The efficacy and safety of articaine versus lignocaine in dental treatments: A meta-analysis

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ABSTRACT

Objectives: Although articaine has been recommended for providing an improved local anaesthetic effect in patients presenting for dental treatments, a relevant meta-analysis has been lacking. Despite articaine's popularity, there is contradictory evidence to support the claims. The aim of this systematic review was to compare the efficacy and safety of articaine with lignocaine in maxillary and mandibular infiltrations and block anaesthesia in patients presenting for routine dental treatments.

Data sources: The following databases were searched: Cochrane Central, Medline, Embase, and ProQuest Health and Medical Complete. In addition, the metaRegister of the controlled trials database was searched to identify dissertations and ongoing or unpublished trials, and the Australian division of Septodont (the manufacturer of articaine and lignocaine) was contacted. The bibliographies of identified articles were also searched.

Study selection: Inclusion was limited to: (1) randomized controlled trials in patients requiring non-complex routine dental treatments; (2) interventions comparing 4% articaine (1:100,000 epinephrine) with 2% lignocaine (1:100,000 epinephrine) for maxillary and mandibular infiltrations and block anaesthesia; and (3) with principal outcome measures of anaesthetic success, post-injection adverse events or post-injection pain. Trial quality was evaluated by assessing randomization, allocation concealment, blinding, intention to treat analyses and how losses to follow up were addressed. Treatment effects were combined by meta-analysis using the random effects method.

Results: Articaine is more likely than lignocaine to achieve an anaesthetic success in the posterior first molar area with a relative risk for success at 1.31 (95% CI 1.12–1.54, $P = 0.0009$). There is no difference in post-injection adverse events between articaine and lignocaine with a relative risk of 1.05 (95% CI 0.66–1.65, $P = 0.85$). However, articaine injection results in a higher pain score as measured by Visual Analogue Scale, than lignocaine at the injection site after anaesthetic reversal with a weighted mean difference of 6.49 (95% CI 0.02–12.96, $P = 0.05$) decreasing to 1.10 (95% CI 0.18–2.02, $P = 0.02$) on the third day after injection.

Conclusion: The results of this systematic review provide support for the argument that articaine is more effective than lignocaine in providing anaesthetic success in the first molar region for routine dental procedures. In addition, both drugs appear to have similar adverse effect profiles. The clinical impact of articaine's higher post-injection pain scores than lignocaine is negligible. Hence, articaine is a superior anaesthetic to lignocaine for use in routine dental procedures. Use in children under 4 years of age is not recommended, since no data exists to support such usage.

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1. Introduction

Pain control in dentistry is an important factor for reducing the fear and anxiety associated with dental procedures.[4] Local anaesthetics form the backbone of pain control techniques in dentistry and there has been substantial research interest in finding safer and more effective local anaesthetics.[5] Clinical studies have found failure with inferior alveolar nerve block between 44% and 81% of the time[6,7,21] and for maxillary infiltrations failures range from 0% to 36%.[8,9] Lignocaine was first introduced in the market in 1948.[29] Articaine entered clinical use in 1976 as a unique amide local anaesthetic which contains an ester and a thiophene group increasing its liposolubility.[5] This liposolubility has been suggested to facilitate better diffusion of the anaesthetic solution to the teeth,[12] giving articaine a reputation for providing an improved local anaesthetic effect than lignocaine for dental treatments,[5,13] which would be beneficial in reducing patient anxiety and lead to improved treatment.[4] However, the evidence basis for articaine's reputation is not entirely clear.

The aim of this paper is to compare the efficacy and safety of articaine with that of lignocaine in maxillary and mandibular infiltrations and block anaesthesia in patients presenting for routine non-complex dental treatments through a systematic review and meta-analysis.

2. Materials and methods

2.1. Literature searching

Citations to potentially relevant trials published in journals and dissertations were located by searching the appropriate databases (Medline, Cochrane Central Register of Controlled Trials, Embase, and ProQuest Health and Medical Complete), efforts to identify potentially relevant unpublished or ongoing trials were made by searching the metaRegister of controlled

trials database. The references cited in relevant review articles were also checked. The Australian division of Septodont (manufacturing company for articaine and lignocaine) was contacted for further information on ongoing trials. The search was from 1950 to October 2009. Appendix Table I shows the search strategy for this systematic review with a list of keywords used for the search.

2.2. Selection of studies

Randomized controlled trials (RCTs) appropriate to be included in the review were fulfilling certain criteria concerning study design, participants' characteristics, intervention characteristics, and outcome measures. Inclusion was limited to: (1) RCTs in patients requiring non-complex routine dental treatments; (2) interventions comparing 4% articaine (1:100,000 epinephrine) with 2% lignocaine (1:100,000 epinephrine) for maxillary and mandibular infiltrations and block anaesthesia; and (3) with principal outcome measures of anaesthetic success, onset of action, post-injection adverse events or post-injection pain. Study selection criteria are given in Table 1.

2.3. Data abstraction and study characteristics

The author independently reviewed titles and the abstracts, if available, of identified citations in accordance with the QUOROM statement.[14] All citations were checked as to whether it involved a trial (1) evaluating articaine effectiveness and safety in dental treatments, (2) comparing 4% articaine with 2% lignocaine directly, (3) comparing the 1:100,000 epinephrine concentration in both articaine and lignocaine, and (4) measuring onset of anaesthesia, duration of anaesthesia, anaesthetic success with pain scores using Heft Parker Visual Analogue Scale (VAS), post-injection pain and/or post-injection adverse events. Any trial not fulfilling these criteria was excluded from further evaluation, and the full articles were retrieved for trials meeting the criteria.

Table 1 – Criteria for selecting studies in the meta-analysis.	
Criteria	Definition
Study characteristics	The studies should be randomized controlled trials (RCTs) directly comparing similar volume dose of 4% articaine (1:100,000 epinephrine) with 2% lignocaine (1:100,000 epinephrine).
Patient characteristics	All ages requiring routine non-complex dental treatments such as dental restorations, root planing, periodontal treatments, endodontic therapy, extraction of teeth, crown and bridge preparation, and implant procedures under local anaesthesia in dental surgery. Trials in medically compromised patients and those studying complex dental treatments were excluded.
Intervention characteristics	Studies with only maxillary and mandibular, infiltrations and block anaesthesia administered manually were included. Trials studying computerised delivery routes were excluded as they are not used routinely. Trials evaluating the less commonly used supplemental anaesthetic techniques after the routine infiltration or block anaesthesia, and those involving intraosseous, intraligamentary, intrapulpal and intrapocket routes were also excluded.
Outcome characteristics	Trial included should report outcome measures as below: time taken for onset of anaesthesia and duration of anaesthesia using Electric Pulp Tester (EPT).[22,23] anaesthesia success defined as none or mild pain measured using Heft-Parker Visual Analogue Scale (VAS)[24] during clinical instrumentation or measured by no response by tooth to maximal stimulation (80 μA) on two or more consecutive tests with EPT if there was no instrumentation. evaluation of post-injection pain using VAS, and/or post-injection adverse events reported (eg swelling, bruising, trismus, paraesthesia, etc.)

Data abstraction was performed in Microsoft Excel, with forms noting year of publication, country of study, demographics details of patients, details of study design, verification of study eligibility, quality assessment, participants' characteristics, intervention details including doses and type of needle used, and the measurements of anaesthesia safety and effectiveness. Data on time of onset and duration of onset was extracted as average time in minutes with their standard deviations (SD). Data on pain felt during injection, and after, was extracted as mean Heft-Parker VAS scores with their standard deviations. Finally, data on post-injection sequelae were extracted as mean Heft-Parker VAS score with their standard deviations and number of patient reporting abnormal symptoms post-injection. For the one trial that reported standard error of the mean (SE),[5] SD was calculated using the formula $SD = SE \times \sqrt{N}$ where N is the total number of patients in each arm.

2.4. Statistical analyses

The statistical reporting of one trial lacked important information, and the author was unsuccessfully contacted for the necessary clarifications.[15] Data from eight trials[5,16–20,30,31] were therefore included in this meta-analysis.
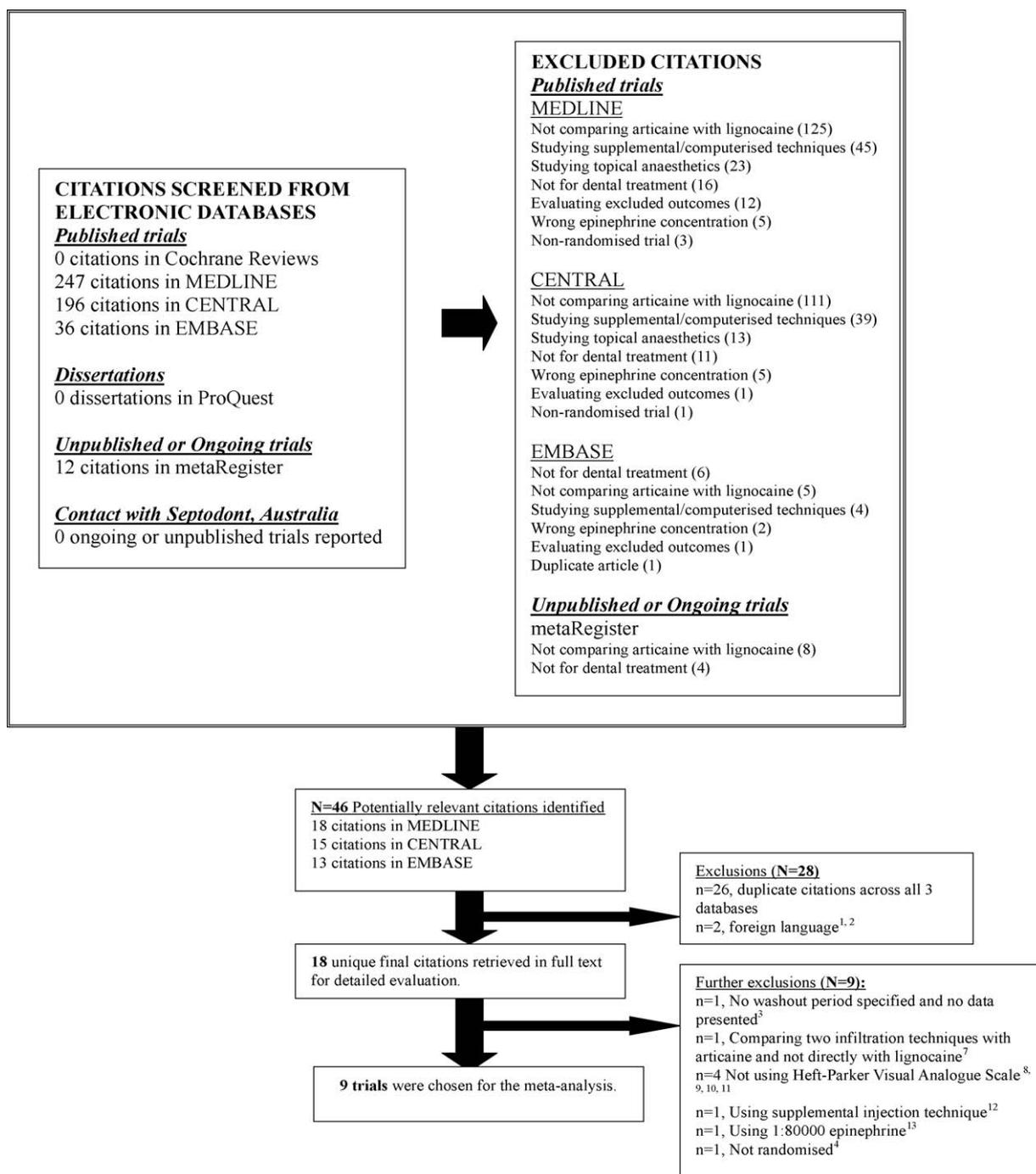

EXCLUDED CITATIONS
Published trials
MEDLINE
Not comparing articaine with lignocaine (125)
Studying supplemental/computerised techniques (45)
Studying topical anaesthetics (23)
Not for dental treatment (16)
Evaluating excluded outcomes (12)
Wrong epinephrine concentration (5)
Non-randomised trial (3)

CENTRAL
Not comparing articaine with lignocaine (111)
Studying supplemental/computerised techniques (39)
Studying topical anaesthetics (13)
Not for dental treatment (11)
Wrong epinephrine concentration (5)
Evaluating excluded outcomes (1)
Non-randomised trial (1)

EMBASE
Not for dental treatment (6)
Not comparing articaine with lignocaine (5)
Studying supplemental/computerised techniques (4)
Wrong epinephrine concentration (2)
Evaluating excluded outcomes (1)
Duplicate article (1)

Unpublished or Ongoing trials
metaRegister
Not comparing articaine with lignocaine (8)
Not for dental treatment (4)

CITATIONS SCREENED FROM ELECTRONIC DATABASES
Published trials
0 citations in Cochrane Reviews
247 citations in MEDLINE
196 citations in CENTRAL
36 citations in EMBASE

Dissertations
0 dissertations in ProQuest

Unpublished or Ongoing trials
12 citations in metaRegister

Contact with Septodont, Australia
0 ongoing or unpublished trials reported

N=46 Potentially relevant citations identified
18 citations in MEDLINE
15 citations in CENTRAL
13 citations in EMBASE

Exclusions (**N=28**)
n=26, duplicate citations across all 3 databases
n=2, foreign language[1,2]

18 unique final citations retrieved in full text for detailed evaluation.

Further exclusions (**N=9**):
n=1, No washout period specified and no data presented[3]
n=1, Comparing two infiltration techniques with articaine and not directly with lignocaine[7]
n=4 Not using Heft-Parker Visual Analogue Scale[8,9,10,11]
n=1, Using supplemental injection technique[12]
n=1, Using 1:80000 epinephrine[13]
n=1, Not randomised[4]

9 trials were chosen for the meta-analysis.

Fig. 1 – Flowchart of the search process.

Table 2 – Summary of Trial Characteristics Included in the Meta-analysis.

Study		Claffey et al.[16]	Evans et al.[17]	Kanaa et al.[18]	Malamed et al.[5]	Mikesell et al.[19]	Robertson et al.[20]	Sherman et al.[15]	Abdulwahab et al.[30]	Tortamano et al.[31]
Characteristics										
Total number		72	80	31	1325	57	60	42	18	40
Mean age in years ± standard deviation and/or (range in years)		(A) 31 ± 8.3 (21–53) (L) 31 ± 8.0 (20–48)	(20–36)	22.8 ± 2.1	(A) 36.2 ± 15.4 (L) 36.5 ± 15.4	28 (19–60)	27 (19–51)	N.A.	24.9 (18–53)	(A) 29.9 (L) 34.1
Gender distribution of patients (females/males)		(A) 24/13 (L) 23/12	34/46	16/15	(A) 464/418 (L) 259/184	27/30	34/26	(A) 13/7 (L) 8/12	12/6 12/6	(A) 10/10 (L) 14/6
Intervention characteristics										
Number of patients	(A) (L)	37 35	80 80	31 31	882 443	57 57	60 60	18 18	20 20	20 20
Anaesthetic dose in mL	(A) (L)	2.2 2.2	1.8 1.8	1.8 1.8	Mean 2.5 ± 1.8 Mean 2.6 ± 1.7	1.8 1.8	1.8 1.8	0.9 0.9	3.6 3.6	1.7 1.8
Injection route—INF: infiltration; IANB: inferior alveolar nerve block		IANB	INF	INF	INF and IANB	IANB	INF	INF and Gow-Gates Block	INF	IANB
Location of teeth anaesthetised—MD: mandibular; MX: maxillary		MD posteriors	MX lateral incisor and MX fist molar	MD first molar	All	MD posteriors	MD posteriors	MX and MD posteriors	MD 1st Molar	MD posteriors
Validity assessment										
Random sequence generation		U	A	A	U	A	A	A	A	U
Allocation concealment		U	U	U	U	A	A	A	A	U
Blinding of examiners		A	A	A	U	A	A	U	A	A
Handling of losses		A	A	A	A	A	A	A	N.A.	N.A.
Analyses for losses		N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	I	A	A

Key: (A) – Articaine group (intervention), (L) – Lignocaine group (comparator), N.A. – Not applicable, A = Adequate, U = Unclear, I = Inadequate.
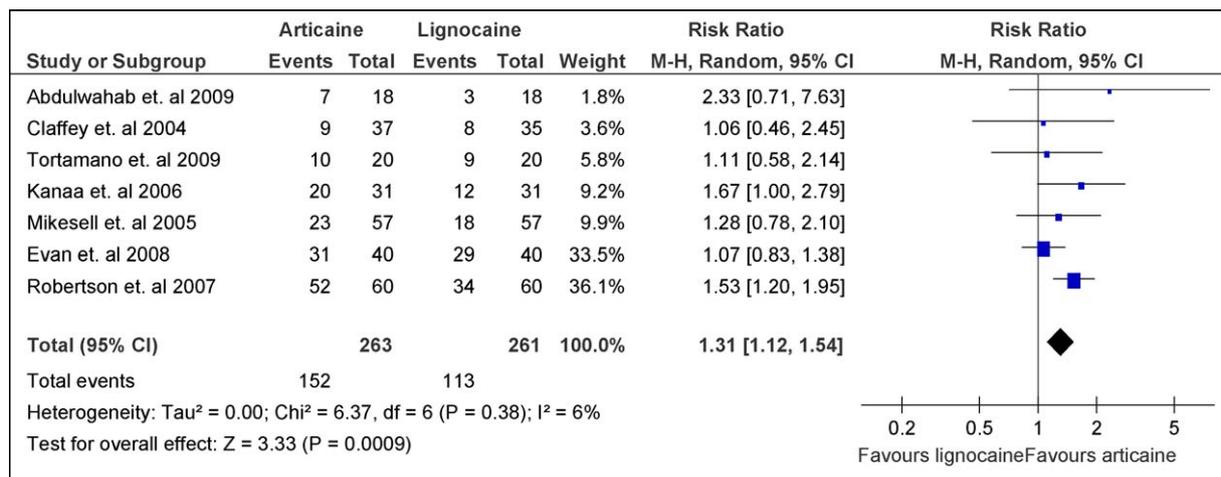
Fig. 2 – Comparative forest plot between articaine and lignocaine showing anaesthetic success achieved in the first molar area.

Revman version 5 software was used for statistical analyses. The data category common amongst all studies was for the posterior first molar and this was used for the pooled analysis. Four outcomes were analyzed: (1) anaesthetic success, (2) time of onset of anaesthesia, (3) post-injection pain from the time of anaesthetic reversal to 3 days after, and (4) adverse effects/events.

Due to the anticipated variability in included trials, a random effects model was chosen. To identify heterogeneity, the overlap of the 95% CI for the results of individual studies was inspected graphically, and the Cochran test for homogeneity and the I^2 test were calculated to check for heterogeneity and inconsistency, respectively.

Planned subgroup analyses were based on age, gender, arch location (maxillary versus mandibular teeth), type of injection (infiltration or block) and the dose of anaesthetic. A sensitivity analysis was also considered to assess the effects of low quality RCTs.

2.5. Validity assessment

The quality of the trials selected was evaluated by assessing the randomization process, allocation concealment, blinding, description of losses, and the use of intention to treat analyses. The assessment criteria are given in Appendix Table II and the individual study rating in Appendix Table III.

3. Results

No restrictions were placed on years. Restrictions were placed on the language and publication status to identify RCTs. Two citations in German language were excluded from the review.[1,2] Nine trials qualified for this meta-analysis. Fig. 1 presents the results of the search process. The characteristics of the included trials, including their methodological quality are summarized in Table 2.

The Heft-Parker Visual Analogue Scale (VAS) used in the included studies has four levels of pain: (1) 0 mm or no pain, (2) more than 0 and less than or equal to 54 mm is mild pain with descriptors like "faint", "weak" and "mild", (3) more than 54 mm to less than 114 mm is moderate pain, and (4) 114 mm or greater is severe pain including the descriptors of "strong", "intense" and "maximum possible".

The comparative anaesthetic success between articaine and lignocaine, adverse events and post-injection pain from anaesthetic reversal to three days later are shown in Figs. 2–4 respectively. The comparative forest plot for onset of anaesthetic action between articaine and lignocaine is
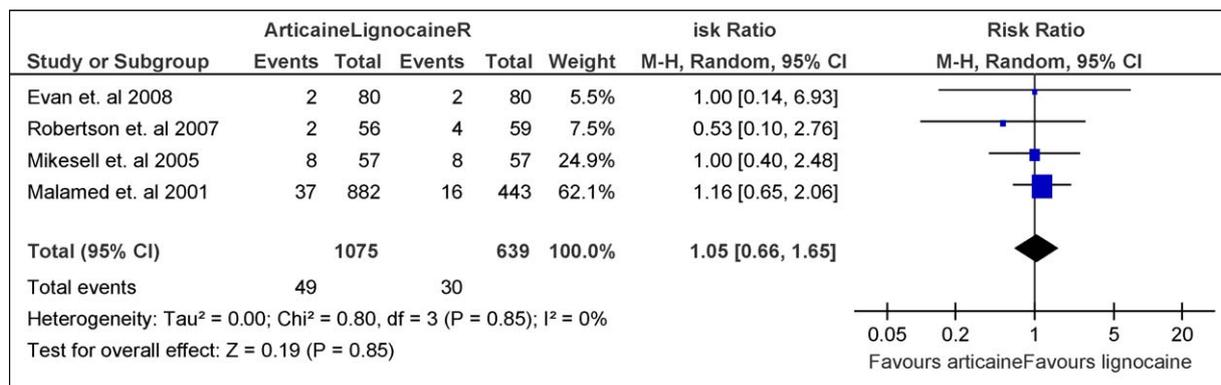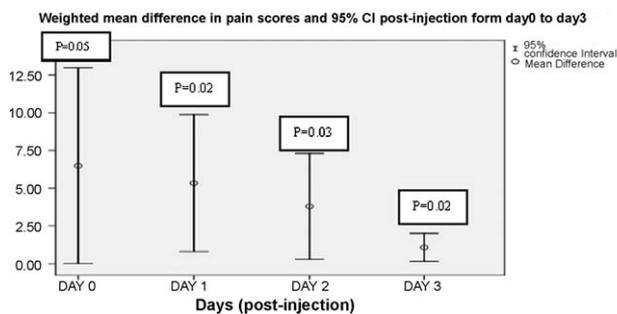

Fig. 3 – Comparative forest plot between articaine and lignocaine showing post-injection adverse events.

Fig. 4 – Weighted mean differences in pain score and 95% CI post-injection from Day 0 to Day 3.

presented in Appendix Fig. I. In addition to basic statistical data, the forest plots for each outcome category are shown. A summary effect measure and the relative weightings for each study were calculated. No significant heterogeneity was noted for any analyses. Neither the planned subgroup analyses assessment nor the publication bias assessed by preparing a funnel plot was implemented because of the small number of studies that eventually qualified.

The relative risk for achieving the event of an anaesthetic success in the first molar area between articaine and lignocaine is 1.31 (95% CI 1.12–1.54, $P = 0.0009$, $Z = 3.33$). The relative risk of adverse post-injection events between articaine and lignocaine is 1.05 (95% CI 0.66–1.65, $P = 0.85$, $Z = 0.19$).

Fig. 4 shows a graph of forest plots from Appendix Figs. III–VI. Articaine scored higher on pain scores post-injection than lignocaine from anaesthetic reversal to third day after, as measured by VAS. Weighted mean difference (WMD) in pain scores between articaine and lignocaine is 6.49 (95% CI 0.02–12.96, $P = 0.05$) upon anaesthetic reversal decreasing to 1.10 (95% CI 0.18–2.02, $P = 0.02$) on the third day after injection.

4. Discussion

4.1. Summary of key findings

This systematic review supports the argument that articaine as compared with lignocaine provides a higher rate of anaesthetic success, with comparable safety to lignocaine when used as infiltration or blocks for routine dental treatments. The improved anaesthetic effect is demonstrated in the data abstracted for first molars. While the findings indicate that articaine injection can cause slightly more post-injection pain in the area injected than lignocaine, the difference is small in clinical terms, and none of the studies reported it as a problem from the patient's perspective. Post-injection adverse events related to articaine and lignocaine in the included trials were reported as swelling, bruising, trismus, soreness, hyperesthesia and/or paraesthesia. Haas and Lennon[32] have demonstrated that articaine increased the risk of non-surgical postoperative paraesthesia. This finding, however, could not be confirmed in a recent study by Pogrel.[33] This meta-analysis thus supports a recommendation for 4% articaine (1:100,000 epinephrine) in routine dental practice over and above 2% lignocaine (1:100,000 epinephrine).

4.2. Biological and clinical interpretation

The findings in this study are consistent with the manufacturer's information on articaine that suggests an improved anaesthetic effect. This may be explained to its chemical structure that increases its liposolubility that permits it to diffuse to the teeth in addition to the main action of blocking nerve action potential, and the 4% concentration used in a cartridge as opposed to 2% for lignocaine. The fact that articaine possesses both an amide and an ester linkage is of clinical significance in minimizing the risk of overdose (toxic reaction).[27] The elimination half-life of most amide local anaesthetics is approximately 90 min and articaine's is 27 min.[27]

Both lignocaine and articaine have the same maximum milligram dose of 500 mg (recommended dose, 6.6–7 mg/kg) for the adult patient.[28] Because articaine is marketed as a 4% solution, the manufacturer's maximum recommended dose for a health 70-kg adult is 7 cartridges of an articaine solution compared with 13 cartridges of a 2% lignocaine solution.[28]

4.3. Limitations

The exhaustive literature search, explicit selection criteria used and validity assessment of the included trials shows a thoroughness and a systematic approach in reaching the conclusion. When information was doubtful in a study, the authors were contacted to clarify.

One limitation of this review is possible language bias, as indicated by the exclusion of two trials[1,2] written in German. However, the effect of this exclusion is probably minor as judged from their conclusions in the English abstract. Hidding and Khoury[1] reported a high standard of security in dental local anaesthesia, and Khoury et al.[2] stated there was no significant difference between articaine and lignocaine as far as effect on blood pressure, pulse, and tissue rehabilitation are concerned. Khoury also stated that the better results of 4% articaine compared to 2% lignocaine were statistically not significant.

Having only one reviewer performed the data abstraction which may increase the likelihood of inaccuracy and bias. However, data abstraction was checked several times to avoid errors in data. Studies using a Heft-Parker Visual Analogue Scale were pooled in this meta-analysis and all modified pain scales were excluded, so the findings are more generalisable to adult patients who are able to score their pain on the scale. Five out of nine studies included in this meta-analysis rated poorly on methodological validity assessment which may bias the results.

4.4. Comparison to previous work

A relevant meta-analysis in the area is lacking for the purpose of comparison. Malamed SF[27] in response to a letter to the editor in JADA 2000 by Schertzer[6] states that clinical observations (as opposed to evidenced-based research) indicate that articaine possesses two features that practicing doctors find important: a faster onset of anaesthesia and ''you don't miss as often.'' This latter claim requires clinical verification in studies which so far have been underpowered. This systematic review provides the power to confirm the higher success rate of anaesthesia with articaine as opposed to lignocaine as witnessed in clinical observations.

Lack in collecting data for onset of anaesthesia across studies is disappointing as it is a very significant clinical property desired by the clinicians.

4.5. Applicability of findings

Articaine is widely available world-wide and as cost-effective as lignocaine. This makes it a practical choice for use in routine dental practices. Articaine's superiority to lignocaine's use in complex dental procedures is not yet illustrated in a relevant study. The use of articaine is not recommended in children under 4 years of age as no data exists to support such use.

4.6. Future research directions

It is suggested that in future, a uniform pain scoring system be developed to study the efficacy and safety of articaine in dental procedures for children. There is lack of data indicating whether articaine has faster onset of anaesthesia than lignocaine as seen by doctors in the clinical setting.[27] This lack needs to be addressed in future trials to give dental practitioners the verification of their experience in practice. It is also suggested to improve the quality of randomized controlled trials particularly in the areas of allocation concealment, handling of losses and intention to treat analysis.

Acknowledgement

Appendix A. Appendix A

See Tables I–III and Figs. I–VI.

Table I – Search strategy.	
Databases	Keywords
Databases of published trials	
MEDLINE	
Searched via OvidSP (1950–October 2009)	(exp carticaine/OR articaine.tw OR septanest.tw OR septocaine.tw OR ultracaine.tw OR exp Anaesthesia, Dental/) and (exp Lidocaine/OR lignocaine.tw OR Xylocaine.tw) and (randomized controlled trial.pt OR clinical trial.pt OR exp Clinical Trial/OR random$.tw OR review.pt and medline.tw) LIMIT to HUMANS
Cochrane Central Register of Controlled Trials (CENTRAL)	
Searched via OvidSP (1991–October 2009)	(exp carticaine/OR exp dental anaesthesia/) and (exp Lidocaine/or lignocaine.mp.)
EMBASE	
Searched via Embase.com (October 2009)	('articaine'/exp OR 'articaine') OR 'dental anaesthesia' AND (('lignocaine'/exp OR 'lignocaine') OR ('lidocaine'/exp OR 'lidocaine')) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim AND [article]/lim AND humans]/lim
Databases of dissertations	
ProQuest Health and Medical Complete at 31st October 2009 Via ProQuest 5000	(articaine OR carticaine) in dissertations
Databases of dissertations	
metaRegister of Controlled Trials searched via www.controlled-trials.com at 31st October 2009	(articaine OR carticaine) AND (lignocaine OR lidocaine)

Table II – Five criteria for assessing quality of included RCTs.	
Criteria factor	Description definition
1. Random sequence generation[25]	*Adequate*: Generated by random numbers or tables, tossed coin, shuffled cards, or any other random sequence generation satisfying the CONSORT criteria. In case of restricted randomization, the method used to restrict randomization and the method used for random selection should be specified. *Unclear*: Just the term randomized or *randomly allocated* without information of the exact randomization method. *Inadequate*: Alternate assignment, case record number, etc.

Table II (*Continued*)

Criteria factor	Description definition
2. Allocation concealment[26]	
Central randomization	*Adequate*: Measures for concealing allocation do not fall into the category of unclear measures. *Unclear*: No reported negation of disclosing participants' prognostic data to central office staff before clinician obtains treatment assignment. No reported information on whether allocation sequence is concealed to central staff before a participant is irreversibly registered and no assurance that the sequence is strictly sequentially administered. Minimization is interpreted as inherently strictly sequentially administered
Envelope method	*Adequate*: Envelopes opaque, sealed, and sequentially numbered. *Unclear*: Above-mentioned criteria not met.
Numbered coded vehicles	*Adequate*: Vehicles were indistinguishable, sequentially numbered, and sequentially administered. No implication that the investigator allocating them knew the contents. *Unclear*: No information on whether vehicles were sequentially administered
All methods	*Adequate*: Other measures of convincing allocation concealment. *Inadequate*: Allocation by alternation, date of birth, case record number, or open table of random numbers.
3. Blinding of examiner[25]	*Adequate*: The outcome assessor could not know to which group the participants had been randomized. *Unclear*: No details in the text on procedures. *Inadequate*: The outcome assessor could assume to which group the participants had been randomized.
4. Handling of losses[25]	*Adequate*: Statement about the participants who were randomized, statement (or inferring from the tables) about the participants that violated the protocol of the study, dropped out, or were withdrawn for each group, and the respective reasons for each group. *Unclear*: No details in the text. *Inadequate*: Numbers randomized not stated or not specified for each group. Numbers of participants lost from analysis without the reasons for each group.
5. Analyses for losses[25]	*Adequate*: Use of intention to treat analyses to include all participants randomized into trial irrespective of what happened. *Unclear*: No details in the text. *Inadequate*: Such approaches were not used. *Not applicable*: No losses occurred.

Table III – Assessing quality of included trials.

| Study	Quality ratings 1	2	3	4	5	Explanation
1. Claffey et al.[16]	U	U	A	A	N	Exact method of randomization not mentioned. No mention if injections were sequentially administered.
2. Evans et al.[17]	A	U	A	A	N	Random number table. No mention if injections were sequentially administered.
3. Kanaa et al.[18]	A	U	A	A	N	Central randomization, computer generated. No mention of allocation concealment measures. The investigator who enrolled the volunteers was blinded to the order of injection. Both the volunteer and the investigator of anesthetic efficacy were blinded to the drug being used.
4. Malamed et al.[5]	U	U	U	A	N	No mention of randomization process. No mention of allocation concealment measures.
5. Mikesell et al.[19]	A	A	A	A	N	The anesthetic solutions administered were blinded by masking the appropriate cartridges with opaque labels, which were labeled with the six-digit numbers.
6. Robertson et al.[20]	A	A	A	A	N	Randomly assigned the two anesthetic formulations six-digit numbers from a random number table. Masked the lignocaine and articaine cartridges with opaque labels and wrote the corresponding six-digit codes on each cartridge. Recorded only the random numbers on the data collection sheets.
7. Sherman et al.[15]	A	A	U	A	I	Random number table. Masking the aluminum caps with a permanent black marker and masking the appropriate cartridges with an opaque label. 2 patients were excluded due to anaesthetic failure. Intention to treat analyses not used.
8. Abdulwahab et al.[30]	A	A	A	N	A	Random number table. 6 × 6 Latin Square.
9. Tortamano et al.[31]	U	U	A	N	A	No mention of randomization process. No explanation of allocation concealment measures.
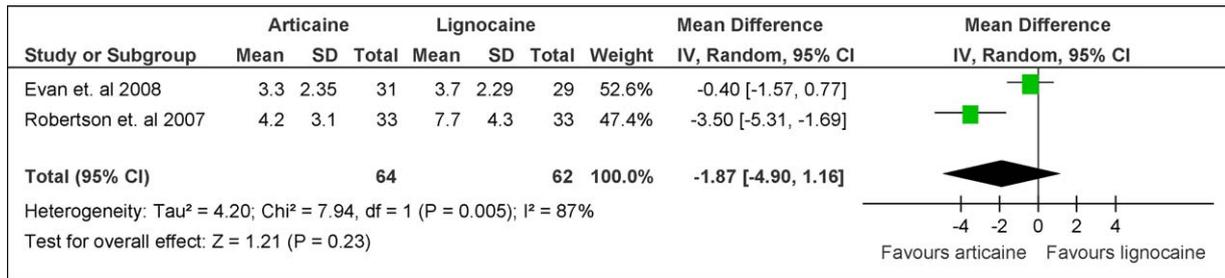
Fig. I – Forest plot for articaine versus lignocaine showing mean onset of action measured in minutes.
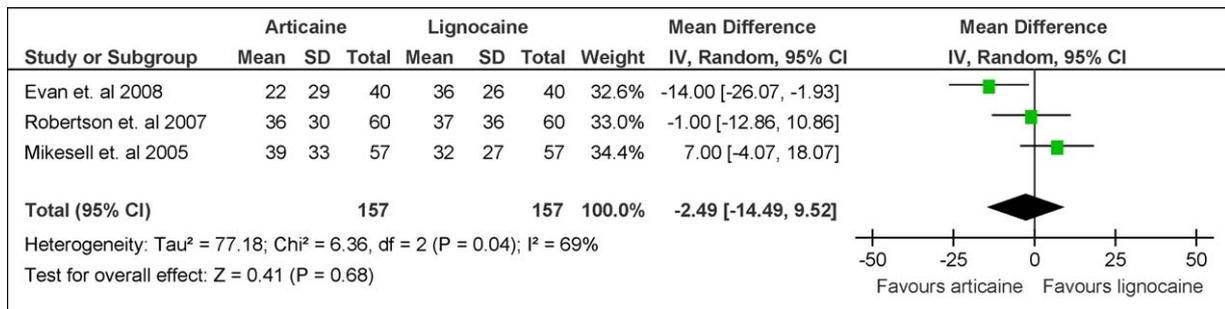

Fig. II – Forest plot for articaine versus lignocaine showing pain as measured by mean VAS scores during solution deposition.
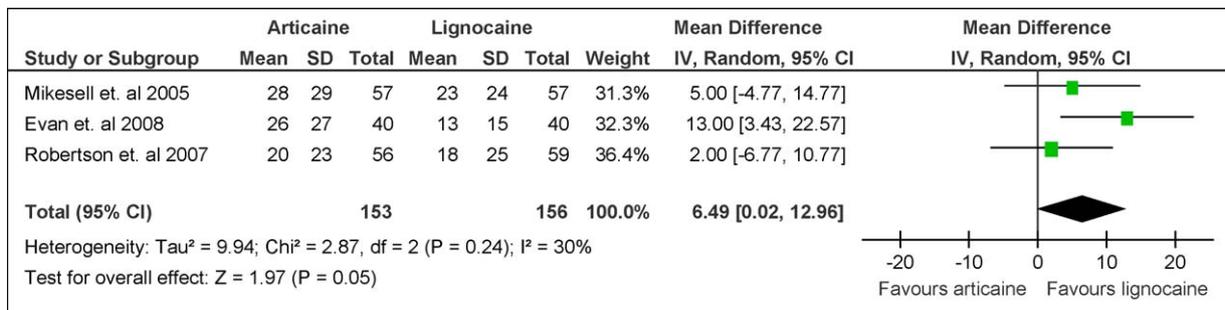

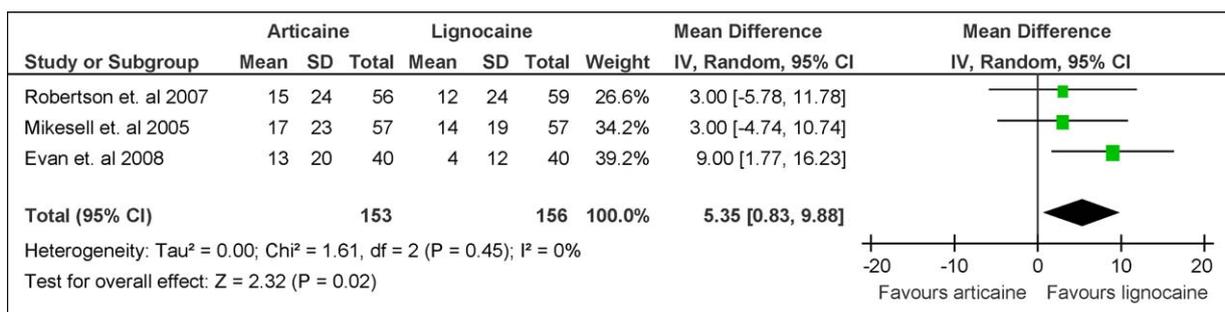Fig. III – Forest plot for articaine versus lignocaine of WMD in pain scores post-injection on Day 0.

Fig. IV – Forest plot for articaine versus lignocaine of WMD in pain scores post-injection on Day 1.
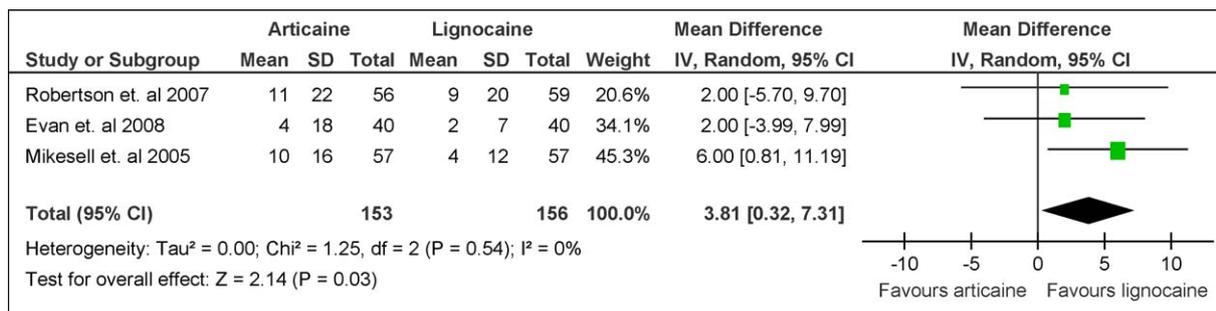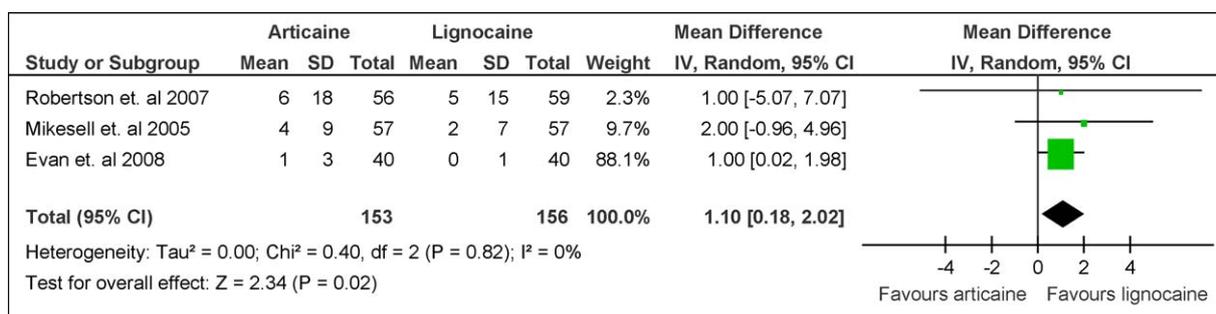
Study or Subgroup	Articaine Mean	SD	Total	Lignocaine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Robertson et. al 2007	11	22	56	9	20	59	20.6%	2.00 [-5.70, 9.70]
Evan et. al 2008	4	18	40	2	7	40	34.1%	2.00 [-3.99, 7.99]
Mikesell et. al 2005	10	16	57	4	12	57	45.3%	6.00 [0.81, 11.19]
Total (95% CI)			153			156	100.0%	3.81 [0.32, 7.31]

Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Fig. V – Forest plot for articaine versus lignocaine of WMD in pain scores post-injection on Day 2.

Study or Subgroup	Articaine Mean	SD	Total	Lignocaine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Robertson et. al 2007	6	18	56	5	15	59	2.3%	1.00 [-5.07, 7.07]
Mikesell et. al 2005	4	9	57	2	7	57	9.7%	2.00 [-0.96, 4.96]
Evan et. al 2008	1	3	40	0	1	40	88.1%	1.00 [0.02, 1.98]
Total (95% CI)			153			156	100.0%	1.10 [0.18, 2.02]

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.34 (P = 0.02)

Fig. VI – Forest plot for articaine versus lignocaine showing of WMD in pain scores post-injection on Day 3.

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