	1) Assessment of pain during injection.: WBFPS: 2) Children's behavior during procedure: MBPS.	1) Evaluation of Pain on Injection: pain score is given by Ram and Peretz. 2) Evaluation of Pain during Pulp Extirpation: SEM scale. 3) Evaluation of Overall Experience of the Patient: HP-VAS.	1) Pain assessment: WBFRS and VAS. 2) Behavior assessment: FBRS.	1) Pain assessment: WBFRS. 2) Behavior assessment: MBPS and FBRS. 3) Adverse events: A phone call after 24 hours.

Findings	1) Blood pressure: No statistically significant difference. 2) Pulse rate: No statistically significant difference. 3) FLACC: No statistically significant difference. 4) WBFPS: No statistically significant difference.	1) WBFPS: No statistically significant difference. 2) MBPS: Patients' behavior during pulpotomy was significantly better in the articaine group	1) Evaluation of Pain on Injection: the pain-related behavior scores were higher for IANB when compared with infiltration. 2) Evaluation of Pain during Pulp Extirpation: SEM ratings for IANB were significantly higher than infiltration. 3) Evaluation of Overall Experience of the Patient: IANB group had higher scores than the articaine infiltration group which renderd them having a better overall experience.	1) During the injection: W-BFRS: success rates were 63.3% for both techniques. VAS: absolute differences in success rates were 0.06. FBRS: absolute differences in success rates were 0.08. 2) During the treatment: FBRS: Positive behaviour for both groups and similar success rates. VAS: results showed similar success rates.	1) Articaine group: - Intra-group comparison: W-BFRS showed no significant difference between the pain experienced at 3 time points. - MBPS: pain increased in the form of cry (P = 0.010) and movements (P = 0.023) and was statistically significant. 2) Lidocaine group: The mean values of W-BFRS and MBPS increased through the 3 points and were statistically significant. 3) FBRS: Intra-group comparison showed no statistically significant difference of mean values for behavior in both groups. 4) Accidental lip injury in 4 patients of Lidocaine group and in 2 patients of the articaine group.

Table 3 cont.: Characteristics of the included studies (Mandible):

Title	**Anaesthetic Efficacy of 4% Articaine Mandibular Buccal Infiltration Compared To 2% Lignocaine Inferior Alveolar Nerve Block in Children with Irreversible Pulpitis.** [63]	**Comparison of Visual Analog Scale Scores in Pain Assessment during Pulpotomy using Different Injection Materials in Children Aged 6 to 8 and 8 to 10 Years.** [64]	**Evaluation of Buccal Infiltration with Articaine and Inferior Alveolar Nerve Block with Lignocaine for Pulp Therapy in Mandibular Primary Molars.** [32]	**Pain perception and efficacy of local analgesia using 2% lignocaine, buffered lignocaine, and 4% articaine in pediatric dental procedures.** [65]	**Comparison of Anaesthetic Efficacy of 4% Articaine Buccal Infiltration Versus 2% Lidocaine Inferior Alveolar Nerve Block for Pulpotomy in Mandibular Primary Second Molars.** [66]
Author	Arali, et al.	Alinejhad, et al.	Chopra, et al.	Afsal, et al.	Daneshvar, et al.
Publication Year	2015	2018	2016	2019	2021
Location	India	Iran	India	India	Iran
Journal	Journal of Clinical and Diagnostic Research	The Journal of Contemporary Dental Practice	The Journal of Clinical Pediatric Dentistry	Journal of Dental Anesthesia and Pain Medicine.	Journal of Indian Society of Pedodontics and Preventive Dentistry
Sample Size	40	40	30	48	40
Age Range	5 - 8 years	6 - 8 years, 8 - 10 years	4 - 8 years	5 - 10 years	5 - 8 years
Gender	Not Specified.	Not Specified.	Females: 18. Males: 12.	Not Specified.	Females: 23. Males: 17.

Study Design	**Crossover design** randomized controlled trial.	**Split-mouth r**andomized controlled trial.	**Crossover design** randomized controlled trial.	**Crossover design** randomized controlled trial.	**Crossover design** randomized controlled trial.
Randomization	Yes.	Yes.	Yes.	Yes.	Yes.
Blinding	Double-blind.	Single-blind.	Not Blinded.	Double-blind.	Double-blind.
Intervention	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:200,000 epinephrine as BI	Group C: 4% articaine with 1:200,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI
Comparison	2% Lidocaine with 1:100,000 epinephrine as IANB	2% Lidocaine with 1:100,000 epinephrine as IANB	2% Lidocaine with 1:80,000 epinephrine as IANB	Group A: 2% lignocaine with 1:200,000 epinephrine. Group B: buffered lignocaine.	2% Lidocaine with 1:80,000 epinephrine as IANB
Presence of control group.	NO control group. The same patient served as the control and the intervention.	Each age group was divided into 2 groups. The same patient served as the control and the intervention.	NO control group. The same patient served as the control and the intervention.	Yes	NO control group. The same patient served as the control and the intervention.
Time frame and visits	2 visits / at least 1 week apart.	2 visits.	2 visits.	3 visits.	2 visits / at least 1 week apart.

Teeth included / Procedure	Primary mandibular molars / Pulp therapy	Primary mandibular second molars / Pulpotomy	Primary mandibular molars / Pulp therapy	Primary mandibular molars / Pulp therapy and Extraction	Mandibular primary second molars / Pulpotomy
Waiting time	N/A	Lidocaine: 15 minutes. Articaine: 10 minutes.	N/A	N/A	10 - 15 minutes.
Outcome Variable	1) Onset and duration of anesthesia. 2) Efficacy of the anesthetic agent.	Success Rate of anesthesia through assessment of pain perception.	Efficacy of the anesthetic agent.	1) Assessment of pain perception. 2) Time of onset and efficacy of analgesia.	Anesthetic efficacy based on Pain intensity.

Outcome measurements and scales	1) Behavior assessment: MBPS. 2) Pain assessment: VAS.	Pain evaluation: VAS.	1) Pain during injection: The Pain score given by Ram & Peretz. 2) Pain during procedure: SEM score. 3) After the procedure: FI score and HP-VAS.	1) Pain evaluation: WBFPS. 2) Objective evaluation: SEM scale. 3) Onset of anesthesia: Objectively by gingival probing. 4) Efficacy of anesthesia: - Subjectively: by asking the patient. - Objectively: gingival probing until complete anesthesia.	1) Initiation of the procedure: FI score.. 2) Patients' behavior during the procedure: SEM.

Findings	1) Onset of anesthesia with articaine infiltration was faster as compared to lidocaine. 2) Articaine has a shorter duration of action. 3) VAS scale: Less pain with articaine group as compared to the lignocaine group. Results are statistically significant. 3) Behavioral changes with articaine group were less when compared to the lignocaine group.	6 to 8 years group: * The mean VAS in the lidocaine group was 1.85 ± 1.08 * The mean VAS in the articaine group 0.55 ± 0.68 8 to 10 years group: * The mean VAS in the lidocaine group was2.3 ± 1.26 * The mean VAS in the articaine group 0.4 ± 0.75 - The mean VAS score between both groups was not significantly different.	1) Pain during injection: Pain-related behavior scores were higher for IANB. 2) Pain during procedure: The SEM scores were higher for lidocaine regardless of gender and age groups. 3) After the procedure: The scores from both scales were higher for lidocaine group concluding a better overall experience in the articaine group.	1) Wong-Baker scale: Statistically significant between buffered lidocaine and lidocaine ($P < 0.001$), and buffered lignocaine and articaine ($P = 0.041$). 2) SEM scale: There was a difference in the scores obtained for all the three agents, but it was not statistically significant. 3) Mean time of onset: * Lidocaine: 73.63 (± 13.45) seconds. * Articaine: 68.38 (± 16.555) seconds. * Buffered lidocaine: 60.00 (± 10.37) seconds.	1) Mean of Facial image scale scores: Lidocaine group 2.17 ± 0.75, articaine group 2.52 ± 0.78. Better pain experience in the lidocaine group ($P = 0.028$). 2) The means of SEM values: lidocaine group 5.52 ± 1.47, articaine group 6.35 ± 1.73. Better patient behavior in the lidocaine group ($P = 0.028$).

Table 3 cont.: Characteristics of the included studies (Mandible):

Title	**Articaine efficacy and safety in young children below the age of four years: An equivalent parallel randomized control trial.** [67]	**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.** [68]	**Articaine Infiltration Versus Lidocaine Inferior Alveolar Nerve Block for Anesthetizing Primary Mandibular Molars: A Randomized, Controlled, Double-Blind Pilot Study.** [8]
Author	Hamid Elheeny	Khanna, et al	Zhang, et al.
Publication Year	2020	2021	2021
Location	Egypt	India	USA
Journal	International Journal of Pediatric Dentistry	QUINTESSENCE INTERNATIONAL	PEDIATRIC DENTISTRY
Sample Size	184	100	30
Age Range	36 to 47 months	6 - 8 years	4 - 10 years
Gender	Not Specified.	Females: 34. Males: 66.	Females: 14. Males: 16.

Study Design	Randomized control trial	**Split-mouth** randomized controlled trial.	Randomized Controlled Pilot Study
Randomization	Yes.	Yes.	Yes.
Blinding	Triple-blind.	Not Blinded.	Double-blind.
Intervention	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI	4% articaine with 1:100,000 epinephrine as BI
Comparison	2% Lidocaine with 1:100,000 epinephrine as IANB	2% Lidocaine with 1:80,000 epinephrine as IANB	2% Lidocaine with 1:80,000 epinephrine as IANB
Presence of control group.	Yes	NO control group. The same patient served as the control and the intervention.	Yes
Time frame and visits	1 visit.	2 visits / 1 week apart.	1 visit.

Teeth included / Procedure	Mandibular primary molars / Pulpotomy	Mandibular primary molars / Any dental procedure.	Mandibular primary molars / Restorative treatment.
Waiting time	N/A	N/A	N/A
Outcome Variable	Anesthetic success.	1) Efficacy of anesthesia. 2) Onset of anesthesia. 3) Adverse events.	Effectiveness of anesthesia.

Outcome measurements and scales	1) Anesthetic success. 2) Pain assessment: FLACC. 3) Behavior assessment: FBRS. 4) Parents' post-operative pain measure (PPPM). 5) Adverse effects.	1) Onset of anesthesia: Pulp sensitivity using an electric pulp tester. 2) Subjective assessment: VAS and WBFPS. 3) Heart rate and oxygen saturation levels	1) Objective assessment: MBPS. 2) Subjective assessment: WBFPS. 3) Physiological parameters: Blood pressure and pulse.

Findings	1) FLACC pain scale: No statistically significant difference between groups. 2) Success rate: - Articaine: * During injection: 81.5%. * During procedure: 87%. - Lidocaine: * During injection: 79.3%. * During procedure: 78.3%. 3) Parents' post-operative pain measure (PPPM) Absolute difference between the groups 0.033 (−0.036;0.101). 4) Post-operative complications: No statistically significant difference between groups.	1) The mean onset of anesthesia of 4% articaine (2.08 ± 0.79 minutes) and 2% lidocaine (3.78 ± 0.6 minutes). 2) Anesthetic success was seen in both the groups when tested using an electric pulp tester. No significant difference. 3) VAS and WBFPRS: Significant difference between both groups. 4) Pulse rate and oxygen saturation levels: There was significant difference in both groups at each interval. 5) No significant differences were observed in postoperative complications.	1) The mean MBPS: crying score was the only parameter with a statistically significant difference between groups. 2) The mean WBS score: Lidocaine group 1.33±1.45 and articaine group 0.53±0.92. 3) BP: No statistically significant difference in mean BP between groups. 4) Pulse: statistically significant difference over three different time points between both groups.

Table 4: Characteristics of the included studies (Maxilla and Mandible):

Title	**Anesthetic Efficacy of Buccal Infiltration Articaine versus Lidocaine for Extraction of Primary Molar Teeth.** [69]	**Comparison of articaine 4% and lidocaine 2% in paediatric dental patients.** [35]	**A comparison between Articaine HCl and Lidocaine HCl in pediatric dental patients.** [26]	**Efficacy and adverse events of 4% articaine compared with 2% lidocaine on primary molar extraction: A randomised controlled trial.** [70]
Author	Rathi, et al.	Ram, et al.	Malamed, et al.	Massignan, et al.
Publication Year	2018	2006	2000	2020
Location	India	Israel	Multicenter studies	Brazil
Journal	American Dental Society of Anesthesiology	International Journal of Pediatric Dentistry	Pediatric Dentistry	Journal of Oral Rehabilitation
Sample Size	100	62	70	43
Age Range	7 - 12 years	5 - 13 years	4 - 13 years.	6 - 10 years
Gender	Females: 50. Males: 50.	Females: 34. Males: 28.	Females: 34. Males: 36.	Females: 19. Males: 24.
Study Design	Randomized clinical trial.	**Crossover design** randomized controlled trial.	Randomized parallel controlled clinical trial.	Parallel randomized controlled trial.
Randomization	Yes.	Yes.	Yes.	Yes.
Blinding	Triple-blind.	Single-blind.	double-blind	Triple-blind.

Intervention	4% articaine Buccal infiltration.	4% articaine Buccal infiltration in Maxilla and Mandible.	4% articaine.	4% articaine Buccal infiltration.
Comparison	2% Lidocaine Buccal infiltration.	2% Lidocaine Buccal infiltration in Maxilla and IANB in Mandible.	2% Lidocaine.	2% Lidocaine Buccal infiltration.
Presence of control group.	Yes	Each child served as his or her own control.	Yes	Yes
Time frame and visits	1 visit.	2 visits.	1 visit.	1 visit.
Teeth included / Procedure	Primary maxillary and mandibular molars / Extraction	Maxillary and Mandibular arches	Simple and complex dental procedures	Primary maxillary and mandibular molars / Extraction
Waiting time	5 minutes.	N/A	N/A	5 minutes.

Outcome Variable	Anesthetic efficacy was evaluated by the assessment of pain perception.	1) Onset of anesthesia. 2) Duration of action. 3) Efficacy of LA agent. 4) Adverse effects.	1) Anesthetic efficacy. 2) Adverse effects.	1) Anesthetic efficacy. 2) Onset of anesthesia. 3) Duration of anesthesia. 4) Adverse events. 5) The child's experience.

Outcome measurements and scales	1) Subjective assessment of pain: WBFPS. 2) Objective evaluation of pain: Heart rate and blood pressure.	1) Onset: asking the patient about the sensation. 2) Offset time: parents recorded the time when the sensation disappeared. 3) Objective evaluation: MBPS. 4) Subjective assessment of pain: WBFPS. 5) Adverse effects: phone call after the treatment.	1) Pain evaluation: VAS. 2) Safety: vital signs recorded before and after the administration of the LA agent and assessing adverse events.	Pain assessment: FPS-R scale and VAS.

Findings	1) The mean FPS value was higher in lidocaine group (5.6 ± 1.8) and was statistically significant ($p \leq 0.05$). 2) The difference in mean of heart rate recorded before and during the intervention in the articaine group was lower than the lidocaine group and was statistically significant ($P = 0.003$). 3) The difference in mean systolic blood pressure ($P = 0.303$) and the mean diastolic blood pressure ($P = 0.898$) recorded before and during the intervention in the articaine group was statistically not significant.	1) No differences were seen between the 2 agents in onset time. 2) No significant difference in Wong–Baker Faces scale between the 2 agents. 3) No significant difference in the objective evaluation according to Taddio's scale. 4) Duration of numbness of the soft tissue in articaine was longer than for lidocaine. This difference was statistically significant ($P = 0{\cdot}003$) 5) Adverse events related to articaine and lidocaine were not statistically significant.	1) Mean patient VAS scores: - Articaine: 0.5±0.18 for simple procedures and 1.1±0.33 for complex procedures. - Lidocaine: 0.7±0.26 for simple procedures and 2.3±2.25 for complex procedures. 2) Adverse events: No serious adverse events occurred.	There was a mean increase in pain during articaine injection by 2.43 units on the FPS-R scale compared to lidocaine. Articaine was more painful.

Table 5: Characteristics of the included studies (Primary and Permanent teeth in mandibular arch):

Title	**Comparison of the efficacy of a standard inferior alveolar nerve block versus articaine infiltration for invasive dental treatment in permanent mandibular molars in children: a pilot study.** [72]	**A comparison of articaine 4% and lignocaine 2% in block and infiltration analgesia in children.** [71]
Author	Jorgenson, et al.	P Arrow
Publication Year	2020	2012
Location	UK	Australia
Journal	European Archives of Paediatric Dentistry	Australian Dental Journal.
Sample Size	22	57
Age Range	8 - 15 years	5 - 13 years
Gender	Not Specified.	Not Specified.
Study Design	Prospective randomized controlled clinical trial.	Parallel group and **split-mouth** randomized controlled design.
Randomization	Yes.	Yes.
Blinding	Double - blind.	Triple-blinded to the anesthetic agent but not the technique.
Intervention	4% articaine with 1:100,000 epinephrine Buccal infiltration.	4% articaine with 1:100,000 epinephrine BI
Comparison	2% lidocaine with 1:80,000 epinephrine IANB	2% Lidocaine with 1:80,000 epinephrine IANB
Presence of control group.	Yes, but if the patient required a treatment in the contralateral tooth, they received the alternative local anesthetic on their second visit.	NO control group. The same patient served as the control and the intervention.

Time frame and visits	1 visit.	2 visits / 1 week apart.
Teeth included / Procedure	Mandibular permanent molars / Restorative and Extraction	Mandibular 1st and 2nd permanent molars and 2nd primary molars / Restorative
Waiting time	N/A	5 minutes.
Outcome Variable	Success of Anesthesia	Analgesia success, report on the pain experienced and occurrence of adverse events
Outcome measurements and scales	1) Pain perception by the patient: VAS. 2) Depth of anesthesia by the operator: Three-point scale: 1 inadequate 2 satisfactory 3 good	1) Success of local anesthesia: Testing of the soft tissue and pain reported during the procedure. 2) Evaluation of pain: FPS - R. 3) Behavior and Observer rating of pain: CHEOPS. 4) post-anesthetic events: Parents were contacted.

Findings	1) The mean VAS score for pain of injection was higher with IANB with lidocaine than a BI with articaine (Not statistically significant P = 0.239). 2) The mean VAS score for pain of treatment was higher with IANB with lidocaine than a BI with articaine (Not statistically significant P = 0.480).	1) Type of LA did not affect the success of anesthesia. LA technique was significantly associated with LA success. Greater success was obtained with IANB than BI. The success rate for articaine with BI was 71% and lidocaine BI was 64%, this difference was not statistically significant. 2) Adverse events: 8 events reported, tests of association between postoperative complications and LA technique and type showed no statistical significance. 3) Onset of anesthesia: No statistically significant differences in onset time by LA technique and type.

Year of publication of the included studies and Age range of the participants:

All included studies were published between the years 2000 and 2022. Of those, 23 studies were conducted in pediatric patients whom their age ranged from 5 to 15 years. Only one study was conducted in pediatric patients below the age of 4 (Hamid Elheeny [(67)]). Primarily, the inclusion criteria stated

Study design and randomization:

All studies were Randomized Clinical Trials. However, 12 studies were conducted as crossover/split mouth design where the child served as his or her own control, while the remaining 12 studies had separate control groups. All the crossover/split mouth design studies reported that the two visits of the child were of a minimum of 1 week apart to allow for the washout period and prevent bias.

Intervention and Comparison:

All the studies used 4% articaine as the intervention with variable dosage of epinephrine whether 1.8 ml or 1.7 ml. Of those 24, three studies used three-armed trials. Manisha Nair, et al. and Kolli, et al. compared buccal infiltration using 4% articaine with 2% lidocaine injected buccally and palatally, and 2% lidocaine injected only buccally in the maxillary arch. In the mandibular arch, Afsal et al. compared buccal infiltration using 4% articaine versus 2% lignocaine versus buffered lignocaine.

Blinding:

There were 20 studies blinded whereas 4 were not blinded (Khanna, et al., Chopra, et al., Manisha Nair, et al., Velagala Daneswari, et al.). Studies were either single-blinded (Zahra Bahrololoomi, et al., Fatma Alzahrani, et al., Alinejhad, et al., Ram, et al.), double-blinded (Jorgenson, et al., Malamed, et al., Zhang, et al., Daneshvar, et al, Afsal, et al., Arali, et al., Jain, et al., Zahra Bahrololoomi, et al., Sara Ghadimi, et al.) or triple-blinded (Kolli, et al., Mittal, et al., Jaikaria, et al., Massignan, et al., Hamid Elheeny, Rathi, et al., P Arrow).

Teeth included and procedures:

The studies were conducted mainly on posterior teeth, namely primary maxillary molars, primary mandibular molars, permanent mandibular molars which were treated with extractions, pulp therapy (pulpotomy or pulpectomy) and restorative treatments. All the studies used the same technique when local anesthetic injection was administered.

Waiting time:

There were 11 studies that recorded the time they waited prior to the initiation of the treatment. All other studies did not report the waiting time.

Outcome assessment:

The included studies in this review were analyzed according to the pain and behavior scale used in order to evaluate the effect of articaine and lidocaine on pain perception and behavior depicted by pediatric patients during dental procedures. Moreover, the onset of anesthesia was assessed according to the method used in each study, for instance assessing the onset of symptoms of anesthesia, such as the feeling numbness at the injected site, by electric pulp testing, by gingival probing or simply by asking the patient about the sensation. In addition, duration of action and adverse events were evaluated by contacting the parents after the procedure.

- **Maxillary arch studies:**

All studies have evaluated the anesthetic efficacy of articaine versus lidocaine by the assessment of pain perception. Zahra Bahrololoomi, et al., Mittal, et al. and Jaikaria, et al. used the Wong-Baker FACES Pain scale (WBFPS) for the subjective evaluation of pain. Whereas, Nair, et al. used the Visual Analog Scale (VAS) and Kolli, et al. used Faces Pain Scale Revised (FPS-R).

For the objective evaluation of pain, Zahra Bahrololoomi, et al., Jaikaria, et al. and Kolli, et al. used Face, Legs, Activity, Cry, Consolability (FLACC) scale. Mittal, et al. used the Modified Behavior Pain Scale (MBPS). However, Nair, et al. did not perform any objective evaluation. Physiological parameters, blood pressure and pulse rate, were recorded by all the studies except Nair, et al.

All of the maxillary arch studies did not evaluate the onset time for both agents. Only 2 studies reported adverse events associated with the administration of articaine and lidocaine (Zahra Bahrololoomi, et al. and Kolli, et al.) and there were no side effects recorded in both articaine and lidocaine groups.

- **Mandibular arch studies:**

Anesthetic efficacy was evaluated by the assessment of pain perception and child's behavior. The Wong-Baker FACES Pain scale (WBFPS) was used for subjective evaluation of pain in the following studies: Zahra Bahrololoomi, et al., Sara Ghadimi, et al., Jain, et al., Afsal, et al. and Zhang, et al. The Visual Analog Scale (VAS) was used by Arali, et al. and Alinejhad, et al. However, Fatma AL Zahrani, et al. and Khanna, et al. recorded pain perception subjectively using both WBFPS and VAS. Furthermore, Daneshvar, et al used Facial Image scale (FIS) to evaluate pain intensity during the procedure.

For the objective evaluation of pain and behavior assessment, Zahra Bahrololoomi, et al. and Hamid Elheeny used Face, Leg, Activity, Cry, and Consolability (FLACC) scale. Modified Behavioral Pain Scale (MBPS) was used by Sara Ghadimi, et al., Arali, et al. and Zhang, et al. whereas, Fatma Alzahrani, et al. used Frankl Behavior Rating Scale (FBRS) for the assessment child's behavior during the procedure. Both scales FLACC and MBPS were used in Jain, et al. Lastly, Afsal, et al. and Daneshvar, et al. evaluated patients' behavior using Sound, Eye, Motor (SEM) scale.

Velagala Daneswari, et al. and Chopra, et al. evaluated pain in 3 points of time, namely during injection using the Pain score given by Ram & Peretz, during procedure using Sound, Eye, Motor scale (SEM), and after the procedure using Facial Image (FI) score and Heft-Parker Visual Analogue Score (HP-VAS). Among all the studies, Hamid Elheeny was the only study that used Parents' post-operative pain measure (PPPM) to assess pain after the procedure.

In regards of the physiological parameters only Zhang, et al. and Zahra Bahrololoomi, et al. evaluated blood pressure and heart rate. In addition, Khanna, et al. evaluated heart rate and oxygen saturation levels.

Onset of anesthesia was reported in Afsal, et al. and Khanna, et al. Duration of action was not recorded in any of the studies. Jain, et al. and Hamid Elheeny recorded the adverse events associated with the administration of both local anesthetic agents.

- **Both arches' studies:**

For the subjective evaluation of pain, Rathi, et al. and Ram, et al. used the Wong-Baker FACES Pain scale (WBFPS) while, Malamed, et al. used The Visual Analog Scale (VAS). Additionally, Massignan, et al. used both Faces Pain Scale Revised (FPS-R) and VAS scale.

Only Ram, et al. assessed pain objectively using the Modified Behavior Pain Scale (MBPS). Moreover, Ram, et al. recorded the onset and offset time of anesthesia whereas, the other two studies did not. Rathi, et al. and Malamed, et al. recorded the vital signs which are the heart rate and blood pressure. The occurrence of adverse events was reported in Ram, et al. and Malamed, et al.

- **Primary and permanent teeth in mandibular arch studies:**

Jorgenson, et al. assessed the success of anesthesia by using the patient's and the operator's report. Pain perception was recorded subjectively by the patient using the Visual Analog Scale (VAS), while the operator reported the depth of anesthesia using three-point scale: inadequate, satisfactory and good. P Arrow measured the success of local anesthesia by testing the soft tissue and pain reported during the dental procedure. Faces Pain Scale Revised (FPS-R) was used to evaluate pain subjectively. Objective evaluation of pain was done using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Furthermore, it evaluated the post operative adverse events.

Risk of Bias assessment results:

After the assessment of risk of bias among the included studies, eight studies had low risk of bias, nine studies had moderate risk of bias and seven studies had high risk of bias. Therefore, the overall risk of bias across the studies was deemed to be moderate. Figure 15 shows risk of bias graph and Figure 16 shows risk bias summary. It is noteworthy that Bahrololoomi 2021 is Zahra Bahrololoomi, et al. conducted on the maxillary arch [(31)], whereas Bahrololoomi 2021 is Zahra Bahrololoomi, et al. conducted on the mandibular arch. [(7)]

Randomization and allocation concealment were the biggest issue in most of the high risk of bias studies. Based on the author's judgment, appropriate methods of randomization and allocation concealment were reported by 11 RCTs (Zahra Bahrololoomi, et al., Hamid Elheeny, Jaikaria, et al., Jorgenson, et al., Jain, et al.). Blinding of outcome assessment was not carried out in 5 studies (Fatma AL Zahrani, et al., Chopra, et al., Khanna, et al., Velagala Daneswari, et al., Manisha Nair, et al.). Due to the lack of blinding, Khanna, et al., Chopra, et al., Manisha Nair, et al. and Velagala Daneswari, et al. are more prone to outcome ascertainment bias and assessment bias. 2 studies (Manisha Nair, et al. and Velagala Daneswari, et al.) scored high risk of bias in most of the assessment domains.

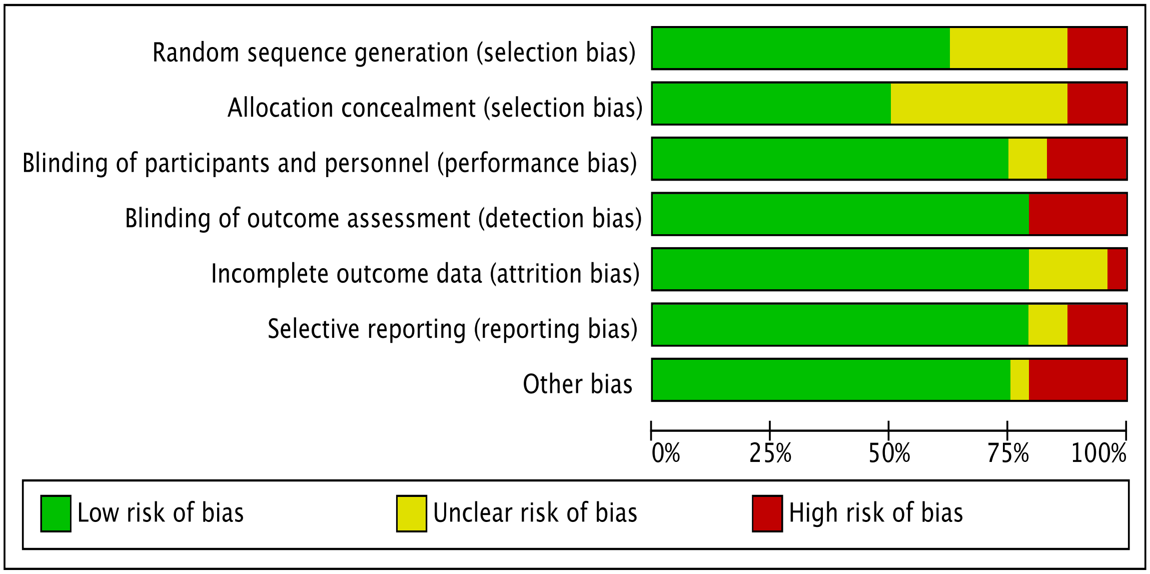

Figure 15: Risk of Bias graph.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Afsal 2019	+	?	+	+	+	+	+
Alinejhad 2018	−	−	+	+	+	+	+
Alzahrani 2018	?	+	?	−	−	+	+
Arali 2015	?	?	+	+	+	?	?
Bahrololoomi 2021	+	+	+	+	?	+	+
Chopra 2016	?	?	−	−	+	−	−
Daneshvar 2021	+	?	+	+	+	+	+
Hamid Elheeny 2020	+	+	+	+	+	+	+
Jaikaria 2017	+	+	+	+	+	+	+
Jain 2022	+	+	+	+	+	+	+
Jorgenson 2020	+	+	+	+	?	−	−
Khanna 2021	?	?	−	−	+	+	−
Kolli 2017	+	?	+	+	+	+	+
Malamed 2000	?	?	+	+	+	?	+
Massignan 2020	+	+	+	+	+	+	+
Mittal 2015	+	+	+	+	+	+	+
Nair 2018	−	−	−	−	?	−	−
P Arrow 2012	+	+	+	+	+	+	+
Ram 2006	?	?	?	+	+	+	+
Rathi 2018	+	?	+	+	+	+	+
Sara Ghadimi 2018	+	+	+	+	+	+	+
Velagala Daneswari 2021	−	−	−	−	+	+	−
Zahra Bahrololoomi 2021	+	+	+	+	?	+	+
Zhang 2021	+	+	+	+	+	+	+

Figure 16: Risk of bias summary.

DISCUSSION

One of the most important advances in dental science in the past years is the emergence of new agents and techniques for local anesthesia. Local anesthetic injections have been always known to be the most unpleasant event during dental treatments in pediatric patients. Therefore, pain management is a necessity to ensure a successful treatment.

Several randomized clinical trials were conducted to evaluate the success and effectiveness of articaine when used among pediatric patients. To ensure comprehensive results in these trials, self-report pain scales, behavioral scales and physiological parameters were assessed to provide a multidimensional evaluation of pain. [7] In this systematic review, the effect of articaine and lidocaine on pain perception and child's behavior was evaluated.

It should be emphasized that several studies assessed pain perception and behavior during or after conducting the procedure and not during local anesthetic administration. One of these procedures is extraction, which is known as a painful procedure, therefore evaluating pain after the procedure could bias the perceived pain during injection. Moreover, performance bias among different clinicians remains unclear and cannot be evaluated within the capacity of this review. It would be remarkable to improve study designs in future trials.

The detailed and comprehensive search strategy rendered this review consisting of a greater number of articles than previously published systematic reviews. On the other hand, one of the limitations of the current review that it was conducted by one reviewer. It is recommended that systematic reviews are performed by multiple reviewers to reduce errors in assessments and prevent the influence of a single person's perspective. [73] Moreover, most of the included studies exhibited a moderate risk of bias which can affect the overall evidence judgments. Additionally, there were possible biases due to randomization, allocation concealment and blinding in the included studies which may have affected the results of each trial.

To minimize bias in this review and to better interpret the current evidence, the studies included in this qualitative analysis were grouped according to the arch treated during the trial. 2 studies included permanent teeth in the trial and they were analyzed separately. Comparison of outcomes has been made between groups.

1) **Maxilla:** It is noteworthy that all the trials conducted on the maxillary arch performed extractions in pediatric patients.

   - **Pain perception among the included studies:**

The WBFPS was used by Zahra Bahrololoomi, et al., Mittal, et al. and Jaikaria, et al. to evaluate pain perception immediately after extraction. All three studies reported a higher WBFPS mean values in the lidocaine group than the articaine group. Mittal, et al. (Lidocaine: 1.88 ± 1.688, Articaine: 1.31 ± 1.13), (P = 0.085), and Jaikaria, et al. (Lidocaine: 2.200 ± 2.148, Articaine: 1.400 ± 1.294), (*P* = 0.089) reported that the difference between the groups was not statistically significant, whereas Zahra Bahrololoomi, et al. (Lidocaine: 2.36, Articaine: 1.43) showed a statistical difference between the groups (P = 0.013).

Nair, et al. and Kolli, et al. are 3-armed clinical trials. The highest mean values of VAS in Nair, et al. study was seen in lidocaine buccal infiltration group. The results exhibited a statistically significant difference between the groups. Furthermore, Kolli, et al. used FPS-R scale to evaluate pain perception. When the conventional buccal and palatal infiltration with lidocaine compared with the articaine group, there was no statistically significant difference in the mean values. Also, FPS-R scores were found to be higher in the lidocaine group when administered only buccally, compared to the articaine group, indicating a statistically significant difference between both groups.

- **Child's behavior:**

Zahra Bahrololoomi, et al., Jaikaria, et al., and Kolli, et al. used FLACC scale to evaluate child's behavior during the procedure. Zahra Bahrololoomi, et al. reported that the mean values of FLACC scale were 1.18 in the lidocaine group and 1.39 in the articaine group and there were no statistically significant differences between the two groups. The mean values of FLACC scale in Kolli, et al. were the highest in the lidocaine single buccal infiltration group which was 2.17 ± 1.46. The differences between this group and articaine group was statistically significant. Moreover, the mean values of FLACC scale in the lidocaine buccal and palatal infiltration group was 0.80 ± 0.84 and 1.27 ± 1.28 in the articaine group and there was no statistically significant difference between the two groups. Jaikaria, et al. did not report the mean values of FLACC, rather it showed that the percentage of patients in articaine group was lower in all the categories in the scale which indicates a profound anesthesia achieved and better patients' behavior during the procedure. There was no statistically significant difference in all the categories

Mittal, et al. used the Modified Behavior Pain Scale (MBPS) by Taddio et al. and showed that articaine group exhibited lower values in all the categories, with the association between the agents and eye squeezing, Hand movement and Leg movement statistically significant (P =

0.015, P = 0.003, P = 0.046, respectively). However, Torso movement and Crying were not statistically significant (P = 0.135. P = 0.248, respectively).

- **Secondary outcomes:**

Time of onset and duration of action were not studied in any of the studies, but adverse events were addressed in Zahra Bahrololoomi, et al. and Kolli, et al. They reported no adverse events with both articaine and lidocaine. This is indicative of articaine safety in pediatric patients.

2) Mandible:

- **Pain perception among the included studies:**

There were a consistent lower mean WBFPS scores with articaine with the differences between the groups not statistically significant among Zhang, et al., Jain, et al., Afsal, et al. and Sara Ghadimi, et al. In Zhang, et al. the mean scores were 1.33 ± 1.45 for the lidocaine group and 0.53 ± 0.92 for the articaine group. Jain, et al. reported a mean score of 4.46 in articaine group and 5.07 in lidocaine group. Similarly, Sara Ghadimi, et al. reported mean scores 2.87 ± 2.88 in the articaine group and 3.30 ± 2.93 in the lidocaine group. Moreover, when articaine was compared with buffered lidocaine and lidocaine in Afsal, et al., WBFPS mean score were similar among the patients received articaine and buffered lidocaine. These scores were lower than lidocaine group. On the other hand, Zahra Bahrololoomi, et al. also used WBFPS to evaluate pain subjectively during LA injection. Although, it showed a higher mean score when articaine was used compared to lidocaine (2.21 ± 1.663, 1.64 ±1.224, respectively), score 0 which indicates no pain was higher in the articaine group. The difference between the groups was not statistically significant. Furthermore, Daneshvar, et al. reported similar results where the mean FI scale scores were higher in the articaine group 2.52 ± 0.78 whereas, 2.17 ± 0.75 in the lidocaine group. The difference was statistically significant (P = 0.028). These results support findings from similar studies in which higher pain scores were generally associated with articaine. [69-70]

Velagala Daneswari, et al. and Chopra, et al. used both FI score and HP-VAS scores to evaluate the subjective overall experience of the patient after dental treatment. Both studies suggest a better experience with articaine, as the results showed higher mean scores for lidocaine group when compared to the articaine group. The difference between the groups was statistically significant.

Al Zahrani, et al. and Khanna, et al. used VAS and WBFPS for the subjective assessment of pain during local anesthetics administration. The two studies differ in terms of statistical significance difference. Khanna, et al. reported higher mean scores when lidocaine was used with both scales and the results were statistically significant (VAS in lidocaine 7.45 ± 1.08, in articaine 5.00 ± 0.69, WBFPRS in lidocaine 6.90 ± 1.19, in articaine 4.30 ± 1.22). However, Al Zahrani showed equal pain perception with both agents when WBFPS was used. When VAS was used results were higher in the lidocaine group. There was no statistically significant difference in the results.

Similarly, Arali, et al. and Alinejhad, et al. used VAS scale to assess pain perceived during treatment. Both studies reported lower mean VAS scores among the patients received articaine as LA agent. Moreover, the results were statistically significant. The mean score in articaine group in Arali, et al. was 0.5 ± 0.18 while lidocaine group had 0.7 ± 0.26. Likewise, the mean scores in Alinejhad, et al. was 0.55 ± 0.68 in articaine group and 1.85 ± 1.08 in lidocaine group among patients aged 6 to 8 years, whereas these scores were 0.4 ± 0.75 in articaine group and 2.3 ± 1.26 in lidocaine group among 8 to 10 years patients. Hamid Elheeny was the only clinical trial conducted on the mandibular arch and did not evaluate pain subjectively due to the younger age group included in the study.

- **Child's behavior:**

Based on FLACC and FBRS used to evaluate children's behavior, Elheeny reported that there was an equivalence during LA injection between both agents. While during treatment, depicted behavior was better in the articaine group when compared to lidocaine. Conversely, Zahra Bahrololoomi, et al. registered the mean FLACC scores between the groups and it was higher in the articaine group (articaine 1.36 ± 1.062, lidocaine 0.89 ± 0.916). Both studies reported no statistically significant difference in the results. This is in accordance with other studies reported. [29]

MBPS was used by Arali, et al., Sara Ghadimi, et al. and Zhang, et al. as an observational tool of child behavior during dental treatment. All three studies showed lower MBPS mean values when articaine was used and this is indicative of better behavior among children. The means of MBPS values in Sara Ghadimi, et al. in the articaine group and lidocaine group were 3.13 ± 1.86 and 4.52 ± 2.55, respectively. Likewise, Zhang, et al. showed a mean score of 2.13 ± 0.915 in the articaine group and 3.07 ± 1.624 in the lidocaine group. Arali, et al. and Sara Ghadimi, et al. reported statistically significant results, whereas Zhang, et al. showed a statistically significant result in cry category only. Jain, et al. showed a comparable results to

Zhang, et al. with cry category being statistically significant (P = 0.024). Moreover, there was a positive behavior with both LA agents seen in Alzahrani, et al. using FBPS.

When comparing the studies that used SEM scale to evaluate the behavior of the patient, Afsal, et al. and Daneshvar, et al. reported higher mean scores when articaine was used. Afsal, et al. showed a significant difference in the motor component of SEM between buffered lidocaine and articaine (P = 0.018) which was attributed to the higher pH of buffered lidocaine than articaine which reduced tissue irritation and consequently pain. Similarly, SEM mean values were 5.52 ± 1.47 in the lidocaine group and 6.35 ± 1.73 in the articaine group in Daneshvar, et al. implying a significant better behavior among the lidocaine group (P = 0.028). On the contrary, Velagala Daneswari, et al. and Chopra, et al. showed a statistically significant higher SEM mean scores when lidocaine was used.

- **Secondary outcomes:**

Afsal, et al., Khanna, et al. and Arali, et al. reported that the mean onset time of anesthesia was faster when articaine was used. Moreover, only Arali, et al. reported that the duration of action for both agents. The anesthetic effect persisted for 160 minutes with articaine, whereas lidocaine persisted for 200 minutes. Accidental lip injury and post operative pain were the main adverse events reported in Jain, et al., Khanna, et al. and Hamid Elheeny.

3) **Both arches:**

- **Pain perception among the included studies:**

Malamed, et al. grouped patients according to the complexity of procedure into simple and complex. Based on the VAS scores, articaine group exhibited a lower mean values than the lidocaine group. The mean VAS scores for simple procedures with articaine group was 0.5 ± 0.18 and for complex procedures 1.1 ± 0.33. For the lidocaine group, mean VAS scores were 0.7 ± 0.26 in simple procedures and 2.3 ± 2.25 for complex procedures. Malamed, et al. concluded that articaine 4% provided pain relief during most of the dental procedures, although there was no significant difference observed between the groups. Similarly, The WBFPS values in Rathi, et al. were lower in the articaine group than in the lidocaine group (1.52 ± 1.64, 5.6 ± 1.8 respectively) and it was statistically significant.

On the other hand, Ram, et al. and Massignan, et al. reported higher mean pain scales' scores in the articaine group. Ram, et al used WBFPS to measure pain perception after the administration of the injection. The results were 1.06 ± 0.73 in the lidocaine group whereas, 1.08 ± 0.79 in the articaine group. There was no statistically significant difference in the results. On the contrary, Massignan, et al. stated that there was a mean increase in pain during articaine injection by 2.43 units on the FPS-R scale compared to lidocaine and it showed a statistically significant difference (95% CI 0.28; 4.57; P = 0.02). Those results confirm that buccal infiltration with articaine was more painful than lidocaine. Massignan, et al. explained that articaine exhibit lower pH than lidocaine, which could be the reason in the difference in pain on injection.

- **Child's behavior:**

Only, Ram, et al. evaluated child behavior using the MBPS. The study reported no significant difference between articaine and lidocaine during injection.

- **Secondary outcomes:**

Ram, et al. reported no differences between agents in onset time, with immediate onset of action in more than 80% of cases. This is in accordance with Massignan, et al. which found that within one minute after completion of the injection, most of the patients were anesthetized. This is in contrary with what is present in the literature which indicates a faster onset time with articaine. [26]

It was shown in Ram, et al. that soft tissues' numbness was longer in the articaine group. The mean duration of action was 3.43 ± 0.7 hours for articaine and 3.0 ± 0.8 hours for lidocaine. This difference was statistically significant ($P = 0.003$). Likewise, Massignan, et al. reported that 63.2% of the patients in the articaine group were still anesthetized after 2 hours of procedure completion.

Malamed, et al., Ram, et al., and Massignan, et al. recorded the adverse events associated with both agents. Post operative pain, headache, pain at the injection site, and accidental lip injury were noted with articaine. However, accidental lip injury was the only adverse event directly related to articaine. [26] Moreover, Ram, et al. stated that there was no statistically significant difference in the adverse events between both agents. Additionally, Massignan, et al. registered nausea with articaine and edema with both agents.

4) **Permanent teeth in mandibular arch:**

- **Pain perception among the included studies:**

The mean VAS score for the pain perceived during LA injection in Jorgenson, et al. was higher with lidocaine compared to when articaine was used (24, 14.62 respectively). The differences were not statistically significant (P = 0.239). Conversely, P Arrow used FPS-R to evaluate pain during injection subjectively. Although, the results were not statistically significant, but it showed that during LA administration less patients reported no or mild pain and more patients reported moderate or severe pain in the articaine group. This was mainly related to the LA technique rather than the agent itself. These results are in accordance with Ram, et al. and Massignan, et al.

- **Child's behavior:**

Children's behavior was reported in P Arrow, and it showed better behavior in CHEOPS ratings during the LA administration with articaine. However, the differences were not statistically significant (P = 0.86).

- **Secondary outcomes:**

Secondary outcomes were reported only in P Arrow. The study registered the mean onset time based on the LA type and technique Table. 2. The results were longer

	Lip symptoms	Tongue symptoms
Articaine / IANB	129 seconds	85 seconds
Articaine / BI	115 seconds	-
Lidocaine/ IANB	119 seconds	104 seconds
Lidocaine / BI	170 seconds	-

Table 6: Onset of action based on the LA agent and technique reported by P Arrow [71].

than observed in Arali, et al. as which reported onset of action of 50 seconds with articaine buccal infiltration and 60 seconds with lidocaine inferior alveolar nerve block.

There were eight postoperative complications noted in the study that varies with LA type and technique. Tests of association between these complications and LA type and technique were not statistically significant. Lip and cheek bite, pain at the injection site, tenderness of the tooth and painful jaw were seen.

CONCLUSION

In conclusion, within the limitations of this review, the results suggest that although there was a clear variability in the statistical significance of the results, most of the articles included in the current systematic review showed a lower pain perception values and a better behavior when articaine was used among pediatric patients. Furthermore, articaine exhibited a faster onset of action and similar safety and possible adverse events as lidocaine. Based on the findings of the current review, articaine may substitute the gold standard local anesthetic agent; lidocaine, with the advantage of better management of pediatric patients during dental procedures. More clinical trials with larger sample size and standardized methodology are required to confirm these findings.

APPENDIX – 1

Keywords used in the search:

PICO	Keywords	# of Articles
P	"Pediatric Dentistry"[Mesh]	4727
	pedodontics[Text Word]	832
CONCEPT 1	"pediatric dentistry"[MeSH Terms] OR pediatric dentistry[Text Word] OR pedodontics[Text Word] OR "child"[MeSH Terms] OR children[Text Word]	
I	"Carticaine"[Mesh]	624
	articaine[Text Word]	625
	"carticaine"[MeSH Terms] OR articaine[Text Word] AND children	97
	(carticaine) AND (pediatric dentistry)	37
	(carticaine OR Articaine) AND (pediatric dentistry)	52
	(carticaine OR Articaine OR Carticaine* OR Articaine*) AND (pediatric dentistry)	52
CONCEPT 2	"carticaine"[MeSH Terms] OR articaine[Text Word]	
C	"Lidocaine"[Mesh] AND children	1877
	"lidocaine"[MeSH Terms] OR lidocaine[Text Word] AND children	2,482
	(lidocaine) AND (pediatric dentistry)	161
CONCEPT 3	"lidocaine"[MeSH Terms] OR lidocaine[Text Word]	
O	"pain perception"[MeSH Terms] OR pain perception[Text Word] AND "Child Behavior"[Mesh]	34
CONCEPT 4	"pain perception"[MeSH Terms] OR pain perception[Text Word] AND "Child Behavior"[Mesh]	
FULL SEARCH STRING	((("carticaine"[MeSH Terms] OR articaine[Text Word])) AND "Lidocaine"[Mesh]) AND "Pediatric Dentistry"[Mesh]OR pediatric dentistry[Text Word]	6,277
	"pediatric dentistry"[MeSH Terms] OR pediatric dentistry[Text Word] OR pedodontics[Text Word] OR "child"[MeSH Terms] OR children[Text Word] AND "carticaine"[MeSH Terms] OR articaine[Text Word] AND "lidocaine"[MeSH Terms] OR lidocaine[Text Word] AND "pain perception"[MeSH Terms] OR pain perception[Text Word] AND "Child Behavior"[Mesh]	33

Search strategy:

Pubmed

Concept 1 (children)	"pediatric dentistry"[MeSH Terms] OR pediatric dentistry[Text Word] OR pedodontics[Text Word] OR "child"[MeSH Terms] OR children[Text Word]
AND	
Concept 2 (articaine)	"carticaine"[MeSH Terms] OR articaine[Text Word]
AND	
Concept 3 (lidocaine)	"lidocaine"[MeSH Terms] OR lidocaine[Text Word]
AND	
Concept 4 (pain perception AND child behavior)	"pain perception"[MeSH Terms] OR pain perception[Text Word] AND "Child Behavior"[Mesh] AND "anesthesia, dental"[MeSH Terms] OR dental anesthesia[Text Word]
Full search string	"pediatric dentistry"[MeSH Terms] OR pediatric dentistry[Text Word] OR pedodontics[Text Word] OR "child"[MeSH Terms] OR children[Text Word] AND "carticaine"[MeSH Terms] OR articaine[Text Word] AND "lidocaine"[MeSH Terms] OR lidocaine[Text Word] AND "pain perception"[MeSH Terms] OR pain perception[Text Word] AND "Child Behavior"[Mesh] AND "anesthesia, dental"[MeSH Terms] OR dental anesthesia[Text Word]

Embase

Concept 1 (children)	('child'/exp OR 'child' OR 'children' OR 'pediatric dentistry'/exp OR 'paediatric dentistry' OR 'paedodontics' OR 'pediatric dentistry' OR 'pedodontics')
AND	
Concept 2 (articaine)	('articaine'/exp OR '2 methoxycarbonyl 4 methyl 3 (alpha propionylamino) thiophene' OR '4 methyl 3 (2 propylaminopropionamido) 2 thiophenecarboxylic acid methyl ester' OR 'articaine' OR 'articaine hydrochloride' OR 'carticaine' OR 'carticaine hydrochloride' OR 'hoe 045' OR 'hoe 40045' OR 'methyl 4 methyl 3 [2 (propylamino) propionamido] 2 thiophenecarboxylate' OR 'ultracain' OR 'ultracaine')
AND	
Concept 3 (lidocaine)	('lidocaine'/exp OR 'lidocaine' OR 'lidocaine hydrochloride' OR 'lignocaine' OR 'xylocaine' OR 'xylocaine dental' OR 'xylocaine dental cartridges' OR 'xylocaine hcl' OR 'xylocaine solution')
AND	
Concept 4 (pain perception AND child behavior)	('nociception'/exp OR 'nociception' OR 'nociperception' OR 'pain perception' OR 'pain sensation' OR 'pain sense' OR 'pain sensitivity' OR 'sensitivity, pain' OR 'behavior'/exp OR 'behavior' OR 'behavior and behavior mechanisms' OR 'behavior development' OR 'behavior facilitation' OR 'behavior pattern' OR 'behavior variable' OR 'behavioral activity' OR 'behavioral characteristic' OR 'behavioral response' OR 'behavioral specificity' OR 'behavioral symptoms' OR 'behavioral variable' OR 'behaviour' OR 'behaviour and behavior mechanisms' OR 'behaviour development' OR 'behaviour facilitation' OR 'behaviour pattern' OR 'behaviour variable' OR 'behavioural activity' OR 'behavioural characteristic' OR 'behavioural response' OR 'behavioural specificity' OR 'behavioural symptoms' OR 'behavioural variable' OR 'human behavior' OR 'human behaviour' OR 'intention' OR 'manual behavior' OR 'manual behaviour' OR 'marking behavior' OR 'marking behaviour' OR 'multitasking behavior' OR 'power (psychology)' OR 'power, psychological' OR 'psychological and psychiatric phenomena' OR 'psychological and psychosocial phenomena' OR 'refractory behavior' OR 'refractory behaviour' OR 'schedule controlled behavior' OR 'schedule controlled behaviour')

Cochrane

ID	Search Hits
#1	MeSH descriptor: [Child] this term only 53754
#2	MeSH descriptor: [Adolescent] this term only 110346
#3	MeSH descriptor: [Carticaine] explode all trees 281
#4	MeSH descriptor: [Lidocaine] explode all trees 6427
#5	MeSH descriptor: [Pain Perception] explode all trees 535
#6	MeSH descriptor: [Child Behavior] explode all trees 2327
#7	pediatric dentistry OR pedodontics 2744
#8	MeSH descriptor: [Anesthesia, Dental] explode all trees 1187
#9	#3 AND #7 17
#10	#4 AND #7 72
#11	#3 AND #4 AND #5 2
#12	#5 AND #6 AND #7 AND #82
#13	#3 AND #4 AND #5 AND #71
#14	#1 AND #2 AND #3 11
#15	#1 AND #2 AND #3 AND 4 8
#16	#1 AND #2 AND #5 AND #61

Web of science

Concept 1 (children)	TS=("pediatric dentistry" OR pediatric OR child* OR adolescent OR "young people")
AND	
Concept 2 (articaine)	TS=(carticaine OR articaine OR "carticaine hydrochloride" OR ultracaine)
AND	
Concept 3 (lidocaine)	TS=("lidocaine" OR "lidocaine hydrochloride" OR "lignocaine" OR "xylocaine" OR "xylocaine dental" OR "xylocaine dental cartridges" OR "xylocaine hcl" OR "xylocaine solution")
AND	
Concept 4 (pain perception AND child behavior)	TS=(("pain perception" OR "pain sensitivity" OR "pain sense") AND ("child behavior" OR "behavior development" OR psychological))
Full search string	(((TS=("pediatric dentistry" OR pediatric OR child* OR adolescent OR "young people")) AND TS=(carbocaine OR articaine OR "carbocaine hydrochloride" OR ultracaina)) AND TS=("lidocaine" OR "lidocaine hydrochloride" OR "lignocaine" OR "xylocaine" OR "xylocaine dental" OR "xylocaine dental cartridges" OR "xylocaine hcl" OR "xylocaine solution")) AND TS=("pain perception" OR "pain sensitivity" OR "'pain sense" AND "child behavior" OR "behavior development" OR psychological)

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CURRICULUM VITAE

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