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Local Anesthetic Used for Dental Treatment in Children- Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author NR designed the study, wrote the protocol and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: To analyse the existing literature on the effectiveness of various injectable amide local anaesthetic agents for children undergoing routine dental treatment.
Design: A systematic search was carried out for the databases of PubMed, Central, LILACS, Science direct, Metapress and SIGLE to identify clinical trials published on the effectiveness of injectable amide local anaesthetic agents in dental journals from the inception of the databases up to July 2015.
Results: The systematic search gave nine studies. Four of out seven studies found articaine to more effective. No significant difference in anaesthetic effectiveness of the agents were found in seven studies. One study reported significant difference in the anaesthetic effectiveness in favour to articaine. Two studies reported articaine to have longer duration of action.
Conclusion: With the available evidence, this review may suggest that articaine is an effective amide anesthetic agent. Lignocaine is most effective at 2% concentration. Prilocaine and mepivacaine show comparable effectiveness. As eight of the studies have high risk of bias, there is a greater need for well-designed randomized controlled studies to be conducted to assess

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effectiveness of various injectable amide local anaesthetics to be used in children for routine dental treatment.

Keywords: Local anesthetics; dental; children; systematic review.

1. INTRODUCTION

A successful outcome in paediatric dental treatment is largely dependent on efficient pain control. The concept of pain control is very pertinent in the management of children [1]. Local anaesthetics are a predominant way of achieving pain control in dental procedures, and can be a challenging aspect of paediatric dentistry [2]. Although local anaesthesia allows dental treatment to be virtually pain free, it still causes many anxious thoughts in paediatric patients [3]. An ideal agent should possess characteristics of providing maximum efficacy using a minimum number of injections while causing negligible adverse effects [2].

The introduction of lidocaine in 1948 replaced procaine as the drug of choice for pain control due to its rapid onset of action, more profound anaesthesia, greater potency and longer duration of action. Allergy to amide local anaesthetics is virtually non-existent, thereby giving a clinical advantage of amide anaesthetics over ester-type local anesthetics [5]. Lidocaine represents the "gold standard" of local anesthetics [4]. The most important advancement to have occurred in dentistry in the past 100 years is probably the improvement in agents for local anesthesia [5].

Originally synthesized as carticaine in 1969, articaine is unique in its chemical structure [4]. The presence of the thiophene group increases its lipid solubility thereby giving it a faster onset of action, and the ester group enables its rapid biotransformation into an inactive metabolite, hence, reducing its systemic toxicity [4].

Bupivacaine, ropivacaine, prilocaine, mepivacaine were subsequently introduced. McLean et al. [6] reported 3% mepivacaine as equivalent to other anaesthetic solutions for achieving pulpal anaesthesia. Haas et al. [7] found a higher success rate with articaine in obtaining pulpal anesthesia than prilocaine.

To the best knowledge of the author, amide anaesthetics have not been evaluated and compared with one another to establish the most effective injectable amide local anaesthetic.

The aim of this paper is to systematically review available evidence on the clinical effectiveness of injectable amide local anaesthetic agents administered to children undergoing routine dental treatment.

2. MATERIALS AND METHODS

Electronic search and hand search were carried out and articles were selected based on-

2.1 Inclusion Criteria

Randomized controlled trials and prospective clinical trials in which injectable amide local anaesthetics have been evaluated in children; Patients aged 4 - 13 years undergoing routine dental treatment; Amide anaesthetic agents namely articaine, lignocaine, bupivacaine, mepivacaine, prilocaine and ropivacaine; Anaesthetic effectiveness based on pain scales.

2.2 Exclusion Criteria

Ester anaesthetic agents; Studies comparing the technique of delivering local anaesthesia.

Electronic search was carried out using the keywords in the Search engines- PubMed, Science Direct, Cochrane, LILACS, SIGLE and Metapress up to July 2015, which yielded a total of 531 articles (Fig. 1). Hand search was done in International Journal of Pediatric Dentistry (IJPD), Journal of Clinical Pediatric Dentistry (JCPD) and Pediatric Dentistry by one of the authors (NR), which yielded no articles. Based on pre-set inclusion and exclusion criteria, the titles of the studies identified from the search were assessed independently by four review authors. Conflicts concerning inclusion of the studies were resolved by discussion. Thirteen titles were identified from the search after excluding duplications. Abstracts of selected articles were reviewed independently. Articles were selected following discussion and three articles were eliminated. Full text articles were retrieved for ten relevant studies. After reviewing the articles independently, nine articles were selected (Table 2). Discussion was held to resolve conflicts concerning inclusion of a study [9] (Fig. 1).

The reference list of the full text articles were reviewed for identifying additional studies. Titles of articles relevant to the review were selected by discussion. Abstracts of the three selected articles were reviewed. Difference of opinion concerning inclusion of a study was resolved by discussion and one article was eliminated after reviewing abstracts. Full text articles were retrieved for selected studies and two more articles were eliminated following discussion [10,11] (Table 4).

Quality Assessment criteria to evaluate the studies were decided by four review authors in accordance with CONSORT guidelines based on sample size determination, allocation concealment, blinding and random sequence generation (Table 1). Data extraction for variables of outcome was done by NR (Table 2). The available data was extracted from the articles. There was no need to contact the paper authors for additional details. The risk of bias for each study was independently assessed by the four review authors and conflicts concerning risk of bias was sorted by discussion (Table 3). Each study was rated as “High risk” of bias if it did record a “Poor” in any one category, “Low Risk” if all the four categories recorded “Good”.

3. RESULTS

The search identified 531 publications from electronic search. Full text articles were obtained for ten studies. One article was excluded after reading the full text articles. Cross References revealed three articles, of which one was eliminated at abstract stage and two were eliminated after reviewing full text articles. Therefore, a total of nine articles fulfilled all the criteria for inclusion (Fig. 1).

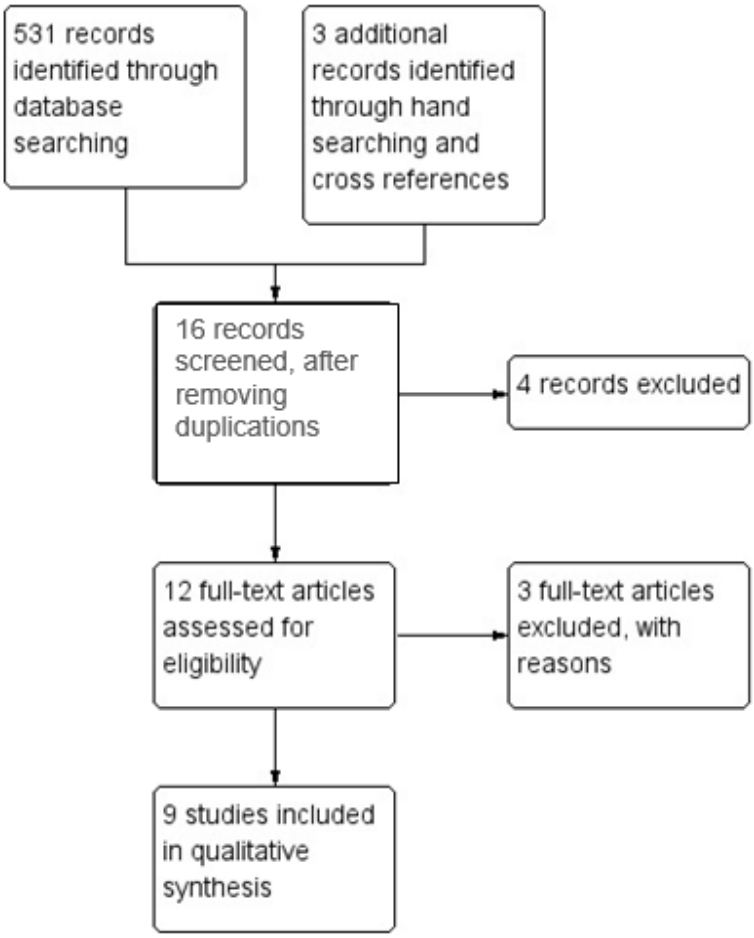

Fig. 1. Search flow chart


((((((((((child) OR children) OR middle year child) OR child, preschool))))) OR mixed dentition) OR primary dentition)) AND ((((((((dentistry) OR dental care for children) OR children, dentistry for) OR dental treatment) OR pulpotomy) OR pulpotomies) OR pulpectomy) OR pulpectomies) OR extraction))) AND ((((((((((((((((((((((((((local anesthetics) OR anesthetics, topical) OR conduction-blocking anesthetics) OR conduction blocking anesthetics) OR anesthetics, conduction-blocking) OR anesthetics, conduction blocking)) OR anesthetics, local))) OR ((((((((((propitocaine) OR astra brand of prilocaine hydrochloride) OR prilocaine hydrochloride) OR devlet brand of prilocaine hydrochloride) OR parnell brand of prilocaine hydrochloride) OR citanest octapressin) OR citanest) OR xylonest) OR astrazeneca brand of prilocaine hydrochloride) OR inibsa brand of prilocaine hydrochloride)) OR prilocaine)) ((((((((((((((((((((((((((((((((((isocaine) OR pascoe brand of mepivacaine hydrochloride) OR novosel brand of mepivacaine hydrochloride) OR ibogaine) OR clarren brand of mepivacaine hydrochloride) OR aventis brand of mepivacaine hydrochloride) OR meaverin) OR mechain) OR curasan brand of mepivacaine hydrochloride) OR mepilexag) OR hexyl brand of mepivacaine hydrochloride) OR mepivacaine braun, mepivacaine) OR braun brand of mepivacaine hydrochloride) OR mepivacaine hydrochloride) OR hydrochloride, mepivacaine) OR mepivacaine monohydrochloride) OR monohydrochloride, mepivacaine) OR mepivastesin) OR 3m brand of mepivacaine hydrochloride) OR polocaine) OR scand inibsa) OR inibsa brand of mepivacaine hydrochloride) OR scandonest) OR dentsply brand of mepivacaine hydrochloride) OR carbocaine) OR sanofi brand of mepivacaine hydrochloride) OR astra brand of mepivacaine hydrochloride) OR astrazeneca brand of mepivacaine hydrochloride) OR carbocaine) OR scandicaine) OR mepivacaine injectors) OR mepivacaine injectors)) OR mepivacaine)) OR ((((((((((((((((((((((((((((((((((1-Butyl-N- (2,6-dimethylphenyl) -2-piperidinecarboxamide) OR bupivacaine carbonate) OR jenapharm brand of bupivacaine hydrochloride) OR jenapharm, bupivacaine) OR bupivacaine jenapharm) OR astrazeneca brand of bupivacaine hydrochloride) OR abbott brand of bupivacaine hydrochloride) OR carbostesin) OR marcaine) OR marcain) OR astra brand of bupivacaine hydrochloride) OR sensorcaine) OR dvanaest) OR strathmann brand of bupivacaine hydrochloride) OR pisa brand of bupivacaine hydrochloride) OR butacaine) OR bupivacaine monohydrochloride, monohydrate) OR carbonate, bupivacaine) OR hydrochloride, bupivacaine) OR bupivacaine hydrochloride) OR inibsa brand of bupivacaine hydrochloride) OR anhydrous, bupivacaine) OR sved cain sin vasoconstror) OR bupivacaine anhydrous) OR braun brand of bupivacaine hydrochloride) OR braun, bupivacaine) OR bupivacaine braun) OR aventis brand of bupivacaine hydrochloride) OR bupivacaine rpr) OR bupivacaine rpr)) OR bupivacaine))) OR ((((((((((1-propyl-2',6'-pipecoloxylidide) OR naropin) OR astrazeneca brand of ropivacaine monohydrochloride) OR naropeine) OR astra brand of ropivacaine monohydrochloride) OR AL 381) OR AL-381) OR ropivacaine monohydrochloride, (S) isomer) OR LEA 103) OR LEA-103) OR ropivacaine monohydrochloride) OR ropivacaine hydrochloride) OR ropivacaine)) OR amide anesthetics)) OR dental anesthesia) OR anesthesia, dental)) OR ((((((((((((carticaine) OR articaine) OR carticaine) OR Hoe-40045) OR Hoe 40045) OR Hoe40045) OR Hoe-045) OR Hoe045) OR ultracaine) OR hoechst brand of carticaine hydrochloride) OR carticaine hydrochloride) OR hydrochloride, carticaine)) OR articaine))))) OR infiltration anesthesia) OR inferior alveolar nerve block) OR subperiosteal anesthesia) OR infra orbital nerve block))AND ((((((((((((((((((((((((((((((measurement, pain) OR measurements, pain) OR pain measurements) OR assessment, pain) OR assessments, pain) OR pain assessments) OR pain assessment) OR analgesia tests) OR analgesia test) OR test, analgesia) OR nociception tests) OR nociception test) OR test, nociception) OR tests, nociception) OR visual analog pain scale) OR visual analogue pain scale) OR analogue pain scale) OR analogue pain scales) OR pain scale, analogue) OR pain scales, analogue) OR scale, analogue pain) OR scales, analogue pain) OR analog pain scale) OR analog pain scales) OR pain scale, analog) OR pain scales, analog) OR scale, analog pain) OR scales, analog pain) OR onset) OR duration))

Fig. 2. Search words

Table 1. Quality assessment

Criteria for assessing quality of included studies		
S. No	**Criteria factor**	**Description definition**
1	Sample size	**Good:** Explanation on how sample size was determined. **Poor:** No details on sample size determination.
2	Blinding [Katyal V, 2010] [8]	**Good:** The outcome assessor could not know to which group the participants had been randomized. **Fair:** Just the usage of the Blinding without information of the exact details.
3	Random sequence generation [Katyal V, 2010] [8]	**Good:** Generated by random numbers or tables, tossed coin, shuffled cards, or any other random sequence generation satisfying consort criteria. **Fair:** Just the usage of the term randomization or randomly allocated without information of the exact randomization method **Poor:** Alternate assignment, case record, number etc.
4	Allocation concealment [Katyal V, 2010] [8]	
	Central randomization	**Good:** Measures for concealing allocation do not fall into the category of unclear measures. **Poor:** No reported negation of disclosing participants' prognostic data to central office staff before clinician obtains treatment assignment
	envelope method	**Good:** Envelopes opaque, sealed and sequentially numbered. **Poor:** Above-mentioned criteria not met.
	Numbered coded vehicles	**Good:** Vehicles were indistinguishable, sequentially numbered, and sequentially administered. **Poor:** No information on whether vehicles were sequentially administered.
	All methods	**Good:** Other measures of convincing allocation concealment **Poor:** Allocation by alternation, date of birth, case record number, or open table of random numbers.

Table 2. Summation of outcome of variables

Variable	Author/ Year								
	Wilson et al. 1990 [12]	**Malamed et al. 2000 [1]**	**Ram and Amir 2006 [13]**	**Van de hoef and Van Amerongen 2007 [14]**	**Yilmaz et al. 2011 [15]**	**Odabas et al. 2012 [5]**	**Arrow 2012 [16]**	**Arali and PM 2015 [17]**	**Zurfluh et al. 2015 [18]**
Materials used	2% lignocaine in 1:1,00,000 1% lignocaine in 1:1, 00, 000.	4% Articaine in 1:1,00,000 2% lignocaine in 1:1,00,000	4% articaine in 1:2,00,000 2% lignocaine in 1:1,00,000	4% articaine	4% articaine with 1:1,00,000 epinephrine	4% articaine with 1:2,00,000 3% mepivacaine	4% articaine in 1:1,00,000 2% lignocaine in 1:80,000	4% articaine n 1:1,00,000 2% lignocaine in 1:1,00,000	4% articaine in 1:1,00,000 4% articaine in 1:4,00,000
Anesthetic effectiveness	1% observed a higher percentage of failures. No statistical significant difference. p=0.147)	Pain scores are higher in lignocaine group (2.3) than articaine (1.1) No statistical significant difference in pain control was observed.	Comparable effectiveness between the two solutions. No statistical significance was observed.(p>0.05)	There is no statistically significant difference in the measure of discomfort irrespective of whether LA is used.	Pain related scores are higher in prilocaine anesthetized group. Not statitstically significant.	Comparable pain scores between the two agents. No statistical significance.(p=0.07,p=0.89, p=0.77)	Success rate for articaine (71%) is higher than lignocaine (64%). Difference is not statistically significant.	Articaine was found to be more effective than lignocaine. Difference was found to be statistically significant.	Not evaluated using pain scales
Duration	*Not evaluated*	*Not evaluated*	Articaine was significantly longer lasting when compared to lignocaine.	*Not evaluated*	*Not evaluated*	Articaine was significantly longer lasting when compared to mepivacaine.	*Not evaluated*	Articaine had shorter duration of action(no statistically significant difference)	4% articaine in 1:1,00,000 Had a longer duration of action than 4% articaine in 1:4,00,000 (statistically significant)
Onset	*Not evaluated*	*Not evaluated*	Values given according to type of anesthetic (infiltration or block)	*Not evaluated*	*Not evaluated*	No significant difference was found.	There were no statistically significant differences in time to appearance of lip symptoms.	There was no statistically significant difference.	Not evaluated

Table 3. Risk of bias

S. No	Study	Sample size determination	Random sequence generation	Allocation concealment	Blinding	Risk of bias
1	Wilson et al. 1990 [12]	Poor	Poor	Good	Good	High
2	Malamed et al. 2000 [1]	Poor	Good	Poor	Fair	High
3	Ram and Amir 2006 [13]	Poor	Fair	Poor	Good	High
4	Van de hoef and Van Amerongen 2007 [14]	Poor	Good	N.A	Good	High
5	Yilmaz et al. 2011 [15]	Poor	Fair	Good	Good	High
6	Odabas et al. 2012 [5]	Poor	Fair	Poor	Good	High
7	Arrow 2012 [16]	Good	Good	Good	Good	Low
8	Arali V and PM 2015 [17]	Poor	Fair	Poor	Good	High
9	Zurfluh et al. 2015 [18]	Poor	Fair	Poor	Poor	High

Table 4. Characteristics of excluded studies

S. No	Author	Year	Reason for exclusion
1.	Nakai et al. [9]	2000	In conjunction with sedative agents
2.	Rozanski et al. [10]	1988	No available data from 12-13 years
3.	Dudekeiwicz et al.	1987	No pain scale was used

Eight clinical trials in the review evaluated anaesthetic effectiveness in children undergoing dental treatment (Table 2). [1,5,12-16] Zurfluh et al. [18] evaluated effectiveness but pain scales were not used, hence it was not included in this aspect of the review. To evaluate anaesthetic effectiveness of 4% articaine and 2% lignocaine, Malamed et al. [1], Arrow [16], Ram and Amir [13] and Arali V and PM [17] adopted different methods. The results of Malamed et al. [1] were consistent with that of Arrow [16] who found articaine to have better effectiveness but no statistically significant difference between the anaesthetic agents. Ram and Amir [13] found articaine and lignocaine to have comparable efficacy. Odabas et al. [5] found articaine and mepivacine to have comparable efficacy. Arali V and PM [17] found 4% articaine to be more effective than 2% lignocaine and the results of this study were statistically significant.

Wilson et al. [12] compared 1% lignocaine with 2% lignocaine and found 1% lignocaine to have a higher percentage of failures. Yilmaz et al. [15] found higher pain scores when prilocaine HCl group was used during coronal pulp extirpation. He found no statistically significant difference between prilocaine and articaine in his double blind clinical study. Van de hoef and Van Amerongen [14] conducted a study to investigate the influence of local anaesthesia on the quality of Class 2 restorations and found no significant difference in the measure of discomfort irrespective of whether 4% articaine is used or not.

Ram and Amir, 2006[13], Odabas et al. [5], Arali V and PM [17] and Zurfluh et al. [18] evaluated the duration of anaesthesia. Ram and Amir, [13] and Odabas et al. [5] evaluated by instructing parents to ask the child and record time taken for the feeling of numbness to disappear and found articaine to be significantly long lasting when compared to lignocaine and mepivacaine [5,13]. Arali V and PM [17] found 4% articaine infiltration to have shorter duration of action. Zurfluh et al. [18] found 4% articaine in 1:1,00,000 adrenaline to have longer duration than 4% articaine in 1:4,00,000 adrenaline.

Ram and Amir [13], Odabas et al. [5], Arrow [16] and Arali V and PM [17] evaluated the onset of anaesthesia. Ram and Amir [13] recorded the onset of 4% articaine and 2% lignocaine but the onset was described based on type of anaesthetic technique. Odabas et al. [5] evaluated the onset of 3% mepivacaine and 4% articaine. Arali V and PM [17] evaluated the onset between 4%articaine and 2% lignocaine. The method of evaluation is not described. Arrow [16] evaluated the onset as the mean time to appearance of lip symptoms. The authors found no statistically significant difference in onset of anaesthetic agents.

4. DISCUSSION

Fear related behaviour and anxiety are recognized barriers to good dental treatment and hence, dentistry has been in the fore front in seeking more effective and safer local anaesthetics.

The hierarchy of evidence has assessed Randomized Controlled Trials above other forms of study [19] and hence randomized controlled trials and prospective clinical trials were selected in this review. Amide anaesthetics have superseded the use of ester anaesthetic agents owing to its allergic properties and hence, this review excluded ester local anaesthetic agents.

The term 'Anaesthetic Effectiveness' in this review meant absence of pain during routine dental procedure. Six out of eight included studies in this review evaluated the presence of pain used self-report scales [1,5,12,13,16,17]. While Malamed et al. [1] and Arali V and PM [17] used Visual Analog Scale (VAS), Ram and Amir [13] and Odabas et al. [5] used Wong Baker's Faces pain scale to evaluate pain. Arrow [16] used Faces Pain scale-Revised and Wilson et al. [12] used Faces Scale by McGrath. Wong and Baker [20] stated that children aged 3 to 18 years prefer Faces pain scales over the other scales. Tomlinson et al. [21] concluded that FPS-R is highly recommended for use in clinical trials as the lack of tears on the faces eliminate confounding effects, although the neutral faces are not preferred by children. He also reported that Wong Bakers Faces Pain Scale can have a confounding effect due to the presence of tears on the faces [20]. However, Hain [22] stated that in conjunction with self-report pain scales, observational and/or physiological measures should also be used. All eight studies also used objective evaluation [1,5,12,13,16,17]. Malamed et al. [1] and Arali V and PM [17] used a 10 cm VAS while Ram and Amir [13] and Odabas et al. [5] used Modified behavioural scale by Taddio for objective evaluation. CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) was used by Arrow [16]. Van de hoef and Van Amerongen [14] used Modified Venham scale and Wilson et al. [12] used 'Faces scale', Yilmaz et al. [15] evaluated pain during treatment by using a previously published pain related behaviour score [18]. In this review, the injectable amide local aesthetics were evaluated for anaesthetic effectiveness and different scales were used by each author to evaluate anaesthetic effectiveness thereby giving heterogeneous results.

Duration of anaesthesia is a very significant factor in assessing the effectiveness. While prolonged duration can cause adverse effects like self-inflicted trauma, reduced duration can impede dental treatment and result in multiple injections thereby provoking anxiety in the patient. Articaine was found to have longer duration of action as compared to mepivacaine and lignocaine [5,13]. Ram and Amir [13] state that duration is related to degree of protein binding. Articane, with a protein binding capacity of 95%, has a longer duration compared to lignocaine, which has protein binding capacity of 65%. This can be clinically beneficial by precluding the need for conscious sedation in cooperative patients requiring multiple treatments in one quadrant. However, Arali V and PM [17] found articaine infiltration to have shorter duration of action. Arali V and PM compared the onset of articaine to 2% lignocaine administered through an IANB. Zurfluh et al. [18] found adrenaline concentration to influence the duration of anesthetic agent. Amide anaesthetics have comparable degrees of protein binding and hence duration of action must be evaluated for all amide anaesthetic agents.

A faster onset of action is a primary requisite in paediatric patients. Rapid onset of action can ensure less chair time for the patient and aid in good dental treatment. Studies carried out by Odabas et al. [5] Ram and Amir [13], Arrow [16] and Arali V and PM [17] evaluated the onset of anaesthesia and found no significant difference in the onset of anaesthesia.

Most of the studies did not specify how the sample size was calculated. Although the importance of appropriate sample size considerations cannot be overemphasized, a study may be flawed if sample size and power considerations are not explicitly addressed [23]. With the exception of one study, [13] no other study in the review emphasized on sample size calculation. In these studies, Convenience sampling method was used, hence giving these studies a high risk of bias. The strength of RCT stems from randomization. By generating two groups of subjects with similar characteristics, the randomization minimizes confounding bias. Arrow [16] explains the method of randomization in detail while Ram and Amir [13], Odabas et al. [5], Yilmaz et al. [15] and Arali V and PM [17] only mention the word 'randomly assigned'. Malamed et al. [1] mentions that the study protocol had randomized participants to receive articaine and lignocaine in the ratio of 2:1 and Van de hoef and Van Amerongen14 mention the use of SPSS to generate randomization sequence. Adequate Allocation concealment can also increase the possibility of proper randomization. The absence of it can subvert even properly developed random allocation

sequences [24]. In this review, three studies have ensured adequate allocation concealment (Wilson et al. [12] Arrow [16] Yilmaz et al. [15], whereas Malamed et al. [1] Ram and Amir [13], Odabas et al. [5] and Arali V and PM [17] have not described method of allocation concealment, hence having an increased risk of bias. Allocation concealment was not applicable in the study by Van de hoef and Van Amerongen [14] as only one anaesthetic agent (4% articaine) was used. Blinding the outcomes to the evaluators is of essential importance [25] and all eight studies ensured adequate blinding although Malamed et al. [1] does not mention the method of blinding.

Hence, eight studies in this review were rated as having high risk of bias. One study was rated low risk of bias and the study found no significant difference in the anaesthetic effectiveness between articaine and lignocaine in its interim analysis [16].

The studies measured the effectiveness on different scales and hence it was not possible to compare the studies based on the type of outcome measurement, that is, dichotomous, percentages or continuous.

Bhanenkar et al. conducted a study to evaluate the role of morphine as an adjuvant to local anesthetics. He found that there was no benefit of adding morphine to local anesthetics for analgesia after pediatric dental extractions. Further research should be done in using an adjuvant with local anesthetics that can help reduce post extraction dental pain.

One limitation of the review is the possible language bias in the systematic search. However the effect is negligible as judged from the abstract of the articles which did not fulfil the inclusion criteria. The results of the review are in agreement with relevant meta-analyses [8,26] which determined articaine to be more effective when compared to lignocaine.

5. CONCLUSION

With the available evidence, this review may suggest that articaine is an effective amide anesthetic agent. Lignocaine is most effective at 2% concentration. Prilocaine and mepivacaine show comparable effectiveness. However, no significant difference between the agents was observed in eight studies. The presence of high risk of bias across all the included studies revealed the necessity for well conducted studies. Trials comparing bupivacaine, ropivacaine and 2% articaine in children are not available in the literature. A properly designed randomized controlled study must be performed to give concrete evidence on the clinical performance of anaesthetic agents.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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