Martin, Erica Madeleine

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Articaine in dentistry: Safety, efficacy, practitioner perception and evidence-based practice

Master of Philosophy (Health)

College of Medicine and Dentistry
James Cook University

Table of Contents

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Advisors: Dr Ernest Jennings, Associate Professor Andrew Lee, Professor Alan Nimmo

Peers: Dr Rita Louise, Dr Andrea James

Mentors: Dr Ernest Jennings, Dr Michelle Redman-MacLaren, Professor John Abbott

Personal: My family

Statement of Contribution:

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Statement of Contributions

Thesis Part	Publication on which based	Role of each author
Introduction		Martin authored the introduction with proof-reading conducted by Jennings
PART 1	Martin, E., Nimmo, A., Lee, A. Jennings, E. Articaine in dentistry: an overview of the evidence and meta-analysis of the latest randomised controlled trials on articaine safety and efficacy compared to lidocaine for routine dental treatment. *BDJ Open* **7,** 27 (2021). https://doi.org/10.1038/s41405-021-00082-5	Martin, Nimmo, Lee and Jennings refined the study questions based upon a topic suggested by Martin. Martin conducted the data collection, data analysis, interpretation of the results, and authored the publication. Jennings and Lee edited the publication and gave intellectual and research support throughout the process.
PART 2	Martin, E., Lee, A. & Jennings, E. Articaine: dental practitioner use, basis of perception and evidence-based dentistry—a cross-sectional study. *BDJ Open* **8,** 20 (2022). https://doi.org/10.1038/s41405-022-00113-9	Martin, Lee and Jennings conceptualised the research question and methodology. Martin conducted the data collection, data analysis, data interpretation and research writing. Jennings validated the data, provided resources, administered/supported the research project, provided support with funds acquisition and edited the publication. Lee assisted with supervision and provided clinical dental support
Conclusion		Martin authored the conclusion with proof-reading conducted by Jennings

Thesis Abstract

Aim/Objectives: The aim of this Master of Philosophy (Health) research project was to determine evidence-based dental practice in relation to the dental anaesthetic, articaine, by achieving two objectives. Objective one was to synthesise and review the conclusions of existing studies to determine articaine's status in dental clinical practice. Objective two was to collect data on dental practitioner use of articaine and the basis of their perceptions about articaine, clarify evidence-based dental practice regarding articaine use and suggest a future direction of research involving articaine in dentistry.

Methodologies: Our first objective was fulfilled by comprehensively reviewing the latest randomised controlled trials involving articaine in dentistry and conducting a systematic review and meta-analysis to answer the question: "Is articaine a safe and efficacious local anaesthetic for routine dental treatment compared to lidocaine?". The review incorporated the PRISMA guidelines for systematic reviews and meta-analysis, the Cochrane Risk of Bias 2 guidelines and utilised the Cochrane Review Manager 5.3 software (RevMan Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for statistical analysis of the principal outcome.

Our second objective was achieved by surveying dental practitioners online using the Qualtrics SAP Core XM software. The software generated a link that was disseminated via social media as an anonymous questionnaire which included a plain language information sheet and 15 questions, including a request for participant consent. The Qualtrics link was available online from December 2020 to January 2021. The collected data was downloaded from the Qualtrics website, and the answers were arranged into recurrent themes using a Microsoft™ Excel spreadsheet. The data from objectives one and two were analysed, discussed and a future direction for further research was suggested.

Results: Our systematic review and meta-analysis found that articaine is a safe and efficacious dental local anaesthetic and achieved anaesthetic success more frequently than the gold standard LA, lidocaine, in all subgroup analyses and overall.

Our survey found that while twenty-three percent of surveyed dental practitioners used articaine for all their dental procedures including inferior alveolar nerve blocks, forty percent

of respondents did not use articaine for inferior alveolar nerve blocks. The predominant influence on dental practitioner use and perceptions of articaine were the dental guidelines of their country dental registration.

Conclusions: For all routine dental procedures, articaine is a safe and efficacious dental local anaesthetic. Articaine is more likely to achieve successful anaesthesia than lidocaine. Both LAs had similar incidences of anaesthetic related adverse effects.

Whilst a review of the clinical evidence, as illustrated by our systematic review, indicates that articaine is a safe and efficacious dental anaesthetic for all routine dental procedures including inferior alveolar nerve blocks, forty percent of surveyed dental practitioners reportedly avoid articaine use for their inferior alveolar nerve blocks. The discrepancy between reported clinical practice and current research evidence found in our study warrants further investigation and clarification to achieve ubiquitous practice of evidence-based dentistry

Introduction

This Master of Philosophy (Health) research project aimed to synthesise results from existing studies, gather new data and ascertain whether further research is needed to clarify articaine's place in evidence-based dental clinical practice. Articaine is a local anaesthetic (LA) which has gained popularity worldwide since its clinical release in 1976.[1]

This Master of Philosophy research project consisted of two components. The first component reviewed the existing literature on articaine and conducted a meta-analysis comparing the safety and efficacy of articaine to the current gold standard dental LA, lidocaine. The second component collected data about dental practitioner use of LA in routine dental practice, and the basis of their perceptions about articaine via an online, anonymous survey disseminated on social media.

The final analysis aimed to compare the data collected from the systematic review with survey data results and discern any discrepancy in current evidence-based dental clinical practice that may define a future research pathway in this field.

Background

Effective pain control forms the backbone of successful dental patient care. Articaine, a local anaesthetic (LA) used for routine dental treatment worldwide, is a relative newcomer in the LA field, released for clinical use in 1976.[1] The current gold standard of dental local anaesthetics, lidocaine, was released for clinical use in 1948. Both articaine and lidocaine are popular LAs used for routine dental treatment.

Several anaesthesia techniques are used for routine dental treatment – local infiltrations and nerve blocks.[2] The first, a local infiltration or LA administration close to terminal nerve endings adjacent to the target tooth, is where the anaesthetic infiltrates from the injection site through porous bone, anaesthetising the tooth. The local infiltration may be used to anaesthetise maxillary teeth and mandibular teeth anterior to the molars.

The second technique, a nerve block, anaesthetises nerves or nerve bundles by depositing anaesthetic further up a nerve branch.[2] The mandibular nerve block refers to the traditional inferior alveolar nerve block used by dental practitioners to anaesthetise mandibular premolars, molars or multiple teeth on one side of the lower jaw.

The inferior alveolar nerve enervates mandibular teeth. The nerves of the lower molars are commonly encased within dense buccal bone that cannot be effectively penetrated by LA infiltration. The mandibular nerve block aims to anesthetise the inferior alveolar nerve along the inner ramus of the mandible at the height of the lingula before it enters the mandibular foramen. The inferior alveolar nerve block requires a deeper injection than the infiltration that passes through facial soft tissue, the buccinator muscle and proximal to the lingual nerve. The lingual nerve enervates the tongue and soft tissues on the tongue-side of the lower teeth.[2]

Objective and scholarly context

Previous randomised controlled trials (RCT) and systematic reviews have found that articaine is as safe, and equal to or more efficacious a dental LA as lidocaine. Despite these findings, dental practitioners may be influenced by a few potentially flawed and biased reviews that hypothesised articaine's association with higher rates of lingual nerve paraesthesia following mandibular block anaesthesia[3] resulting in avoidance of articaine use for this anaesthetic technique. Based upon the conclusions of the latest reviews and randomised controlled trials involving articaine, the avoidance of articaine use for mandibular block anaesthesia indicates a discrepancy in dental evidence-based clinical practice.

The aim of this research project was to clarify evidence-based practice regarding use of articaine in dentistry. The research project consisted of three objectives. The first was to systematically review the latest research findings on articaine safety and efficacy. The second was to gather data on dental practitioner use of articaine in their daily practice, their perceptions of dental LA and the basis of their perception. Once we fulfilled these two objectives, we could compare the findings and evaluate if dental practitioners were following evidence-based dental practice.

The following thesis consists of three parts: part one, the systematic review and meta-analysis of the latest RCTs on articaine safety and efficacy compared to the current gold standard dental LA, lidocaine for routine dental treatment; part two, a cross-sectional study of dental practitioner use, basis of perception and evidence-based dentistry and part three, a brief conclusion summarising the data analysis of the two previous parts to summarise the status of evidence-based dental practice regarding articaine use.

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Part I

Articaine in dentistry: An overview of the evidence and meta-analysis of the latest randomised-controlled trials on articaine safety and efficacy compared to lidocaine for routine dental treatment

Link to publication: https://doi.org/10.1038/s41405-021-00082-5.

ABSTRACT

Key words: Dentistry, local anaesthetic, articaine, lidocaine

Objectives: To comprehensively review the existing studies of articaine in dentistry and conduct a systematic review and meta-analysis to answer the following Population, Intervention, Comparison and Outcome question: "Is articaine a safe and efficacious local anaesthetic for routine dental treatment compared to lidocaine?"

Methods: Database searches were conducted in Medline Ovid, Medline Pubmed, Scopus, Emcare, Proquest and the Cochrane Central register of Controlled Trials. Inclusion criteria were all existing English, human, randomised controlled trials of interventions involving 4% articaine and 2% lidocaine in routine dental treatment. Twelve studies were included for meta-analysis using Cochrane Review Manager 5 software. Anaesthetic success odds ratios were calculated using a random-effects model.

Results: Articaine had a higher likelihood of achieving anaesthetic success than lidocaine overall and in all subgroup analyses with varying degrees of significance. Overall (OR: 2.17, 95% CI: 1.50, 3.15, $I^2 = 62\%$) articaine had 2.17 times the likelihood of anaesthetic success of lidocaine ($P < 0.0001$). For mandibular blocks (OR: 1.50, 95% CI: 1.14, 1.98, $I^2 = 0\%$) articaine had 1.5 times the likelihood of anaesthetic success of lidocaine ($P = 0.004$). For all infiltrations, maxillary and mandibular (OR: 2.78, 95% CI: 1.61, 4.79, $I^2 = 66\%$) articaine had 2.78 times the likelihood of anaesthetic success of lidocaine ($P = 0.0002$). None of the studies reported any major local anaesthetic-related adverse effects as a result of the interventions.

Conclusions: Articaine is a safe and efficacious local anaesthetic for all routine dental procedures in patients of all ages, and more likely to achieve successful anaesthesia than

lidocaine in routine dental treatment. Neither anaesthetic has a higher association with anaesthetic-related adverse effects.

INTRODUCTION

Local anaesthetics (LA) provide pain-free patient dental care reducing patient anxiety and phobia. Evidence-based dental clinical practice should be based upon the latest clinical research with continuous re-assessment of all available clinical data on dental anaesthetic efficacy and safety.

Purpose of this review

The aim of this research is twofold: to review the existing studies of articaine use for routine dental treatment and to conduct a meta-analysis of randomised control trials answering the following Population, Intervention, Comparison and Outcome question: Is articaine as safe and efficacious as the current gold standard dental anaesthetic, lidocaine for all routine dental treatment? For the purposes of this review, the definition of routine dental treatment are standard dental procedures taught in mainstream undergraduate dental curriculums.

Systematic reviews are considered the most robust method for summarizing large volumes of study evidence, and meta-analyses of research data are considered the highest form of evidence.[1,2] The Cochrane Handbook for Systematic Reviews of Interventions recommends that review data should be updated every two years or when relevant new data emerges in the literature.[3]

The research questions for this systematic review and meta-analysis are: “Is articaine a safe local anaesthetic for all routine dental treatment?” and “Is articaine as safe and efficacious as the current gold standard dental anaesthetic, lidocaine for all routine dental treatment?”

Articaine pharmacology

Articaine, *4-methyl-3[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride,* belongs to the amide family of local anaesthetics which also includes lidocaine, mepivacaine, bupivicaine and prilocaine.[4-6] Articaine is unique amongst the amide family, containing an ester group and having a thiophene instead of a benzene ring.[4-6] The thiophene ring, an integral feature of articaine’s LA potency[7] increases articaine’s lipid

solubility facilitating more efficient diffusion of the anaesthetic through the nerve cell lipid membrane and into surrounding tissue.[8-10] A 2000 pharmacological study of various anaesthetic diffusion across nerve membranes found that articaine's lipid-soluble abilities result in superior diffusive action of articaine when compared with other LA formulas.[7] Articaine has a serum half-life of 20-30 minutes, shorter than the other amide LAs due to the more rapid hydrolysis of the ester group within the plasma.[5,9,11,12] Lidocaine has a half-life of 90-120 minutes.[9] Articaine's ester group allows 90%[5,11] of the anaesthetic to metabolise within the plasma to the inert metabolite, articainic acid, and be excreted via the kidneys resulting in the shorter half-life compared to the other amide LAs. The remaining 10% biotransforms within the liver.[12]

Oertel (1997)[5] concluded that articaine's shorter half-life means that articaine can be given safely at higher concentrations[5], however Paxton and Thorne (2010)[8] argue that lipid solubility may not determine the speed of diffusion across the cell membrane.[8] Other studies have proposed that anaesthetic binding to plasma proteins has greater association with ionic channel action than lipid solubility.[5] Similar to the other amide LAs, articaine anaesthetises tissue by blocking nerve conduction. The addition of a vasoconstrictor prolongs the anaesthetic effect by delaying absorption of the anaesthetic solution.[12]

Studies investigating the pharmacology and toxicology of articaine in animals recognised that articaine had 1.5 times higher anaesthetic efficiency, superior ability in infiltration anaesthesia and low toxicity to local tissues when compared with the other amide LAs.[8] A rat sensory nerve conduction study concluded that 2% and 4% articaine more effectively anaesthetise nerve fibres than other LAs.[13] Articaine's anaesthetic effect lasts approximately 120 minutes which is similar to lidocaine.[5]

Articaine in dentistry

Articaine was first synthesized in Germany in 1969 under the label, HOE 40-045, and then released for clinical use in 1976 under the name, Carticaine hydrochloride.[6,9] Winther and Nathalang conducted the first clinical trials of articaine in 1971 finding that 2% articaine with 1:200,000 adrenaline was superior to 2% lidocaine with 1:200,000 adrenaline in anaesthetic duration and extent, and that articaine produced profound anaesthesia for all teeth except mandibular molars.[4] In 1984, carticaine was renamed to articaine[8] and in 2000, was approved by the US FDA as a 4% formula with 1:100,000 adrenaline under the name Septocaine (Septodont). The FDA approved 4% articaine with 1:200,000 adrenaline in 2006.[6]

Articaine efficacy

Articaine LA onset takes between 1.5-1.8 minutes for a maxillary infiltration and 1.5-3.6 minutes for mandibular block anaesthesia.[4,6,14] Articaine pulpal anaesthesia lasts between 30-120 minutes, a duration longer than lidocaine, mepivacaine and prilocaine.[4] Articaine soft tissue anaesthesia lasts approximately 2.25 hours for maxillary infiltrations and 4 hours for mandibular blocks.[6]

Articaine safety

Malamed et al.'s 2001's multi-centre trial involving the comparison of 2% lidocaine with 4% articaine on 1325 patients aged 4-80 years of age, found that articaine was well-tolerated and safe for use in routine clinical dentistry.[6] Both anaesthetics are appropriate and effective for clinical use. Articaine's toxicity is comparable to that of lidocaine[4,12], but Malamed et al. cautioned use of both lidocaine and articaine in patients with liver or cardiovascular impairment as amide biotransformation occurs in the liver and the anaesthetics can decrease myocardial function for patients with advanced cardiovascular disease.[6]

Lidocaine and articaine use in dentistry

Lidocaine has proven safe and efficacious for routine clinical treatment.[9] Lidocaine entered the clinical market in 1948 and has since been the most common dental LA in most countries.[8] Lidocaine sets the dental LA gold standard against which all new LAs are compared.[9]

Despite the popularity of lidocaine, dental LA reviews in 1995[15] and 2000[16] recognised articaine's growing popularity stating that articaine was the most popular dental anaesthetic in some countries at the time. Oertel's[5] 1997 review of articaine stated that lidocaine was the LA most used in dentistry, but that articaine was well-established as a mainstream dental LA in continental Europe and Canada, and the most widely used dental LA in Germany, Italy and the Netherlands.[5] A 1989 study of German dentists found that articaine is used 72% of the time and lidocaine 13% of the time.[17] A 2005 study by Vree and Gielen stated that "in dentistry, articaine is the drug of choice in the vast majority of the literature."[18]

MATERIAL AND METHODS

Population, Intervention, Comparison and Outcome question: Is articaine as safe and efficacious as the current gold standard dental anaesthetic, lidocaine for all routine dental treatment?"

- Population: All routine dental treatment
- Intervention: 4% articaine dental local anaesthesia
- Comparison: 2% lidocaine dental local anaesthesia
- Outcome: Dental local anaesthesia efficacy and safety

The systematic review was registered in the PROSPERO database prior to the literature search.[19] The search strategy follows the PRISMA preferred reporting items for systematic reviews and meta-analysis.[20]

Search terms

MeSH terms search: Exp dental anaesthetic, Exp articaine, Exp randomized controlled trial

Text word search: "local an?esthetic" OR "dental an?esthetic"; carticaine OR articaine OR septanest OR septocaine OR ultracaine; (randomized controlled trial OR clinical trial OR exp clinical trial OR random* OR trial? OR review)

Databases searched: Medline Ovid, Medline Pubmed, SCOPUS, Cochrane Central Register of Controlled Trials, Emcare Ovid, ProQuest

Ongoing articaine trials were reviewed for redundancy and our study was registered (CRD42020170889) on the PROSPERO International prospective register of systematic reviews

Selection of Studies

Inclusion criteria for the search:

- All existing online studies of interventions involving articaine from its release to February 2020
- Randomised controlled trials
- Studies of routine dental procedures

- Studies published in English

The outcomes measures for the systematic review included: anaesthetic success, anaesthetic onset and duration, and post intervention LA-related adverse events.

The initial search of the listed databases resulted in 1449 studies.

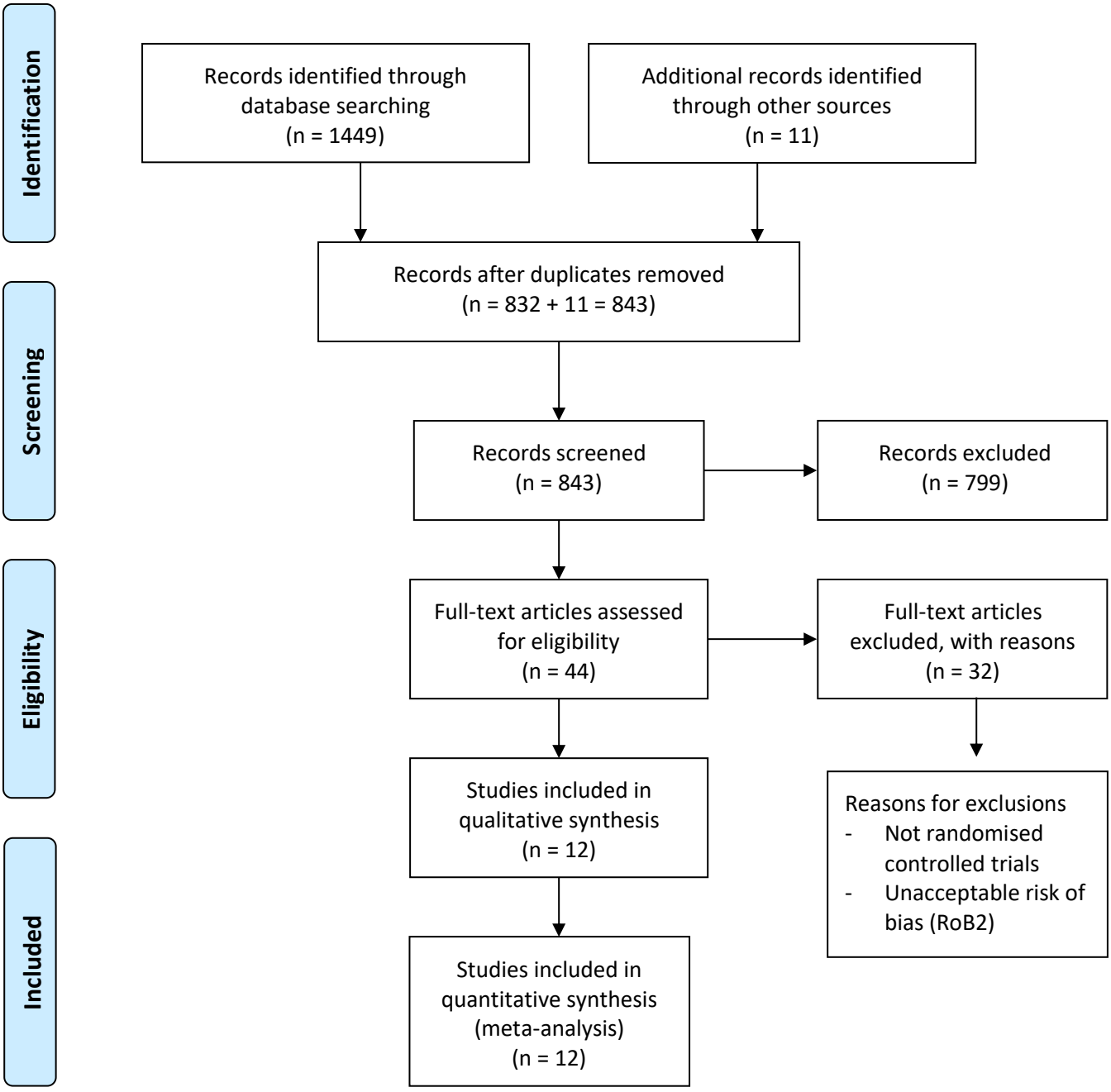
Search Methodology

From the initial 1449 results, a subsequent title and abstract review excluded 617 duplicates and 832 studies based upon the following exclusion criteria:

- Non-English studies
- Trials on non-humans
- Complex dental procedures involving soft tissue surgery and bone removal
- Medically compromised patients
- Digital anaesthesia and non-routine dental anaesthetic techniques eg. Intraosseous, intraligamentary, intra-pulpal, intra-pocket anaesthesia, non-standard mandibular block techniques (Gow-Gates and Vazarani-Akinosi techniques)
- Unrecognised duplicates
- Interventions not including lidocaine or articaine
- Full text not available

A full text review was conducted on 42 studies, of which, nine were further excluded for being incomplete or not randomised controlled trials. A review of citations from previous systematic reviews of articaine and the included studies revealed 11 more sources. A search of the grey literature databases did not produce any further sources. The final search resulted in 44 randomised controlled studies comparing 4% articaine to 2% lidocaine (Figure 1).

Figure 1: PRISMA flowchart - systematic review search process



Risk of Bias Assessment

Forty-four randomised controlled trials were reviewed by the researcher for risk of bias according to Cochrane Risk of Bias 2 guidelines.[21]

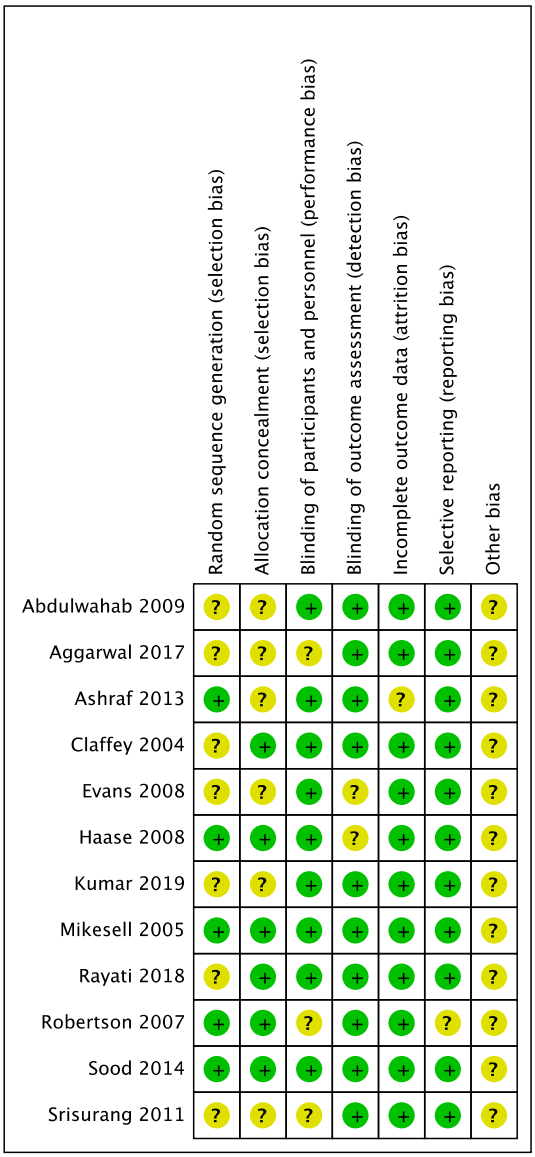
Cochrane Risk of Bias 2 guidelines include assessments of bias from:

- The randomization process (allocation sequence and concealment),
- Deviations from intended interventions (extent/quality of blinding and balanced interventions),
- Missing outcome data
- Measurement of the outcome (quality and appropriateness)
- Selection of the reported result

The risk of bias was assessed as: low risk, high risk, unknown risk or some concerns. Low risk studies had no concerns judged in any domains. Any study with a single concern was judged as “some concerns”. Studies with multiple concerns or deemed high risk in any domain was judged as “high risk” and studies with no information were deemed “unknown risk”. Studies with multiple concerns or any high-risk category were excluded from the meta-analysis.

Thirteen studies were assessed as “low” or “some concern” risk of bias. One study from 1993 was not included for meta-analysis due to lack of appropriate study data measurements. Twelve studies were included in the meta-analysis (Figure 2).

Figure 2: Risk of bias summary



The process was assessed by another of the authors and any differences were resolved for final consensus by an independent third-party reviewer.

Data Extraction/Study Characteristics

Data from the final 12 studies were extracted onto a Microsoft EXCEL spreadsheet (Table 1)

Table 1: Characteristics of included studies

Reference	Sample size	Age range (m)	Sex distribution	Arch	Teeth	Pre-operative tooth status	Anaesthetic technique	Anaesthetic dose	Vasoconstrictor concentration	Assessment method	Anaesthetic success %	Adverse effects
Abdulwahab et al., 2009 [40]	18	18-53 m=24.9	M6 F12	Md	Molar	Healthy asymptomatic	BI	0.9mLs	A 1:100,000 L 1:100,000	EPT	A38.9 L16.7	Minor/No reported paraesthesia
Aggarwal, 2017 [34]	91	24-47 m=34	M57 F34	Md	Molar	Irreversible pulpitis	IANB	1.8mLs	A 1:100,000 L 1:200,000	Endo access	A33 L23	No data
Ashraf et al., 2013 [36]	102	20-60	M47 F55	Md	Molar	Irreversible pulpitis	BI following failed IANB	1.5mLs	A 1:100,000 L 1:100,000	Endo access	A71 L29	No data
Claffey et al., 2004 [31]	72	20-53 m=31	M25 F47	Md	Molar or premolar	Irreversible pulpitis	IANB	2.2mLs	A 1:100,000 L 1:100,000	Endo access	A24 L23	No data
Evans et al., 2008 [37]	80	20-36 m=25	M46 F34	Mx	Lat. Incisor/Molar	Healthy asymptomatic	Infiltration	1.8mLs	A 1:100,000 L 1:100,000	EPT	LI A88 L62/ Molar A78 L72	Minor/No reported paraesthesia
Haase et al., 2008 [35]	73	20-36 m=27	M46 F27	Md	Molar	Healthy asymptomatic	BI following failed IANB	1.8mLs	A 1:100,000 L 1:100,000	EPT	A88 L71	Minor/No reported paraesthesia
Kumar et al., 2019 [41]	100	20-59 m=27	M54 F46	Mx	Molar	Needing extraction	Infiltration	1.8mLs	A 1:100,000 L 1:100,000	EPT	A44 L48	No adverse effects/No reported paresthesia
Mikesell et al., 2005 [32]	57	m=28	M30 F27	Md	Molars, premolars	Healthy asymptomatic	IANB	1.8mLs	A 1:100,000 L 1:100,000	EPT	A48.6 L37.7	Minor/No reported paraesthesia
Rayati et al., 2018 [39]	133	20-50	M65 F68	Md	Molars	Needing extraction	BI	1.8mLs	A 1:100,000 L 1:100,000	Extraction	A18 L1	No data
Robertson et al., 2007 [38]	60	19-51 m=27	M26 F34	Md	Molar or premolar	Healthy asymptomatic	BI	1.8mLs	A 1:100,000 L 1:100,000	EPT	A84.8 L57.3	Minor/No reported paraesthesia
Sood et al., 2014 [33]	100	18-50 m=27	no data	Md	Molars	Irreversible pulpitis	IANB	1.8mLs	A 1:100,000 L 1:80,000	Endo access	A88 L82	No data
Srisurang et al., 2011 [43]	33	13-45 m=18.2	no data	Mx	Premolars	Needing extraction	Infiltrations	1.2mLs	A 1:100,000 L 1:100,000	EPT	A100 L97	Minor/No reported paraesthesia

Key
Md = mandibular
Mx = maxillary
IANB = inferior alveolar nerve block
BI = buccal infiltration
EPT = electronic pulp tester

Data Analysis

Data from 919 interventions were included in the meta-analyses.

Cochrane Review Manager 5.3 software (RevMan Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to statistically analyse the principal outcome - anaesthetic success.

Analysis was performed for:

- All interventions in the studies - maxillary and mandibular infiltrations, and mandibular blocks*
- All mandibular interventions - block and infiltration studies
- Only mandibular block studies
- Only mandibular infiltration studies
- All infiltrations studies - maxillary and mandibular
- Only maxillary infiltration studies
- Preoperative pulp status - asymptomatic versus symptomatic
- Study design - parallel versus crossover

**Mandibular block anaesthesia refers to inferior alveolar nerve blocks, as none of the included studies involved mental or incisive nerve blocks*

The principal summary measures were odd ratios calculated using a Mantel-Haenszel random-effects model for dichotomous data. Treatment differences between articaine and lidocaine were illustrated through forest plots.

Statistical heterogeneity was assessed using Tau^2, Cochran Q test (Chi^2) and the I^2 test for inconsistency. Significance was set at $P <= 0.05$. Heterogeneity refers to variability in the intervention effects being evaluated and is a consequence of clinical or methodological diversity. Tau^2 reflects the amount of variation found among the different studies in a random-effects model and reflects the amount of true heterogeneity. The Cochran Q-test assesses whether the true treatment effects are the same in all the primary studies and is expressed as a P-value determining significant heterogeneity or not. I^2 quantifies the statistical heterogeneity and represents the amount of variability in effect estimates.[22]

A sensitivity analysis of individual study effects on the pooled effects were assessed by omitting studies one by one and noting the change in overall odds ratio.

Funnel plots were used for assessment of publication bias (Figure 3 and 4). Funnel plots are scatterplots used in meta-analysis for publication bias. They estimate the effect each study has against a standard of precision and if the size of the effect is expected or could have occurred by chance.[22] Other than publication bias, funnel plot asymmetry can also be explained by unrobust methodology, inaccurate data analysis or data tampering.[22]

Figure 3: Funnel plot of all studies including outlier (Rayati et al.).

Legend: x-axis = standard error SE(log[OR]), y-axis = log risk ratio (OR)

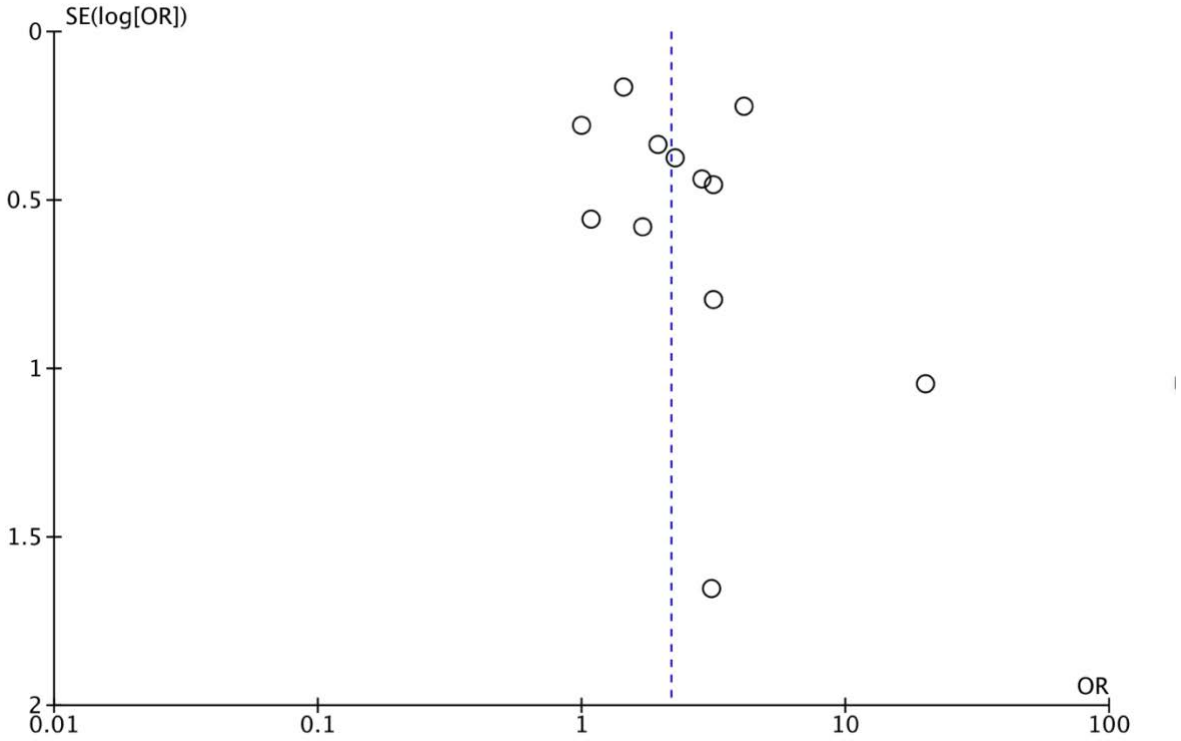
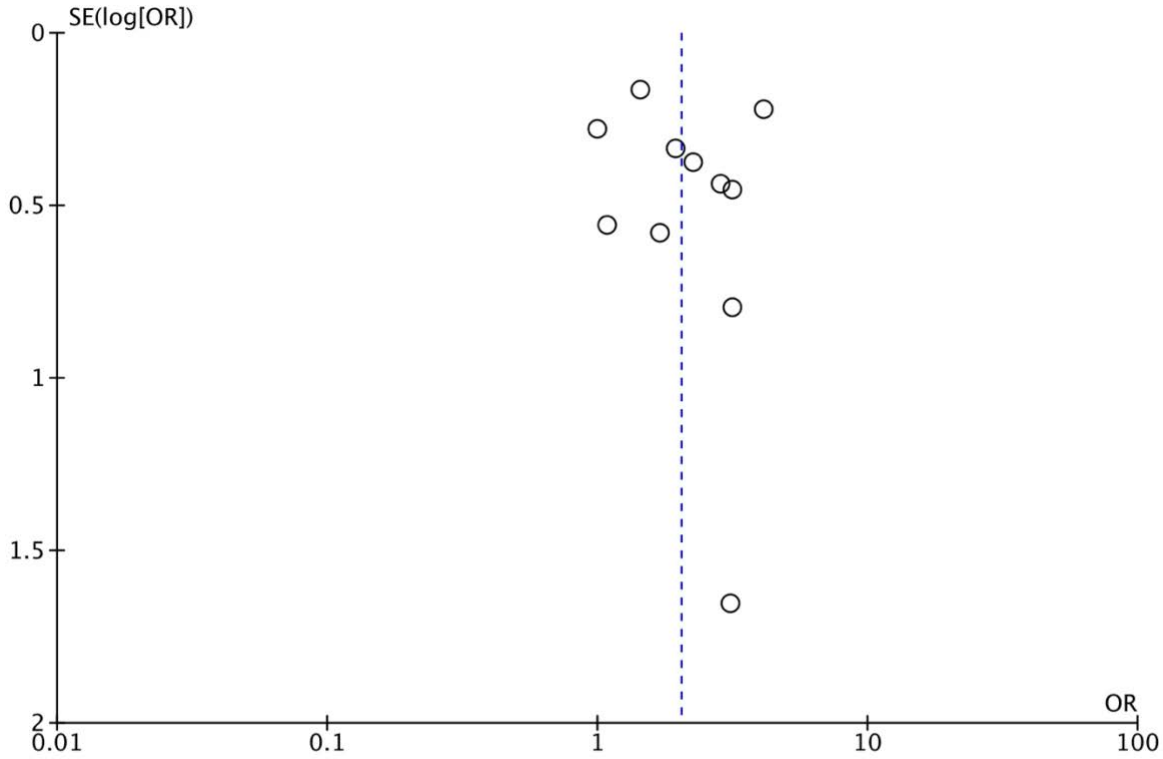


Figure 4: Funnel plot of all studies excluding outlier



RESULTS

Meta-analysis

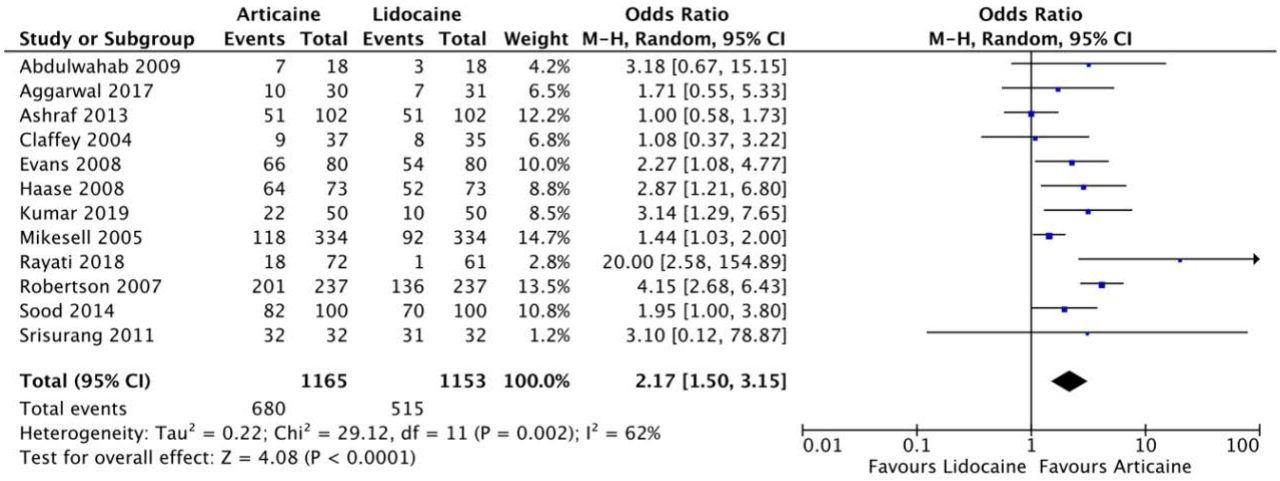
The included studies showed medium to high levels of heterogeneity, therefore, a random-effects model and the Mantel-Haenszel statistical method was used for data analysis. Tooth and arch location, anaesthetic delivery method, anaesthetic volume, vasoconstrictor volume, pre-intervention tooth status and study type accounted for the variations between the studies.

In overall and subgroup analyses, articaine showed a higher likelihood of successful anaesthesia than lidocaine, with varying degrees of significance.

Group Analysis

For all LA interventions (OR: 2.17, 95% CI: 1.50, 3.15, I^2 = 62%) articaine had 2.21 times the likelihood of anaesthetic success of lidocaine. The results were significant (P < 0.0001). (Figure 5)

Figure 5: Forest plot – all local anaesthetic interventions.

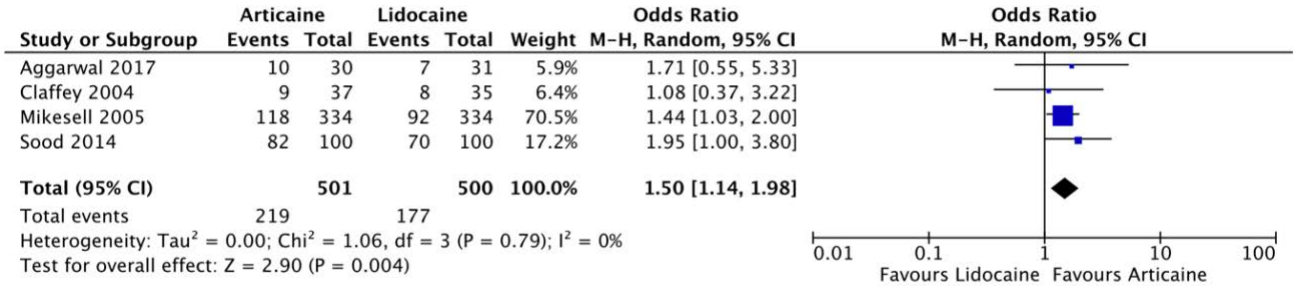


Subgroup Analyses

Anaesthetic delivery method

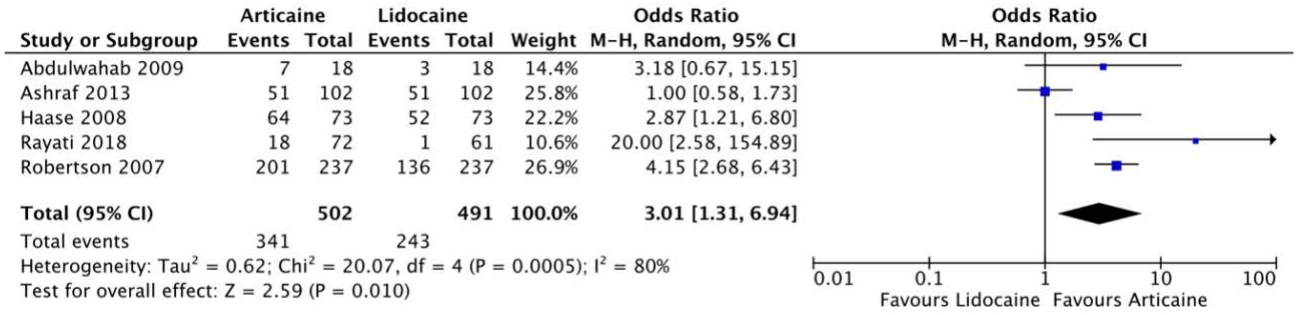
For mandibular blocks (OR: 1.50, 95% CI: 1.14, 1.98, I^2 = 0%) articaine had 1.5 times the likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.004) (Figure 6).

Figure 6: Forest plot – mandibular inferior alveolar nerve blocks



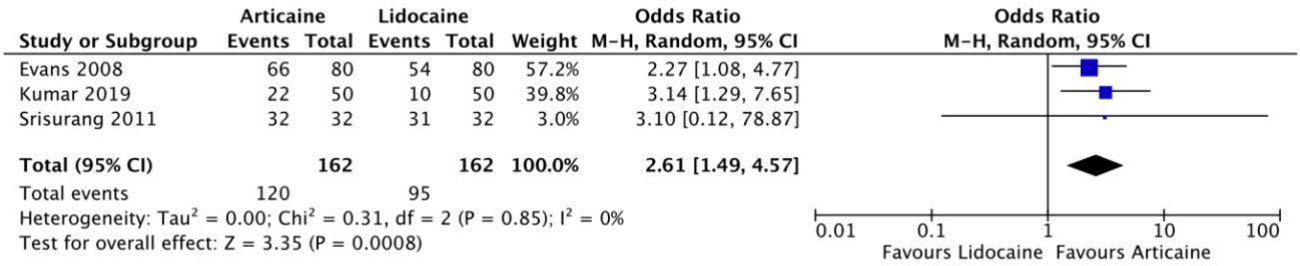
For mandibular infiltrations (OR: 3.01, 95% CI: 1.31, 6.94, I^2 = 80%) articaine had 3.01 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.010) (Figure 7).

Figure 7: Forest plot – mandibular infiltrations



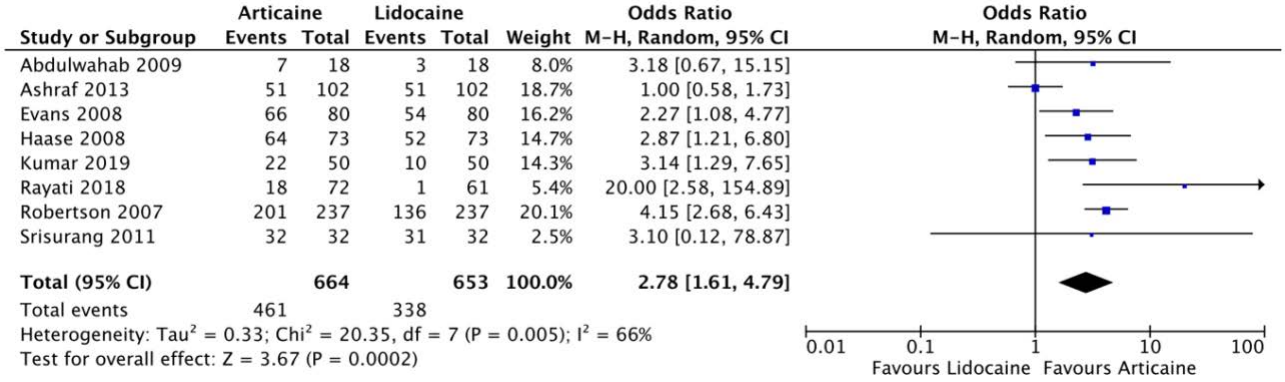
For maxillary interventions (infiltrations) (OR: 2.61, 95% CI: 1.49, 4.57, I^2 = 0%) articaine had 2.62 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.0008) (Figure 8).

Figure 8: Forest plot – maxillary infiltrations.



For all infiltrations, maxillary and mandibular (OR: 2.78, 95% CI: 1.61, 4.79, $I^2 = 66\%$), articaine had 2.78 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.0002) (Figure 9).

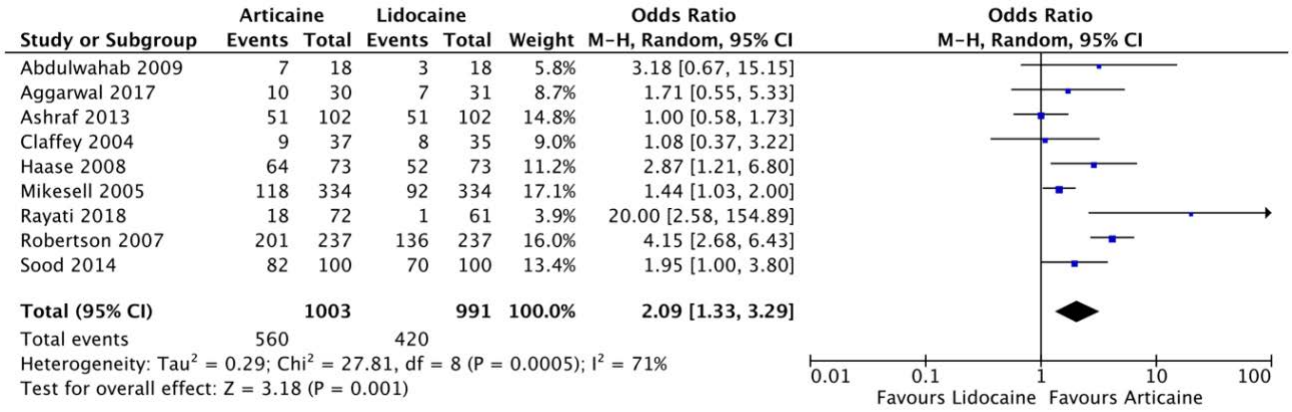
Figure 9: Forest plot – all infiltrations, maxillary and mandibular



Arch difference

For all mandibular interventions (OR: 2.09, 95% CI: 1.33, 3.29, $I^2 = 71\%$) articaine had 2.09 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.001) (Figure 10).

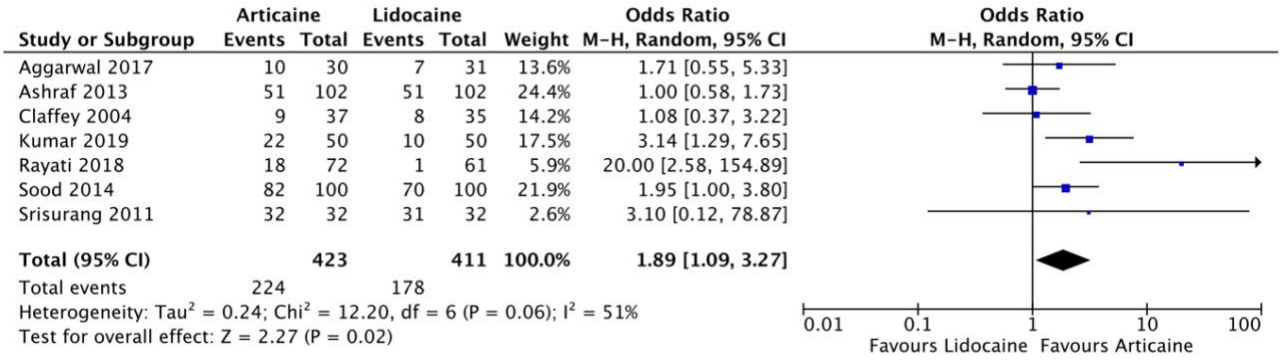
Figure 10: Forest plot – all mandibular interventions – blocks and infiltrations



Pre-intervention pulp status

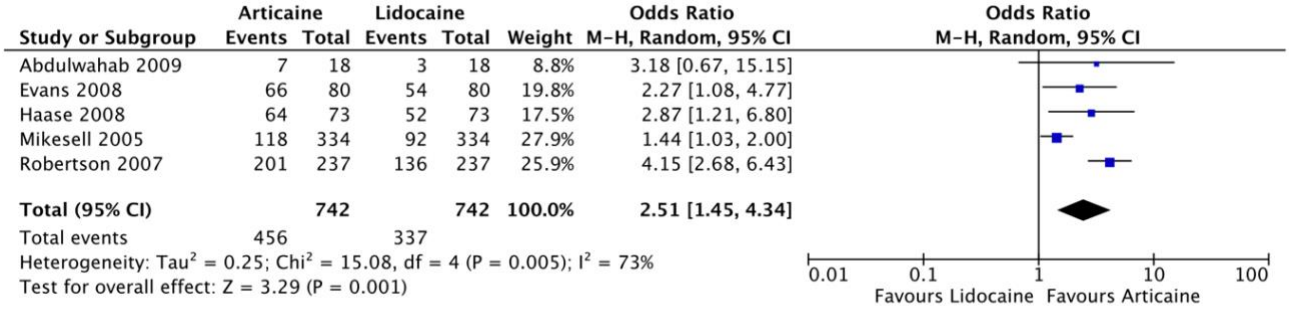
For all symptomatic teeth in the meta-analysis (OR: 1.89, 95% CI: 1.09, 3.27, I^2 = 51%) articaine had 1.89 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.02) (Figure 11).

Figure 11: Forest plot– studies with pre-operative symptomatic teeth.



For all asymptomatic teeth in the meta-analysis (OR: 2.51, 95% CI: 1.47, 4.34, I^2 = 73%) articaine had 2.51 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.001) (Figure 12).

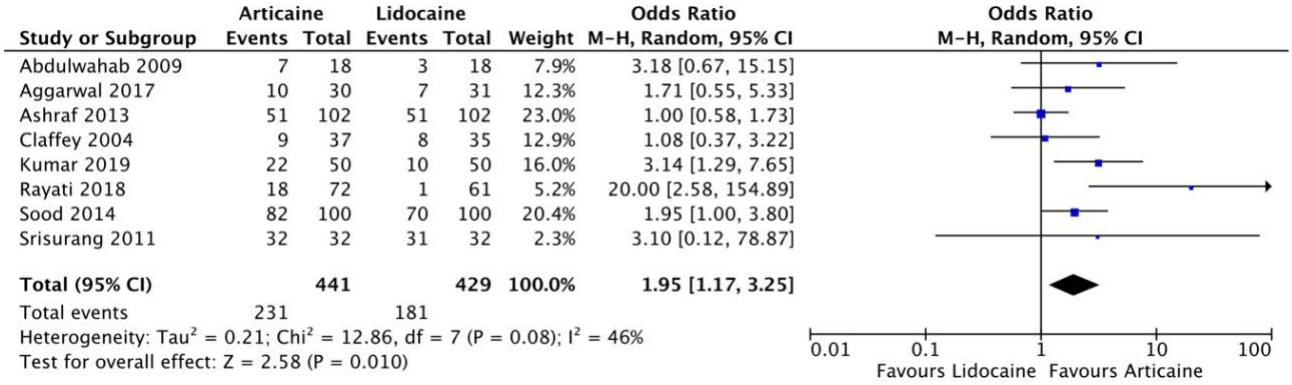
Figure 12: Forest plot – studies with pre-operative healthy teeth.



Study Design

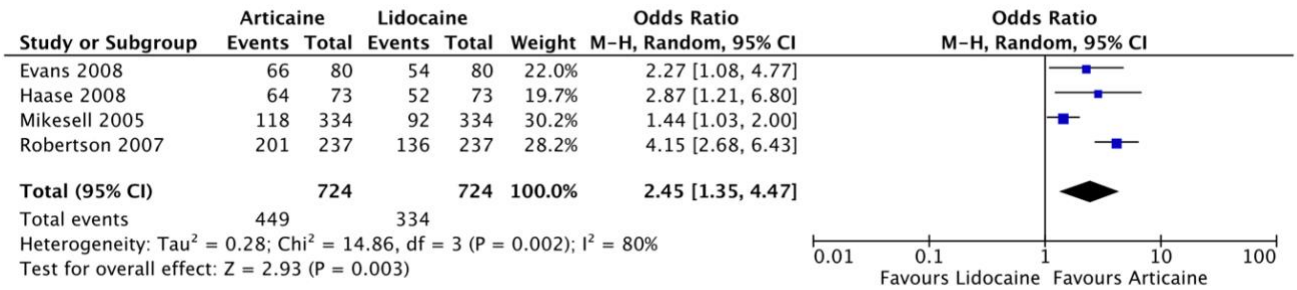
For all parallel studies (OR: 1.95, 95% CI: 1.17, 3.25, I^2 = 46%) articaine had 1.95 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.010) (Figure 13).

Figure 13: Forest plot – all parallel RCT studies



For all crossover studies (OR: 2.45, 95% CI: 1.35, 4.47, I^2 = 80%) articaine had 2.40 times likelihood of anaesthetic success of lidocaine. The results were significant (P = 0.003) (Figure 14).

Figure 14: Forest plot – all crossover RCT studies



Publication bias funnel plot

A funnel plot was used to assess publication bias. Most studies fell within the funnel with one outlier, but the sensitivity effect was insignificant for omission of any of the studies (Figures 3 and 4). Analysis of the group and subgroup forest plots show that all odd ratios favoured articaine, whether the outlier was included in the analysis or not (Figures 5-14). The outlier did not affect the overall conclusions of the meta-analysis.

Adverse effects

Of the 12 included studies in this meta-analysis, four did not include data on LA-related adverse effects, the remaining nine stated that there were only minor temporary side-effects with no reported incidence of paraesthesia.

DISCUSSION

Meta-analysis

The meta-analysis included data from human, randomised-controlled trials based in U.S.A, India, Iran, Thailand, and Finland, published in English between 1993 and 2019 involving intervention on 922 patients with asymptomatic or symptomatic pre-clinical tooth status and anesthetised with 4% articaine and 2% lidocaine anaesthetic for routine dental treatment. The studies included interventions on healthy teeth, teeth diagnosed with symptomatic irreversible pulpitis and teeth requiring extraction. The differences in pre-operative baseline pulp status were analysed for their effect in the meta-analysis because symptomatic teeth have been shown to be more difficult to anaesthetise than asymptomatic teeth.[11,23-26]

Data measurement tools in the studies included assessment of pulp status using electronic pulp testers, pain assessment using the 100mm or 170mm visual analogue scales, endodontic access success and extraction success. Anaesthetic success was the primary outcome measure for all the studies. Other outcome measures were assessment of pain during various stages of anaesthetic administration, pain during intervention, post-operative pain at 0, 24, 48 and 72 hours, onset of pulpal anaesthesia, duration of pulpal anaesthesia and extent of soft tissue anaesthesia.

Electronic pulp testers have been the standard measurement tool used to ascertain pulpal status in quantitative clinical trials of dental anaesthetic setting the score of 80 as the criteria for complete pulpal anaesthesia.[27] Symptomatic teeth may be more difficult to anaesthetise than asymptomatic teeth and pulpal anaesthesia of teeth with irreversible pulpitis is not guaranteed even with an electronic pulp tester score of 80 or more.[27] Visual analogue scales of 100mm and 170mm were used in most of the included studies to quantify subjective pain data for valid analysis.[28,29]

This systematic review and meta-analysis recognise articaine as a safe and efficacious dental local anaesthetic for all routine dental treatment. Compared to lidocaine, articaine is more efficacious in block and infiltration anaesthesia in both arches.

Mandibular block anaesthesia

In this review, mandibular block anaesthesia refers to the traditional inferior alveolar nerve block. Overall, articaine performed better than lidocaine in mandibular block anaesthesia for healthy and symptomatic teeth. Previously, most individual studies found that the differences were not statistically significant.[30-33] Our meta-analysis found that, for mandibular block anaesthesia, articaine had 1.5 times the likelihood of anaesthetic success of lidocaine with statistical significance (P = 0.005). However, neither lidocaine nor articaine mandibular block anaesthesia adequately anaesthetised symptomatic teeth with irreversible pulpitis.[30,32,33]

Supplementary buccal infiltration following failed mandibular block anaesthesia

Our review corroborates previous review findings that articaine gives significantly more efficacious anaesthesia than lidocaine for supplementary buccal infiltration following failed mandibular block anaesthesia for healthy teeth and symptomatic teeth requiring endodontic treatment.[34,35]

Infiltrations

Articaine has a higher likelihood of anaesthesia success than lidocaine for: mandibular molar buccal infiltration anaesthesia,[36-38] maxillary incisor infiltration anaesthesia[39] and maxillary molar infiltration anaesthesia.[40] A 1993 outlier study of maxillary anaesthesia noted no

significant difference in LA success between articaine and lidocaine in terms of onset or duration.[41] Our meta-analysis found that, for infiltrations, articaine had 2.78 times likelihood of anaesthetic success of lidocaine (P = 0.0002), 3.01 times for mandibular infiltrations and 2.61 times for maxillary infiltrations (P = 0.01).

In our study, mandibular infiltrations with articaine compared to lidocaine (3.01x) showed double the odds ratio of mandibular blocks (1.5x). The difference suggests that mandibular infiltrations with articaine are more likely to achieve anaesthetic success compared to lidocaine than mandibular blocks.

Arch

For both arches, the meta-analysis found that articaine had higher likelihood of anaesthesia success than lidocaine, 2.76 times more likely in the mandible (P = 0.0002) and 2.61 times more likely in the maxilla (P = 0.0008).

Pulp status

Meta-analysis was performed for the differences in pre-intervention pulp status between symptomatic and asymptomatic teeth. For asymptomatic teeth, articaine had 2.31 times higher likelihood of anaesthesia success of lidocaine with significance (P = 0.006). For symptomatic teeth, articaine had 1.89 times higher likelihood of anaesthesia success of lidocaine with weak significance (P = 0.02)

Study Design

Meta-analysis was performed for the differences in parallel compared to crossover studies. Study design appeared not to influence anaesthesia outcomes in this meta-analysis. The included parallel and crossover randomised controlled trials showed that articaine had a higher likelihood of anaesthesia than lidocaine.

Extractions

Articaine can be used with buccal infiltration anaesthesia for successful extraction of maxillary premolars[42] and maxillary molars without the need for palatal infiltrations,[40] but should not replace standard mandibular block anaesthesia for extraction of mandibular molars.[38]

Anaesthetic onset and duration

All relevant studies showed faster onset and longer duration for articaine anaesthesia over lidocaine with varying degrees of significance. One study in the meta-analysis recorded data on anaesthetic onset, finding that the onset time for articaine mandibular buccal infiltration anaesthesia ranged from 4.2 - 4.7 minutes compared with 6.1 - 11.1 minutes for lidocaine.[37] Two studies documented anaesthetic duration, one for maxillary molars infiltrations, with approximately 71.70 mins for 1.8mls articaine and 56.25 mins for 1.8mls lidocaine[40], and the other for maxillary incisor labial infiltrations, with 24.5 minutes for 0.6mls articaine and 23.8 minutes for 0.6mls lidocaine.[41]

LA-related adverse effects

As with previous systematic reviews, this systematic review found no incidence of permanent paraesthesia in any of the studies which included follow up for adverse effects. Neither reviews nor individual studies specify a standard definition of “paraesthesia”.

Overview of previous systematic reviews

The broader systematic reviews of articaine all recognise articaine’s equal or superior efficacy when compared with lidocaine for routine dental treatment.[10,43,44] Katyal[10] found articaine superior to lidocaine in posterior first molar anaesthesia.[10] Out of 1022 study participants, Brandt et al.[43] found articaine superior to lidocaine for all dental infiltrations and for mandibular block anaesthesia in healthy teeth.[43] Soysa et al.[44] found articaine superior to lidocaine for all mandibular interventions.[44] None of the reviews reported any short or long-term paraesthesia.

The most recent systematic review by Soysa et al. in 2019 reviewed randomised controlled trials (RCTs) of articaine from 2000-2018.[44] Soysa et al. included eighteen studies for meta-analysis. Twelve of these studies were excluded by this systematic review because one involved non-routine third molar extraction and one involved the non-standard Gow-Gates block technique. The remaining eight studies were assessed by us as having high risk of bias due to lack of description of the allocation or randomisation process, lack of blinding by the person administering the anaesthetic and anaesthetic cartridges not being masked. The meta-analysis in this review included three studies not included in Soysa’s. These were:

Haase et al.[34], Kumar et al.[40] and Srisurang et al.[42]. All were RCTs assessed as low to medium risk of bias using the Cochrane Risk of Bias 2 guidelines.

Other comparisons of this meta-analysis to Soysa et al.'s review[44] are listed below:

- Both reviews had the same outcome measure - anaesthetic success of articaine compared to lidocaine, however Soysa et al. only included studies which measured the efficacy of an agent without requiring re-anaesthesia, whereas this review included studies of supplementary anaesthesia techniques.
- Soysa et al. analysed studies involving posterior teeth only, whereas this review included studies of all teeth.
- Soysa et al. excluded studies using less than 0.9mL of anaesthetic solution, whereas this review included all randomised controlled trials comparing articaine and lidocaine regardless of anaesthetic amount
- Soysa et al. included studies involving the Gow-Gates block anaesthesia technique whereas this review only included studies of routine dental infiltrations and the traditional inferior alveolar nerve blocks.

The overall results from this review also differed slightly from the conclusions made by Soysa et al. Both reviews found that articaine is more likely to achieve anaesthetic success than lidocaine in combined analysis, mandibular infiltration and block anaesthesia. This review found that this conclusion was also true for maxillary infiltrations, unlike Soysa et al. who found no significant difference in anaesthetic success between articaine and lidocaine for maxillary infiltrations. Both reviews note the potential effect of medium to high rates of heterogeneity on the review outcomes.[44]

Paxton and Thome[8] and Yapp et al.[11] conducted literature reviews of articaine both recognising a general trend of articaine outperforming lidocaine in anaesthetic efficacy.[8,11] Yapp et al. stated that articaine is a safe and effective LA for all routine dental procedures for patients of all ages, and that no conclusive evidence demonstrates articaine neurotoxicity over any other dental anaesthetic.[11]

Reviews comparing articaine efficacy to that of lidocaine's in patients with irreversible pulpitis found that both LAs lack efficacy for mandibular block anaesthesia, but that articaine's rate of anaesthetic success was significantly superior to lidocaine for supplementary mandibular infiltrations following failed mandibular block anaesthesia to anaesthetise symptomatic teeth.[45-47] In general, these reviews found articaine superior to lidocaine in achieving anaesthetic success and for pain control in symptomatic teeth.[45-47]

Successful anaesthesia rates for mandibular block anaesthesia in healthy versus inflamed pulps are approximately 70% compared to 30%. Teeth with irreversible pulpitis are more difficult to anaesthetise compared to asymptomatic teeth.[11,23-26]

General overview of previous articaine studies

Anaesthetic efficacy

For mandibular block anaesthesia efficacy in teeth with irreversible pulpitis undergoing endodontic treatment, articaine has an anaesthesia success rate of 87% compared to 60% with lidocaine.[48] For anaesthesia of mandibular teeth following failed mandibular block anaesthesia, intraosseous anaesthesia with articaine has a success rate of approximately 86% in mandibular posterior teeth,[49] and supplementary articaine mandibular buccal infiltrations have a success rate of approximately 42-73%.[50-52]

For mandibular incisors, combined articaine labial and lingual infiltrations provide effective pulpal anaesthesia compared to labial alone with anaesthetic duration less than 60 minutes.[53] However, higher than normal doses of buccal infiltrations of articaine can effectively anaesthetise maxillary teeth for extractions without a need for palatal anaesthesia.[54,55]

Most studies and reviews did not find a significant difference in anaesthesia success comparing articaine buccal infiltration with mandibular block anaesthesia in adults or children, recognising that articaine buccal infiltrations can be used as a substitute for lidocaine mandibular block anaesthesia, especially for paedodontic pulpal treatments.[10,56-64] An outlier study by Arrow in 2012 found that mandibular block anaesthesia of both articaine and lidocaine had higher anaesthetic success than buccal infiltrations of both anaesthetics alone.[65]

For mental/incisive nerve blocks, Batista et al.[66] found that articaine has a higher success rate than lidocaine for anaesthetising mandibular anterior teeth, but that anaesthesia could only be considered successful for premolars, not anterior teeth.[66]

Anaesthetic concentrations

A comparison of mandibular block anaesthesia with 2% and 4% articaine for extraction of mandibular posterior teeth acknowledges that both concentrations give adequate

anaesthesia with no significant difference, except that 2% articaine results in shorter soft tissue anaesthesia.[67] Two percent articaine maybe advantageous for children due to its lower maximum serum concentration and shorter serum half-life.[17]

Vasoconstrictor concentrations

Articaine provides more efficacious anaesthesia when combined with adrenaline than without,[4,8,14,68,69] with no significant difference between the 1:100,000 and 1:200,000 concentrations of the vasoconstrictor.[70] Kammerer et al. stated in 2012 that although articaine with 1:100,000 vasoconstrictor had a faster onset than that with no vasoconstrictor, both provide adequate anaesthesia when administered as mandibular block anaesthesia for mandibular extractions.[71] However, in a subsequent 2014 study, the same researcher recognised that articaine with no vasoconstrictor had a much shorter anaesthetic effect and that LAs with vasoconstrictor produce longer, deeper anaesthesia.[72]

The majority of studies comparing different adrenaline concentrations of 4% articaine found no significant difference in pulpal anaesthesia success rates between 1:100,000 and 1:200,000 concentrations, however the 1:100,000 adrenaline may have an insignificant advantage over the 1:200,000[4,8,68,73-75] and may be more efficacious than the 1:200,000 adrenaline for extractions of maxillary third molars.[76]

Anaesthetic dose

For anaesthesia of mandibular first molars, 3.6mls of articaine as a buccal infiltration provides more effective anaesthesia than 1.8mls, with approximately 70% success rate,[77,78] but as a supplementary anaesthetic to failed mandibular block anaesthesia, there is no difference in anaesthetic efficacy between the two doses.[79,80] In the maxilla, a dose of 1.2mls of articaine as a buccal infiltration is more efficacious than a dose of 0.6 - 0.9mls,[81] meaning a higher dose results in a higher rate of anaesthetic success.

Anaesthesia in children

The safety of articaine use in children under four years of age was documented in a 1989 retrospective report by Wright et al. reviewing 211 paedodontic cases using articaine. No adverse reactions were observed, therefore, the review stated that articaine is safe to use in children under age four.[82] Articaine was recognised as safe and efficacious in children of all ages in a 2011 comprehensive review of articaine.[11] A subsequent 2018 study found that

there is no difference between articaine and lidocaine in frequencies of anaesthetic-related adverse events in children.[83]

Adverse effects

Paraesthesia associated with dental anaesthesia is defined as numbness or tingling of the mouth and face.[12] The hypothesized association of articaine having an increased risk of paraesthesia following mandibular block anaesthesia may have been precipitated with Hass and Lennon's[84] retrospective study of reported paraesthesia cases in Ontario's Professional Liability Program between 1973 and 1993. The study associated articaine with more cases than other LAs by comparing the number of LA cartridges used in relationship to market share of the type of LA.[84]

Follow-up retrospective studies conducted by Gaffen and Haas in 2009, again reviewed the same database from 1999 to 2008, reporting that the incidence of non-surgical paraesthesia during the studied time frame was 1 in 609,000. The same study stated that prospective studies of anaesthesia-related adverse events are challenging to undertake due to difficulty getting ethics approval for a cohort large enough to detect any statistical significance as rarity LA-related paraesthesia occurrence is rare.[85] A subsequent 2010 review involving a researcher from the previous two mentioned studies reported that the incidence of adverse effects from articaine was approximately 1 in 4,159,848 and that 4% LA solutions had the highest incidence of adverse reported events based upon dental LA market share data.[86]

Other systematic reviews and randomised controlled trials have not been able to find any scientific evidence corroborating the hypothesis that articaine is associated with increased risk of permanent paraesthesia.[6,11,87] Three studies in 1995[88], 2000[89]and 2007[90] involving the same researcher revealed equal distributions of nerve damage among anaesthetic solutions, with lidocaine having more associations with LA-related adverse events than articaine. A 2001 study involving 882 articaine interventions revealed no incidences of temporary or permanent nerve damage.[6]

Yapp et al's[11] comprehensive literature review of articaine could not find any scientific evidence supporting articaine's association with increased paraesthesia, stating that LA-related paraesthesia is uncommon, with the incidence was found to be between 1 in 726,000 and 1 in 785,000.[11] The review listed direct needle trauma, intra-neural hematoma formation, fascicular pattern and LA toxicity as the potential explanation for LA-related nerve involvement. Yapp et al.'s review also judged previous retrospective studies from Hass and Lennon,[84] Hillerup and Jensen,[91,92] Gaffen and Haas,[85] Garisto et al..[86] associating articaine

with higher incidence of paraesthesia to be of low-level evidence, biased in data recruitment, and not robust enough in protocol to derive any clinical recommendations.[11]

Toma et al.'s[87] comprehensive 2016 synopsis of studies on dental anaesthetic-related adverse events also could not find any scientific evidence corroborating claims of articaine's association with adverse events. The review stated that the evidence for anaesthetic-related neurotoxicity is lacking and reached the same conclusion as Yapp et al. in 2011, that the reports and studies suggesting that articaine is associated with higher frequency of neurotoxicity are of poor quality and at high risk of bias.[87]

A 2015, in-vitro study of anaesthetic effect on human neuroblastoma cells reported that with increasing concentrations, all anaesthetics eventually resulted in induced cell death, but articaine and ropivacaine were the least neurotoxic; mepivacaine, prilocaine and lidocaine were considered of medium neurotoxicity, and bupivacaine resulted in the most rapid nerve cell death.[93]

Another in-vitro study of anaesthetic effect on rodent neural cells found that articaine resulted in the most effective blocking of nerve action potentials compared to lidocaine and mepivacaine.[13]

Limitations

This systematic review and meta-analysis were limited to English resources and excluded studies involving non-routine dental treatment and anaesthesia techniques, for example, third molar surgery and digital anaesthesia. In addition, the studies included for meta-analysis had a medium to high level of heterogeneity. These factors could have affected the outcomes of the meta-analysis.

Discussion of updated search results from February 2020 to May 2021

The authors conducted an updated search to find studies released between February 2020 and May 2021 that were not available or published at the time of the initial research. The purpose of the exercise was to assess the potential impact of the data of new randomised controlled trials on the current study outcomes.[94] The search discovered nine reviews and ten studies.

Five reviews involved third molar extraction surgeries. Three involved complex surgical extractions and were excluded, and the remaining two systematic reviews with meta-analysis revealed data relevant to this review. The first studied the safety and efficacy of 4% articaine in mandibular third-molar extractions finding that 4% articaine is a safe choice for third molar extractions requiring less supplemental anaesthesia, with a shorter onset time than the other amide LAs.[95] The second study analysed articaine and hypesthesia in third molar extractions concluding that the use of articaine during third molar extraction does not increase the risk of hypesthesia compared to other LAs.[96]

Two reviews involved paediatric dentistry. The first analysed specialist views on articaine administration for children and concluded that articaine use for pediatric dentistry is common but supported by limited evidence.[97] The second compared studies of articaine and lidocaine for dental procedures in paediatric patients finding that articaine is more effective than lidocaine, but the margin of difference in their study was small.[98]

Eleven new studies were assessed for potential inclusion in future meta-analysis. Seven were excluded due to: not being randomised controlled trials, not comparing articaine and lidocaine, only using articaine with no comparison LA, not using a reliable measure of intervention, inadequate blinding and studies involving complex, surgical third molar extractions.

Four studies should be assessed for inclusion in a subsequent meta-analysis comparing articaine and lidocaine for routine dental procedures. The conclusion of these studies is:

- Articaine showed faster onset and duration of anaesthesia than lidocaine for buccal infiltrations.[99]
- Articaine is an efficient and safe LA to treat children between ages three and four.[100]
- Articaine's anaesthetic success rate was significantly higher than lidocaine's and mepivacaine's for supplemental buccal infiltrations.[101]
- Articaine can be used as buccal infiltration for invasive treatment of mandibular molars in children ages eight to fifteen. There was no difference in anaesthesia success between lidocaine mandibular blocks and an articaine buccal infiltrations in this study.[64]

The conclusions from the latest randomised controlled trials that were not available at the time of our meta-analysis aligned with our included studies. The corroboration of these

newer studies give reassurance that our meta-analysis results are relevant to the present day.

CONCLUSION

Our research project aimed to clarify evidence-based dental practice and determine the direction for future investigation regarding the local anaesthetic articaine. By reviewing the latest research on articaine safety and efficacy and gathering data on dental practitioner use and the basis of their perceptions of articaine, we found that discrepancies exist between reported dental clinical practice and current research evidence as of January 2021. Further research and clarifications are needed to align practitioner perception of articaine with their dental clinical practice to achieve ubiquitous practice of evidence-based dentistry regarding articaine use.

Ethics Statement:

The James Cook University Human Research Ethics Committee abides in accordance with the National Statement on Ethical Conduct in Human Research (2007 updated in 2018). The National Statement on Ethical Conduct in Human Research allows certain human research to be exempted from ethical review it is a negligible risk research and involves only the use of existing collections of data or records that contain only non-identifiable data about human beings (Section 5.1.22-23)

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Part II

Articaine: dental practitioner use, basis of perception and evidence-based dentistry - A cross-sectional study

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Abstract

Background: Limited data exists on dental practitioner use and perceptions of articaine. This study is a cross-sectional survey of dental practitioners from January 2021 to ascertain the extent of their use of articaine, the basis of their perceptions about articaine and whether current practices are in line with recent evidence regarding articaine safety and efficacy.

Method: An anonymous survey was designed using the SAP Qualtrics Core XM software platform and a survey link was disseminated from December 2020 to January 2021 via social media. The survey was designed as a five-minute, anonymous, online questionnaire including a plain language information sheet, request for participant consent and 14 questions. Data was entered onto a Microsoft™ Excel spreadsheet and analysed qualitatively, isolating the answers into recurrent themes.

Results: Sixty percent of the surveyed dental practitioner used articaine as their preferred dental anaesthetic. Twenty-three percent of the dental practitioner surveyed used articaine for all of their dental procedures including inferior alveolar nerve blocks, while forty percent of respondents used articaine for all their dental procedures except inferior alveolar nerve blocks. The predominant basis of dental practitioner uses and perception of articaine were their countries dental guidelines.

Conclusion: Despite the latest findings that articaine is as safe and more efficacious as lidocaine for all dental treatment, 40% percent of respondents avoided articaine use for inferior alveolar blocks. Our study found a discrepancy between reported clinical practice and current research evidence. Further research and clarifications are needed to achieve ubiquitous practice of evidence-based dentistry.

Keywords: articaine, dental local anesthetic, evidence-based practice

Introduction

Articaine is an amide local anaesthetic (LA) used routinely in dental practice since its clinical release in 1976.[1,2] Prior to articaine's release, lidocaine was the most commonly used dental LA worldwide.[3] In 1995, Haas and Lennon released a review suggesting a link between articaine use and increased incidence of lingual nerve paraesthesia.[4] In addition, in 2009 and 2010, further reviews involving the same researcher revisited the association and further postulated a link between 4% LA solutions and increased incidence of lingual nerve paraesthesia.[5,6] These reviews approximated the occurrence of LA-related paraesthesia to be approximately 1 in 609,000 in 2009.[5] The rates were then revised to 1 in 4,159,848 in 2010.[6]

Systematic reviews and meta-analysis are considered the highest, most robust analysis of clinical efficacy across multiple trials.[7,8] Multiple systematic reviews have been conducted on articaine efficacy and safety from 2010 to the present. None of them, nor any of the randomised controlled trials analysed by the reviews reported incidence of permanent nerve paraesthesia following articaine use.[9-12]

The latest articaine systematic review with meta-analyses conducted by Martin et al in 2021 stated that articaine is a safe and efficacious LA for all routine dental treatment.[12] None of the participants in the 14 randomised controlled trials reported any major LA-related adverse effects. The results from Martin et al.'s latest systematic review are consistent with older reviews of articaine efficacy and safety.[9-11,13] Despite copious evidence corroborating articaine safety and efficacy, articaine still bears the stigma from the earlier review results that may have been subject to bias and conducted with less-than robust research techniques.

Background

Limited data exist on dental practitioner use and perceptions of articaine, especially related to articaine use for the standard inferior alveolar nerve block (IANB). Yapp, Hofcraft and Parashos surveyed Australian Dental Association members in 2010 to ascertain Australian dental practitioner use of articaine, the reason for their choice of LA and their level of education.[13] Their survey found that most Australian dental professionals used articaine and cited scientific literature, professional education courses and peer reports as the main influences behind their choice of LA. The study further detailed that one third of respondents

used articaine for all procedures except the IANB. [13] In 2010, systematic reviews and randomised controlled trials existed finding articaine to be, equal to or more efficacious, and as safe as lidocaine.[9] Despite the research dictates in 2010, dental practitioners remained cautious in their use articaine for IANBs.

Our cross-sectional study follows a decade on from Yapp, Hofcraft and Parashos's research to determine current dental practitioner use of articaine, the basis of their perceptions and if they are practicing evidence-based dentistry in 2021. Evidence-based dentistry has been defined by the Australian Dental Association as an approach to dental practice that requires integration of systematic assessment and clinically relevant scientific evidence with dental practitioner clinical experience expertise and patient's health perspectives.[14]

The aim of this cross-sectional study was to ascertain if dental practitioners as of January 2021 were enacting evidence-based dentistry. The research process involved two steps. Firstly, the gathering of survey data about dental practitioner use of articaine, their perceptions of articaine and the basis of their perceptions about articaine. Secondly, determining if the survey data results align with the latest evidence about the safety and efficacy of articaine in routine dentistry. Any discrepancy in evidence-based practice indicates a need for further research to clarify any misconceptions about articaine use for routine dental treatment.

Methodology

The research project was approved by the James Cook University Human Research Ethics Committee approval number H8223.

The authors used the SPIDER qualitative/mixed method strategy tool[15] to outline the research questions:

- **S**ample - Dental practitioners
- **P**henomenon of **I**nterest - Use of and perception about dental local LA and basis of their perception
- **D**esign - Survey
- **E**valuation - Experiences and perceptions
- **R**esearch type - Qualitative/quantitative

Research question:

- What percentage of dental practitioners use articaine?

- What are dental practitioner perceptions about the safety and efficacy of articaine compared to other dental LAs?
- What are the factors that influence dental practitioner perceptions about articaine and dental LAs?

An anonymous survey was designed using the SAP Qualtrics Core XM software platform. A pilot validation study was conducted on a group of dental professionals comprised of practicing dentists, dental specialists and university affiliated professors of clinical dentistry. Their feedback was incorporated into the survey before deployment. Validation included survey evaluation for internal consistency, editing of errors and ensuring the questions were not leading, confusing or double-barrelled.[16]

The survey link was disseminated from December 2020 to January 2021 via social media. The Qualtrics survey link was posted on three private Facebook pages dedicated to dental professionals around the world. The reach between the three Facebook groups, at the time, was approximately 80,000 members, with possible overlap in membership between the groups. Given the international membership and accessibility of the private dental Facebook groups, the survey was accessible to dental professionals globally.

Online surveys are a timely, far-reaching and cost-effective method of data collection[17], and participants are more likely to give honest answers if they do not have to disclose personal details.[18] Social media has become an effective avenue for researchers to increase their global reach. In addition, considering the current global climate, the move to online communication is the most COVID-safe data collection strategy.[18]

Our survey was designed as a five-minute, anonymous, online questionnaire including a plain language information sheet (Appendix 1), request for participant consent and 14 questions (Appendix 2). The survey questions consisted of mixed multiple-choice answers and text boxes that requested information about participant:

- Demographics - practice field, sector of practice and country of registration
- Dental local anaesthetic use and preference
- Use of articaine in dental practice and for inferior alveolar nerve blocks
- View of articaine safety and efficacy
- Basis of perceptions of articaine use in routine dental practice
- Views of articaine compared to lidocaine in terms of safety and efficacy
- Experience of adverse reactions on any LA following inferior alveolar nerve blocks. If any:

    - Which LA was used?
    - What adverse reactions were experienced by the patient?
    - Were there any changes in clinical practice following the experience?
- Any further information they would like to share about LA-related adverse events

Data was extraction onto a Microsoft™ Excel spreadsheet and analysed qualitatively using thematic analysis. Survey text answers were listed separately onto a spreadsheet, coded, generated into themes which were defined and analysed.[19]

Results

A total of 325 completed surveys were returned out of 358 respondents. All respondents consented to participating in the survey study. The remaining 33 surveys were incomplete or blank possibly due connectivity issues, hard/software issues, or human factors.

Three-quarters of survey respondents were Australian-registered general dentists working in the private and public sectors (Table 1), with the United Kingdom having the second most survey respondents at seven percent.

Table 1: Survey demographics

Profession	Sector of practice	Country of registration
General dentist 83%	Private 69%	Australia 76%
Dental specialists 7.4%	Public 18%	United Kingdom 7%
Oral Health Therapists 4%	Education 8%	New Zealand 3%
Dental students 3%	Research 2%	Canada 2%
Dental Therapists 1%	Other 3%	U.S.A. 2%
Dental Hygienists 1%		Singapore 0.5%
Post graduate student 0.5%		Pakistan 0.5%
		Scotland 0.5%
		Malaysia 0.5%
		Ireland 0.5%
		India 0.3%
		Romania 0.3%
		Trindad Tobego 0.3%
		Slovenia 0.3%
		Israel 0.3%
		Switzerland 0.3%
		Hungary 0.3%
		Norway 0.3%
		Germany 0.3%
		Wales 0.3%
		Barbados 0.3%

What percentage of dental practitioners use articaine?

Sixty percent of the dental practitioner surveyed used articaine as their preferred dental anaesthetic. Thirty-five percent preferred lidocaine, two percent preferred mepivacaine and one percent preferred prilocaine as their primary dental anaesthetic.

What are dental practitioner perceptions about the safety and efficacy of articaine compared to other dental LAs?

Twenty-three percent of the dental practitioner surveyed use articaine for all their dental procedures including inferior alveolar nerve blocks. Forty percent of respondents use articaine for all their dental procedures except those requiring inferior alveolar nerve blocks. Other variations of this answer were:

- Mainly use articaine except for pregnant women
- Mainly use articaine except for children under five years of age
- Mainly use articaine except for when contraindicated (no further details given)

Fifty-six percent of dental practitioners surveyed felt confident using articaine for all routine dental procedures, thirty-eight percent felt confident using articaine for some dental procedures, and two percent did not feel confident using articaine for any dental procedures.

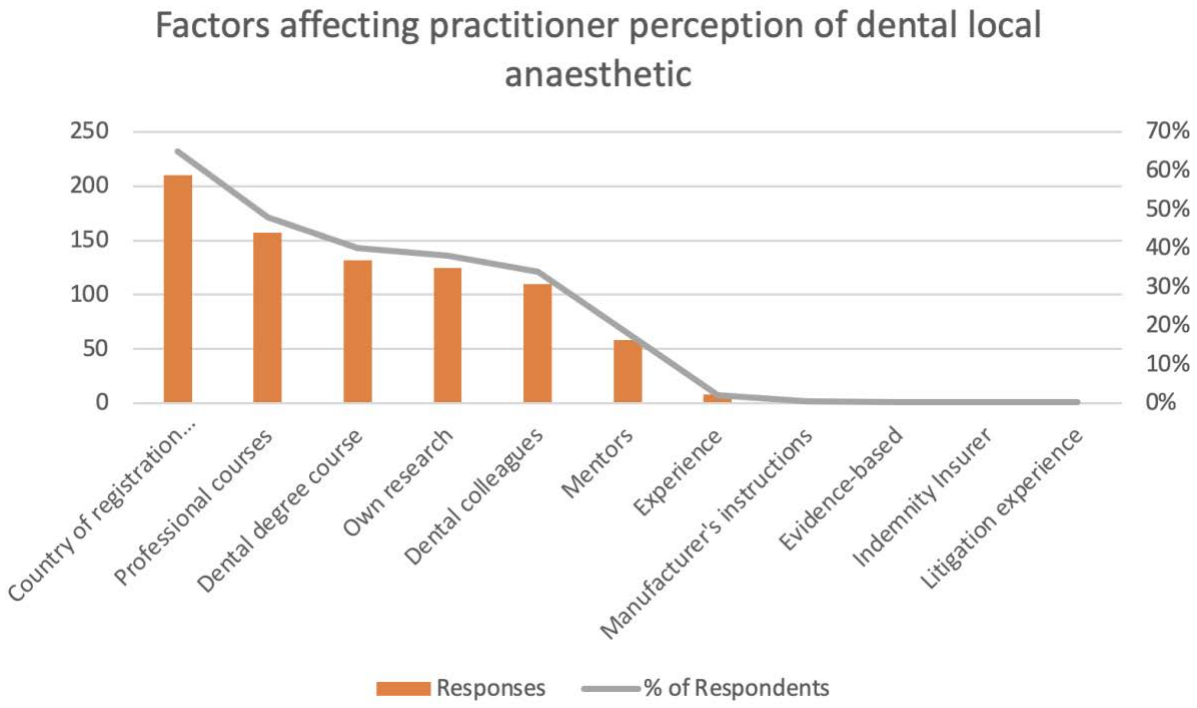
Regarding articaine safety and efficacy compared to lidocaine:

- Forty-six percent of survey respondent felt articaine to be as safe and more efficacious compared to lidocaine
- Thirty-one percent felt articaine to be more efficacious, but less safe than lidocaine
- Eighteen percent felt articaine to be as safe and efficacious as lidocaine
- Two respondents felt that articaine is not safe to be used as a dental LA.

What are the factors that influence their perceptions?

The main basis of dental practitioner uses and perception of articaine according to our survey were: their countries dental guidelines, ongoing professional development courses, their university teachings, their own research, advice from dental colleagues and advice from their dental mentors. Other sources listed were indemnity insurer advice, experience, and manufacture's advice (Table 3).

Table 3: Factors affecting practitioner perception of dental local anaesthetic



Note: Factors: experience, manufacturer's instructions, evidence-based, indemnity insurer, litigation experience had 1-2 responses each which accounted for 0.25-0.5% of respondents (shown as 0% on the chart)

What LA-related adverse effects have dental practitioners experienced following administering of an inferior alveolar nerve block?

Of the 325 respondents, thirteen percent had experienced a patient with LA-related adverse effects more than one day after the administration of a standard IANB.

The dental LA's which caused these adverse effects were lidocaine (47%), articaine (47%), prilocaine (4%) and mepivicaine (2%).

The adverse effects experienced were paraesthesia (38%); palpitations, anxiety, shaking (13%); swelling and bruising (11%); trismus (10%), hematoma (7%), neuropathy (6%), palsy (4%), vision changes (3%) and syncope (1%). Other adverse effects (4%) included breathing and swallowing difficulties, numbness under the eye, pain lasting over two weeks in the

injection site and grand mal seizures. The breakdown of adverse effects by local anaesthetic can be found in Table 2.

Table 2: Adverse effects by anaesthetic type

Adverse Effects	Articaine	Lidocaine	Prilocaine	Mepivicaine	Other	Total
Paraesthesia	15	10		1	1	27
Neuropathy	3	1				4
Trismus		6			1	7
Haematoma		3	1			4
Palsy	1	2				3
Palpitations/anxiety/shaking	2	7				9
Syncope		1				1
Breathing/swallowing difficulty		1				1
Swelling/bruising	1	6	1	1		9
Pain >2 week	1					1
Numbness under the eye	1					1
Vision changes	1				1	2

Sixty-eight of the dental practitioners surveyed who experienced LA-related adverse effects in their patients did not change their clinical procedure following the experience. Fourteen percent did not repeat the procedure using the LA that caused the adverse effects. Five percent stopped using the LA associated with the adverse effect. Other clinical changes (12%) were: changing to a smaller gauge needle, practicing their mandibular block technique, stopping administering LA when the patient experiences unusual pain, and stopping using the LA for inferior alveolar nerve blocks.

Respondents were asked if they wanted to share any further information about their adverse effect experiences. The general themes were:

- The need to review their injection technique and not blame the dental LA for the adverse reaction experienced by their patient.
- The awareness of needle technique when the patient feels an electric shock during needle insertion and not to blame the LA for the adverse effect.
- Only one adverse effect in 20 years of practice, and in another case, in 15 years of practice, only one case of paraesthesia, and, with 50 years of experience has only experienced minor reactions with one case of prolonged paraesthesia that resolved after a year.
- The temporary nature of the adverse effects.

Two further experiences shared were of:

- Lidocaine used for maxillary infiltration that caused the patient to have grand mal seizures and they were in hospital for four days with no history of epilepsy.

- Lingual paraesthesia following using articaine for inferior alveolar nerve blocks, but all reported cases resolved.

Discussion

Survey results 2010 vs 2021

Most dental practitioners who responded to our 2021 survey used articaine as their preferred dental LA. Our study data corroborates the results published by a similar 2010 study.[13] In contrast, our study found that 40% of survey respondents avoided articaine use for inferior alveolar nerve blocks, an increase of 10% from the 2010 study.

The authors of the current study published a 2021 systematic review of randomised controlled trials ascertaining the safety and efficacy of articaine which concluded that articaine is a safe and efficacious dental LA for all routine dental procedures. Thus, the current survey study reveals a potential discrepancy in evidence-based dental practice related to dental LA use and the underlying factors that should be addressed.

Factors influencing practitioner perceptions about dental LA

Our study aimed to ascertain the basis for dental practitioner perceptions for their use of dental LA, including the factors that influence their LA choice for various dental procedures. The top three factors determining dental practitioner perceptions of dental LA were: their countries dental guidelines, continuing professional development courses and their university teachings (Table 3). The most common basis that influenced dental LA choice was country dental guidelines.

In addition to the influences mentioned above, some of the respondents avoided articaine use in pregnant women, children under the age of five and where contraindicated (no specifics given).

Articaine use in children under four years of age

A 2020 randomized controlled trial assessed articaine's efficacy and safety in children under four years of age.[20] One hundred and eighty-four children aged 36-47 months were anaesthetised with either articaine or lidocaine for dental pulpotomies. The study concluded

that children administered articaine experienced less pain during treatment and there was no statistical difference detected between the two LAs regarding post-operative complications.[20]

The most recent systematic review and meta-analysis reviewing articaine and lidocaine in children's dentistry concluded that there was no difference in the occurrence of adverse events between articaine and lidocaine following treatment in paediatric patients.[21] The review only included studies of children aged 5-16.

Ezzeldin, Hanks and Collard published a 2020 review of United Kingdom paediatric specialist views of the use of articaine in paediatric dentistry.[22] The review concluded that participants of the study reported more adverse effects with lidocaine than with articaine. Also, that use of articaine in paediatric dentistry is common, but limited evidence exists to support its use for children under four years of age.[22] More research is needed on the subject.

Articaine and pregnancy

Scarce research exists on the use of dental LA on pregnant women; therefore, this section will focus on articaine pharmacology and the few in-vitro studies of dental LA on human and rodent neuronal cells.

Articaine is an amide anaesthetic containing an ester group and a thiophene ring.[1,23,24] These features are integral part of articaine's LA efficacy[25] and rapid plasma hydrolysis.[2,3,9] The thiophene ring facilitates articaine diffusion through the nerve cell membrane and into the soft tissue. [2,3,9] The ester group allows for rapid plasma hydrolysis.[13,24]

This explains articaine's shorter half-life of 20-30 mins compared to the half-life of lidocaine and the other amide LA of 90-120mins that require hepatic clearance.[1,2,9,24] In addition, 90% of articaine is broken down into its inert form, articainic acid in the plasma sparing liver biotransformation.[1] Articaine's shorter half-life becomes relevant during lengthy procedures where additional LA needs to be administered or if attempting to minimise systemic or liver toxicity.[26]

A 2015 preclinical, in-vitro study of dental anaesthetic reported that the studied LAs, lidocaine, articaine, mepivacaine, bupivacaine, prilocaine and ropivicane, all induced human neuroblastoma cell death in increased concentration.[27] The study concluded that articaine and ropivacaine were the least neurotoxic. Lidocaine, mepivicaine and prilocaine were of

medium neurotoxicity, and bupivicaine was found to be the most neurotoxic. Neurotoxicity was defined in this study as LD_{50} or the amount needed to achieve 50% cell death.[27]

Potocnik et al.'s 2006 study of LA and rodent nerve cells found that 4% articaine was the most effective at blocking nerve conduction of action potentials compared to 2% lidocaine and 3% mepivacaine.[28]

Practitioner perceptions about articaine

Half the survey respondents felt confident using articaine for all their routine dental procedures. With 38% feeling confident to use articaine for some procedures and two respondents (0.0006%) not confident to use articaine at all. With strong data corroborating articaine's safety, the question should be asked: what factors have influenced the practitioners who do not feel confident using articaine for some or any dental procedures?

Articaine vs lidocaine

Three quarters of survey respondents felt that articaine is more efficacious a dental LA than lidocaine, which is in line with the conclusions from current research about articaine efficacy. Half of the respondents feel that articaine is equally as safe to use as a dental LA as lidocaine, which is also in line with the current research about articaine safety.

Discrepancies between dental evidence-based practice and current clinical practice about articaine safety were found in our study, with one third of all respondents feeling articaine to be less safe than lidocaine. Another question arises: what factors have influenced practitioners to believe that articaine is less safe than lidocaine?

As outlined in Table 3, the major factors contributing to practitioner perception of dental LA use were countries dental guidelines, continuing professional development courses, university teachings, advice from colleagues, advice from mentors, advice from indemnity insurers and personal experience.

Adverse reaction experience - standard inferior alveolar nerve block

Thirteen percent of all survey respondents had experienced a patient with LA-related adverse effect following administration of a standard inferior alveolar nerve block. Of these adverse effects, the majority occurred with use of lidocaine (47%) and articaine (47%). Forty

percent of these patients who had suffered LA-related adverse effect experienced nerve paraesthesia as one of the adverse effects. In other words, 0.8% of total respondents had patients who experienced nerve paraesthesia after administration of an IANB. The specific nerve affected was not detailed.

Two respondents had two separate occasions of patients experiencing paraesthesia after an IANB, one with lidocaine and one with articaine. Eight respondents had patients experience paraesthesia in addition to multiple other adverse effects such as palsy, trismus, palpitations, anxiety, shakes, vision changes, swelling and bruising. These simultaneous, multiple adverse reactions following administration of an IANB may have us query what other factors could have caused the reactions other than a reaction to the dental LA? Some hypothesized reasons are incorrect injection technique, soft tissue trauma, depositing LA too rapidly into the injection site, injection of LA into a blood vessel and blood pooling following injection withdrawal.

Seventeen of the 26 (0.05%) adverse effects respondents had patients who only experienced paraesthesia after the IANB with no other adverse effects. Of these, 13 were administered articaine and four were administered lidocaine.

The respondents who had these experiences were queried about how the experience affected their future treatment decisions. Three-quarters answered that they made no changes to their clinical procedures after having an adverse experience with their IANB. The remaining respondents answered that they either: practiced or studied to improve their IANB technique, changed their LA type for IANBs, started using smaller gauge needles for their IANBs or made changes to their IANB technique.

The respondents who had these experiences were also given an opportunity to add their thoughts about their experiences. Three recurring themes emerged from this query: adverse effects compared to years of dental experience, awareness that needle technique could be a cause of the adverse effects and the temporary nature of the adverse effects they experienced. Three respondents commented that they had only observed one case of temporary paraesthesia or only minor LA reactions in their 15, 20 and 50 years of dental practice, adding that LA-related adverse effects are rare in their experience. The longest serving practitioner had only experienced one case of LA-related paraesthesia in their 50 years of dental practice and that case resolved after one year.

Other personal experiences were a patient who had a grand mal seizure and were hospitalised for four days after lidocaine was used for a maxillary infiltration, and another practitioner who had multiple experiences of patients with lingual paraesthesia after using articaine for IANBs, all of which resolved within a short time period.

Perception of risk

The overall occurrence of IANB, LA-related adverse effects in our study was 13%. The occurrence of paraesthesia was 0.08%. The risk of LA-related paraesthesia in previous studies has been approximated to be between 1 in 726,000 and 1 in 785,000.[29] One of the given reasons why robust studies are not available associating nerve paraesthesia to articaine IANBs is because the incidence is so rare.[4,5] Dental researchers continue to debate about the possible and probable causes of nerve paraesthesia following IANBs , especially about its increased affectation of the lingual nerve.[6] Suggested causes by these researchers are: direct needle trauma, intra-neural haematoma formation, fascicular pattern and LA toxicity.[29]

Limitations

Sample representativeness may be questionable as non-technology savvy and offline dental practitioners were not included, and participants were not globally representative. Seventy-five percent of participants were dental practitioners registered in Australia. The cost of dental LA could be a factor that influences dental practitioner choice of LA, but this was not queried in the survey. In Australia, articaine costs more than lidocaine.

Despite surveys being cost-effective, time-effective and convenient, low response rates may result in non-response bias, unclear responses that cannot be clarified and limited sampling may impact population generalisability.[30]

Conclusion

Our research found that the majority (60%) of queried dental practitioners used articaine as their preferred dental LA. Despite the latest findings that articaine is as safe and more efficacious as lidocaine for all dental treatment, forty percent avoided articaine use for inferior alveolar blocks citing their countries dental guidelines, ongoing professional development courses and their university teachings as the main factors that influenced their perceptions about dental LA. Our study found a discrepancy between reported clinical

practice and current research evidence. Further research and clarifications are needed to achieve ubiquitous practice of evidence-based dentistry.

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APPENDIX 1

Survey Information Sheet

Project: Articaine in dentistry: dental practitioner perception

Researchers:
Dr Erica Martin
Dr Ernest Jennings
Prof Alan Nimmo
A/Prof Andrew Lee

Introduction
We would like to invite you to participate in an online survey for our dental research project investigating dental practitioner use of articaine and perception of articaine's safety and efficacy in routine dental procedures.
This project has been approved by the Research Ethics Committee at James Cook University (HREC #H8223)

What is the aim of the research?
The aim of this research is to evaluate the use of articaine in routine dental practice and dental practitioner perception of the safety and efficacy of the local anaesthetic, articaine, for use in all routine dental procedures, and the basis for the perception.

What will participants be asked to do?
Participants who choose to participate will remain anonymous and be asked to answer 12 questions about their dental local anaesthetic choices and views. The answers will help us understand the prevailing views of articaine in dentistry and ascertain the basis for these views.

How long will the survey take to complete?
The survey consists of 12 questions and should take approximately 5-7 minutes to complete

Can participants withdraw from the study at any time?
Participants can withdraw from participation in the survey at any time during the survey until they choose to submit their data. After submission, being de-identified, data cannot be withdrawn.

What are the possible risks?
There are no risks involved in participating in this research.
Will participants get access to the results?
Participants will be able to access results of this survey through publication of the research in the dental literature

What will happen to participant information?
Participant answers are anonymous with no personal association or possibility of identification. The researchers will have no means of identifying the responses. All collected data will be kept

confidential and securely stored locked with password protection according to JCU Code for the Responsible Conduct of Research. The JCU Code is adapted from the National Code (2007). Section 2.

Are there any potential conflicts of interest?
Dr Erica Martin is a dental practitioner in Australia and is conducting her Master of Philosophy (Health) at James Cook University in Cairns. She has no conflicts of interest.

Where can participants get further information?
Please contact Dr Erica Martin for further information: erica.martin@jcu.edu.au

Who to contact about concerns/complaints about the project?
Human Ethics Officer, *Research Office*, *James Cook University*, *Townsville, Qld, 4811*
Email: ethics@jcu.edu.au Ph*: (07) 4781 5011 Fax: (07) 4781 5521*

APPENDIX 2

Survey questions

Articaine in dentistry: dental practitioner perception

Do you consent to participate in this anonymous survey?

a. Yes, I have read the informed consent information above
b. No

Survey questions

1. My profession:
    a. General dentist
    b. Dental specialist (Specialty_____)
    c. Oral health therapist
    d. Dental therapist
    e. Dental hygienist
    f. Dental student
    g. Other _____

2. In which country are you registered as a dental practitioner? _____

3. In what sector do you primarily practice? Please tick applicable
    a. Private
    b. Public
    c. Education
    d. Research
    e. Other _____

4. Which dental local anaesthetic would you use for routine (non-surgical) dental procedures, if you had no financial or practice constraints?
    a. Lidocaine
    b. Articaine
    c. Mepivacaine
    d. Prilocaine
    e. Other_____

5. Which dental local anaesthetic do you currently use for routine (non-surgical) dental procedures? Please tick all applicable:
    a. Lidocaine
    b. Articaine
    c. Mepivacaine
    d. Prilocaine
    e. Other_____

6. If using articaine, do you use it for all your dental procedures?
    a. Yes
    b. No
    c. All except inferior alveolar nerve blocks
    d. Other _____

7. What is your current view of articaine in terms of safety and efficacy?
    a. I am confident using articaine for all routine dental procedures
    b. I am confident using articaine for some dental procedures
    c. I am not confident using articaine for any dental procedures
    d. Other _____

8. What currently influences for your perception of articaine in routine dental practice? (please click all applicable - multiple responses allowed)
    a. Australian Dental Association guidelines
    b. My country's dental guidelines
    c. My dental degree course
    d. Ongoing continuing professional development courses
    e. My own research
    f. My dental colleagues
    g. My mentor
    h. Other _____

9. What are your views of articaine compared to lidocaine for use as a dental local anaesthetic for ALL routine dental procedures?
    a. Articaine is as safe and efficacious as lidocaine
    b. Articaine is as safe and more efficacious than lidocaine
    c. Articaine is more efficacious than lidocaine, but not as safe
    d. Articaine is not safe to use as a dental local anaesthetic
    e. Other_____

10. Have you had any direct experience of your patients experiencing ongoing adverse reactions (>1 day) following administration of an inferior alveolar nerve block?
    a. No
    b. Yes (if yes please go to the next question)

11. If yes to the question 10, what anaesthetic was used for the IANB? Multiple answers possible: _____

12. If yes to question 10, what type of adverse reaction was experienced by the patient after the inferior alveolar nerve block (please click all applicable - multiple responses allowed)
    a. Paraesthesia (1)
    b. Neuropathy (2)
    c. Palsy (3)
    d. Swelling, bruising (4)
    e. Hematoma (5)
    f. Palpitations, anxiety, shakes (6)
    g. Syncope (7)
    h. Vision changes (8)
    i. Trismus (9)
    j. Infection (10)
    k. Other _____ (11, plus new variable/value for text answer)

13. If yes to question 10, did you subsequently change your clinical practice?
    a. No change to clinical practice
    b. Continued using the LA, but not for all procedures
    c. Stopped using that LA all together
    d. Other _____

14. Is there any further information you would like to share about your personal experience with an LA-related adverse event? _____

Thesis Conclusion

Our research project aimed to clarify evidence-based dental practice and determine the direction for future investigation regarding the local anaesthetic articaine. By reviewing the latest research on articaine safety and efficacy and gathering data on dental practitioner use and the basis of their perceptions of articaine, we found that discrepancies exist between reported dental clinical practice and current research evidence as of January 2021. Further research and clarifications are needed to align practitioner perception of articaine with their dental clinical practice to achieve ubiquitous practice of evidence-based dentistry regarding articaine use.