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Is articaine more effective than lidocaine in patients with irreversible pulpitis: An umbrella review.

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Abstract

Background: Pain management can be challenging during root canal treatment of teeth with irreversible pulpitis.

Aim: To identify whether articaine or lidocaine is the most appropriate local anaesthetic solution for teeth with irreversible pulpitis undergoing root canal treatment.

Data source: The protocol of this umbrella review is registered in the PROSPERO database (CRD42019137624). PubMed, EBSCHO host and Scopus databases were searched until June 2019.

Study eligibility criteria, participants, and interventions: Systematic reviews published in English comparing the effectiveness of local anaesthesia following administration of articaine or lidocaine in patients undergoing root canal treatment of teeth diagnosed with irreversible pulpitis were included. Two independent reviewers selected the studies, carried out the data extraction and the appraisal of the included reviews. Disagreements were resolved in consultation with a third reviewer.

Study appraisal and synthesis methods: The quality of the included reviews was appraised by two independent reviewers using the AMSTAR tool (A measurement tool to assess systematic reviews). Each of the 11 AMSTAR items, was given a score of 1 if the specific criterion was met, or 0 if the criterion was not met or the information was unclear.

Results: Five systematic reviews with meta-analyses were included. The AMSTAR score for the reviews ranged from 8-11, out of a maximum score of 11, and all reviews were categorized as "high" quality. Two reviews scored 0 for item 8 in AMSTAR because the scientific quality of the clinical trials included in these reviews was not used in the formulation of the conclusions.

Limitations: Systematic reviews published only in English language were included. Only a small number of studies were available to assess pain intensity during the injection phase, the time until the onset of anaesthesia and the occurrence of adverse events.

Conclusions and implications of key findings: Articaine is more effective than lidocaine for local anaesthesia of teeth with irreversible pulpitis undergoing root canal treatment. There is limited evidence that injection of articaine is less painful, has more rapid onset and has fewer adverse events compared with lidocaine.

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Keywords: Articaine, irreversible pulpitis, lidocaine, meta-analysis, umbrella review, systematic review

Introduction

Adequate pain management is essential to ensure patient comfort and reduce fear and anxiety during dental treatment (Scott *et al.* 1982, Khan *et al.* 2016). Achieving profound anaesthesia during root canal treatment is often challenging, particularly in teeth with symptomatic irreversible pulpitis (Modaresi *et al.* 2006, Segura-Egea *et al.* 2009). This may be attributed to a range of factors, central sensitization including, prostaglandin-induced sensitization of peripheral nociceptors, acute tachyphylaxis, inflammatory responses affecting local tissue pH and blood flow, and psychological factors (Hargreaves & Keiser 2004, Henry & Hargreaves 2007, Khann *et al.* 2007, Owatz *et al.* 2007).

Lidocaine (or lignocaine) is the most commonly used local anaesthetic solution in dentistry (Gaffen & Haas 2009, Oliver *et al.* 2016). Chemically classed as an amide anaesthetic, lidocaine has a rapid onset of action and an intermediate duration of anaesthesia when combined with adrenaline. It is generally accepted that this combination has the ability to produce pulpal anaesthesia for approximately 60 minutes and soft tissue anaesthesia for 3–5 hours (Malamed 2006, Kung *et al.* 2015). Articaine is another amide local anaesthetic solution that substitutes a thiophene ring for the benzene ring present in lidocaine. This modification allows articaine molecules to diffuse through nerve membranes more effectively than lidocaine molecules, due to increased lipid solubility. The two solutions further differ by the incorporation of an ester linkage into the articaine molecule, which results in hydrolysis of articaine by plasma esterases (Malamed *et al.* 2001). Ninety to 95% of articaine is metabolized in the blood by plasma esterases, with the remainder being broken down in the liver, whereas 90% of lidocaine is metabolized in the liver (Oertel *et al.* 1997, Brandt *et al.* 2011).

Several randomised clinical trials have reported that articaine is more effective than lidocaine in achieving profound dental pulp anaesthesia particularly following infiltration in the maxilla (Evans *et al.* 2008, Srinivasan *et al.* 2009) and as a supplementary infiltration following inferior alveolar nerve block (IANB) in the mandible (Aggarwal *et al.* 2009, Ashraf *et al.* 2013, Rogers *et al.* 2014). Conversely, other clinical trials have reported no benefit of

articaine over lidocaine for pulpal anaesthesia in irreversibly pulpitic mandibular teeth after IANB (Tortamano *et al.* 2009, Aggarwal *et al.* 2017).

In an attempt to better understand the inconsistent results of these randomised clinical trials, several systematic reviews and meta-analyses comparing the efficacy of articaine and lidocaine have been published. The first systematic review comparing articaine with lidocaine (Katyal 2010) concluded that articaine was more effective than lidocaine for successful local anaesthesia during routine dentistry following infiltration in the first maxillary molar region and after IANB in the mandibular molar region. However, this systematic review included teeth with a range of pulpal diagnoses and did not select specifically for irreversible pulpitis. Another review (Brandt *et al.* 2011) compared the anaesthetic efficacy of lidocaine with articaine for pulpal anaesthesia in maxillary and mandibular posterior teeth, after infiltration or block routes of administration respectively. It concluded that while there was no difference in efficacy between articaine and lidocaine it was too early to recommend articaine for mandibular block anaesthesia for teeth with irreversible pulpitis (Brandt *et al.* 2011). Since then, four additional systematic reviews have concluded that articaine is superior to lidocaine for pulpal anaesthesia, at least by some routes of administration, for teeth with irreversible pulpitis (Kung *et al.* 2015, Su et al. 2016, St George *et al.* 2018, Nagendrababu *et al.* 2019). The review by Kung *et al.* (2015) analysed studies on infiltration and block anaesthetic techniques separately and concluded that there was no difference in the efficacy of articaine and lidocaine for mandibular block or maxillary infiltration, with the only benefit of articaine being for supplementary infiltrations in mandibular teeth. The more recent reviews reported that articaine was superior to lidocaine for pulpal anaesthesia following IANB during treatment of mandibular posterior teeth with irreversible pulpitis in both children (Su *et al.* 2016) and adults (Nagendrababu *et al.* 2019), whereas the review by St George *et al.* (2018) reported that there was no evidence of a difference between the anaesthetic solutions.

An "umbrella" review represents an overview of systematic reviews and is a new approach to analyse a collection of systematic reviews on a defined topic or question. An umbrella review should identify both the strengths and shortcomings of existing systematic

reviews that could affect the quality of the results obtained. Such reviews also help to identify consistent or contradictory findings when considering whether the independent systematic reviews assessed the question and arrived at reliable conclusions (Aromataris *et al.* 2015, 2017).

This umbrella review was undertaken to analyse the results of previous systematic reviews in order to determine:

1. The most effective local anaesthetic solution for teeth with irreversible pulpitis when comparing articaine and lidocaine;

2. The anaesthetic solution associated with the least pain during injection when comparing articaine and lidocaine;

3. The anaesthetic solution with the most rapid onset of pulpal anaesthesia when comparing articaine and lidocaine;

4. The anaesthetic solution with the fewest adverse events when comparing articaine and lidocaine; and

5. Reporting deficiencies and gaps in knowledge in this area.

Methods

This current umbrella review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2019). The protocol of the review was registered in the PROSPERO database (CRD42019137624).

Review questions

The review questions were developed based on the PICO (population, intervention, control, and outcome) framework:

1. Is articaine (I) more effective than lidocaine (C) for dental pulp anaesthesia (O) in maxillary and mandibular teeth with irreversible pulpitis undergoing root canal treatment (P)?

2. Does articaine (I) result in more rapid onset of pulpal anaesthesia (O) than lidocaine (C) in maxillary and mandibular teeth with irreversible pulpitis undergoing root canal treatment (P)?

3. Does the injection of articaine (I) cause less pain (O) than the injection of lidocaine (C) in patients (P) with irreversibly pulpitic maxillary and mandibular teeth undergoing root canal treatment?

4. Does articaine (I) result in fewer adverse events (O) than lidocaine (C) following administration in the maxilla and mandible for root canal treatment of patients (P) with irreversible pulpitis?

Selection criteria

Articles were included if they satisfied the following criteria:

- systematic reviews with or without meta-analysis;
- published in English;
- reviews comparing anaesthetic efficacy between articaine and lidocaine/lignocaine in patients undergoing root canal treatment in maxillary and/or mandibular teeth with irreversible pulpitis.

Narrative reviews, case reports and individual clinical trials were excluded.

Data source and search strategy

The literature search was performed in PubMed, EBSCOhost and Scopus electronic databases from inception to June 2019 using the following search strategy: (((((articaine) OR lidocaine) OR lignocaine)) AND (((((((root canal) OR endod) OR irreversible pulpitis) OR inferior alveolar nerve block) OR Gow-Gates) OR mental incisive nerve block) OR Vazirani-Akinosi) OR maxillary infiltration)) AND ((systematic review) OR meta-analysis). Reference lists of included systematic reviews were also hand searched to identify other relevant systematic reviews. Initially, two independent reviewers (VN, SP) screened the titles and abstracts of identified reviews to decide on inclusion or exclusion. In cases of doubt after reading the title and abstract, the full-text of each systematic review was read to decide on their inclusion/exclusion. Disagreements were resolved with the help of a third reviewer

(PD). If needed, the authors of included reviews were contacted to provide missing data and/or clarify information that was unclear.

Data extraction

Two independent reviewers (NV, SP) performed the data extraction. Disagreements were resolved by consulting with the third reviewer (PD). Two separate data extraction forms were created:

i) *General characteristics of the included systematic reviews and meta-analyses*: name and country of the first author, year of publication, name of the journal published, database searched, search period during which the original included studies were published, languages included, interventions, number of studies included for meta-analysis, number of participants, type of study design included, instrument used to assess the quality of included studies and outcome assessed;

ii) *Summary of the meta-analyses*: meta-analysis model, number of samples in intervention and comparison group (total and events), study-specific relative risk estimates (risk ratio, odds ratio, or standardized mean differences) along with the corresponding 95% confidence intervals (CI), I2 statistic and publication bias.

Primary outcome

Successful pulpal anaesthesia in maxillary and mandibular teeth with irreversible pulpitis undergoing root canal treatment. The diagnostic criteria for irreversible pulpitis were: moderate to severe spontaneous pain, prolonged response to a cold test and a positive response to an electric pulp test. Anaesthetic success was defined as: no pain or mild pain according to patient-reported pain scores during access cavity preparation and instrumentation or no response to pulp sensibility testing (heat/cold/electric pulp tester).

Secondary outcomes

1. Pain intensity during local anaesthetic injection, 2. Time of onset of pulpal anaesthesia, and 3. Adverse events reported.

Methodological quality assessment

Two independent reviewers (VN, SP) appraised the methodological quality of included systematic reviews using the AMSTAR tool (A measurement tool to assess systematic reviews) (Shea *et al.* 2007). A third reviewer (PD) resolved doubts or discrepancies between the two reviewers. The AMSTAR checklist consists of 11 items. Each item was given a score of 1 if the specific criterion was met, or 0 if the criterion was not met or information was unclear. Missing information was obtained by contacting the authors; if there was no response the item was scored as 0. After scoring, each systematic review was categorised into high, medium and low quality, if it received a score between 8 to 11, 4 to 7 and 0 to 3, respectively (Rangel-Rincón *et al.* 2018). The degree of agreement between the two independent reviewers (VN and SP) and intra-examiner agreement in assessing the methodological quality of included systematic reviews was calculated by Cohen's kappa analysis.

Results

Literature search

Relevant systematic reviews were identified and selected (Figure 1). The initial search resulted in 863 reviews and of these, 107 were removed as they were duplicates. Following title and abstract screening a total of 748 studies were excluded, because they did not satisfy the inclusion criteria with eight studies being shortlisted for full text retrieval. After reading the full text, three reviews were excluded for the following reasons: inclusion of studies with other anaesthetic solutions in the meta-analysis (Tupyota *et al.* 2018), inclusion of studies with a range of pulpal diagnoses and not limited to irreversible pulpitis (Katyal 2010, Bartlett *et al.* 2016). Finally, five systematic reviews with meta-analysis were included for the current umbrella review (Brandt *et al.* 2011, Kung *et al.* 2015, Su *et al.* 2016, St George *et al.* 2018, Nagendrababu *et al.* 2019).

Characteristics of the included systematic reviews

The general characteristics of the included systematic reviews with meta-analysis are summarized in Table 1. Figure 2 provides a summary of the meta-analyses for pulpal anaesthesia and adverse events, whereas Figure 3 provides the summary of the meta-analyses for pain intensity during injection and onset time of pulpal anaesthesia. Among the five included reviews, two were from the USA, with one each from the UK, China and Malaysia. The number of databases searched by the authors of the included reviews ranged from two to five and the reviews included between 3 and 15 randomised clinical trials. No other type of experimental clinical study was included in any review. Su *et al*. (2016) included amongst the 15 individual randomised clinical trials they analysed, four that included children under 16 years of age; all other reviews included only adults (>16 years).

Three of the reviews used the Cochrane Collaboration "Risk of Bias" tool for quality assessment (Kung *et al*. 2015, Su *et al.* 2016, St George *et al.* 2018), whereas one review used the more recently introduced Cochrane risk of bias tool (RoB 2.0) (Nagendrababu *et al*. 2019). Brandt *et al*. (2011) assessed the methodological quality of the trials they included within five domains, namely: randomization, allocation concealment, outcome assessment, adverse events reporting and loss to follow-up; as indicators of quality. All the systematic reviews were published in SCImago tier1/tier2 journals such as: *International Endodontic Journal* (Nagendrababu *et al*. 2019)*, Journal of Endodontics (*Kung *et al*. 2015)*, Australian Endodontic Journal (*Su *et al.* 2016) and *Journal of the American Dental Association (*Brandt *et al.* 2011). One review was published in the *Cochrane database* (St George *et al.* 2018).

Heterogeneity and publication bias in the included systematic reviews
Each systematic review used funnel plots to detect publication bias. The plots in two of the reviews were symmetrical and revealed no evidence of bias (Su *et al*. 2016, Nagendrababu *et al*. 2019), whereas the review by Kung *et al.* (2015) revealed asymmetry in the base of the funnel, indicative of potential publication bias. In the review by Brandt *et al.* (2011) publication bias was not assessed, with no reason being provided, while in the review by St George *et al.* (2018), publication bias was not assessed due to the small number of trials selected. In the meta-analyses of two studies (Kung *et al*. 2015, Su *et al.* 2016) comparing the anaesthetic efficacy of articaine with lidocaine including all delivery routes (combined with

infiltration, mandibular blocks, supplemental infiltration), there was moderate heterogeneity (30-60% [Higgins & Green 2011]), whereas in the review by Brand *et al.* (2011) 0% heterogeneity was observed.

Methodological quality

A quality assessment of the five systematic reviews with meta-analysis included in this umbrella review is provided in Supplementary Table 1. The AMSTAR score for the included systematic reviews ranged from 8-11. Two reviews (Brandt *et al.* 2011, Kung *et al.* 2015) were scored as 0 for "scientific quality of the included studies used appropriately in formulating conclusions". All the systematic reviews were categorized as "high" quality. The intra and inter-examiner reliability scores (VK and SP) for scoring the AMSTAR items of the included studies based on the Kappa statistics was 1 and 0.88 (p<0.001) respectively. This equates to "almost perfect" agreement.

Principal findings

Five systematic reviews were finally included in this review, which contained 35 individual meta-analyses addressing four unique outcomes:

1. Pulpal anaesthesia success rate from 31 meta-analyses;
2. Pain intensity during injection from 1 meta-analysis;
3. Onset time of pulpal anaesthesia from 1 meta-analyses;
4. Adverse events from 1 meta-analysis.

i. Pulpal anaesthesia

Three reviews reported that articaine had a 1.15 – 2.3 times greater success rate than lidocaine (Kung *et al*. 2015, Su *et al*. 2016, St George *et al.* 2018), whereas Brant *et al*. (2011) concluded there was no difference between the solutions. Nagendrababu *et al*. (2019) included 8 clinical trials in their meta-analysis and concluded that articaine had a 1.16 times higher anaesthetic success rate than lidocaine, when the solutions were delivered as an IANB.

Tooth and jaw: Generally, infiltrations are the preferred local anaesthetic technique for maxillary teeth with irreversible pulpitis. Three of the five reviews (Kung *et al.* 2015, Su *et al.* 2016, St George *et al.* 2018) performed a separate analysis for maxillary teeth. Among these, two reviews (Su *et al*. 2016, St George *et al.* 2018) concluded that articaine had a superior success rate than lidocaine, whereas another (Kung *et al*. 2015) concluded there was no difference between the two anaesthetic solutions for maxillary teeth. Four of the reviews performed analyses separately for mandibular teeth with irreversible pulpitis. They concluded that articaine had a greater anaesthetic success rate compared with lidocaine when the anaesthetic solution was delivered by any technique for anaesthetising mandibular molars.

Technique: Three reviews (Kung *et al.* 2015, Su *et al.* 2016, St George *et al.* 2018) combined studies assessing the effectiveness of anaesthesia using various techniques of conventional IANB alone and conventional IANB supplemented by buccal infiltration. The other two reviews (Su *et al*. 2016, Nagendrababu *et al*. 2019) evaluated studies that used only IANBs. The analysis in these reviews revealed that articaine was superior to lidocaine for mandibular molars with irreversible pulpitis undergoing root canal treatment.

Overall, four of the reviews concluded that articaine had a greater anaesthetic success rate than lidocaine during treatment of teeth with irreversible pulpitis.

ii. Pain during injection
Su *et al*. (2016) reported that articaine was associated with a lower pain (VAS) score during injection than lidocaine, however, this data was taken from only one clinical trial (Kanaa *et al*. 2012).

iii. Onset of anaesthesia

Su *et al.* (2016), taking into account the outcome of a meta-analyses from four pooled clinical trials, reported that articaine was associated with a more rapid onset of pulpal anaesthesia than lidocaine.

iv. Adverse events

Kung *et al.* (2015) highlighted that one trial they included reported the absence of adverse events, whereas no mention was made in the other studies they included. In contrast, Su *et al.* (2016) performed a meta-analysis for adverse events and reported that articaine was associated with a lower percentage of patients suffering adverse events than lidocaine, including oedema, haematoma, dizziness, nausea, allergy and shock. Thus, they concluded that articaine is less toxic and safer to use than to lidocaine (Su *et al.* 2016). None of the systematic reviews mentioned paraesthesia as an adverse event; however, this may not have been possible to identify and report since there was no long term follow-up of patients.

Discussion

The inability to achieve pulpal anaesthesia during root canal treatment has the potential to increase fear and anxiety in patients and thus make patient management more challenging, prolong the duration of appointments and create concerns in the mind of patients about the competence of the clinician. It may also exacerbate systemic medical conditions (Kung *et al.* 2015). In an umbrella review, the results of multiple systematic reviews are compiled into a single overarching review, before synthesizing the data in an attempt to integrate all relevant information. The intention is to create greater clarity, reduce uncertainty for decision-making, identify residual gaps in knowledge and provide a reference publication that contains the essential information on that topic. An umbrella review is considered to provide the highest level of scientific evidence, and thus the benchmark for clinical decision-making (Silva *et al.* 2012, 2015). Therefore, an umbrella review approach was used in this study to provide clear and unambiguous recommendations to clinicians when selecting articaine or lidocaine anaesthetic solutions for local anaesthesia of their adult patients presenting with irreversible pulpitis and requiring root canal treatment. The authors of the current umbrella review had planned to perform a meta-analysis, if the primary outcome of the five included

reviews revealed a disagreement. However, the more recent systematic reviews (Kung *et al*. 2015, Su *et al*. 2016, St George *et al*. 2018, Nagendrababu *et al*. 2019) all concluded that articaine was more effective than lidocaine, whereas Brant *et al*. (2011) reported no difference, probably due to the small number of clinical trials included. As a consequence of the consistent conclusions, it was considered that there was no need for a meta-analysis.

Quality of systematic reviews

The quality of the individual systematic reviews included in this umbrella review was categorised as "high" when using the AMSTAR tool. AMSTAR has been reported to provide good evidence of validity and reliability, and helps the reader to appraise the critical components that a systematic review should include in order to appropriately interpret the results and its implications (Shea *et al.* 2007). AMSTAR has 11 domains namely: priori design, study selection and data extraction process, literature search, status of publication, studies list, characteristics of included studies, scientific quality of the included studies assessed and documented, scientific quality of the included studies used appropriately in formulating conclusions, methods to combine findings, publication bias and conflict of interest (Shea *et al.* 2007). A high AMSTAR score for a systematic review does not necessarily mean that the original randomised clinical trials they included were of high quality. However, carrying out a quality assessment of the individual randomised clinical trials included in a systematic review is important in order to evaluate the quality of evidence obtained by a subsequent meta-analysis. Two of the systematic reviews failed to formulate their conclusions based on the quality of the randomised trials they included (Brandt *et al*. 2011, Kung *et al*. 2015). This is a critical flaw of these reviews as it will affect the results and conclusions, which may be used subsequently to develop clinical practice guidelines that directly influence patient care.

Strengths

The current umbrella review was conducted with a robust methodology as it used three electronic databases to search for and identify suitable systematic reviews and two independent reviewers were involved in systematic review selection and data extraction. This rigorous methodology improves the quality of the review process. The umbrella review

only included systematic reviews that contained randomized clinical trials, to provide the highest level of evidence. Furthermore, *a priori* protocol registration in the PROSPERO database improves the methodological and reporting quality of a review, promoting transparency and reducing potential for bias, and helping to avoid unintended duplication of reviews.

Limitations

The heterogeneity among the randomized clinical trials included within each systematic review is by extension also a limitation of this umbrella review. Study heterogeneity included factors such as: geographic location, sample size, experience of operators, criteria for defining the diagnosis of symptomatic irreversible pulpitis, volume of anaesthetic solution, the concentration of vasoconstrictor and speed of injection. Systematic reviews published in language other than English were excluded, which creates a degree of selection bias. Among the five reviews, four included randomised clinical trials with only adult patients, whereas Su *et al.* (2016) included both children (<16 years) and adult patients.

Flaws and inconsistencies at the primary research level further complicates the interpretation within this umbrella review, as the outcome measure used to assess the efficacy of local anaesthetic solutions in randomised clinical trials varied between studies. In some clinical trials, local anaesthetic efficacy was assessed by pulp sensibility testing (cold test/electric pulp tester) (Hsiao-Wu *et al*. 2007, Evans *et al*. 2008), while in others, efficacy was assessed by asking the patient to indicate discomfort/pain using a visual analogue scale (VAS) during access cavity preparation or pulp extirpation (Tortamano *et al*. 2009, Aggarwal *et al.* 2017). Nusstein *et al.* (1998) reported 42% of posterior teeth that had responded negatively to an electric pulp test, were associated with pain during root canal treatment. Thus, pulp sensibility testing is not a reliable indicator for assessing anaesthetic efficacy during actual treatment. The systematic review by Kung *et al*. (2015) combined clinical trials that assessed the outcome using pulp sensibility tests and patient pain ratings, whereas Nagendrababu *et al*. (2019) combined studies only using a patient rating scale or VAS. This variation in outcome measures creates uncertainty and confusion in the subsequent

systematic review, with the result that clinicians are unsure of the best anaesthetic solution to use during root canal treatment of teeth with irreversible pulpitis.

Reporting deficiencies and gaps in knowledge/methodology

On reviewing the randomised clinical trials and systematic reviews on the topic of anaesthetic efficacy, several deficiencies in methodology and reporting were identified. To improve the quality of clinical trials and systematic reviews, the following recommendations are proposed on their conduct and reporting.

Recommendations for conducting randomised clinical trials on anaesthetic solutions
1. Adhere to CONSORT guidelines:

The quality of evidence from this umbrella review is affected by the quality of the included systematic reviews and meta-analyses, as well as the quality of the individual randomised clinical trials included in each meta-analysis. For primary research studies, researchers must adhere to CONSORT guidelines and should register their clinical trial in advance in clinical trial registries such as ClinicalTrials.gov, Health Canada Clinical Trial Database, Iranian Registry of Clinical Trials, EU Clinical Trials Register, Australian New Zealand Clinical Trials Registry.

2. Diagnosis – irreversible pulpitis:

(i) Randomised clinical trials comparing the anaesthetic efficacy of various local anaesthetic solutions need to adhere to an accepted definition of irreversible pulpitis, for example the American Association of Endodontists (AAE 2013) defines irreversible pulpitis as "Symptomatic irreversible pulpitis may include sharp pain upon thermal stimulus, lingering pain (often 30 seconds or longer after stimulus removal), spontaneity (unprovoked pain) and referred pain. Sometimes the pain may be accentuated by postural changes such as lying down or bending over and over-the-counter analgesics are typically ineffective".

(ii) The presence or absence of an apical radiolucency/widening of the apical periodontal ligament should be included in the results. If teeth exhibiting an apical radiolucency are to be excluded, this must be made explicit and a clear rationale provided. Details of the radiographic technique (e.g. films, exposure conditions, use of paralleling devices etc) and

under what conditions the radiographs were interpreted must be included, e.g. the experience of each examiner and the degree of agreement (intrarater or interrater agreement) if two or more examiners were involved in the interpretation of radiographs.

(iii) Details of the clinical process for establishing a pulpal diagnosis, as well as the techniques and devices used for pulp sensibility testing (manufacturer, city, country) must be described accurately.

(iv) The experience of the operator(s) (undergraduate/postgraduate/endodontist) who performed the clinical examination, pulp sensibility tests and interpretation of radiographs to confirm the pulp status must be provided. The operator who performs the pulp sensibility tests should ideally be independent of the research team. Even with a clear definition of irreversible pulpitis and an independent evaluator of pulpal status, consistently diagnosing irreversible pulpitis can be difficult. Although, spontaneous, radiating pain that lingers after removal of the stimulus tends to indicate irreversible pulpitis (ESE 2019), it should be remembered that this is a dynamic clinical diagnosis, which does not always accurately reflect the histological inflammatory state of the pulp (Dummer *et al*. 1980). Indeed, irreversible pulpitis can be symptomless in anywhere between 14-60 % of cases (Seltzer *et al*. 1963, Michaelson & Holland 2002). This makes an accurate diagnosis of irreversible pulpitis difficult and often unreliable even for experienced operators, which adds a potential bias into a clinical trial.

3. Inclusion/exclusion criteria:

The selection criteria of patients/volunteers must be described clearly. The age of the patients, preoperative pain status and how it was measured, radiographic status and medical and dental history (such as history of trauma, previous restorative and orthodontic treatments, previous pain from the tooth) are essential. Patients taking medication that could interfere with the action of any of the anaesthetic solutions must be excluded and reasons for their exclusion highlighted in the results section.

4. Anaesthetic solution:

Details of the anaesthetic solutions must be provided including: volume, concentration, vasoconstrictor used, and temperature when injected.

5. Delivery of anaesthetic solution:

The length and gauge of the needle used to deliver the anaesthetic solution(s) must be provided as well as the estimated average injection speed.

6. Blinding:

The blinding method and individuals involved in the blinding process must be described fully including operator, patient and evaluator.

7. Time before intervention:

The period between delivery of an anaesthetic solution and the assessment of anaesthetic efficacy must be standardised and reported (e.g. lip numbness, patient self-reported assessment [Visual Aanalog Scale]).

8. Outcome measure:

In teeth with irreversible pulpitis, the lack of a response to pulp sensibility tests might not guarantee profound pulpal anaesthesia for painless treatment. The waiting time between sensibility tests may also have an effect with evidence that the result of the first test may have an effect on the reaction to subsequent tests to give a false negative result (Nusstein et al. 2010). Hence, a more reliable indicator for assessing anaesthetic efficacy in clinical trials is to record pain during the endodontic procedure (e.g. access cavity preparation, pulp tissue manipulation, canal instrumentation). It would be best practice to report the success of anaesthesia separately for access cavity preparation, initial pulp penetration and canal instrumentation procedures (Poorni *et al.* 2011). Details of the individual(s) who performed the root canal treatment procedure(s) must be described, for example, were they blinded to the experimental groups, how many operators were involved, their status (undergraduate/postgraduate/endodontist) and their relative experience.

9. Clinical significance of the results:

When planning randomised clinical trials comparing two local anaesthetic solutions, it is critical that the study be adequately powered. Several randomised clinical trials that have

compared articaine with lidocaine in teeth with irreversible pulpitis and used a VAS to measure pain during root canal instrumentation, have reported a trend for more effective anaesthesia, albeit non-significant, results with articaine (Poorni *et al.* 2011, Sood *et al.* 2014, Allegretti *et al.* 2016). For example, Sood *et al.* (2014) reported 88% success with articaine and 82% success with lidocaine, while Poorni *et al.* (2011) reported 69% with articaine and 65% with lidocaine, and Allegretti *et al.* (2016) 63.6% for articaine and 54.5% for lidocaine. In addition to the lack of statistical significance, the number of participants was also relatively small (<55 patients in each arm) increasing the potential for type II error as the studies were underpowered. It is essential that new studies investigating articaine and lidocaine use previously published percentage differences to establish the sample size.

10. Adverse event:

The occurrence of adverse event(s) during clinical trials and how they are managed must be carefully described. If no adverse event(s) occur this should also be mentioned.

Recommendations for conducting systematic reviews and meta-analyses on anaesthetic solutions

The quality of evidence from this umbrella review is affected by the methodological and reporting quality of the included systematic reviews and meta-analyses. All systematic reviews and meta-analyses must adhere to the AMSTAR and PRISMA guidelines and additionally authors need to consider the following parameters, while conducting and reporting systematic reviews and meta-analyses on local anaesthetic solutions:

i. The results of the scientific quality assessment (risk of bias) of the primary randomised trials they include and use that information to formulate the conclusions;

ii. Sub-group and sensitivity analysis based on outcome measures (pulp sensibility, record pain during the endodontic procedure), and local anaesthetic solution (volume, concentration, vasoconstrictor used, and temperature);

iii. Evaluation of adverse events associated with commonly used local anaesthetic solutions;

iv. A clear and consistently applied definition of pulpal status must be used.

These recommendations will help to increase the accuracy, validity and credibility of publications through the development of high-quality manuscripts. They will also help researchers to effectively plan and design randomised clinical studies and systematic reviews for the benefit of clinicians and patients.

Concluding remarks

This umbrella review collated evidence from existing systematic reviews and draws the following conclusions:

i. There is sufficient evidence to conclude that articaine is associated with greater local anaesthetic success rates than lidocaine following IANBs, infiltrations and supplemental injections during root canal treatment of teeth with irreversible pulpitis;

ii. There is limited evidence to suggest that the injection of articaine is less painful than the injection of lidocaine in patients with irreversible pulpitis undergoing root canal treatment;

iii. There is limited evidence to suggest that articaine is associated with a more rapid onset of pulpal local anaesthesia than lidocaine in teeth with irreversible pulpitis undergoing root canal treatment;

iv. There is limited evidence to suggest that articaine local anaesthetic injections are associated with fewer adverse events than lidocaine;

v. Numerous reporting deficiencies and gaps in knowledge have been identified.

It is hoped that these recommendations will help researchers to effectively plan and design randomised clinical trials and systematic reviews for the benefit of clinicians and patients and also help to increase the accuracy, validity and credibility of publications through the development of high-quality manuscripts.

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Legends

Figure 1: Search process.

Figure 2: Meta-analyses summary for pulpal anaesthesia and adverse events outcomes. Note: CI- Confidence Interval, MD- Mean difference, NR- Not reported, NA- Not applicable, RR- Risk Ratio, OR- Odds Ratio,

Figure 3: Meta-analyses summary for pain intensity during injection and onset time of pulpal anaesthesia. Note: CI- Confidence Interval, MD- Mean difference, NR- Not reported, NA- Not applicable, RR- Risk Ratio, OR- Odds Ratio,

Table 1: Main characteristics of the included systematic reviews and meta-analysis

S No	Author, year	Name of the journal published	Database searched	Country of the first author	Search Period	Language	Groups	Number of studies included for meta-analysis	Study design – included studies	Instrument of quality Assessment
1	Brandt *et al.* 2011	*Journal of American Dental Association*	MEDLINE and Embase	USA	1970 to 2009	English, German, Croatian and Russian	4% Articaine, 2% Lidocaine in combination with vasoconstrictor	3	Randomised clinical trials	Five domains namely: randomization, allocation concealment, outcome assessment, adverse effect reporting and loss to follow-up
2.	Kung *et al.* 2015	*Journal of Endodontics*	MEDLINE, Scopus and Cochrane Library	USA	1976 to 2013	No language restriction. (if an abstract was not available in English for screening purposes, the article was not included)	4% Articaine, 2% Lidocaine in combination with vasoconstrictor	10	Randomised clinical trials	Cochrane Collaboration
3	Su *et al.* 2016	*Australian Endodontic Journal*	MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE,	China	1946 to 2015	No language restriction	4% Articaine, 2% Lidocaine in combination with vasoconstrictor	15	Randomised clinical trials	Cochrane Collaboration "Risk of Bias" tool

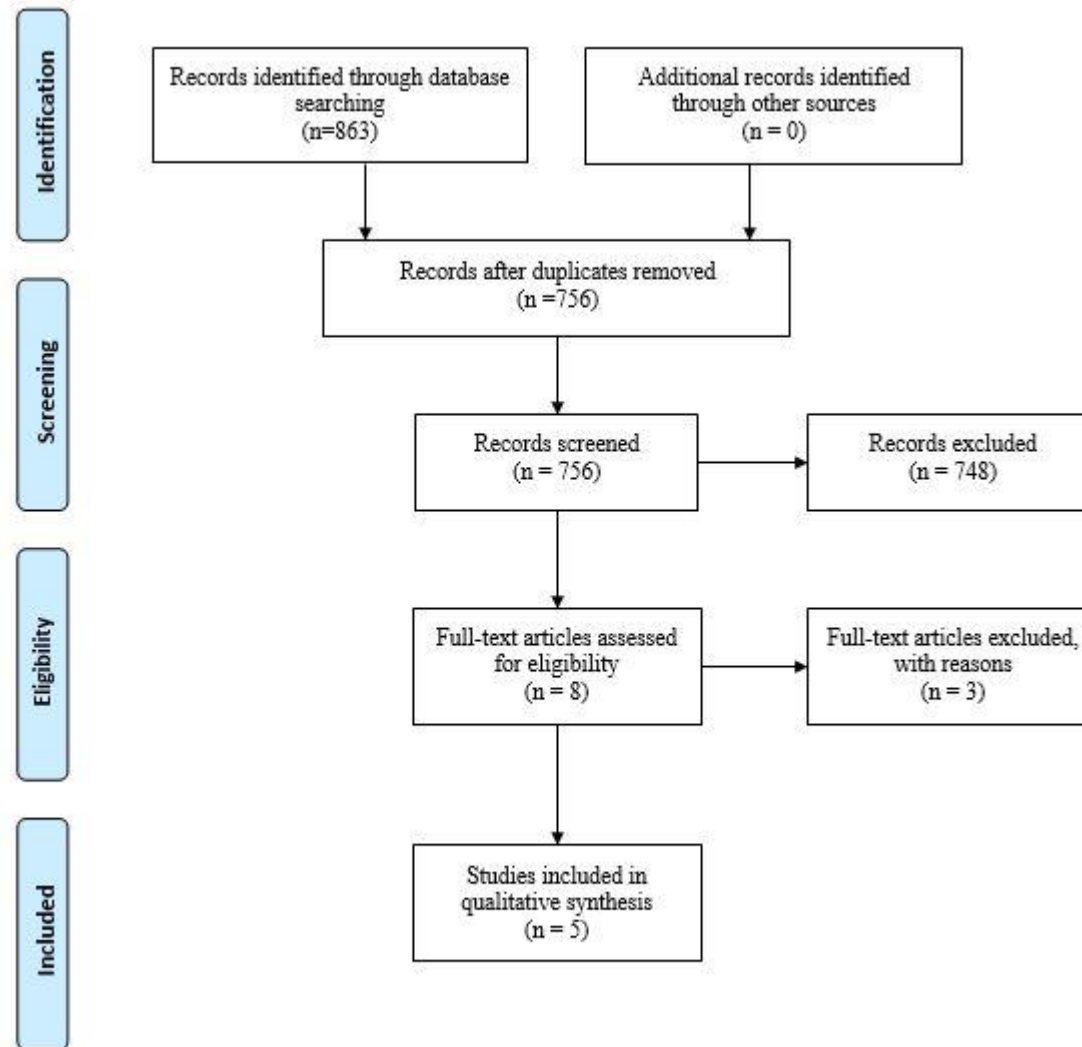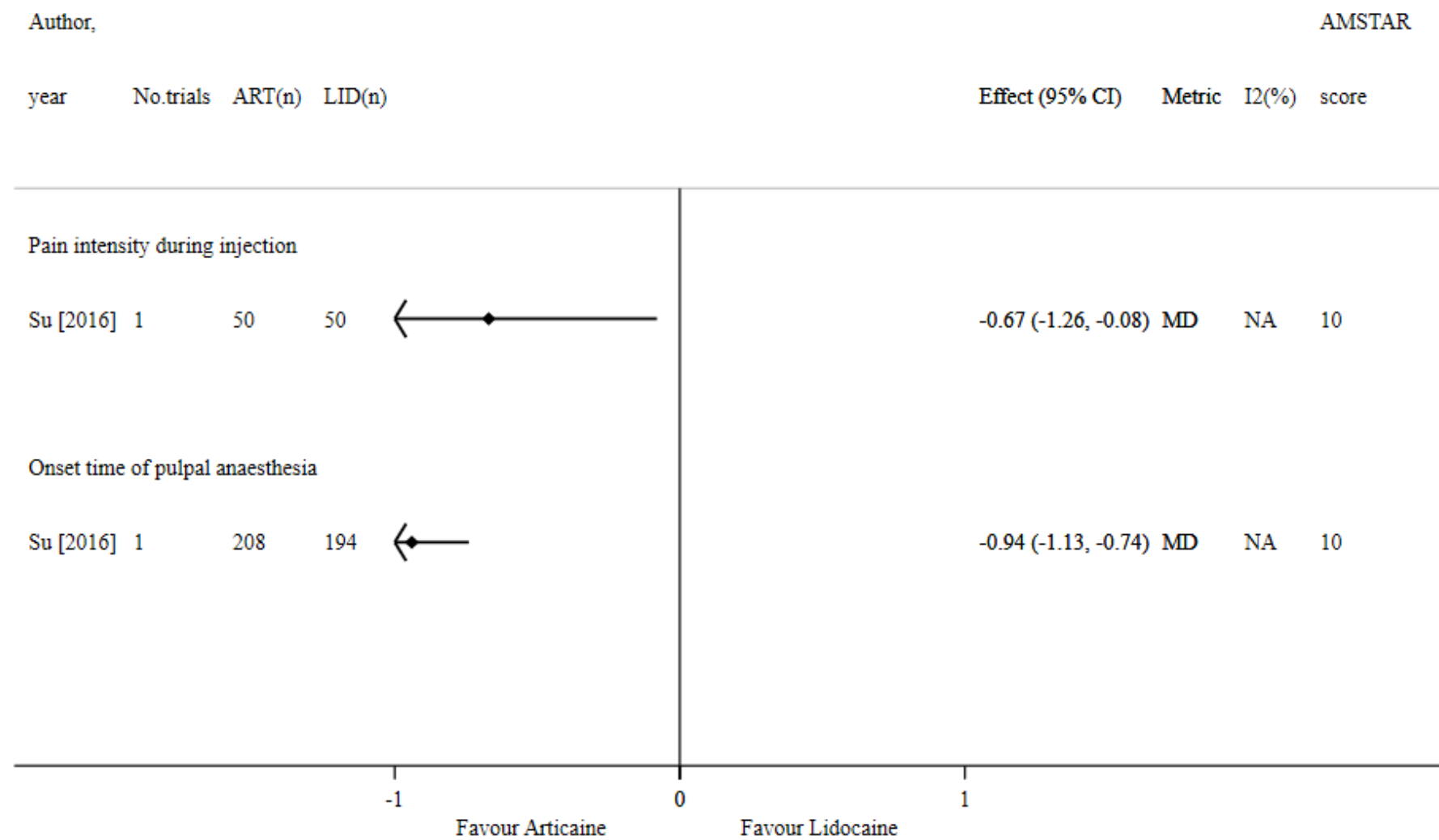| 4 | St George *et al.* 2018 | *Cochrane Database of Systematic Reviews* | Chinese BioMedical Literature Database and China National Knowledge Infrastructure Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library; 2018, Issue 1), MEDLINE (OVID SP), Embase, CINAHL PLUS, WEB OF SCIENCE, PubMed, Scopus | UK | Until 2018 | No language restriction | 4% Articaine, 2% Lidocaine in combination with vasoconstrictor | 4 | Randomised clinical trials | Cochrane Collaboration "Risk of Bias" tool |
| 5 | Nagendrababu *et al.* 2019 | *International Endodontic Journal* | | Malaysia | Inception to 2018 | English | 4% Articaine, 2% Lidocaine in combination with vasoconstrictor | 15 | Randomised clinical trials | Cochrane risk of bias (RoB 2.0) |

Fig 1

Fig 2

Author, year	No.trials	ART(n)	LID(n)		Effect (95% CI)	Metric	I2(%)	AMSTAR score

Pain intensity during injection

Su [2016] 1   50   50   -0.67 (-1.26, -0.08) MD   NA   10

Onset time of pulpal anaesthesia

Su [2016] 1   208   194   -0.94 (-1.13, -0.74) MD   NA   10

-1   0   1

Favour Articaine   Favour Lidocaine

Fig 3