DOES ARTICAINE PROVIDE AN ADVANTAGE OVER LIDOCAINE IN PATIENTS WITH SYMPTOMATIC IRREVERSIBLE PULPITIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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Abstract

Introduction: Profound pulpal anesthesia can be difficult to achieve for patients with irreversible pulpitis due to factors such as altered resting potentials, reduced thresholds of excitability and the tetrodotoxin-resistant (TTXr) class of sodium channels. Clinicians might try various strategies to address this problem such as changing the anesthetic agent, for example using articaine instead of lidocaine injection, and by using a supplemental anesthetic injection delivery technique. The principal aim of this study was to provide a systematic review and meta-analysis to address the PICO question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events? The secondary aim was to identify, characterize and assess the quality of peer-reviewed clinical studies that investigated pulpal anesthesia achieved by the administration of supplemental anesthetic solution following prior anesthesia delivered via any route in adults with symptomatic irreversible pulpitis.

*Methods***:** In Part 1, a protocol was prepared and registered on PROSPERO. Electronic searches were conducted in MEDLINE, Scopus, Cochrane Library and ClinicalTrials.gov using strict inclusion and exclusion criteria. Two independent reviewers assessed eligibility for inclusion and quality with any disagreements resolved by consensus. Using RevMan software, weighted anesthesia success rates and 95% confidence intervals (CI) were estimated and compared using a random-effects model. In Part 2, electronic searches were conducted in MEDLINE, Scopus, Cochrane Library and ClinicalTrials.gov for clinical trials published in peer-reviewed journals that investigated pulpal anesthesia achieved by administration of supplemental anesthetic solution delivered via any route following prior anesthesia in adults with symptomatic irreversible pulpitis. Studies were characterized and, if applicable, assessed for quality using the Cochrane Collaboration Risk of Bias tool.

Results: In Part 1, 275 studies were initially identified from the search; ten double-blind, randomized clinical trials met the inclusion criteria. For combined studies, articaine was more likely than lidocaine to achieve successful anesthesia [n=10, OR=2.21 (95% CI, 1.41-3.47; P=0.0006), I^2=40%]. Maxillary infiltration subgroup analysis showed no significant difference between articaine and lidocaine [n=3, OR=3.99 (95% CI, 0.50-31.62; P=0.19), I^2=59%]. For combined mandibular anesthesia studies articaine was superior to lidocaine [n=8, OR=2.20 (95% CI, 1.40-3.44; P=0.0006), I^2=30%] with further subgroup analysis showing no difference for mandibular block anesthesia [n=5, OR=1.44 (95% CI, 0.87-2.38;P=0.16), I^2=0%]. When used for supplemental infiltration following successful mandibular block anesthesia, articaine was significantly more effective than lidocaine [n=3, OR=3.55 (95% CI, 1.97-6.39; P<0.0001), I^2= 9%]. There were no reports of adverse events. In Part 2, 16 studies were identified, characterized, and assessed for quality. Eight studies evaluated the success of supplemental buccal, lingual, periodontal ligament and intrapulpal infiltration injections. There was considerable heterogeneity between studies in quality and the variable being evaluated: type and/or volume of anesthetic solution and location of injection. Eight other studies evaluated supplemental intraosseous injections using articaine, lidocaine or mepivacaine; all were uncontrolled before-after studies.

Conclusions: The systematic review of double-blind, randomized clinical trials provides level 1 evidence to support the use of articaine for patients with symptomatic irreversible pulpitis. There is a significant advantage to using articaine over lidocaine for supplementary buccal infiltration following mandibular block anesthesia, but no apparent advantage when used for mandibular block anesthesia alone or for maxillary infiltration. There is a need for randomized double-blind studies that evaluate the efficacy and incidence of adverse events from articaine and lidocaine delivered by intraosseous, intraligamental and intrapulpal routes to reduce pain in patients with symptomatic irreversible pulpitis.

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Chapter 1: Introduction and Review of the Literature

The clinical diagnosis of symptomatic irreversible pulpitis is based on subjective and objective findings signifying that the vital inflamed pulp is "incapable of healing", with subjective descriptors that include lingering thermal pain, spontaneous pain and referred pain (1). Root canal treatment has been described as significantly more painful for teeth with irreversible pulpitis and symptomatic apical periodontitis compared to teeth with necrotic pulps and asymptomatic apical periodontitis (2). In addition, achieving profound pulpal anesthesia can be challenging in these cases (3, 4). For example, anesthesia may be sufficiently profound to access the pulp chamber, but canal instrumentation can result in severe pain (4). In a survey of Diplomates of the American Board of Endodontics, 84% of respondents reported experiencing difficulties in anesthetizing acutely painful mandibular molars (5). The inability to achieve pulpal anesthesia has been shown to increase a patient's fear and anxiety, exacerbate systemic medical issues, extend the appointment duration, and generate doubt in the operator; any of these factors can contribute to the impression that receiving root canal treatment is a painful procedure (6). Clinicians might try various strategies to address this problem such as changing the anesthetic agent, for example using articaine instead of lidocaine injection, and by using a supplemental anesthetic injection delivery technique (7).

Lidocaine, also known as lignocaine, is an amino-amide anesthetic introduced to the market in 1948, that has been described as the most commonly utilized local anesthetic for dental use in the United States (US) (8) and elsewhere (9, 10). This anesthetic provides pulpal anesthesia for approximately one hour and soft tissue anesthesia for three to five hours (8). Articaine, the second most commonly used dental anesthetic, was first introduced to the European market in 1976 and entered the US market in 2000 (11). By 2007, articaine was

described as accounting for approximately 25% of total sales, second only to lidocaine at 54% (12). The chemical composition of articaine contains a unique thiophene ring, instead of the benzene ring found in lidocaine and other amide local anesthetics. This difference increases lipid solubility, thereby increasing diffusion through the lipid membrane of the epineurium, which purportedly explains its faster onset and higher success rate when compared to lidocaine (11, 13).

In cases of teeth with symptomatic irreversible pulpitis the inadequacy of the primary local anesthetic procedure requires the clinician to employ alternative strategies to attain good pulpal anesthesia in order to proceed with treatment (14). These strategies include utilizing a different anesthetic solution, or adding an additional supplemental injection (15, 16). Several supplemental injection techniques are available: infiltration, intraligamentary, and intraosseous. The infiltration injection involves the deposition of anesthetic solution intrapulpally or in the soft tissue at the buccal or lingual region of the tooth. The intraligamentary injection, also known as the periodontal ligament (PDL), allows the deposition of the anesthetic solution directly into the periodontal ligament area; this forces anesthetic solution through the cribriform plate and into the cancellous bone that surrounds the tooth (17-20). The intraosseous injection allows the placement of the local anesthetic solution directly into the cancellous bone near the tooth. A clinical advantage of the intraosseous injection over the intraligamental injection may lie in the more apical insertion of the perforator and needle through non-keratinized tissue (21). This approach has been practiced in dentistry since beginning of the twentieth century (22). More recently, it has been accomplished by a delivery system. The two most commonly evaluated systems are the Stabident® (Fairfax Dental Inc., Miami, FL) and X-Tip® (Dentsply Maillefer, Tulsa, OK). The Stabident® system consists of a 27-gauge perforator driven by a slow-speed handpiece to perforate the buccal cortical bone. The opening allows the clinician to then place a

short needle in the hole and deliver anesthetic solution (23). The X-Tip® system consists of a 2-part perforator/guide sleeve component. Similarly to the Stabident® system, the first step uses a perforator driven by a slow speed hand piece to penetrate the cortical bone. The difference is that once the perforation is accomplished, the perforator is withdrawn, leaving the sleeve in the bone to function as an insertion guide for the needle.

Systematic reviews are an integral component of evidence-based medicine, or "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (24). A systematic review aims to "collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question" (25). Systematic reviews of randomized trials are considered as level 1 evidence by the Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) (Appendix 1) (26). OCEBM levels provide a "hierarchy of the likely best evidence" that can be used as a "short-cut for busy clinician researchers, or patients, to find the likely best evidence" (27). In general, the steps required to perform a systematic review are to: (i) assess and develop a question, (ii) develop inclusion and exclusion criteria, (iii) search, select, and identify primary studies, (iv) analyze and perform meta-analysis if applicable, (v) address and report any potential biases, and (vi) interpret results to answer research questions. It is recommended that early in the process the systematic review protocol be registered with an electronic database such as PROSPERO (28). Registration has numerous functions. Primarily, it avoids bias in the conduct and reporting of systematic reviews and also helps to avoid unintended duplication (29).

Systematic reviews with meta-analysis that have focused on the efficacy of articaine compared to lidocaine for dental anesthesia have been published in a Chinese language journal

(30) and in English language journals (31, 32). Xiao et al. concluded that for cases of irreversible pulpitis, articaine was superior to lidocaine both overall and for maxillary anesthesia, but that there was no difference between the two solutions in achieving mandibular anesthesia; however, six of the nine papers included for analyses were Chinese language reports that were unable to be accessed (30). Katyal reported that articaine was more effective than lidocaine (also known as lignocaine) for anesthetizing maxillary and mandibular "1st molar region" teeth, and concluded that articaine is a superior anesthetic for use in routine dental procedures (31). Brandt et al. reported that articaine provided superior pulpal anesthesia when administered by infiltration but concluded that it was premature to recommend articaine over lidocaine for mandibular block anesthesia in cases of irreversible pulpitis (32). However, both of these reviews were based on searches conducted in 2009 that analyzed data from combined asymptomatic and symptomatic subjects enrolled in either crossover or parallel designed random controlled trials (31, 32). A preliminary electronic search revealed that since their publication, several randomized clinical trials comparing articaine and lidocaine for patients with symptomatic irreversible pulpitis had been published.

Purpose of the Study

The purpose of this study was two-fold:

1. The principal aim was to provide a systematic review and meta-analysis to address the PICO question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events?

2. The secondary aim was to identify, characterize and assess the quality of peer-reviewed clinical studies that investigated pulpal anesthesia achieved by the administration of supplemental anesthetic solution following prior anesthesia delivered via any route in adults with symptomatic irreversible pulpitis.

Chapter 2: Materials and Methods

Methods were based on the Institute of Medicine Standards for a comprehensive search (33), the Cochrane Handbook for Systematic Reviews of Interventions (25), and the Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Systematic Reviews in Health Care (34).

2.1 Systematic review and meta-analysis

Aim: to provide a systematic review and meta-analysis to address the PICO question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events?

Searches conducted in October 2013 for existing registered systematic reviews of similar topics on PROSPERO (28), the Cochrane Collaboration (25), and Joanna Brigg's Institute (35) revealed none in progress. A protocol was prepared and registered in the PROSPERO database (CRD42014005794), an international prospective registrar of systematic reviews (28).

2.1.1 Systematic review: Inclusion criteria

Studies were included that evaluated the pulpal anesthetic solutions of 4% articaine compared with 2% lidocaine, delivered as a similar volume dose of at least 1.0 mL per injection in combination with vasoconstrictor, in adult patients with symptomatic irreversible pulpitis. Studies employing anesthetic delivery via any delivery route were included. Additional criteria for eligibility were that the study provided original data and was a randomized, double-blind

clinical trial published in a peer-reviewed journal. Non-English language articles without English abstracts were excluded.

The primary outcome measure was the reduction of pulpal pain to a level that would allow endodontic treatment to proceed within 20 minutes of administration of local anesthetic, as defined by each trial [for example, by using Verbal Analog Scale, Visual Analog Scale (VAS), Heft Parker-Visual Analogue Scale (HP-VAS) and electric pulp tests and/or by initiating endodontic treatment procedures]. Data were presented as dichotomous outcomes of "successful anesthesia" or "unsuccessful anesthesia". Secondary outcomes to be measured were any adverse event. Studies were excluded if: (1) there was insufficient information about the diagnosis of symptomatic irreversible pulpitis and the definition of anesthetic success, and (2) dichotomous data for anesthesia outcome was unavailable.

2.1.2 Systematic review: Search methods

A comprehensive search of the electronic databases was conducted and reviewed by a medical librarian to identify eligible studies through electronic searches from 1976, when articaine was first introduced to the market (11), to October 2013. The search was subsequently updated in February 2015 (Table 1). The following electronic databases were searched: MEDLINE using PubMed search engine (http://www.ncbi.nlm.nih.gov/pubmed/) (36), Scopus (37), and the Cochrane Library (http://www.cochrane.org). ClinicalTrials.gov was searched to identify completed studies that were not yet published (keywords used were "lidocaine articaine"). Reference lists from identified trials and review articles were manually scanned to identify additional relevant studies. The search was also supplemented by hand searching major textbooks: *Handbook of Local Anesthesia 6th edition* (38), and *Successful Local Anesthesia for*

Restorative Dentistry and Endodontics (39). Two reviewers independently assessed eligibility of the studies by reading the title and the abstract. Potentially eligible studies were then assessed by reading the full text, and the final decision on inclusion was determined. Discrepancies between reviewers were resolved by consensus with a third person.

Table 1. Search strategy: Original search October 2013, last updated February 2015

Database	No.	Search History	Results
MEDLINE	1	exp lidocaine/	22095
	2	exp carticaine/	430
	3	ultracaine.mp.	44
	4	articaine.mp.	309
	5	carticaine.mp.	454
	6	2 OR 3 OR 4 OR 5	493
	7	exp Dental Pulp Diseases	9515
	8	1 AND 6 AND 7	14
	9	("root canal" adj3 operat$).mp.	25
	10	exp "Root Canal Therapy"	17651
	11	1 AND 6 AND 10	11
	12	1 AND 7	57
	13	6 AND 7	26
	14	1 AND 10	47
	15	6 AND 10	24
	16	12 OR 14	74
	17	13 OR 15	30
	18	16 OR 17	90
	19	(lidocain$ adj7 (compar$ or versus or vs) adj7 (carticain$ or ultracain$ or articain$)).mp.	48
	20	18 OR 19	**138**
Scopus	1	TITLE-ABS-KEY (lidocaine*)	64766
	2	TITLE-ABS-KEY (Carticain* OR articaine* OR ultracain*)	897
	3	1 AND 2	461
	4	TITLE-ABS-KEY ((dental pulp disease*) OR pulpi* OR canine* OR (oral pathology*) OR endodon* OR root* OR canal* OR tooth* OR dentis*)	1130989
	5	3 AND 4	**133**
Cochrane Library	1	MeSH descriptor [Carticaine] explode all trees	3
	2	MeSH descriptor: [Lidocaine] explode all trees	20
	3	MeSH descriptor: [Pulpitis] explode all trees	2
	4	#1 AND #2 AND #3	**1**

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

2.1.3 Systematic review: Data extraction

A data extraction sheet based on the Cochrane Consumers and Communication Review Groups data extraction template (40) was used by reviewers to record data extracted from the full-text article. In the event that details were not clear to the reviewers the authors were contacted for clarification. The data extracted from each included article was:

1. Article identifying information (author, year, country, title, journal),
2. Article characteristics (sample size, type of study design),
3. Characteristics of trial participants (number of patients for each intervention, mean age, gender distribution, preoperative pulpal diagnosis, method(s) to determine pre-operative pulpal diagnosis),
4. Type of intervention (anesthetic(s) used, anesthetic dose, injection route/delivery method),
5. Type of outcome measure (method to assess anesthesia success, time post injection to start assessing success, definition of success, adverse event),
6. Miscellaneous (conclusion, and source of funding/conflict of interest).

2.1.4 Systematic review: Risk of Bias assessment

The Cochrane Collaboration 'Risk of Bias' tool was used to assess the methodological quality of the included studies by ascertaining their validity, potentially identifying any egregiously biased studies, and determining variability in study results (heterogeneity) (25). Risk of bias domains assessed were selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other potential sources of bias. Risk of bias judgments were indicated as 'Low

risk', 'High risk' or 'Unclear risk' (25). Criteria for judging risk of bias follows Cochrane's Handbook Table 8.5.d (25). Assessments were made independently by the two reviewers, with any disagreements resolved by consensus. Studies with any high risk assessments were not included in the systematic review.

2.1.5 Systematic review: Data analysis

The outcomes "successful anesthesia" or "unsuccessful anesthesia" in accordance with the criteria of each study were recorded as dichotomous data. Meta-analysis was performed on the following groups of data:

1. Combined: all data obtained using any maxillary and mandibular anesthetic delivery route,

2. Subgroup: maxillary anesthesia using any delivery route,

3. Subgroup: combined mandibular anesthesia using any delivery route,

    3.1. Mandibular anesthesia using block anesthesia only,

    3.2. Mandibular anesthesia using supplemental infiltration when pulpal pain persisted despite clinical evidence of successful mandibular block anesthesia (defined as lip numbness).

The principal summary measures were odds ratios (ORs) that were calculated using a random effects model and the Mantel-Haenszel statistical method (RevMan Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis. Treatment differences were expressed graphically in forest plots. To assess the influence of an individual study on the pooled effect, sensitivity analysis was performed by omitting one study at a time. Statistical heterogeneity was assessed using the Q statistic value calculated according to the method of Cochrane Q test, and the I^2 test for inconsistency;

significance was set at $P \leq 0.1$ rather than the conventional $P \leq 0.05$ based on the Cochrane Collaboration recommendations (25). To assess publication bias, a funnel plot was created by plotting the log estimates of all studies against their standard error.

2.2 Supplemental anesthesia

Aim: to identify, characterize and assess the quality of peer-reviewed clinical studies that investigated pulpal anesthesia achieved by the administration of supplemental anesthetic solution following prior anesthesia delivered via any route in adults with symptomatic irreversible pulpitis.

2.2.1 Supplemental anesthesia: Inclusion criteria

Studies were included that evaluated the anesthetic solutions of articaine or lidocaine delivered via supplemental delivery route following prior anesthesia in adult patients with symptomatic irreversible pulpitis. Additional criteria for eligibility were that the study provided original data published in a peer-reviewed journal. Non-English language articles without English abstracts were excluded.

2.2.2 Supplemental anesthesia: Search methods, Data extraction and Risk of Bias assessment

A comprehensive search was conducted as previously described in Section 2.1.2. Two reviewers assessed eligibility of the studies by reading the title and the abstract. Potentially eligible studies were then assessed by reading the full text, and the final decision on inclusion was determined.

The same data extraction sheet previously described in Section 2.1.3, based on the Cochrane Consumers and Communication Review Groups data extraction template (40) was used by to record data extracted from the full-text.

The Cochrane Collaboration 'Risk of Bias' tool was used to assess the methodological quality of applicable studies as previously described in Section 2.1.4.

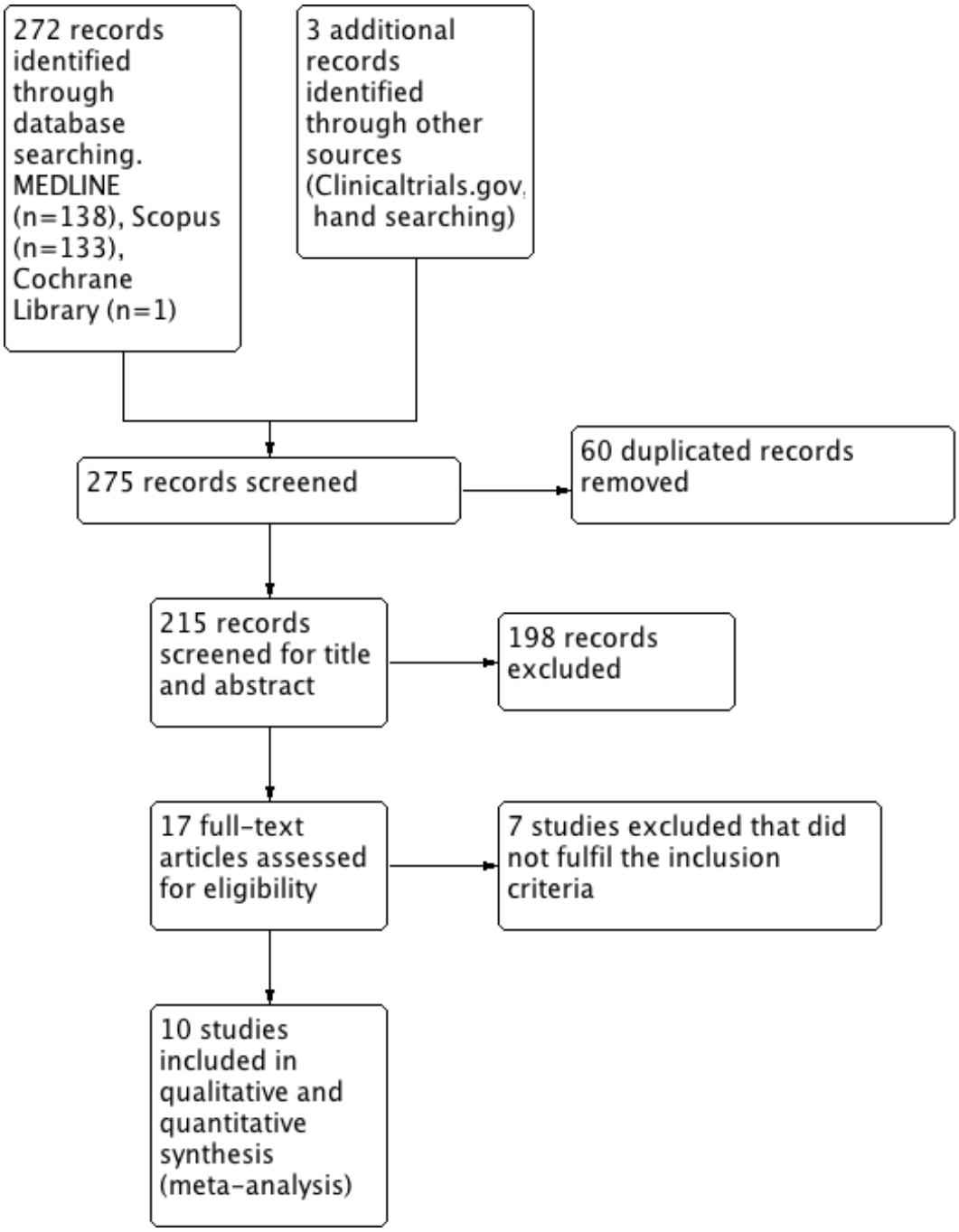
Chapter 3: Results

3.1 Systematic review and meta-analysis

3.1.1 Systematic review: Data extraction

Figure 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) study flow diagram describing the article inclusion process. A total of 275 records were initially screened and the full text of 17 studies were fully assessed. Seven studies were excluded because they did not meet the inclusion criteria: not a randomized double-blind study (41-44), did not compare articaine and lidocaine (42, 45, 46), or did not provide dichotomous data (47). The remaining ten studies met the inclusion criteria and were included in the meta-analysis (48-57).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) study flow diagram



3.1.2 Systematic review: Characteristics of included studies

The studies were unicentric trials published between 2004 and 2014 and involved a total of 746 adult patients diagnosed with symptomatic irreversible pulpitis and anesthetized with either articaine or lidocaine (Table 2). The trials were conducted in India (48, 49, 52, 56), the United States (50, 53, 54), Brazil (57) and England (51). Information about participant age was provided for all except one study (54); written communication with these authors confirmed that all participants were adults. For the remaining studies the mean ages ranged from 23 to 38 years. No significant associations between anesthesia outcome and age or gender were reported.

Table 2. Characteristics of studies included in meta-analysis

Author, year	Patients in meta-analysis (n)	Preoperative pulpal diagnosis	Location and tooth type	Anesthesic delivery route	Interventions compared	Epinephrine concentration	Method to assess pain	Definition of successful anesthesia	Results reported for anesthesia success
Aggarwal et al. 2009 (48)	60	Prolonged response to cold, positive response to EPT, absence of PARL, vital coronal pulp on access opening	Mand molars	All received IANB 1.7 mL of lido Then 2 min later received SupManBI and SupManLI of either 1.7 mL 4% arti or 1.7 mL 2% lido#	SupManBI 1.7mL + SupManLi 1.7mL arti Vs lido	1:200,000	HP-VAS*	No or mild pain during access cavity preparation and instrumentation	Arti: 20/30=67%, Lido: 14/30=47%
Ashraf et al. 2013 (49)	125	Prolonged response to cold, vital pulp tissue during access opening, absence of PARL	Mand molars	All received IANB 1.5 mL and LBI 0.3 mL of either 4% arti or 2% lido. If VAS score was moderate or higher then received 1.8 mL SupManBI of same anesthetic used for IANB	SupManBI 1.8mL arti Vs 1.8mL lido	1:100,000	HP-VAS*	No or mild pain during access cavity preparation and instrumentation	Arti: 41/58=71%, Lido: 17/58=29%
Claffey et al. 2004 (50)	72	Actively experiencing pain, prolonged response to cold, absence of PARL	Mand molars (n=65) premolars (n=7)	Patients received IANB of either 2.2 mL 4% arti or 2.2 mL 2% lido	IANB 2.2mL arti Vs 2.2mL lido	1:100,000	HP-VAS*	No or mild pain during access cavity preparation and instrumentation	Arti: 9/37=24%, Lido: 8/35=23%
Kanaa et al. 2012 (51)	100	Spontaneous pain or pain lasting over 1 min when provoked by thermal stimuli#	Max molars (n=44), premolars (n=24) anteriors (n=5)	Patients received MaxBI of either 2.0 mL 4% arti or 2% lido	MaxBI 2.0mL arti Vs 2.0mL lido	1:100,000 (arti) 1:80,000 (lido)	EPT	No response to EPT (reading >80)	Arti: 38/50=76%, Lido: 35/50=70%
Poorni et al. 2011 (52)	104	Prolonged response to cold, positive response to EPT, absence of PARL, vital coronal pulp on access opening	Mand molars	Patients received IANB of either 1.8 mL 4% arti or 1.8 mL 2% lido	IANB 1.8mL arti Vs 1.8mL lido	1:100,000	HP-VAS*	No or mild pain during access cavity preparation and instrumentation	Arti: 36/52=69%, Lido: 35/50=65%
Rogers et al. 2014 (53)	74	Greater than moderate pain, spontaneous and prolonged response to cold, absence of PARL, vital coronal pulp tissue on access opening	Mand molars	All received IANB 1.7 mL 4% arti Then if VAS pain score was moderate or higher received supManBI of either 1.7 mL 4% arti or 1.7 mL 2% lido	SupManBI 1.7mL arti Vs 1.7mL lido	1:100,000	HP-VAS*	No or mild pain during access cavity preparation and instrumentation	Arti: 24/39=62%, Lido: 13/35=37%
Sherman et al. 2008 (54)	40	Prolonged symptomatic response to cold, intact lamina dura	Posterior Mand (n=21) and Max (n=19) teeth	Patients received either 1.7 mL 4% arti or 1.8 mL of 2% lido by using either a GG block (mand teeth) or MaxBI (max teeth)	Mand: GG 1.7mL arti Vs 1.8mL lido; Max: MaxMI 1.7mL arti Vs 1.8mL lido	1:100,000	HP-VAS*	No or mild pain during access cavity preparation	Overall: Arti: 19/20=95%, Lido:16/20=80% Mandibular: Arti: 9/00=90%, Lido:8/11=73% Maxilllary: Arti: 10/10=100%, Lido:8/9=89%
Sood et al. 2014 (55)	100	Prolonged response to cold, positive response to EPT, absence of PARL	Mand molars (n=92) premolars (n=8)	Patients received IANB of either 1.8 mL 4% arti or 1.8 mL 2% lido	IANB 1.8mL arti Vs 1.8mL lido	1:100,000 (arti) 1:80,000 (lido)	EPT and VAS^	No or mild pain during access cavity preparation	Arti: 44/50=88%, Lido: 41/50=82%

Srinivasan et al. 2009 (56)	40	Prolonged response to cold, positive response to EPT, absence of PARL, vital coronal pulp on access opening	Max molars (n=20) premolars (n=20)	Patients received MaxBI of either 1.7 mL 4% arti or 2% lido	MaxBI 1.7mL arti Vs 1.7mL lido	1:100,000	VAS^	No or mild pain during access cavity preparation and instrumentation	Overall: Arti: 20/20=100%, Lido: 11/20=55% Molars: Arti: 10/10=100%, Lido: 3/10=30% Premolars: Arti: 10/10=100%, Lido: 8/10=80%
Tortamano et al. 2009 (57)	40	Moderate to severe spontaneous pain, prolonged response to cold, positive response to EPT	Mand molars (n=30) premolars (n=10)	Patients received IANB of either 3.6 mL 4% arti or 3.6 mL 2% lido	IANB 3.6mL arti Vs 3.6mL lido	1:100,000	EPT, verbal analog scale~	No or mild bearable pain when accessing pulp chamber	Arti: 13/20=65%, Lido: 9/20=45%

arti, articaine; EPT, electric pulp tester; GG, Gow Gates block; HP-VAS, Heft Parker Visual analogue scale; IANB, inferior alveolar nerve block; LBI, long buccal infiltration; lido, lidocaine; mand, mandibular; ManLI, mandibular lingual infiltration; max, maxillary; MaxBI, maxillary buccal infiltration; PARL, periapical radiolucency; SupManBI, supplemental buccal infiltration; SupManLI, supplemental lingual infiltration; VAS, visual analog scale

*HP-VAS categories:Mild pain >0 mm and ≤54 mm; Moderate pain >54 and <114 mm; Severe pain >114mm

^VAS categories: 0 - no pain; 1- mild discomfort; 10 - severe pain (Srinivasan et al 2009); 0 - no pain; 1- mild bearable pain; 2, moderate, unbearable pain; 3 - severe, intense and unbearable pain (Sood et al 2014)
~Verbal analog scale: 0 - no pain; 1- mild bearable pain; 2, moderate, unbearable pain; 3 - severe, intense and unbearable pain (Tortamano et al 2009)

Information confirmed in written correspondence with authors

3.1.3 Systematic review: Intervention

The intervention compared was the use of either articaine or lidocaine to anesthetize teeth with symptomatic irreversible pulpitis. There was considerable methodological heterogeneity between studies that included differences in anatomic location of teeth being anesthetized (maxilla or mandible, anterior or posterior), tooth type (molars, premolars or anterior teeth), volume of anesthetic solution administered during the intervention (1.7 mL, 1.8 mL, 2.0 mL, 3.6 mL), concentration of epinephrine (1:80,000, 1:100,000, 1:200,000) and anesthetic solution delivery route. Anesthetic solutions were delivered via Gow Gates block (GG), inferior alveolar nerve block (IANB), long buccal infiltration (LBI), mandibular lingual infiltration (ManLI), maxillary buccal infiltration (MaxBI), supplemental buccal infiltration (SupManBI) and supplemental lingual infiltration (SupManLI) (Table 2). Studies comparing articaine and lidocaine delivered by intraosseous, intraligamental and intrapulpal routes were not found.

3.1.4 Systematic review: Outcomes

The primary outcome assessed was successful anesthesia based on each study's criteria. Success was defined in nine studies as no pain or mild/bearable pain/discomfort according to patient-reported pain scores (e.g. HP-VAS) during endodontic treatment access cavity preparation and instrumentation; one study defined successful anesthesia as no response to the electric pulp tester (51). The timing of the assessment following administration of the anesthetic ranged from 5 to 20 minutes. The secondary outcome assessed was adverse events; one study reported the absence of adverse events (52) while no mention was made in the other studies.

3.1.5 Systematic review: Quality assessment using the Risk of Bias tool

Evaluations for risk of bias categories are shown in Table 3, using the same Risk of Bias tool previously described in Section 2.1.4. There were no studies with high risk assessments. However, in one study the risks were unclear across all categories (56). Conflict of interest was denied in four studies (49, 52, 53, 55) and not mentioned in the other six studies. One study disclosed receiving financial support from a pharmaceutical company that provided materials and supplies (53), and four studies disclosed receiving academic institution financial support (50, 52-54).

Table 3. Risk of bias

	Selection		Performance	Detection	Attrition	Reporting
Author, Year (Ref)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Aggarwal et al. 2009 (48)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ashraf et al. 2013 (49)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Claffey et al. 2004 (49)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kanaa et al. 2012 (51)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Poorni et al. 2011 (52)	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Rogers et al. 2014 (53)	Low risk	Low risk#	Low risk	Low risk	Low risk	Low risk
Sherman et al. 2008 (54)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Sood et al. 2014 (55)	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk
Srinivasan et al. 2009 (56)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Tortamano et al. 2009 (57)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk

Anesthetic cartridges were masked (confirmed in written correspondence with author)

3.1.6 Systematic review: Meta-analyses

Success rates for articaine and lidocaine ranged from lows of 24% and 23%, respectively, for IANB delivery to 100% and 89%, respectively, for maxillary infiltration (Table 2). For combined studies, articaine was more likely than lidocaine to achieve successful anesthesia [OR=2.21 (95% CI, 1.41-3.47; P=0.0006), I^2 = 40%] (Figure 2A). A potential outlier study was identified as Srinivasan et al. (56), a trial that evaluated maxillary infiltrations and for which all risk of bias categories were assessed as unclear; sensitivity analysis showed that exclusion of this study did not substantially alter the combined studies results [OR=2.08 (95% CI, 1.38-3.14; P=0.0005, I^2=30%)].

Within the maxillary infiltration subgroup, there was no significant difference between articaine and lidocaine [OR=3.99 (95% CI, 0.50-31.62; P=0.19), I^2 = 59%] (Figure 2B). Sensitivity analysis that excluded Srinivasan et al. (56) reduced the OR from OR=3.99 to OR=1.45, and heterogeneity (I^2) from I^2=59% to I^2=0%, with the absence of a significant difference between articaine and lidocaine remaining unchanged (Figures 2B and 2C).

For combined mandibular anesthesia studies using any delivery route articaine was superior to lidocaine [OR=2.20 (95% CI, 1.40-3.44; P=0.0006), I^2 = 30%] (Figure 3A). Further subgroup analysis showed no difference when used for mandibular block anesthesia alone [OR=1.44 (95% CI, 0.87-2.38;P=0.16), I^2 = 0%] (Figure 3B). However, when used for supplemental infiltration following (successful) mandibular block anesthesia, articaine was significantly more effective than lidocaine [OR=3.55 (95% CI, 1.97-6.39; P<0.0001), I^2 = 19%] (Figure 3C).

Publication bias was evaluated by using a funnel plot (Figure 4). This showed asymmetry in the base of the funnel with more studies on the right compared to the left of the centerline. This asymmetry could represent a lack of available publications describing small studies with interventions that were found to be not significantly effective; the omission of these types of unpublished studies may result in an overestimation of the true effect of an intervention (25).

Figure 2A**.** Forest plots of odds ratios of articaine versus lidocaine from all 10 trials, showing articaine to have treatment effect 2.30 (P=0.0006) times greater than lidocaine.

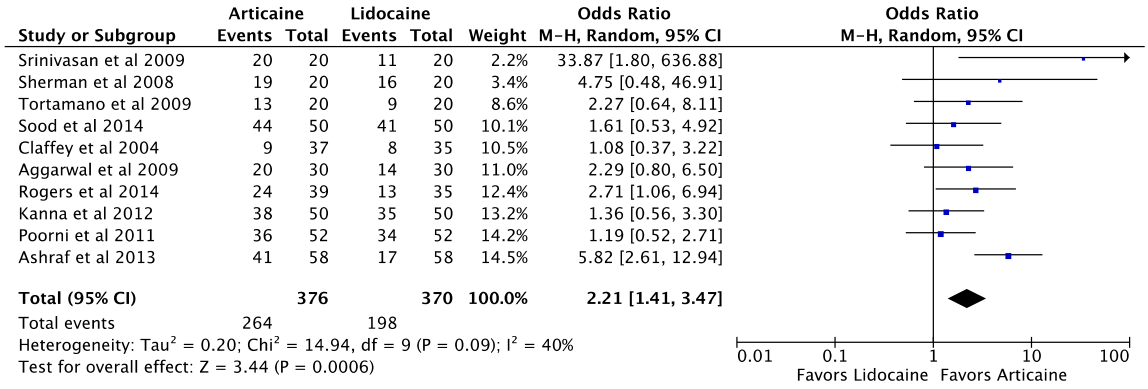


Figure 2B. Forest plots of odds ratios of articaine versus lidocaine. Subgroup maxillary infiltration trials showing no significant difference between articaine and lidocaine (P=0.19).

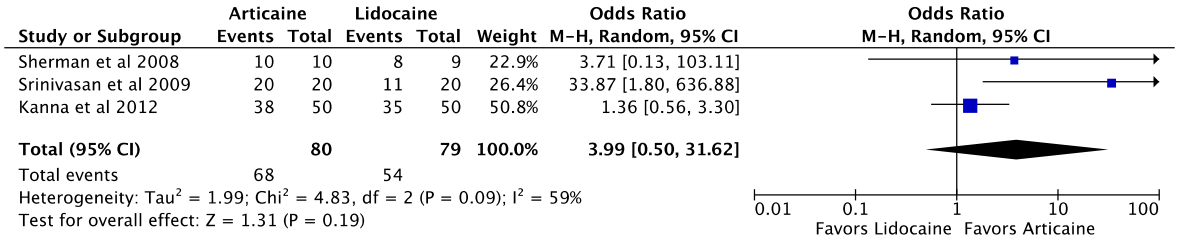


Figure 2C. Forest plots of odds ratios of articaine versus lidocaine. Subgroup maxillary infiltration sensitivity analysis that excludes Srinivasan et al. 2009 (56) which shows a reduced OR and I2, and no significant difference (P=0.39).

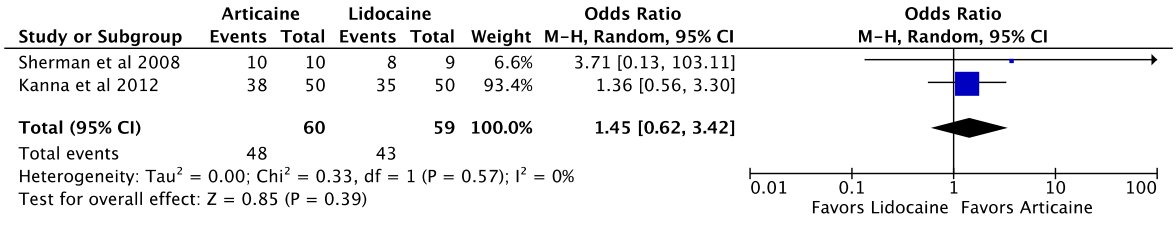


Figure 3A. Forest plots of odds ratios of articaine versus lidocaine from subgroups: all mandibular trials, showing articaine to have a treatment effect 2.20 times greater than lidocaine.

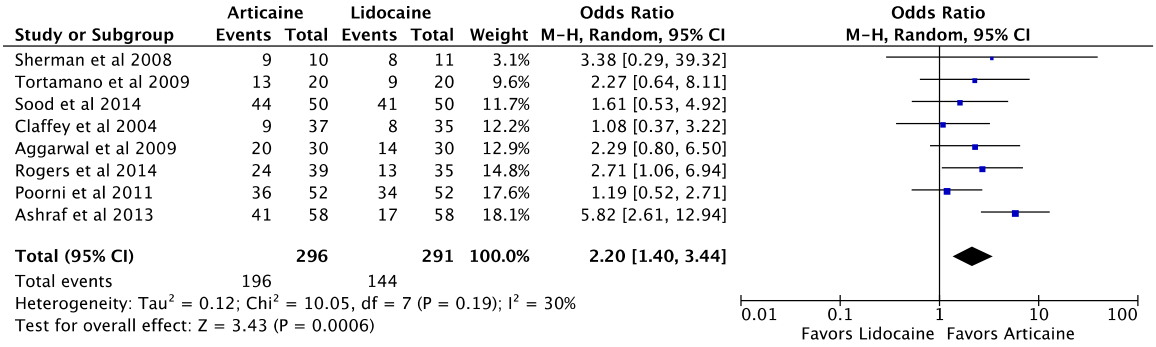


Figure 3B. Forest plots of odds ratios of articaine versus lidocaine from subgroups: trials limited to mandibular block anesthesia only, showing no difference between articaine and lidocaine

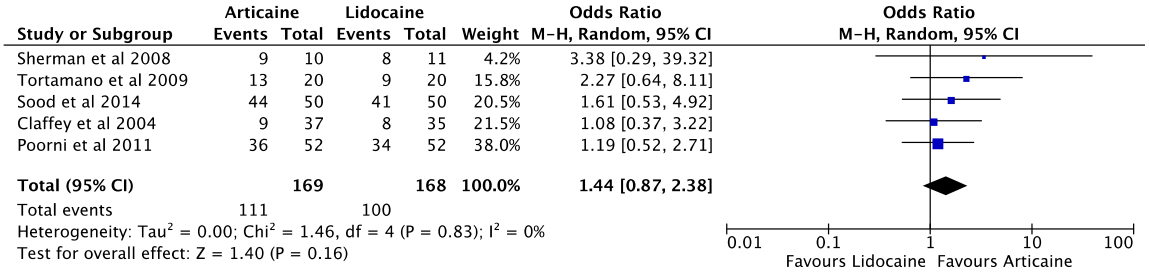


Figure 3C. Forest plots of odds ratios of articaine versus lidocaine from subgroups: Trials using supplemental infiltration in cases where pulpal pain persisted despite successful mandibular block anesthesia (defined as lip numbness), showing articaine to have a treatment effect 3.55 times greater than lidocaine.

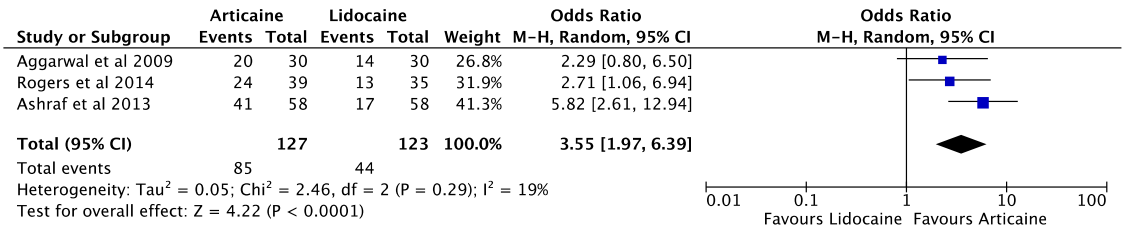
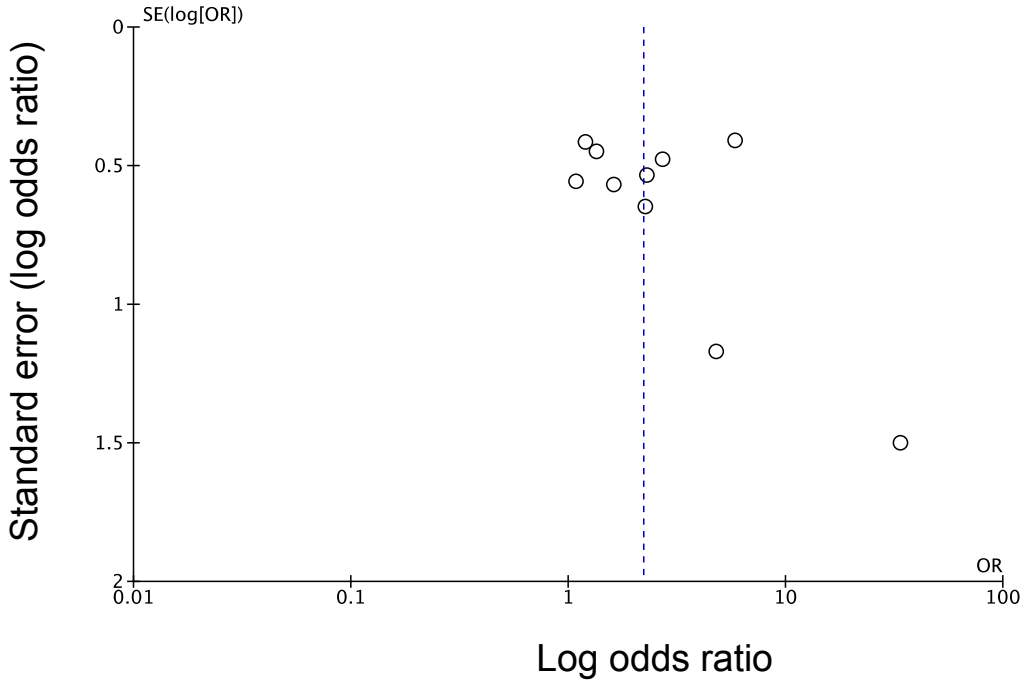


Figure 4. Funnel plot to detect publication bias. Outlier on lower right represents Srinivasan et al. (2009) (56).



3.2 Supplemental anesthesia

3.2.1 Characteristics of included studies

Searches identified a total of 16 studies. Eight studies evaluated the success of supplemental buccal, lingual, periodontal ligament and/or intrapulpal infiltration anesthesia (42-46, 48, 49, 53)(Table 4); three of these studies were also identified in the searches described in Section 3.1 (48, 49, 53) and are included in the systematic review and meta-analysis. Eight other studies evaluated supplemental intraosseous injections in uncontrolled before-after studies (21, 58-64)(Table 5). Randomized double-blind studies comparing articaine and lidocaine delivered by intraosseous, intraligamental or intrapulpal routes were not found. No mention was made of adverse events.

Table 4. Characteristics of studies on pulpal anesthesia achieved by administration of supplemental anesthetic solution following prior anesthesia in cases of symptomatic irreversible pulpitis

Author, Year (Ref)	Patients (n)	Preoperative pulpal diagnosis	Location and tooth type	Prior anesthesia procedures	Interventions	Interventions compared	Epinephrine concentration	Definition of successful anesthesia (Method to assess pain)	Results reported for anesthesia success	Significance
Aggarwal et al. 2009 (48)	60	Prolonged response to cold, positive response to EPT, absence of PARL, vital coronal pulp on access opening	Mand molars	All received IANB 1.7 mL of lido Then 2 min later received SupManBI and SupManLI of either 1.7 mL 4% arti or 1.7 mL 2% lido	SupManBI 1.7mL + SupManLi 1.7mL 4% arti vs 2% lido	Solution (arti vs lido)	1:200,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	Arti: 20/30=67%, Lido: 14/30=47%	p<0.05
Ashraf et al. 2013 (49)	125	Prolonged response to cold, vital pulp tissue during access opening, absence of PARL	Mand molars	All received IANB 1.5 mL and LBI 0.3 mL of either 4% arti or 2% lido. If VAS score was moderate or higher then received 1.8 mL SupManBI of same anesthetic used for IANB	SupManBI 1.8mL 4% arti vs 1.8mL 2% lido	Solution (arti vs lido)	1:100,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	Arti: 41/58=71%, Lido: 17/58=29%	p<0.001
Dou et al. 2013 (42)	80	Responded to cold stimulation using an ice stick with moderate to severe, prolonged pain, and normal periapical radiographc appearance	Mand molars	All received IANB 4 mL of lido. 10 min later, if lip numb received SupManBI 0.9 mL 4% arti or SupManBI 0.9 mL 4% arti plus SupManLI 0.9 mL 4% arti	SupManBI 0.9mL arti vs SupManBI 0.9 mL 4% arti + SupManLI 0.9 mL 4% arti	Location, Volume (SupManBI vs SupManBI + SupManLI)	1:100,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	SupManBI: 28/40=70%, SupManBI+SupManLI: 25/40=62.5%	n.s.
Fan et al. 2009 (45)	57	Spontaneous pain, positive response to EPT, prolonged response to cold, absence of periradicular pathosis	Mand molars	All received IANB 1.7 mL of arti. Then 5 min later, if lip numb then received SupManBI 0.4 mL 4% arti or PDLI 0.4 mL 4% arti	SupManBI 0.4 mL 4% arti vs PDLI 0.4 mL 4% arti	Location (SupManBI vs PDLI)	1:100,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	SupManBI: 22/27=81.5%, PDLI: 25/30=83.3%	n.s.

Kanaa et al. 2012 (43)	182	Unclear explanation of how investigators arrived at the definition of irreversible pulpitis: "Pulp sensitivity of the tooth with irreversible pulpitis was recorded by electronic pulp tester"	Mand molars	All received IANB. Then 10 min later, if tooth achieved 80 with EPT then received repeat IANB 2.0 mL 2% lido, SupManBI 2mL 4% arti, PDLI 0.18 mL 2% lido, or IOI 0.2 mL 2% lido	Repeat IANB 2 mL 2% lido, SupManBI 2 mL 4% arti, PDLI 0.18 mL 2% lido, IOI 0.2 mL 2% lido	Location, Solution (Repeat IANB vs SupManBI vs PDLI vs IO; arti vs lido)	1:100,000 1:80,000	No pain during treatment	Repeat IANB 2 mL lido: 8/25=32%, SupManBI 2 mL arti: 21/25=84%, PDLI 0.18 mL lido: 12/25=48%, IOI 0.2 mL lido: 17/25=68%	p=0.001 (SupMan BI and IOI sig higher success rate than PDL or repeat IANB)
Monteiro et al. 2014 (44)	20	Spontaneous pain, long-lasting moderate to severe pain to cold, bleeding pulp during access, absence of PARL	Mand molars	#Multiple. See footnote	SupManBI 1.7 mL 4% arti	#Multiple. See footnote	1:100,000	Pain-free emergency root canal treatment able to be initiated	1°(BI+LI)+ supp(PDLI +IANB+IP): 21/30=70%; 1°IANB+ supp(BI+PDLI +IP): 16/20=80%	n.s.
Rogers et al. 2014 (53)	74	Greater than moderate pain, spontaneous and prolonged response to cold, absence of PARL, vital coronal pulp tissue on access	Mand molars	All received IANB 1.7 mL 4% arti Then if VAS pain score was moderate or higher received SupManBI of either 1.7 mL 4% arti or 1.7 mL 2% lido	SupManBI 1.7mL 4% arti vs 1.7mL 2% lido	Solution (arti vs lido)	1:100,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	Arti: 24/39=62%, Lido: 13/35=37%	p<0.05
Singla et al. 2015 (46)	147	Active pain, prolonged response to cold, positive response to EPT, absence of PARL, vital coronal pulp tissue on access	Mand molars	All received IANB 1.8 mL 4% arti then 15 min later if lip numb, access initiated. If painful, received either SupManBI 1.8mL 4% arti Vs. SupManBI 3.6mL 4% arti	SupManBI 1.8mL 4% arti vs SupMamBI 3.6mL 4% arti	Volume (1.8mL arti vs 3.6mL arti)	1:100,000	No or mild pain during access cavity preparation and instrumentation (HP-VAS*)	Arti 1.8mL: 45/73=62%, Arti 3.6mL: 47/74=64%	n.s.

arti, articaine; BI, buccal infiltration; EPT, electric pulp tester; GG, Gow Gates block; HP-VAS, Heft Parker Visual analogue scale; IANB, inferior alveolar nerve block; IOI, intraosseous injection; IP, intrapulpal; LBI, long buccal infiltration; LI, lingual infiltration; lido, lidocaine; mand, mandibular; ManLI, mandibular lingual infiltration; max, maxillary; MaxBI, maxillary buccal infiltration; NA, not applicable; n.s., not significant; PARL, periapical radiolucency; PDLI, periodontal ligament infiltration; SupManBI, supplemental buccal infiltration; SupManLI, supplemental lingual infiltration; VAS, visual analog scale; vs, versus
*HP-VAS categories:Mild pain >0 mm and ≤54 mm; Moderate pain >54 and <114 mm; Severe pain >114mm

#2 groups. Primary injection: Grp 1 received 1.8 mL 4% arti BI and 0.6 mL 4% arti LI. Grp 2 received 1.8 mL 2% lido IANB. Supplemental: If pain after 10 min then Grp 1 received 0.9 mL 4% arti PDLI, then 1.8 mL 2% lido IANB, then 0.4 mL 4% arti IP. Grp 2 received 1.8 mL 4% arti BI, then 0.9 mL 4% arti PDLI then 0.4 mL 4% arti or 2% lido IP

Table 5. Characteristics of studies on pulpal anesthesia achieved by intraosseous injection (IOI) following prior anesthesia in cases of symptomatic irreversible pulpitis

Author, Year (Ref)	Patients (n)	Preoperative pulpal diagnosis	Location and tooth type	Prior anesthesia procedures	Intervention	IOI delivery device	Epinephrine concentration	Definition of successful anesthesia (Method to assess pain)	Results reported for anesthesia success
Bhuyan et al. 2014. (58)	30	Prolonged response to cold and EPT	Mand Molars	Patients received IANB 1.7 mL 4% arti	IOI 1.7 mL arti	X-tip	1:100,000	No or mild pain during access cavity or initial instrumentation	Arti: 25/30=83%
Bigby et al. 2006 (59)	37	Prolonged response to cold, vital coronal pulp tissue upon access	Mand Molars	All received IANB and long buccal injections (solutions not identified)	IOI 1.8mL arti	Stabident	1:100,000	No or mild pain during access cavity or initial instrumentation	Arti: 32/37=86%
Idris et al. 2015 (60)	24	Unclear. "Pulpalgia" "criteria for clinical diagnosis of symptomatic irreversible pulpitis."	Mand Molars	All received IANB 1.5 mL 2% arti	IOI 0.9 mL arti	X-tip	1:100,000	No or mild pain during access cavity or initial instrumentation	Arti: 21/24=87.5%
Nusstein et al. 1998 (61)	24	Positive response to cold and EPT, sensitivity to percussion, radiographically widened PDL space	Mand Molars Max Molars	Patients received IANB or MaxBI of 2% lido	IOI 1.8 mL lido	Stabident	1:100,000	No or mild pain during access cavity or initial instrumentation	Max: Lido: 2/3=67% Mand: Lido: 19/21=90%
Nusstein et al. 2003 (21)	33	Prolonged response to cold, vital coronal pulp tissue upon access opening	Mand Molars or Premolar	All received IANB 1.8 mL of 2% lido	IOI 1.8 mL lido	X-tip	1:100,000	No or mild pain during access cavity or initial instrumentation	Lido: 27/33=82%
Parente et al. 1998 (62)	37	Unclear. "irreversible pulpitis", "pulpalgia refractory to conventional methods of local anesthesia"	Mand Molars:34 Max:3	Patients received IANB or MaxBI of 2% lido (minimum volume of 3.6 mL)	IOI 0.45-0.9 mL lido	Stabident	1:100,000	No pain during access cavity and comfortably complete endodontic treatment	Mand: lido: 31/34=91%* Max: lido:2/3=67%
Reisman et al. 1997 (63)	44**	Active pain, positive response to EPT and cold, sensitivity to percussion, radiograph-ically widened PDL	Mand Molars or Premolar	All received IANB 1.8 mL 2% lido. If lip not numb after 5 mins, given IANB. 5 min after successful IANB, given IOI	IOI 1.8 mL 3% mepivacaine	Stabident	zero	No pain during access cavity and ability to complete treatment without pain following negative EPT reading	Mand: 1st IOI 35/44=80% Mand: 2nd IOI 43/44=98%***
Verma et al. 2013 (64)	30	Prolonged response to cold, vital coronal pulp tissue upon access opening, no periapical pathosis	Mand Molars	All received IANB 1-1.8 mL 2% Lido. If after 15 min, pain when access started, then IOI given	IOI 1.8 mL lido	X-tip	1:80,000	No or mild pain during access cavity or initial instrumentation	Lido: 26/28=93%****

arti, articaine; EPT, electric pulp tester; IANB, inferior alveolar nerve block; IOI, intraosseous injection; lido, lidocaine; mand, mandibular; max, maxillary; MaxBI, maxillary buccal infiltration; PDL, periodontal ligament

* For 4 of 31 mandibular teeth, a second IOI was required, no further details provided

** Sample size of 44 could have been 48 because 4 cases were excluded due to technical "failure to perforate the full depth of cancellous bone" and not due to anesthetic solution

*** Second IOI was given through the same previous perforation site, 1.8 mL of 3% mepivacaine was slowly deposited over 2 minutes. If patient still felt pain, an intrapulpal injection was administered.

**** Two cases had anesthetic solution backflow and were excluded as technical failures

3.2.1.1 Supplemental infiltration injections

The characteristics of eight studies that evaluated the success of supplemental buccal, lingual, periodontal ligament and/or intrapulpal infiltration injections are presented in Table 4. All studies used either 4% articaine or 2% lidocaine for mandibular molars with successful block anesthesia (42-46, 48, 49, 53). The supplemental infiltration trials were conducted in India (46, 48, 49), China (42, 45) the United States (53), Brazil (44) and England (43). Three studies reported that success of supplemental anesthesia was significantly greater using articaine compared to lidocaine (48, 49, 53). In terms of location of delivery, there was no difference in success between mandibular buccal sulcus versus periodontal ligament injections (45) when using articaine for supplemental infiltration anesthesia. With regards to volume of anesthetic solution, doubling the volume of articaine for mandibular buccal infiltrations did not significantly affect the anesthesia outcome (42, 46).

3.2.1.2 Supplemental intraosseous injections

The characteristics of the eight uncontrolled before-after studies that evaluated supplemental intraosseous injections are presented in Table 5. Either 4% articaine, 2% lidocaine or 3% mepivacaine were used (21, 58-64). The trials were conducted in the United States (21, 59, 61-63) and India (58, 60, 64). The Stabident® system was used for anesthetic delivery in four of the studies (59, 61-63); the remaining four studies used the X-Tip® system (21, 58, 60, 64). For maxillary posterior teeth success rates using intraosseous injections were reported to be 67% (61, 62). For mandibular posterior teeth, success rates ranged from 80% to 93% (21, 58-64), reaching up to 98% after a second intraosseous injection. In some cases additional intrapulpal anesthesia was still required after an intraosseous injection (61, 62).

3.2.2 Quality assessment using the Risk of Bias tool

The assessments for risk of bias categories for the eight studies that evaluated the success of supplemental buccal, lingual or periodontal ligament infiltration injections are presented in Table 6. In four of the studies the risks were unclear or high in several categories (42-45). The intraosseous injections articles, all of which used an uncontrolled before-after study design, did not qualify for quality assessment by the Risk of Bias tool.

Table 6. Quality evaluations (risk of bias) for studies on pulpal anesthesia achieved by administration of supplemental anesthetic solution following prior anesthesia in cases of symptomatic irreversible pulpitis

Author, Year (Ref)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Aggarwal et al. 2009 (48)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ashraf et al. 2013 (49)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dou et al. 2013 (42)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk
Fan et al. 2009 (45)	Unclear risk	Unclear	Unclear	Low risk	Low risk	Low risk
Kanaa et al. 2012 (43)	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk
Monteiro et al. 2014 (44)	Low risk	Unclear	High risk	High risk	High risk	High risk
Rogers et al. 2014 (53)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Singla et al. 2015 (46)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Chapter 4: Discussion

The systematic review of double-blind, randomized clinical trials comparing the use of articaine and lidocaine in patients with symptomatic irreversible pulpitis provides level 1 evidence based on the criteria given by the Oxford Centre for Evidence-based Medicine (26). The main conclusions that can be drawn from this study are that there is a significant advantage to using articaine over lidocaine for supplementary infiltration following mandibular block anesthesia, but no advantage when used for mandibular block anesthesia alone or for maxillary infiltration.

While there were no specific language exclusion criteria as part of the search strategy for the present reviews, if an abstract was not available in English for screening purposes, the article was not included. Therefore it should be acknowledged that any existing non-English publications may not have been included in the present reviews. It is also important to acknowledge that, in common with previous reviews (31, 32), the underlying heterogeneity of the included studies presents limitations. Such heterogeneity includes geographic location, sample size, number and experience of operators, potential variations in approaches to diagnose symptomatic irreversible pulpitis (cold test, electric pulp test, and patient history), the volume of anesthetic, the concentration of epinephrine, reproducibility of injection route, and evaluation scale used to assess pain and definition of success (VAS, HP-VAS, access cavity, endodontic instrumentation). In one study injection speed was standardized by using a digitally controlled injection system at a standardized injection rate (45). It should be noted that Poorni et al. included three test arms in their trial, two arms comparing articaine and lidocaine mandibular block anesthesia, and a third "control" test arm that employed articaine buccal infiltration (52);

data from the third test arm were not included in this study since there was no lidocaine group comparison.

In an effect to allow for heterogeneity issues, the meta-analysis used a random-effects model of statistical analysis, as opposed to the fixed-effects model that is used in cases with no evidence of heterogeneity. One study in particular was identified as potentially contributing to heterogeneity; this study met the eligibility criteria but was assessed as having unclear reporting (56). In addition, forest plot analysis showed wide confidence intervals that potentially contributed to heterogeneity as shown by I^2 estimates of 40% and 59% (Figures 2A and 2B). Excluding outlier studies from a meta-analysis is not recommended since doing so might introduce bias (25). However, in order to evaluate whether the final results were dependent on a study with unclear reporting, a sensitivity analysis was performed by conducting a meta-analysis that excluded the study in question. The sensitivity analysis confirmed that, while exclusion of the study reduced the odds ratios and heterogeneity, the overall results were unchanged (Figure 2C).

The meta-analysis included several studies not previously reviewed. Four of these studies evaluated mandibular molars (48, 49, 52, 55) and one evaluated maxillary teeth (51). One study in symptomatic patients had been excluded from a previous review (32) because of concerns that the comparisons were confounded by the pre-administration of additional anesthetic before the comparison (48). Three studies in the present review included patients who had already received block anesthesia prior to the intervention (supplemental infiltration) (48, 49, 53). For the systematic review it was considered that pre-administration of anesthetic solution should not be an exclusion criterion as long as both groups received the same pre-administration

anesthetic solution. Both groups receiving different anesthetic solution would add a confounding variable.

The Cochrane Handbook for Systematic Reviews of Interventions recommends updating existing reviews every two years or when potentially relevant studies surface in the literature (25). A Chinese language systematic review published in 2010 reviewed six Chinese language reports that were unable to be accessed (30); consequently, since this review was unable to be fully evaluated it is not discussed further. Comparisons with previous English language systematic reviews (31, 32) reveals some similarities, and some notable differences (Table 7). For example, all three reviews included an intention to evaluate the incidence of adverse events, but few studies mentioned adverse events at all. Katyal reported that a meta-analysis of four studies evaluating post-injection adverse events showed no difference between articaine and lidocaine (31). In the present review only one of the ten studies reported the absence of adverse events (52) while the other studies made no mention. It is important that future clinical studies incorporate the reporting of adverse events in their methodology. A review published in 2011 concluded that reports of articaine neurotoxicity were low level and based on retrospective studies with biased data recruitment, with no scientific evidence demonstrating that 4% articaine solution is "neurotoxic or unsafe to use in any aspect of clinical dentistry" (65).

The main difference between the present systematic review and previous English language reviews (31, 32) is that all participants in this review were diagnosed with irreversible pulpitis compared to previous reviews that had a broader participant base (patients and non-patient volunteers with or without pain). In addition, in the present review all studies were parallel designed random controlled trials that evaluated independent samples. Previous reviews

also included studies with crossover design which, while minimizing variability, are not practical or ethically appropriate for patients in pain. Another difference was the number of participants with symptomatic irreversible pulpitis: 746 compared with 152 (31) and 133 (32) in previous reviews. The start of the search period in this study was selected based on the introduction of articaine to the market in 1976 (11). In comparison, the search period was started in 1950 by Katyal (31) and in 1970 by Brandt et al. (32), with the publication dates of their earliest studies reviewed being 2001 and 1972, respectively.

Previously Brandt et al. reported that articaine was 3.81 times more likely than lidocaine to achieve anesthetic success when delivered "when the infiltration mode of administration is used" (32). The odds ratio of all studies from Brand et al. [OR=2.44 (95% CI, 1.59-3.76, P<0.0001)] is similar to this study [OR=2.21 (95% CI, 1.41-3.47), P=0.0006]. However, their conclusions were based on data from combined maxillary and mandibular teeth in patients and non-patient (asymptomatic) volunteers. In contrast, the present study, which included only symptomatic patients, found no difference between articaine and lidocaine for maxillary infiltration (Figure 2B), and mandibular infiltration-only studies in symptomatic patients were not found. However, it should be noted that this subgroup numbering 159 patients may have insufficient power; post-hoc power analysis (using ClinCalc.com with the articaine anticipated incidence set at 85%, lidocaine anticipated incidence at 68%, alpha at 0.05 and power at 80%) indicated a study sample of 192 patients would be needed for sufficient power.

The addition of epinephrine to local anesthetic solutions facilitates vasoconstriction, slows systemic absorption and thus prolongs the anesthetic effect. The previous systematic reviews included only studies using the epinephrine concentration of 1:100,000 (31, 32). In this

review seven of the ten studies used 1:100,000 epinephrine (Table 2). One study compared articaine and lidocaine solutions with 1:200,000 epinephrine (48) and another study compared articaine with 1:100,000 epinephrine to lidocaine with 1:80,000 epinephrine (51). Dagher et al found no significant differences in degree of anesthesia obtained using 2% lidocaine with either 1:50,000, 1:80,000, or 1:100,000 concentrations of epinephrine (66). The same onset and duration of pulpal anesthesia has been reported for articaine with either 1:100,000 or 1:200,000 epinephrine (2-3 minutes onset and 60 minutes pulpal anesthesia) and for lidocaine 1:50,000 and 100,000 (onset for both 3-5 minutes, duration 10 minutes for 1:50,000 and 60 minutes for 1:100,000) (8). Considering that evaluations for the determination of anesthetic success were made by 10 minutes (51) and 15 minutes (48) after injection, it is reasonable to expect that these variations in epinephrine concentration would not likely have a major impact on the outcomes evaluated in the systematic review. Clinical trials on the efficacy of supplemental injections for pulpal anesthesia in patients with symptomatic irreversible pulpitis utilized the following local anesthetic solutions and vasoconstrictors: 4% articaine with 1:100,000 epinephrine, 2% lidocaine with 1:100,000 epinephrine, and 3% mepivacaine (Tables 4 and 5). Because of the absence of epinephrine 3% mepivacaine solutions are indicated for patients with untreated hyperthyroidism (67) and pheochromocytoma, high blood pressure (excess of 200 mm Hg systolic or 115 mm Hg diastolic), cardiac dysrhythmias, and severe cardiovascular disease (68).

With regard to supplemental anesthesia, no randomized double-blind studies were found that compared articaine and lidocaine delivered by the intraosseous, intraligamental and intrapulpal routes to anesthetize symptomatic teeth undergoing endodontic treatment. Further, there was considerable heterogeneity between the eight supplemental infiltration studies in terms of intervention categories evaluated: type of solution (articaine versus lidocaine) (48, 49, 53),

location of anesthetic solution delivery (e.g. buccal infiltration versus periodontal ligament injection, intrapulpal) (43-45) and volume of anesthetic solution delivered (42, 44, 46). The three studies that evaluated multiple variables also had multiple high risk of bias (42-44) (Tables 4 and 5). In addition, all the clinical trials that evaluated intraosseous injection were designed as uncontrolled before-after studies that estimated the efficacy of intraosseous injections administered as supplemental injections when anesthesia was inadequate following prior administration of anesthetic via inferior alveolar nerve block or maxillary buccal infiltration Table 6). While this study design might provide a convenient approach to evaluating an intervention, the limitations include lack of randomization, risk of selection bias, the introduction of confounders that cannot be identified, and a risk of overestimation of effect (69, 70). There is a need for randomized double-blind studies that evaluate the efficacy and incidence of adverse events from articaine and lidocaine delivered by intraosseous, intraligamental and intrapulpal routes to reduce pain in patients with symptomatic irreversible pulpitis.

Table 7. Comparison with other systematic reviews

	Katyal 2010 (31)	Brandt et al. 2011 (32)	This study
Aim of study	"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"	"broad comparison regarding the efficacy of articaine and lidocaine solutions when used to achieve profound anesthesia in adults"	PICO question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events?
Search period	1950 - October 2009	Jan 1970 to Dec 2009	Jan 1976 - February 2015
Search strategies	MEDLINE, Cochrane, Embase, Proquest, metaRegister of controlled trial database	MEDLINE, Embase, hand search, journal table-of-contents searches, books, conference proceedings, recommendations from experts in field	MEDLINE, Scopus, Cochrane Library, ClinicalTrials.gov, hand search, journal table-of-contents searches, books, conference proceedings
Reviewers	One	Two, with third available to resolve discrepancies between reviewers	Two, with third available to resolve discrepancies between reviewers
Interventions compared	Similar volume dose of 4% articaine (1:100,000 epinephrine) and 2% lignocaine (1:100,000)	4% articaine (1:100,000 epinephrine) and 2% lignocaine (1:100,000)	Same volume dose of at least 1.0 mL per administration of 4% articaine and 2% lidocaine in combination with epinephrine
Anesthetic delivery routes included	Maxillary and mandibular infiltrations and block anesthesia administered manually	Inferior alveolar nerve block, Gow-Gates block, maxillary buccal and lingual infiltration	Inferior alveolar nerve block, Gow-Gates block, long buccal nerve infiltration, maxillary buccal infiltration, supplemental mandibular buccal and lingual infiltration
Exclusion factors not excluded in this review	Computerized delivery routes	Preadministration of additional anesthetic before the intervention	Not applicable

Meta-analysis			
Total studies included in meta-analysis	8 (both crossover and independent-sample studies)	13 (both crossover and independent-sample studies)	10 (independent-sample studies only)
Participants	1, 725 patients of all ages requiring routine non-complex dental treatment with and without pain	560 adult human participants (including non-patient volunteers) with and without pain	746 adult human patients with symptomatic irreversible pulpitis
Studies restricted to irreversible pulpitis	2 (Claffey et al 2004, Tortamano et al 2009)	4 (Claffey et al 2004, Sherman et al 2008, Srinivasan et al 2009, Tortamano et al 2009)	10
Participants with irreversible pulpitis	77 (articaine); 75 (lidocaine)	67 (articaine); 66 (lidocaine)	376 (articaine); 370 (lidocaine)
Analysis of all studies	Not available	13 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=2.44 (95% CI, 1.59-3.76, P<0.0001)]	10 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=2.21 (95% CI, 1.41-3.47), P=0.0006]
Infiltration only (maxillary+mandibular)	Not available	9 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=3.81 (95% CI, 2.71-5.36, P<0.00001)]	Not available
Infiltration only (maxillary)	Not available	Not available	3 studies: no difference between articaine and lidocaine
Mandibular (combined block and infiltration)	Not available	Not available	8 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=2.20 (95% CI, 1.40-3.44, P<0.0006)]
Mandibular block only (combined crossover and independent-samples studies)	7 studies: articaine more likely than lidocaine to achieve anesthetic success in posterior first molar area [OR=1.31 (95% CI, 1.12-1.54, P-0.0009)]	4 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=1.57 (95% CI, 1.12-2.21, P<0.00001)]	Not available

Mandibular block only (independent-samples studies only)	Not available	3 studies: no difference between articaine and lidocaine	5 studies: no difference between articaine and lidocaine
Supplemental Infiltration after mandibular block	Not available	Not available	3 studies: articaine more likely than lidocaine to achieve anesthetic success [OR=3.55 (95% CI, 1.97-6.39; P<0.0001)]
Adverse events	No difference between articaine and lidocaine	No reports of adverse events, or not mentioned	No reports of adverse events, or not mentioned
Pain	3 studies: articaine results in a higher VAS pain score than lidocaine at injection site OR=6.49 (95% CI, 0.02–12.96, P=0.05)] at day zero decreasing to OR=1.10 (95% CI, 0.18–2.02, P = 0.02) on 3rd day after injection	Not available	Not available
Onset of action	2 studies: No difference between articaine and lidocaine	Not available	Not available

Chapter 5: Summary and Conclusions

Achieving profound pulpal anesthesia can be difficult in patients with symptomatic irreversible pulpitis. Clinicians might try various strategies to address this problem such as changing the anesthetic agent, for example using articaine instead of lidocaine injection, and by using a supplemental anesthetic injection delivery technique (7). The overall purpose of this study was to review the available literature on the use of local anesthesia in patients with systematic irreversible pulpitis, a clinical presentation known to produce challenges to adequately achieving profound anesthesia. There were two parts to the study:

In Part 1 a systematic review and meta-analysis was conducted that addressed the following PICO (population, intervention, comparison, outcome) question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and the comparative incidence of adverse events? The main conclusions of the meta-analysis were:

1. Articaine is an effective local anesthetic in cases of symptomatic irreversible pulpitis.
2. There is no significant difference in efficacy between articaine and lidocaine for maxillary infiltration and mandibular block anesthesia.
3. Where pulpal pain persists despite successful mandibular block anesthesia, supplemental infiltration with articaine is significantly more likely (OR=3.55) than lidocaine to achieve successful anesthesia.

In Part 2 a search of the electronic databases was conducted to identify, characterize and assess the quality of peer-reviewed clinical studies that investigated the success of supplemental pulpal anesthesia in patients with symptomatic irreversible pulpitis. The main findings were:

1. Randomized double-blind trials that evaluated supplemental infiltration compared type and volume of anesthetic solution, and location of injection. There was no difference in success between mandibular buccal sulcus versus periodontal ligament injections when using articaine (45). Doubling the volume of articaine for mandibular buccal infiltrations did not significantly affect the anesthesia (42, 46).
2. Clinical trials that evaluated intraosseous injection were all designed as uncontrolled before-after studies; success rates were reported to be 67% (61, 62) for maxillary posterior teeth and 80%-93% reaching up to 98% after a second intraosseous injection for mandibular posterior teeth (21, 58-64).
3. There is a need for randomized double-blind studies that evaluate the efficacy and incidence of adverse events from articaine and lidocaine delivered by intraosseous, intraligamental and intrapulpal routes to reduce pain in patients with symptomatic irreversible pulpitis.

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Appendix 1. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

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Appendix 2. Journal of endodontics publication

Kung J, McDonagh M, Sedgley CM. Does Articaine Provide an Advantage over Lidocaine in Patients with Symptomatic Irreversible Pulpitis? A Systematic Review and Meta-analysis. Journal of Endodontics 2015 Nov; 41:1784-1794.

Does Articaine Provide an Advantage over Lidocaine in Patients with Symptomatic Irreversible Pulpitis? A Systematic Review and Meta-analysis

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Abstract

Introduction: Achieving profound pulpal anesthesia can be difficult in patients with symptomatic irreversible pulpitis. This study provides a systematic review and meta-analysis to address the population, intervention, comparison, outcome (PICO) question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events? **Methods:** A protocol was prepared and registered on PROSPERO. Electronic searches were conducted in MEDLINE, Scopus, Cochrane Library, and ClinicalTrials.gov by using strict inclusion and exclusion criteria. Two independent reviewers assessed eligibility for inclusion and quality. Weighted anesthesia success rates and 95% confidence intervals (CIs) were estimated and compared by using a random-effects model. **Results:** Two hundred seventy-five studies were initially identified from the search; 10 double-blind, randomized clinical trials met the inclusion criteria. For combined studies, articaine was more likely than lidocaine to achieve successful anesthesia (odds ratio [OR], 2.21; 95% CI, 1.41–3.47; $P = .0006$; $I^2 = 40\%$). Maxillary infiltration subgroup analysis showed no significant difference between articaine and lidocaine (OR, 3.99; 95% CI, 0.50–31.62; $P = .19$; $I^2 = 59\%$). For combined mandibular anesthesia studies articaine was superior to lidocaine (OR, 2.20; 95% CI, 1.40–3.44; $P = .0006$; $I^2 = 30\%$), with further subgroup analysis showing no difference for mandibular block anesthesia (OR, 1.44; 95% CI, 0.87–2.38; $P = .16$; $I^2 = 0\%$). When used for supplemental infiltration after successful mandibular block anesthesia, articaine was significantly more effective than lidocaine (OR, 3.55; 95% CI, 1.97–6.39; $P < .0001$; $I^2 = 9\%$). There were no reports of adverse events. **Conclusions:** This systematic review of double-blind, randomized clinical trials provides level 1 evidence to support the use of articaine for patients with symptomatic irreversible pulpitis. There is a significant advantage to using articaine over lidocaine for supplementary infiltration after mandibular block anesthesia but no advantage when used for mandibular block anesthesia alone or for maxillary infiltration. *(J Endod 2015;41:1784–1794)*

Key Words

Articaine, carticaine, irreversible pulpitis, lidocaine, local anesthesia, meta-analysis, symptomatic irreversible pulpitis, systematic review, ultracaine

The clinical diagnosis of symptomatic irreversible pulpitis is based on subjective and objective findings signifying that the vital inflamed pulp is incapable of healing, with subjective descriptors that include lingering thermal pain, spontaneous pain, and referred pain (1). Root canal treatment has been described as significantly more painful for teeth with irreversible pulpitis and symptomatic apical periodontitis compared with teeth with necrotic pulps and asymptomatic apical periodontitis (2). In addition, achieving profound pulpal anesthesia can be challenging in these cases (3, 4). For example, anesthesia may be sufficiently profound to access the pulp chamber, but canal instrumentation can result in severe pain (4). In a survey of Diplomates of the American Board of Endodontics, 84% of respondents reported experiencing difficulties in anesthetizing acutely painful mandibular molars (5). The inability to achieve pulpal anesthesia has been shown to increase a patient's fear and anxiety, exacerbate systemic medical issues, extend the appointment duration, and generate doubt in the operator; any of these factors can contribute to the impression that receiving root canal treatment is a painful procedure (6).

Lidocaine, also known as lignocaine, is an amino-amide anesthetic introduced to the market in 1948 that has been described as the most commonly used local anesthetic for dental use in the United States (7) and elsewhere (8, 9). This anesthetic provides pulpal anesthesia for approximately 1 hour and soft tissue anesthesia for 3–5 hours (7). Articaine, the second most commonly used dental anesthetic, was first introduced to the European market in 1976 and entered the U.S. market in 2000 (10). By 2007, articaine was described as accounting for approximately 25% of total sales, second only to lidocaine at 54% (11). The chemical composition of articaine contains a unique thiophene ring instead of the benzene ring found in lidocaine and other amide local anesthetics. This difference increases lipid solubility, thereby increasing diffusion through the lipid membrane of the epineurium, which purportedly explains its faster onset and higher success rate when compared with lidocaine (10, 12).

Systematic reviews are an integral component of evidence-based medicine or "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (13). A systematic review aims to "collate all

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empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question" (14). In general, the steps required to perform a systematic review are as follows:

1. Assess and develop a question.
2. Develop inclusion and exclusion criteria.
3. Search, select, and identify primary studies.
4. Analyze and perform meta-analysis if applicable.
5. Address and report any potential biases.
6. Interpret results to answer research questions.

It is recommended that early in the process the review protocol be registered with an electronic database such as PROSPERO (15). Registration has numerous functions. Primarily, it avoids bias in the conduct and reporting of systematic reviews and also helps to avoid unintended duplication (16).

Systematic reviews with meta-analysis that have focused on the efficacy of articaine compared with lidocaine for dental anesthesia have been published in a Chinese language journal (17) and in English language journals (18, 19). Xiao et al (17) concluded that for cases of irreversible pulpitis, articaine was superior to lidocaine both overall and for maxillary anesthesia, but that there was no difference between the 2 solutions in achieving mandibular anesthesia; however, 6 of the 9 articles included for analyses were Chinese language reports that were unable to be accessed. Katyal (18) reported that articaine was more effective than lidocaine (lignocaine) for anesthetizing maxillary and mandibular "1st molar region" teeth and concluded that articaine is a superior anesthetic for use in routine dental procedures. Brandt et al (19) reported that articaine provided superior pulpal anesthesia when administered by infiltration but concluded that it was premature to recommend articaine over lidocaine for mandibular block anesthesia in cases of irreversible pulpitis. However, both of these reviews were based on searches conducted in 2009 that analyzed data from combined asymptomatic and symptomatic subjects enrolled in either crossover or parallel designed random controlled trials (18, 19). A preliminary electronic search revealed that since their publication, several randomized clinical trials comparing articaine and lidocaine for patients with symptomatic irreversible pulpitis had been published.

The purpose of this study was to conduct a systematic review and meta-analysis that addressed the following population, intervention, comparison, outcome (PICO) question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and the comparative incidence of adverse events? Searches conducted in October 2013 for existing registered systematic reviews of similar topics on PROSPERO (15), the Cochrane Collaboration (14), and Joanna Brigg's Institute (20) revealed none in progress.

Materials and Methods

Methods were based on the Institute of Medicine Standards for a comprehensive search (21), the Cochrane Handbook for Systematic Reviews of Interventions (14), and the Centre for Reviews and Dissemination Guidance for Undertaking Systematic Reviews in Health Care (22). A protocol was prepared and registered in the PROSPERO database (CRD42014005794), an international prospective registrar of systematic reviews (15).

Inclusion Criteria

Studies were included that evaluated the pulpal anesthetic solutions of 4% articaine compared with 2% lidocaine, delivered as a similar volume dose of at least 1.0 mL per injection in combination with vasoconstrictor, in adult patients with symptomatic irreversible pulpitis. Studies that used anesthetic delivery via any delivery route were included. Additional criteria for eligibility were that the study provided original data and was a randomized, double-blind clinical trial published in a peer-reviewed journal. Non-English language articles without English abstracts were excluded.

The primary outcome measure was the reduction of pulpal pain to a level that would allow endodontic treatment to proceed within 20 minutes of administration of local anesthetic, as defined by each trial (for example, by using Verbal Analog Scale, Visual Analogue Scale (VAS), Heft Parker-Visual Analogue Scale (HP-VAS), and electric pulp tests and/or by initiating endodontic treatment procedures). Data were presented as dichotomous outcomes of "successful anesthesia" or "unsuccessful anesthesia." Secondary outcomes to be measured were any adverse event. Studies were excluded in the following circumstances:

1. There was insufficient information about the diagnosis of symptomatic irreversible pulpitis and the definition of anesthetic success.
2. Dichotomous data for anesthesia outcome were unavailable.

Search Methods

A comprehensive search of the electronic databases was conducted and reviewed by a medical librarian to identify eligible studies through electronic searches from 1976, when articaine was first introduced to the market (10), to October 2013. The search was subsequently updated in February 2015 (Table 1). The following electronic databases were searched: MEDLINE by using PubMed search engine (http://www.ncbi.nlm.nih.gov/pubmed/) (23), Scopus (24), and the Cochrane Library (http://www.cochrane.org). ClinicalTrials.gov was searched to identify completed studies that were not yet published (keywords used were "lidocaine articaine"). Reference lists from identified trials and review articles were manually scanned to identify additional relevant studies. The search was also supplemented by hand searching major textbooks: *Handbook of Local Anesthesia*, 6th edition (25) and *Successful Local Anesthesia for Restorative Dentistry and Endodontics* (26). Two reviewers independently assessed eligibility of the studies by reading the title and the abstract. Potentially eligible studies were then assessed by reading the full text, and the final decision on inclusion was determined. Discrepancies between reviewers were resolved by consensus with a third person.

Data Extraction

A data extraction sheet based on the Cochrane Consumers and Communication Review Groups data extraction template (27) was used by reviewers to record data extracted from the full-text article. In the event that details were not clear to the reviewers, the authors were contacted for clarification. The data extracted from each included article were the following:

1. Article identifying information (author, year, country, title, journal)
2. Article characteristics (sample size, type of study design)
3. Characteristics of trial participants (number of patients for each intervention, mean age, gender distribution, preoperative pulpal diagnosis, method[s] to determine preoperative pulpal diagnosis)
4. Type of intervention (anesthetic[s] used, anesthetic dose, injection route/delivery method)
5. Type of outcome measure (method to assess anesthesia success, time after injection to start assessing success, definition of success, adverse event)
6. Miscellaneous (conclusion and source of funding/conflict of interest)

TABLE 1. Search Strategy: Original Search October 2013, Last Updated February 2015

Database	No.	Search history	Results
MEDLINE	1	exp lidocaine/	22,095
	2	exp carticaine/	430
	3	ultracaine.mp.	44
	4	articaine.mp.	309
	5	carticaine.mp.	454
	6	2 OR 3 OR 4 OR 5	493
	7	exp Dental Pulp Diseases	9515
	8	1 AND 6 AND 7	14
	9	("root canal" adj3 operat$).mp.	25
	10	exp "Root Canal Therapy"	17,651
	11	1 AND 6 AND 10	11
	12	8 OR 11	14
	13	1 AND 7	57
	14	6 AND 7	26
	15	1 AND 10	47
	16	6 AND 10	24
	17	13 OR 15	74
	18	14 OR 16	30
	19	17 OR 18	90
	20	(lidocain$ adj7 (compar$ or versus or vs) adj7 articain$)).mp.	48
	21	19 OR 20	**138**
Scopus	1	TITLE-ABS-KEY (lidocaine*)	64,766
	2	TITLE-ABS-KEY (Carticain* OR articaine* OR	897
	3	1 AND 2	461
	4	TITLE-ABS-KEY ((dental pulp disease*) OR pulpi* OR canine* OR (oral pathology*) OR endodon* OR root* OR canal* OR tooth* OR dentis*)	113,0989
	5	3 AND 4	**133**
Cochrane Library	1	MeSH descriptor [Carticaine] explode all trees	3
	2	MeSH descriptor: [Lidocaine] explode all trees	20
	3	MeSH descriptor: [Pulpitis] explode all trees	2
	4	#1 AND #2 AND #3	**1**

mp, title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier. Bold font shows the final number of articles for each of the 3 databases searched.

Risk of Bias Assessment

The Cochrane Collaboration "Risk of Bias" tool was used to assess the methodological quality of the included studies by ascertaining their validity, potentially identifying any egregiously biased studies, and determining variability in study results (heterogeneity) (14). Risks of bias domains assessed were selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other potential sources of bias. Risks of bias judgments were indicated as low risk, high risk, or unclear risk (14). Criteria for judging risk of bias follow Cochrane's Handbook Table 8.5.d (14). Assessments were made independently by the 2 reviewers, with any disagreements resolved by consensus.

Data Analysis

The outcomes "successful anesthesia" or "unsuccessful anesthesia" in accordance with the criteria of each study were recorded as dichotomous data. Meta-analysis was performed on the following groups of data:

1. *Combined:* All data obtained by using any maxillary and mandibular anesthetic delivery route
2. *Subgroup:* Maxillary anesthesia by using any delivery route
3. *Subgroup:* Combined mandibular anesthesia by using any delivery route
   - Mandibular anesthesia by using block anesthesia only
   - Mandibular anesthesia by using supplemental infiltration when pulpal pain persisted despite clinical evidence of successful mandibular block anesthesia (defined as lip numbness)

The principal summary measures were odds ratios (ORs) that were calculated by using a random-effects model and the Mantel-Haenszel statistical method (RevMan Version 5.3; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis. Treatment differences were expressed graphically in forest plots. To assess the influence of an individual study on the pooled effect, sensitivity analysis was performed by omitting one study at a time. Statistical heterogeneity was assessed by using the Q statistic value calculated according to the method of Cochrane Q test and the I^2 test for inconsistency; significance was set at $P \leq .1$ rather than the conventional $P \leq .05$ on the basis of the Cochrane Collaboration recommendations (14). To assess publication bias, a funnel plot was created by plotting the log estimates of all studies against their standard error.

Results

Data Extraction

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) study flow diagram describing the article inclusion process. A total of 275 records were initially screened, and the full texts of 17 studies were fully assessed. Seven studies were excluded because they did not meet the inclusion criteria: not a randomized double-blind study (28–31), did not compare articaine and lidocaine (29, 32, 33), or did not provide dichotomous data (34). The remaining 10 studies met the inclusion criteria and were included in the meta-analysis (35–44).

Characteristics of Included Studies

The studies were unicentric trials published between 2004 and 2014 and involved a total of 746 adult patients diagnosed with symptomatic irreversible pulpitis and anesthetized with either articaine or lidocaine (Table 2). The clinical trials were conducted in India (35, 36, 39, 43), the United States (37, 40, 41), Brazil (44), and England (38). Information about participant age was provided for all except one study (41); written communication with these authors confirmed that all participants were adults. For the remaining studies the mean ages ranged from 23 to 38 years. No significant associations between anesthesia outcome and age or gender were reported.

Intervention

The intervention compared was the use of either articaine or lidocaine to anesthetize teeth with symptomatic irreversible pulpitis. There was considerable methodological heterogeneity between studies that included differences in anatomic location of teeth being anesthetized (maxilla or mandible, anterior or posterior), tooth type (molars, premolars, or anterior teeth), volume of anesthetic solution

administered during the intervention (1.7 mL, 1.8 mL, 2.0 mL, 3.6 mL), concentration of epinephrine (1:80,000, 1:100,000, 1:200,000), and anesthetic solution delivery route. Anesthetic solutions were delivered via Gow Gates block (GG), inferior alveolar nerve block (IANB), long buccal infiltration (LBI), maxillary buccal infiltration (MaxBI), supplemental buccal infiltration (SupManBI), and supplemental lingual infiltration (SupManLI) (Table 2). Studies comparing articaine and lidocaine delivered by intraosseous, intraligamental, and intrapulpal routes were not found.

Outcomes

The primary outcome assessed was successful anesthesia that was based on each study's criteria. Success was defined in 9 studies as no pain or mild/bearable pain/discomfort according to patient-reported pain scores (eg, HP-VAS) during endodontic treatment access cavity preparation and instrumentation; one study defined successful anesthesia as no response to the electric pulp tester (38). The timing of the assessment after administration of the anesthetic ranged from 5 to 20 minutes. The secondary outcome assessed was adverse events; one study reported the absence of adverse events (39), whereas no mention was made in the other studies.

Quality Assessment

Evaluations for risk of bias categories are shown in Table 3. In one study the risks were unclear across all categories (43). Conflict of interest was denied in 4 studies (36, 39, 40, 42) and not mentioned in the other 6 studies. One study disclosed receiving financial support from a pharmaceutical company that provided materials and supplies (40), and 4 studies disclosed receiving academic institution financial support (37, 39–41).

Meta-analyses

Success rates for articaine and lidocaine ranged from lows of 24% and 23%, respectively, for IANB delivery to 100% and 89%, respectively, for maxillary infiltration (Table 2). For combined studies, articaine was more likely than lidocaine to achieve successful anesthesia (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.41–3.47; $P = .0006$; $I^2 = 40\%$) (Fig. 2*A*). A potential outlier study was identified as that of Srinivasan et al (43), a trial that evaluated maxillary infiltrations and for which all risks of bias categories were assessed as unclear; sensitivity analysis showed that exclusion of this study did not substantially alter the combined studies results (OR, 2.08; 95% CI, 1.38–3.14; $P = .0005$; $I^2 = 30\%$).

Within the maxillary infiltration subgroup, there was no significant difference between articaine and lidocaine (OR, 3.99; 95% CI, 0.50–31.62; $P = .19$; $I^2 = 59\%$) (Fig. 2*B*). Sensitivity analysis that excluded Srinivasan et al (43) reduced the OR from OR = 3.99 to OR = 1.45 and heterogeneity (I^2) from $I^2 = 59\%$ to $I^2 = 0\%$, with the absence of significant difference between articaine and lidocaine remaining unchanged (Fig. 2*B* and *C*).

For combined mandibular anesthesia studies that used any delivery route, articaine was superior to lidocaine (OR, 2.20; 95% CI, 1.40–3.44; $P = .0006$; $I^2 = 30\%$) (Fig. 3*A*). Further subgroup analysis showed no difference when used for mandibular block anesthesia alone (OR, 1.44; 95% CI, 0.87–2.38; $P = .16$; $I^2 = 0\%$) (Fig. 3*B*). However, when used for supplemental infiltration after (successful) mandibular block anesthesia, articaine was significantly more effective than lidocaine (OR, 3.55; 95% CI, 1.97–6.39; $P < .0001$; $I^2 = 19\%$) (Fig. 3*C*).

Publication bias was evaluated by using a funnel plot (Fig. 4). This showed asymmetry in the base of the funnel, with more studies on the right compared with the left of the center line. This asymmetry could represent a lack of available publications describing interventions that were found to be not significantly effective; the omission of these types of unpublished studies may result in an overestimation of the true effect of an intervention (14).

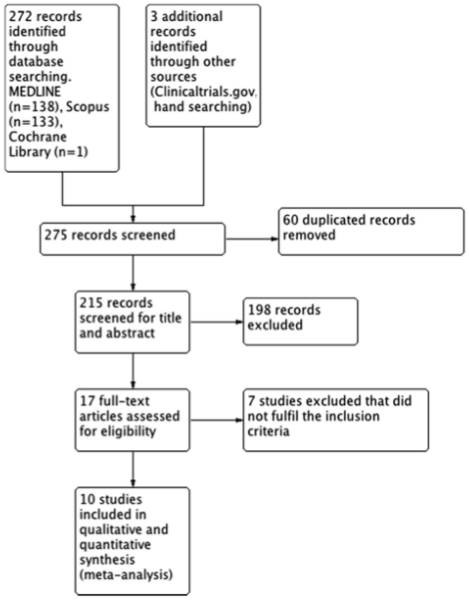

Figure 1. Study flow diagram.

Discussion

This systematic review of double-blind, randomized clinical trials comparing the use of articaine and lidocaine in patients with symptomatic irreversible pulpitis provides level 1 evidence that is based on the criteria given by the Oxford Centre for Evidence-based Medicine (4). The main conclusions that can be drawn from this study are that there is a significant advantage to using articaine over lidocaine for supplementary infiltration after mandibular block anesthesia but no advantage when used for mandibular block anesthesia alone or for maxillary infiltration.

Although there were no specific language exclusion criteria as part of the search strategy for the present review, if an abstract was not available in English for screening purposes, the article was not included. Therefore, it should be acknowledged that any existing non-English publications may not have been included in the present review. In addition, it is important to acknowledge that in common with previous reviews (18, 19), the underlying heterogeneity of the included studies presents limitations. Such heterogeneity includes geographic location, sample size, number and experience of operators, potential variations in approaches to diagnose symptomatic irreversible pulpitis (cold test, electric pulp test, and patient history), the volume of anesthetic, the concentration of epinephrine, reproducibility of injection route, and evaluation scale used to assess pain and definition of success (VAS, HP-VAS, access cavity, endodontic

TABLE 2. Characteristics of Studies Included in Meta-analysis

Author, year	Patients in meta-analysis (*n*)	Preoperative pulpal diagnosis	Location and tooth type	Anesthetic delivery route	Interventions compared	Epinephrine concentration	Definition of successful anesthesia (method to assess pain)	Results reported for anesthesia success
Aggarwal et al, 2009 (35)	60	Prolonged response to cold testing with ice stick and electric pulp tester, absence of PARL, vital coronal pulp on access opening	Mandibular molars	All received IANB 1.7 mL lidocaine. Then 2 minutes later received SupManBI and SupManLI of either 1.7 mL 4% articaine or 1.7 mL 2% lidocaine.*	SupManBI 1.7 mL + SupManLi 1.7 mL articaine vs lidocaine	1:200,000	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS†)	Articaine: 20/30 = 67% Lidocaine: 14/30 = 47%
Ashraf et al, 2013 (36)	125	Prolonged response to cold testing by using ice stick, vital pulp tissue during access opening, and absence of PARL	Mandibular molars	All received IANB 1.5 mL and LBI 0.3 mL of either 4% articaine or 2% lidocaine. If VAS score was moderate or higher, then received 1.8 mL SupManBI of same anesthetic used for IANB.	SupManBI 1.8 mL articaine vs 1.8 mL lidocaine	1:100,000	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS†)	Articaine: 41/58 = 71% Lidocaine: 17/58 = 29%
Claffey et al, 2004 (37)	72	Actively experiencing pain, prolonged response to cold testing with Endo-ice, absence of radiographic evidence of periapical pathosis	Mandibular molars (*n* = 65) Premolars (*n* = 7)	Patients received IANB of either 2.2 mL 4% articaine or 2.2 mL 2% lidocaine.	IANB 2.2 mL articaine vs 2.2 mL lidocaine	1:100,000	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS†)	Articaine: 9/37 = 24% Lidocaine: 8/35 = 23%
Kanaa et al, 2012 (38)	100	Irreversible pulpitis (diagnosed by spontaneous pain or pain lasting over 1 minute when provoked by thermal stimuli)*	Maxillary molars (*n* = 44) Premolars (*n* = 24) Anteriors (*n* = 5)	Patients received MaxBI of either 2.0 mL 4% articaine or 2% lidocaine.	MaxBI 2.0 mL articaine vs 2.0 mL lidocaine	1:100,000 (articaine) 1:80,000 (lidocaine)	No response to EPT (reading >80)	Articaine: 38/50 = 76% Lidocaine: 35/50 = 70%
Poorni et al, 2011 (39)	104	Prolonged response to cold testing with ice stick and electric pulp tester, absence of PARL, vital coronal pulp on access opening	Mandibular molars	Patients received IANB of either 1.8 mL 4% articaine or 1.8 mL 2% lidocaine.	IANB 1.8 mL articaine vs 1.8 mL lidocaine	1:100,000	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS†)	Articaine: 36/52 = 69% Lidocaine: 35/50 = 65%

Rogers et al, 2014 (40)	74	Greater than moderate pain and spontaneous and prolonged response to cold testing with Endo-Ice, absence of radiographic evidence of periapical pathosis, vital coronal pulp tissue on access	Mandibular molars	All received IANB 1.7 mL 4% articaine. Then if VAS pain score was moderate or higher, received SupManBI of either 1.7 mL 4% articaine or 1.7 mL 2% lidocaine.	SupManBI 1.7 mL articaine vs 1.7 mL lidocaine	1:100,000	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS[†])	Articaine: 24/39 = 62% Lidocaine: 13/35 = 37%	
Sherman et al, 2008 (41)	40	Prolonged symptomatic response to cold stimuli and intact lamina dura	Posterior mandibular (n = 21) and maxillary (n = 19) teeth	Patients received either 1.7 mL 4% articaine or 1.8 mL of 2% lidocaine by using either GG block (mandibular teeth) or MaxBI (maxillary teeth).	Mandibular GG 1.7 mL articaine vs 1.8 mL lidocaine Maxillary MaxBI 1.7 mL articaine vs 1.8 mL lidocaine	1:100,000	No pain or mild pain during access cavity preparation (HP-VAS[†])	Overall: Articaine: 19/20 = 95% Lidocaine:16/20 = 80% Mandibular: Articaine: 9/10 = 90% Lidocaine: 8/11 = 73% Maxillary: Articaine: 10/10 = 100% Lidocaine: 8/9 = 89%	
Sood et al, 2014 (42)	100	Prolonged response to cold testing with ice stick and electric pulp tester, absence of PARL	Mandibular molars (n = 92) Premolars (n = 8)	Patients received IANB of either 1.8 mL 4% articaine or 1.8 mL 2% lidocaine.	IANB 1.8 mL articaine vs 1.8 mL lidocaine	1:100,000 (articaine) 1:80,000 (lidocaine)	No pain or mild pain during access cavity preparation (EPT and VAS[‡])	Articaine: 44/50 = 88% Lidocaine: 41/50 = 82%	
Srinivasan et al, 2009 (43)	40	Prolonged response to cold testing with ice stick and electric pulp tester, absence of PARL, vital coronal pulp on access opening	Maxillary molars (n = 20) Premolars (n = 20)	Patients received MaxBI of either 1.7 mL 4% articaine or 2% lidocaine.	MaxBI 1.7 mL articaine vs 1.7 mL lidocaine	1:100,000	No pain or mild discomfort during access cavity preparation and instrumentation (VAS[‡])	Overall: Articaine: 20/20 = 100% Lidocaine: 11/20 = 55% Molars: Articaine: 10/10 = 100% Lidocaine: 3/10 = 30% Premolars: Articaine: 10/10 = 100% Lidocaine: 8/10 = 80%	
Tortamano et al, 2009 (44)	40	Moderate to severe spontaneous pain and exhibited positive response to EPT and prolonged response to cold testing	Mandibular molars (n = 30) Premolars (n = 10)	Patients received IANB of either 3.6 mL 4% articaine or 3.6 mL 2% lidocaine.	IANB 3.6 mL articaine vs 3.6 mL lidocaine	1:100,000	No pain or mild bearable pain when accessing pulp chamber (EPT and verbal analog scale[§])	Articaine: 13/20 = 65% Lidocaine: 9/20 = 45%	

EPT, electric pulp tester; PARL, periapical radiolucency.
*Information confirmed in written correspondence with authors.
[†]HP-VAS categories: mild pain >0 and ≤54 mm; moderate pain >54 and <114 mm; severe pain >114 mm.
[‡]VAS categories: 0 = no pain; 1 = mild discomfort; 10 = severe pain (Srinivasan et al [43]); 0 = no pain; 1 = mild, bearable pain; 2 = moderate, unbearable pain; 3 = severe, intense, and unbearable pain (Sood et al [42]).
[§]Verbal analog scale: 0 = no pain; 1 = mild, bearable pain; 2 = moderate, unbearable pain; 3 = severe, intense, and unbearable pain (Tortamano et al [44]).

TABLE 3. Risk of Bias

Author, year	Selection		Performance: blinding of participants and personnel	Detection: blinding of outcome assessment	Attrition: incomplete outcome data	Reporting: selective reporting
	Random sequence generation	Allocation concealment				
Aggarwal et al, 2009 (35)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ashraf et al, 2013 (36)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Claffey et al, 2004 (37)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kanaa et al, 2012 (38)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Poorni et al, 2011 (39)	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
Rogers et al, 2014 (40)	Low risk	Low risk*	Low risk	Low risk	Low risk	Low risk
Sherman et al, 2008 (41)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Sood et al, 2014 (42)	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk
Srinivasan et al, 2009 (43)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Tortamano et al, 2009 (44)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk

*Anesthetic cartridges were masked (confirmed in written correspondence with author).

instrumentation). In an effort to allow for heterogeneity issues, the meta-analysis used a random-effects model of statistical analysis, as opposed to the fixed-effects model that is used in cases with no evidence of heterogeneity. Regardless, in the present meta-analysis, one study in particular was identified as potentially contributing to heterogeneity; this study met the eligibility criteria but was assessed as having unclear reporting (43). In addition, forest plot analysis showed wide CIs that potentially contributed to heterogeneity as shown by I^2 estimates of 40% and 59% (Fig. 2*A* and *B*). Excluding outlier studies from a meta-analysis is not recommended because doing so might introduce bias (14). However, to evaluate whether the final results were dependent on a study with unclear reporting, a sensitivity analysis was performed by conducting a meta-analysis that excluded the study in question. The sensitivity analysis confirmed that although exclusion of the study reduced the ORs and heterogeneity, the overall results were unchanged (Fig. 2*C*).

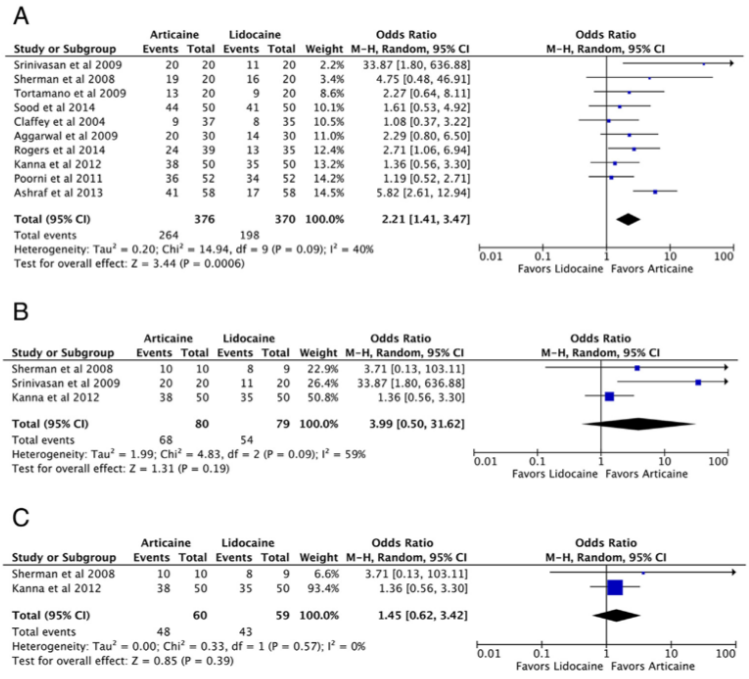

Figure 2. Forest plots of ORs of articaine versus lidocaine from (*A*) all 10 trials, showing articaine to have treatment effect 2.30 times greater than lidocaine (P = .0006), (*B*) subgroup maxillary infiltration trials showing no significant difference between articaine and lidocaine (P = .19), and (*C*) subgroup maxillary infiltration sensitivity analysis that excludes Srinivasan et al (43), which shows reduced OR and I^2 and no significant difference (P = .39). M-H, Mantel-Haenszel.

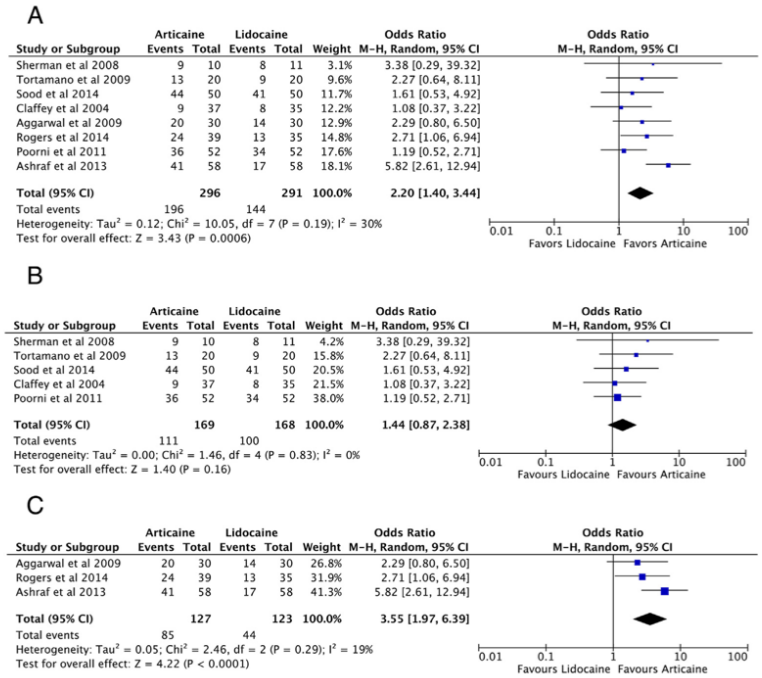

Figure 3. Forest plots of ORs of articaine versus lidocaine from subgroups: (*A*) all mandibular trials, showing articaine to have treatment effect 2.20 times greater than lidocaine, (*B*) trials limited to mandibular block anesthesia only, showing no difference between articaine and lidocaine, and (*C*) trials using supplemental infiltration in cases where pulpal pain persisted despite successful mandibular block anesthesia (defined as lip numbness), showing articaine to have treatment effect 3.55 times greater than lidocaine. M-H, Mantel-Haenszel.

In one study, injection speed was standardized by using a digitally controlled injection system at a standardized injection rate (32). No studies were found that compared articaine and lidocaine delivered by the intraosseous, intraligamental, and intrapulpal routes sometimes used to anesthetize symptomatic teeth undergoing endodontic treatment (45). It should be noted that Poorni et al (39) included 3 test arms in their trial, 2 arms comparing articaine and lidocaine mandibular block anesthesia and a third "control" test arm that used articaine buccal infiltration; data from the third test arm were not included in this study because there was no lidocaine group comparison.

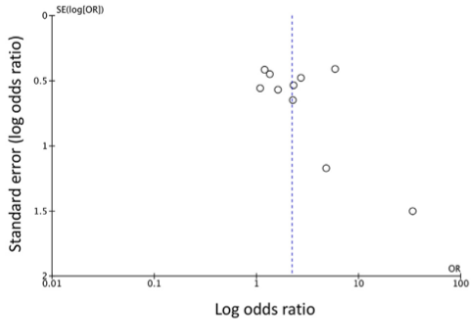

Figure 4. Funnel plot to detect publication bias. Outlier on lower right represents Srinivasan et al (43).

This meta-analysis included several studies not previously reviewed. Four of these studies evaluated mandibular molars (35, 36, 39), and one evaluated maxillary teeth (38). One study in symptomatic patients had been excluded from a previous review (19) because of concerns that the comparisons were confounded by the pre-administration of additional anesthetic before the comparison (35). Three studies in the present review included patients who had already received block anesthesia before the intervention (supplemental infiltration) (35, 36, 40). We considered that pre-administration of anesthetic solution should not be an exclusion criterion as long as both groups received the same pre-administration anesthetic solution.

The Cochrane Handbook for Systematic Reviews of Interventions recommends updating existing reviews every 2 years or when potentially relevant studies surface in the literature (14). A Chinese language systematic review published in 2010 reviewed 6 Chinese language reports that were unable to be accessed (17); consequently, because this review was unable to be fully evaluated, it is not discussed further. Comparisons with previous English language systematic reviews (18, 19) reveal some similarities and some notable differences (Table 4). For example, all 3 reviews included an

TABLE 4. Comparison with Other Systematic Reviews

	Katyal, 2010 (18)	Brandt et al, 2011 (19)	This study
Aim of study	"to compare the efficacy and safety of articaine with that of lignocaine in maxillary and mandibular infiltrations and block anesthesia in patients presenting for routine noncomplex dental treatments"	"broad comparison regarding the efficacy of articaine and lidocaine solutions when used to achieve profound anesthesia in adults"	PICO question: in adults with symptomatic irreversible pulpitis who are undergoing endodontic treatment, what is the comparative efficacy of articaine compared with lidocaine in reducing pain and incidence of adverse events?
Search period	1950–October 2009	January 1970–December 2009	January 1976–February 2015
Search strategies	MEDLINE, Cochrane, Embase, Proquest, metaRegister of controlled trial database	MEDLINE, Embase, hand search, journal table-of-contents searches, books, conference proceedings, recommendations from experts in field	MEDLINE, Scopus, Cochrane Library, ClinicalTrials.gov, hand search, journal table-of-contents searches, books, conference proceedings
Reviewers	1	2, with third available to resolve discrepancies between reviewers	2, with third available to resolve discrepancies between reviewers
Interventions compared	Similar volume dose of 4% articaine (1:100,000 epinephrine) and 2% lignocaine (1:100,000)	4% articaine (1:100,000 epinephrine	Same volume dose of at least 1.0 mL per administration of 4% articaine and 2% lidocaine in combination with epinephrine
Anesthetic delivery routes included	Maxillary and mandibular infiltrations and block anesthesia administered manually	IANB, GG block, maxillary buccal and lingual infiltration	IANB, GG block, long buccal nerve infiltration, maxillary buccal infiltration, supplemental mandibular buccal and lingual infiltration
Exclusion factors not excluded in this review	Computerized delivery routes	Pre-administration of additional anesthetic before intervention	Not applicable
Meta-analysis			
Total studies included in meta-analysis	8 (both crossover and independent-sample studies)	13 (both crossover and independent-sample studies)	10 (independent-sample studies only)
Participants	1725 patients of all ages requiring routine non-complex dental treatment with and without pain	560 adult human participants (including non-patient volunteers) with and without pain	746 adult human patients with symptomatic irreversible pulpitis
Studies restricted to irreversible pulpitis	2 (Claffey et al [37], Tortamano et al [44])	4 (Claffey et al [37], Sherman et al [41], Srinivasan et al [43], Tortamano et al [44])	10
Participants with irreversible pulpitis	77 (articaine), 75 (lidocaine)	67 (articaine), 66 (lidocaine)	376 (articaine), 370 (lidocaine)
Analysis of all studies	Not available	13 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 2.44; 95% CI, 1.59–3.76, $P < .0001$)	10 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 2.21; 95% CI, 1.41–3.47; $P = .0006$)
Infiltration only (maxillary + mandibular)	Not available	9 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 3.81; 95% CI, 2.71–5.36; $P < .00001$)	Not available
Infiltration only (maxillary)	Not available	Not available	3 studies: no difference between articaine and lidocaine
Mandibular (combined block and infiltration)	Not available	Not available	8 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 2.20; 95% CI, 1.40–3.44; $P < .0006$)
Mandibular block only (combined crossover and independent-samples studies)	7 studies: articaine more likely than lidocaine to achieve anesthetic success in posterior first molar area (OR, 1.31; 95% CI, 1.12–1.54; $P = .0009$)	4 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 1.57; 95% CI, 1.12–2.21; $P < .00001$)	Not available
Mandibular block only (independent-samples studies only)	Not available	3 studies: no difference between articaine and lidocaine	5 studies: no difference between articaine and lidocaine

Supplemental infiltration after mandibular block	Not available	Not available	3 studies: articaine more likely than lidocaine to achieve anesthetic success (OR, 3.55; 95% CI, 1.97-6.39; $P < .0001$)
Adverse events	No difference between articaine and lidocaine	No reports of adverse events or not mentioned	No reports of adverse events or not mentioned
Pain	3 studies: articaine results in higher VAS pain score than lidocaine at injection site (OR, 6.49; 95% CI, 0.02–12.96; $P = .05$) at day 0 decreasing to OR, 1.10; 95% CI, 0.18–2.02; $P = .02$ on day 3 after injection	Not available	Not available
Onset of action	2 studies: no difference between articaine and lidocaine	Not available	Not available

intention to evaluate the incidence of adverse events, but few studies mentioned adverse events at all. Katyal (18) reported that a meta-analysis of 4 studies evaluating post-injection adverse events showed no difference between articaine and lidocaine. In the present review only 1 of the 10 studies reported the absence of adverse events (39), whereas the other studies made no mention. It is important that future clinical studies incorporate the reporting of adverse events in their methodology. A review published in 2011 concluded that reports of articaine neurotoxicity were low level and based on retrospective studies with biased data recruitment, with no scientific evidence demonstrating that 4% articaine solution is "neurotoxic or unsafe to use in any aspect of clinical dentistry" (46).

The main difference between the present and previous English language reviews (18, 19) is that all participants in this review were diagnosed with irreversible pulpitis compared with previous reviews that had a broader participant base (patients and non-patient volunteers with or without pain). In addition, in the present review all studies were parallel-designed, random controlled trials that evaluated independent samples. Previous reviews also included studies with crossover design that, while minimizing variability, are not practical or ethically appropriate for patients in pain. Another difference was the number of participants with symptomatic irreversible pulpitis, 746 compared with 152 (18) and 133 (19) in previous reviews. The start of the search period in this study was selected on the basis of the introduction of articaine to the market in 1976 (10). In comparison, the search period was started in 1950 by Katyal (18) and in 1970 by Brandt et al (19), with the publication dates of their earliest studies reviewed being 2001 and 1972, respectively.

The addition of epinephrine to local anesthetic solutions facilitates vasoconstriction, slows systemic absorption, and thus prolongs the anesthetic effect. The previous reviews included only studies that used the epinephrine concentration of 1:100,000 (18, 19). In this review 7 of the 10 studies used 1:100,000 epinephrine (Table 2). One study compared articaine and lidocaine solutions with 1:200,000 epinephrine (35), and another study compared articaine with 1:100,000 epinephrine with lidocaine with 1:80,000 epinephrine (38). Dagher et al (47) found no significant differences in degree of anesthesia obtained by using 2% lidocaine with 1:50,000, 1:80,000, or 1:100,000 concentrations of epinephrine. The same onset and duration of pulpal anesthesia have been reported for articaine with either 1:100,000 or 1:200,000 epinephrine (2- to 3-minute onset and 60-minute pulpal anesthesia) and for lidocaine 1:50,000 and 1:100,000 (onset for both 3–5 minutes, duration 10 minutes for 1:50,000 and 60 minutes for 1:100,000) (7). Considering that evaluations for the determination of anesthetic success were made by 10 minutes (38) and 15 minutes (35) after injection, it is reasonable to expect that these variations in epinephrine concentration would not likely have a major impact on the outcomes evaluated in this review.

Previously Brandt et al (19) reported that articaine was 3.81 times more likely than lidocaine to achieve anesthetic success when delivered "when the infiltration mode of administration is used". However, that was based on data from combined maxillary and mandibular teeth in patients and non-patient (asymptomatic) volunteers. In contrast, the present study, which included only symptomatic patients, found no difference between articaine and lidocaine for maxillary infiltration; mandibular infiltration only studies in symptomatic patients were not found.

In conclusion, the present meta-analysis showed that in patients with symptomatic irreversible pulpitis, articaine is as effective as lidocaine when used for mandibular block or maxillary infiltration

anesthesia. In cases of persistent pulpal pain despite successful mandibular block anesthesia, supplementary infiltration with articaine instead of lidocaine has 3.55 times greater likelihood of achieving successful anesthesia.

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The authors deny any conflicts of interest related to this study.

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The Oregon Health & Science University School of Dentistry

Master of Science in Endodontology Data Sheet

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Brief Summary of Thesis: The present meta-analysis showed that in patients with symptomatic irreversible pulpitis, there is a significant advantage to using articaine over lidocaine for supplementary infiltration after mandibular block anesthesia but no advantage when used for mandibular block anesthesia alone or for maxillary infiltration.