Does the Use of 4% Articaine and 1:100,000 Adrenaline, Rather Than 2% Lidocaine and 1:100,000 Adrenaline, Increase the Risk of Nerve Damage When Administered for Inferior Alveolar Nerve Blocks in Patients Undergoing Local Anaesthesia for Dental Treatment?

A Mini Systematic Review of The Literature.

Manuscript Approved (MSS-2018-270).

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Abstract

This mini systematic review seeks to analyse the available literature and determine if a 4% articaine solution poses a greater risk of inferior alveolar and/or lingual nerve

damage compared to that of 2% lidocaine when administered for an inferior alveolar nerve block.

After a mini systematic review search of the published literature, seven suitable studies were identified, one double blind random controlled trial (DBRCT) and six retrospective cohort studies.

The DBRCT and 2 of the cohort studies concluded that 4% articaine poses no greater risk of nerve damage.

The remaining 4 cohort studies suggested that caution should be exhibited when using a 4% local anaesthetic solution rather than a 2% solution. However, these studies also concluded that no evidence exists to explain the reasons for their results.

The included articles present no conclusive evidence to suggest that 4% articaine causes more nerve damage than 2% lidocaine although some authors advise caution when using this agent.

All studies conclude that further quality research is required and it is therefore suggested that dental practitioners exhibit caution when choosing to use 4% articaine in an inferior alveolar nerve block until further scientific research has been performed

Introduction

Since 1949, lidocaine has been recognised as the “gold standard” of local anaesthetic agents.[1] However, the desire to develop fast acting agents with a short half-life that also produce profound anaesthesia has led to the development of other alternatives. One example is articaine, initially synthesised in 1969 and used for the first time in clinical dental practice in Germany in 1976.

The reason for articaine’s popularity appears to be due to its efficacy. Numerous studies have shown that articaine produces a more profound anaesthesia than that of lidocaine.[2,3,4,5,6,7,8]

Lidocaine is an amide compound, based on a benzene ring structure (C_6H_6). Articaine, in contrast, possesses a thiophene ring (C_4H_4S), providing greater lipid solubility and an increased potency as a greater volume of an administered dose can enter the target neurons. Articaine’s lipid solubility has been quoted at over 4 times greater than that of lidocaine.[9]The same study confirmed that the onset of anaesthesia was achieved in 7.4 mins with articaine as opposed to 8.7 mins with lidocaine.[9] It has also been suggested that articaine provides a longer duration of anaesthesia due to its protein binding characteristics.[10,11]

With these attributes, it is perhaps not surprising that many studies have concluded that articaine is more efficient at producing profound anaesthesia than lidocaine.[6,12,13,14,15] These papers include studies of both infiltration and nerve block anaesthesia. Other authors concluded that articaine has a faster onset than lidocaine[11], and a meta-analysis has proved that articaine is 1.6 – 3.5 times more potent than lidocaine.[2]

Several studies have concluded that articaine should be recommended for use over lidocaine.[2,6,12,16] In 2007, Robertson et al concluded that both the speed of onset and the anaesthetic efficacy of articaine were superior to those of lidocaine when administered via a buccal infiltration technique in the posterior molar region.[14]

Another important attribute of a local anaesthetic agent is that of safety and this is perhaps where articaine compares less favourably. Since its introduction, several articles have been published warning of possible nerve damage when articaine is administered in an inferior alveolar nerve block (IANB).[17,18] These articles indicate a risk of causing temporary or permanent paraesthesia of the inferior alveolar nerve (IAN) but evidence also exists contradicting these claims.[3,19,20]

It appears, therefore, that the dental profession faces a dilemma. Should the more efficient agent be used to achieve faster, more profound anaesthesia or should the profession be wary of an agent that may have the potential to induce nerve damage?

A mini systematic review of the literature was performed by a single researcher with one, clearly focused question[21]. The results of the study will hopefully provide advice to the dental profession, ensuring the continued provision of safe and effective local anaesthesia.

Methodology

The Scottish Intercollegiate Guidelines Network (SIGN) presents eight levels of evidence-based research. The SIGN tool was used in this study according to the criteria set out in Table 1.[22]

The development of the research question was aided using the PICOS method[23], as described in Table 2.

Inclusion and exclusion criteria were applied to the literature search as outlined in Tables 3 and 4.

Basic search terms and medical sub headings terms were developed and detailed in Tables 5 and 6.

3 electronic databases were chosen to systematically search the available literature:

1. Medline with Full Text.
2. Dentistry and Oral Sciences Source.
3. The Cochrane Library

Quality Assessment of Studies

To ensure that the random controlled trials included in the review were accurately assessed against the inclusion and exclusion criteria, the risk of bias tool as described in the Cochrane Handbook for Systemic Reviews of Intervention was applied.[24]

For the selected cohort studies, a Methodology Index for Non Randomised Studies (MINORS) was applied[25], as described in Table 8.

A record sheet was developed, and each study was subsequently scored as directed by Slim and Nini et al 2003[25] as defined in Table 9.

Data Extraction

Specifically designed data extraction forms were developed, allowing uniform data to be extracted under the following headings;

- Study design
- Study objectives
- Geographical origin of the study
- Clinical setting for the study
- Study funding
- Study participants – sex, age, numbers
- Type of anaesthetic agent used
- Study outcome – methods of recording and reporting nerve damage
- Comparison made between “expected” and “observed” outcomes
- Follow up periods
- Attrition bias
- Data analysis of outcomes

Results

Data extraction and results of the mini systematic review are detailed in tables 10 – 18.

Discussion

Malamed and Gagnon's study of 1325 participants enabled a statistical analysis of the results which indicated that the incidence of nerve damage was the same (1%) whether 4% articaine or 2% lidocaine was used as the LA agent. Indeed, this DBRCT concluded that articaine is a "*safe and effective*" local anaesthetic agent.[19]

Both studies conducted by Pogrel[20,26], concluded that the incidence of nerve damage following the use of 4% articaine was in proportion to its market share.

However, 3 of the studies indicated that the use of 4% articaine elicited more adverse outcomes than would be expected when compared to the agent's market share.[17,27,28]

Limitations and Characteristics of Included Studies

Several methodological inconsistencies exist throughout the included studies, making a direct comparison between the chosen articles difficult.

When performing a study comparing 2 pharmaceutical agents, a true comparison can only be achieved with the knowledge of the relative use of the 2 drugs within the studied population.

Haas and Lennon[17], Gaffen and Haas[28] and Garisto, Gaffen et al[27] all used the “null hypothesis” developed by Ronald Fisher.[29]

However, the other included studies failed to indicate any comparison between expected and observed outcome events.

The creation of a “barb” on the tip of the needle resulting from contact with the bone, may also be a factor in the traumatic damage to both the IAN and LN. However, whether or not this event occurred during any of the IANBs included in the studies, the resultant mechanical damage would be the same for both LA solutions.

Of the 7 included papers, only one involves a DBRCT, 3 involve voluntary reporting of nerve damage and the remaining 3 articles elicit their information from patients who have been referred to a specialist centre for the specific reason that they are experiencing some degree of nerve damage. This clearly results in a considerable degree of reporting bias.

With incidences of nerve damage ranging from 1: 27,000 to 1: 785,000[17,30], it is clear that this study’s outcome is extremely rare. To obtain statistically significant results in a DBRCT would require a clinical trial on a very large scale. This could explain the existence of only one such study since 1976.[19]

Both Hillerup and Jensen[18] and Garisto and Gaffen[27] make reference to the possibility of reporting bias in their papers and Gaffen and Haas[28] admit that “*reported incidence*

numbers should be viewed cautiously". In his 2007 paper, Pogrel[26] states that he estimates that his study represents approximately 10% of all cases of nerve damage in the given population per year. However, reporting bias for patients referred to a specialist centre would be the same for both LA solutions.

The only study that included a detailed physical examination of the patient was that of Hillerup and Jensen[18] using a "standardised test of neurosensory functions" by a single operator to determine the presence and extent of any reported nerve damage.[31,32] The remaining included studies merely noted the incidence of "reported" nerve damage.

Pogrel's studies[20,26], using data from a specialist centre and Garisto and Gaffen's paper[27] all failed to accurately examine the patient, relying instead on the patient's own descriptions and a log of reported cases to AERS. Pogrel's description of the patient "examination" lacks sufficient detail to allow exclusion of detection bias.

The description of the reporting of an "electric shock" during the administration of the LA created notable discussion among the included authors. Four of the included papers noted the reporting of this phenomenon[17,18,27,28] and all included these reports in their results as a "nerve injury". The remaining 3 papers failed to mention this possible event.[19,20,26]

Interestingly, Hillerup and Jensen state that "*electric shock per se is probably of minor relevance for the aetiology of injection injuries*".[18] However, they then go on to question the cause of nerve injury, admitting that it is unknown as to whether the nerve is damaged via neurotoxicity or mechanically, via intra-fascicular injection.

Many authors are now advocating the use of 4% articaine in infiltration anaesthesia as an alternative to block anaesthesia due to the increased efficacy of this agent.[33,34,35,36] The evidence presented in these studies indicates a clear efficacy advantage when using 4% articaine as a buccal infiltration compared to 2% lidocaine in an IANB. One author has even suggested that the IANB may now be an unnecessary procedure.[37]

Concentration of the LA agent

Three of the chosen papers postulate that it may be the fact that, because articaine is administered in a 4% solution, it is the concentration of the LA solution rather than the actual pharmacology of the agent that causes damage to the nerve.[17,27,28] This suggestion would appear to be confirmed by another study on rat sciatic nerves, which concluded that significantly more neurotoxic injuries were observed following the direct injection into the nerve of a 4% articaine solution compared to that of a 2% solution.[38]

In a recent in-vitro study, articaine proved to be less neurotoxic than lidocaine, mepivacaine and prilocaine.[39] Indeed, previous studies have concluded that no scientific evidence exists to confirm the suggestion that articaine causes increased paraesthesia and, to date, no causal relationship has been exhibited between an anaesthetic agent's concentration and neurological damage.[40,41]

Implications for Clinical Research

This mini systematic review confirms that controversy still exists over the safety of 4% articaine and 1:100,000 adrenaline as a dental local anaesthetic agent.

The authors of all the included papers admit that, due to the extremely rare occurrence of the outcome, a carefully performed, high quality DBRCT would have to involve such vast numbers of participants that, logistically, such a study would pose certain problems.

It is generally accepted that 4% articaine exhibits greater lipid solubility, faster onset and increased duration of anaesthesia, more profound anaesthesia and reduced toxicity than those of its counterpart, 2% lidocaine. With these favourable attributes, 4% articaine does indeed offer superior properties over 2% lidocaine but would a 2% articaine solution offer the same advantages?

Further research is required into the efficacy and safety of a 2% articaine solution. Indeed, a study in 2006 proved that the 4% articaine solution was not superior in its anaesthetic effect compared to 2% and 3% solutions of the same agent.[42]

Implications for General Dental Practice

The highest level of evidence available to this study was that of Malamed and Gagnon's DBRCT in 2001.[19] Although spread over 27 sites in 2 countries, this trial unfortunately exhibited several potential areas of bias. It did, however, conclude that there was no evidence to suggest that 4% articaine posed a greater risk of nerve damage than 2%

lidocaine and that the use of 4% articaine in general dental practice can therefore be deemed safe and efficient.

3 further papers, not included in this study, also concluded that no conclusive evidence exists to suggest that 4% articaine poses a greater risk of nerve damage compared to other LA agents.[3,10,12]

Conclusion

This mini systematic review of the literature has highlighted the fact that further research is required to determine the relative risks of using 4% articaine compared to 2% lidocaine in IANB's.

Clearly, the use of 4% articaine is becoming increasingly popular as a means of achieving successful dental anaesthesia and, if current trends continue, this agent may become the number one anaesthetic of choice in the future. This steady increase in popularity is likely to be due to the proven efficacy of this LA agent, benefiting both the patient and the operator. Indeed, the incidence of inferior alveolar nerve damage may reduce in the future as more evidence emerges to support infiltration anaesthesia.

With this in mind and, considering the contradictory evidence presented in this study, it is suggested that, until factual evidence becomes available, dental practitioners should consider all the potential risks and benefits of a particular LA agent prior to its administration.

Declaration of Interests

The authors declare no conflicts of interest.

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Appendices

Glossary of Abbreviations

AERS: Adverse Event Reporting System

DBRCT: Double Blind Random Controlled Trial

IAN: Inferior Alveolar Nerve

IANB: Inferior Alveolar Nerve Block

LA: Local Anaesthetic

LN: Lingual Nerve

MeSH: Medical Sub Headings

MINORS: Methodological Index for Non-Randomised Studies

PICOS: Population, Intervention, Comparator, Outcome, Studies

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

SIGN: Scottish Intercollegiate Guidelines Network

UCSF: University of California, San Francisco

Tables

Level of Evidence	Description of Evidence
1++	High quality meta-analysis, systematic reviews of RCT's or very low risk of bias RCT's
1+	Well conducted meta-analysis, systematic reviews of RCT's or very low risk of bias RCT's
1-	Meta-analysis, systematic reviews of RCT's or RCT's with a high risk of bias
2++	High quality systematic reviews of cohort or case-control studies or high quality cohort or case-control studies with a very low risk of confounding bias or chance and a high probability that the relationship is causal
2+	Well conducted cohort or case-control studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Cohort or case-control studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies. Case reports and case series
4	Expert opinion

Table 1: The Hierarchy of Evidence. Adapted from the Scottish Intercollegiate Guidelines Network (SIGN).[43]

PICOS	Search Strategy Application
Population	Patients receiving IANB's with either 4% articaine hydrochloride + 1:100,000 adrenaline or patients receiving IANB's with 2% lidocaine + 1:100,000 adrenaline. Males and females. All ages
Intervention	Studies involving the administration of an IANB with 4% articaine + 1:100,000 adrenaline
Comparison	Studies involving the administration of an IANB with 2% lidocaine +1:100,000 adrenaline
Outcome	Post injection nerve damage indicated by prolonged temporary or permanent anaesthesia, paraesthesia or dysaesthesia in both the intervention and comparison groups.
Studies	Randomised controlled trials comparing 4% articaine + 1:100,000 adrenaline + 2% lidocaine + 1:100,000 adrenaline in IANB's. Cohort studies investigating the use of 4% articaine + 1:100,000 adrenaline as a dental local anaesthetic agent in IANB's.

Table 2: PICOS parameters applied to the study.

Inclusion Criteria	Reason for Inclusion
English language papers	No translation facility. Author only speaks English.
Papers published since 1976	Articaine's first use in clinical dentistry
Human subjects only	Relevant to general dental practice
Male and female subjects	Maximum number of participants
Global participation	Maximum number of participants
Subjects of all ages	Maximum number of participants
Articles involving IANB anaesthesia	Specific to study question
LA agents, lidocaine and articaine only	Specific to study question
Inferior alveolar and/or lingual nerve damage	Anatomical possibility of damage to either nerve during the administration of an IANB.
Permanent and/or temporary nerve damage	Both indicators of nerve damage
Suitable ethical approval obtained	Ethical and moral issues relating to research
Random Controlled Trials	Good quality evidence
Cohort Studies	Large number of subjects

Table 3: Search Inclusion Criteria

Exclusion Criteria	Reason for Exclusion
Articles describing only infiltration anaesthesia	Administration of a nerve block is postulated as a cause of nerve damage
Articles describing the use of anaesthetic agents other than articaine or lignocaine	Other anaesthetic agents not widely used in general dental practice
Studies investigating the use of articaine for “surgical dentistry”	Possible surgical cause of nerve damage
Studies investigating the use of articaine for removal of lower third molars and placement of mandibular implants	Both recognised causes of possible inferior alveolar and lingual nerve paraesthesia
“Sponsored” articles, unless a conflict of interest is declared	Author bias
Case studies	Poor quality evidence
Letters to editors	Personal opinions

Table 4: Search Exclusion Criteria

articaine, carticaine, septanest, ultracaine, septocaine, dental anaesthesia, lignocaine, lidocaine, xylocaine, paraesthesia, paresthesia, anaesthesia, anesthesia, dysaesthesia, dysesthesia, trigeminal nerve injuries, damage, injury, inferior alveolar nerve, inferior dental nerve, mandibular nerve, lingual nerve

Table 5. Basic Search Terms

Articaine, dental anaesthesia, nerve injury

Table 6. Medical Sub Headings Terms (MeSH Terms)

Search No.	Search Term
S1	(MM "Carticaine")
S2	septanest
S3	articaine
S4	ultracaine
S5	septocaine
S6	(MM "Anesthesia, Dental+")
S7	lignocaine
S8	lidocaine
S9	xylocaine
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S11	S7 OR S8 OR S9
S12	paraesthesia
S13	paresthesia
S14	anaesthesia
S15	anesthesia
S16	dysaesthesia
S17	dysesthesia
S18	(MM "Trigeminal Nerve Injuries+")
S19	damage
S20	injury
S21	inferior alveolar nerve
S22	inferior dental nerve
S23	mandibular nerve
S24	lingual nerve
S25	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S26	S21 OR S22 OR S23 OR S24
S27	S10 AND S11 AND S25 AND S26

Table 7: Search Strategy 18/11/16

Methodological Items for Non-Randomised Studies	Item Description
Clearly stated aim	Relevant and precise study question, relating to available literature
Inclusion of consecutive patients	All eligible participants included in study
Prospective collection of data	Data collected as per guidelines established prior to study commencement
Endpoints appropriate to study aim	Clear, quantifiable outcome addressing study question
Unbiased endpoint	Blind assessment of endpoint
Review period appropriate to aim	Review period sufficient to allow outcome occurrence and measurement
Attrition bias less than 5%	All patients should be reviewed
Prospective calculation of study size	Information regarding study population size necessary to achieve 95% confidence interval and level of statistical significance
Additional Items for use in Comparative Studies	**Item Description**
Suitable control	"Gold standard" as per available information
Contemporary groups	Groups studies during the same time period
Baseline equivalent groups	Group criteria similar at start point
Statistical analysis	Suitable statistics with confidence intervals or relative risk

Table 8: Methodology Index for Non Randomised Studies (MINORS).[25]

Item Score	Reason
0	Not reported
1	Reported but inadequate
2	Reported and adequate

Table 9. MINORS criteria scores.

Search No.	Search Term	Dentistry & Oral Science	Medline	Cochrane
S1	(MM "Carticaine")	2	303	3
S2	septanest	2	4	1
S3	articaine	216	398	3
S4	ultracaine	4	47	9
S5	septocaine	6	3	1
S6	(MM "Anesthesia, Dental+")	1,277	5,827	9
S7	lignocaine	332	2,405	11
S8	lidocaine	561	25,426	47
S9	xylocaine	306	713	1
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6	1,429	6,139	9
S11	S7 OR S8 OR S9	592	26,463	55
S12	paraesthesia	117	1,134	195
S13	paresthesia	31	7,415	50
S14	anaesthesia	6,591	65,803	1078
S15	anesthesia	6,591	200,202	334
S16	dysaesthesia	24	265	23
S17	dysesthesia	61	1278	13
S18	(MM "Trigeminal Nerve Injuries+")	84	833	13
S19	damage	3,284	433,750	2,568
S20	injury	9,260	549,161	2,570
S21	inferior alveolar nerve	1124	2,102	13
S22	inferior dental nerve	78	142	18
S23	mandibular nerve	568	3,556	36
S24	lingual nerve	269	1,298	18
S25	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	18,767	1,145,705	4,497
S26	S21 OR S22 OR S23 OR S24	1,492	5281	55
S27	S10 AND S11 AND S25 AND S26	36	170	2

Table 10. Search Strategy and Results (performed on 30-12-16)

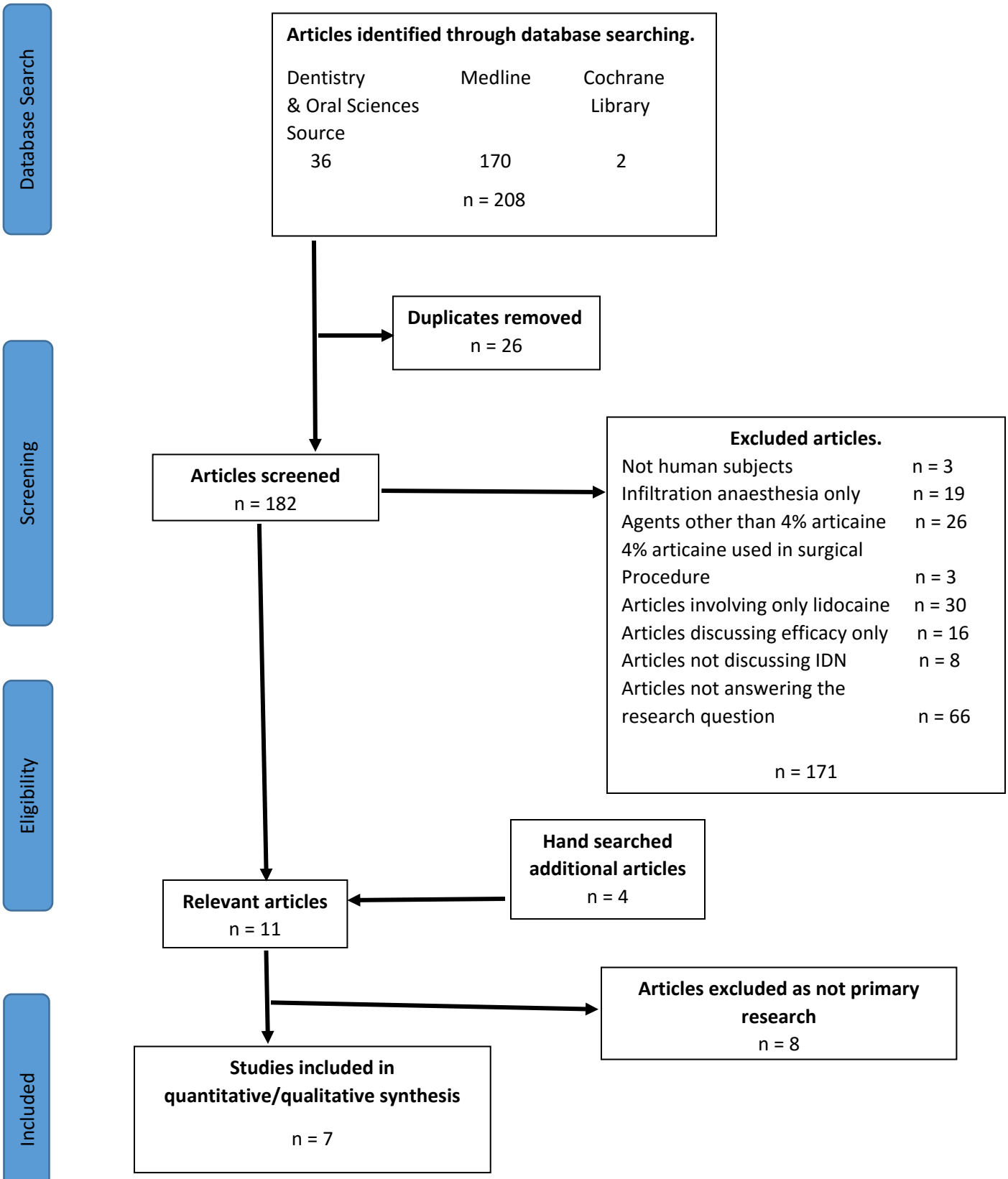

Table 11: PRISMA diagram indicating selection/inclusion process

Title and Author(s)	Year	"SIGN" Level of Evidence	Type of study
A 21 Year Retrospective Study Of Reports Of Paresthesia Following Local Anesthetic Administration. Hass and Lennon[17]	1995	2-	Retrospective Cohort
Retrospective Review Of Voluntary Reports Of Nonsurgical Paresthesia in Dentistry. Gaffen and Haas[28]	2009	2-	Retrospective Cohort
Nerve Injury Caused By Mandibular Block Analgesia. Hillerup and Jenson[18]	2006	2-	Retrospective Cohort
Permanent Nerve Damage From Inferior Alveolar Nerve Blocks – An Update to Include Articaine. Pogrel[26]	2007	2-	Retrospective Cohort
Articaine Hydrochloride: a study of the safety of a new amide local anesthetic. Malamed, Gagnon et al[19]	2001	1-	Random Controlled Trials
Occurrence of paresthesia after dental local anesthetic administration in the United States. Garisto, Gaffen et al[27]	2010	2-	Retrospective Cohort
Permanent Nerve Damage From Inferior Alveolar Nerve Blocks: A Current Update. Pogrel[20]	2012	2-	Retrospective Cohort

Table 12: Included Studies

Article(s)	Reason for Exclusion
Aguiar, Chebroux et al.[44] Hung, Chang et al.[45] Potocnik, Tomsic et al.[46] Sisk.[47] Baroni, Franz-Montan et al.[48] Batista, Berto et al.[49]	**Incorrect Population.** n = 6 Studies on rats and cats. Studies using Cow–Gates and Akinosi IANB. Studies of mental and incisive nerve blocks.
Chopra, Jindal et al.[50] Danielsson, Evers et al.[51] Rood.[52]	**Incorrect Intervention.** n = 48 Studies comparing Lidocaine, etidocaine and bupivacaine.
Rood.[52]	**Incorrect Comparator.** n = 1 5% lidocaine solution used in study.
Ahmad, Ravikumar et al.[53] Kambalimath, Dolas et al.[54] Moorthy, Stassen.[55] Choi, Seo et al.[56] Al-Sandook, Al-Saraj.[57]	**Incorrect Outcome.** n = 42 Studies measuring articaine's efficacy only. Studies detailing damage to nerves other than IAN and/or LN.
Choi, Seo et al.[56] Wyman.[58] Pedlar.[59]	**Incorrect Studies.** n = 8 Case reports and letters to editors.
Fowler, Reader.[60] Steinkruger, Nusstein et al.[61]	**Articles not answering study question.** n = 66 Studies comparing volume of anaesthetic agent and injection technique.

Table 13. Examples of excluded studies

Criteria	Haas & Lennon[17]	Gaffen & Haas[28]	Hillerup & Jenson[18]	Pogrel[26]	Malamed & Gagnon[19]	Garisto & Gaffen[27]	Pogrel[20]
Clearly stated aim	2	2	2	2	2	2	2
Inclusion of consecutive patients	1	2	2	2	1	2	2
Prospective collection of data	2	2	2	2	2	2	2
Endpoint appropriate to study	2	2	2	2	2	2	2
Unbiased assessment of endpoint	1	1	1	1	2	1	1
Appropriate follow up period	0	1	2	2	1	1	2
Loss to follow up less than 5%	1	0	0	0	0	0	0
Prospective calculation of study size	0	0	0	0	0	0	0
Adequate control group	NA	NA	NA	NA	2	NA	NA
Contemporary groups	NA	NA	NA	NA	2	NA	NA
Baseline equivalence groups	NA	NA	NA	NA	2	NA	NA
Adequate statistical analysis	NA	NA	NA	NA	1	NA	NA
Total Score	9	10	11	11	17	10	11

Table 14: MINORS Checklist for Included Studies

Bias	Malamed and Gagnon[19]
Random sequence generation (selection bias)	Low risk "*There were no statistically significant differences in the studies between the articaine and lidocaine treatment groups with respect to age, sex, weight, race distribution or the proportion of subjects undergoing simple or complex procedures*"
Allocation concealment (selection bias)	Unclear risk. Not mentioned in methodology
Blinding of outcome assessment (detection bias)	Unclear risk. "*Randomised, double-blind*…" mentioned in methodology but no other details
Participant awareness (performance bias)	Unclear risk. Not mentioned in methodology
Incomplete outcome data (attrition bias)	High risk. No mention of attrition at 24 hour and 7 day follow up interviews
Sponsorship (funding bias)	Low risk. "*The manufacturer of the drug products used in the three trials…..providing materials and funding*." The same company manufactures both the intervention and comparator drugs.
Selective reporting (reporting bias)	Unclear risk. "*The vast majority of these events are related by (telephone interviews with) patients and are alleged as opposed to confirmed*."
Overall risk of bias	Unclear risk.

Table15: Risk of Assessment Bias (adapted from Higgins, Altman et al.[24]).

Study	Haas & Lennon[17]	Gaffen & Haas[28]	Hillerup & Jensen[18]
Study publication date	April 1995	October 2009	May 2006
Study design	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort
Study objectives	Prolonged paraesthesia following LA in dentistry	Prolonged paraesthesia following LA in dentistry	Prolonged paraesthesia following LA in dentistry
Geographical origin	Ontario, Canada	Ontario, Canada	Denmark
Study setting	Not Stated	Not stated	"*All dental practitioners*"
Study funding	Not stated	"*no declared financial interests*"	Not Stated
Eligible study participants	143, male and female, all ages	172, male and female, 11-80 years	52, male and female, 24 – 81 years
LA agents used	Lidocaine, articaine, prilocaine, mepivacaine, bupivacaine	Lidocaine, articaine, prilocaine, mepivacaine, bupivacaine	Lidocaine, articaine, prilocaine, mepivacaine
Outcome reporting and recording	Voluntary reports to PLP	Voluntary reports to PLP	Telephone call to GDP. Type and volume of LA used. Electric shock experienced? Written questionnaires and patient interviews
Comparison made between "expected" and "observed" outcomes	Yes	Yes	No
Study period	21 years, 1973 - 1993	10 years, 1999 - 2008	8 years, 1997 – June 2004
Attrition bias	Not stated	Not stated	30 patients (58%) lost to follow up after 12 months
Data analysis of outcomes	Chi – square analysis	Chi – square analysis	Chi – square analysis
Ethical approval	Not stated	Stated Obtained	Not stated

Table 16a: Data Extraction

Study	Pogrel[26]	Malamed, Gagnon et al[19]	Garisto, Gaffen et al[27]	Pogrel[20]
Study publication date	April 2007	February 2001	July 2010	October 2012
Study design	Retrospective Cohort	3 Double Blind Random Controlled Trials	Retrospective Cohort	Retrospective Cohort
Study objectives	Prolonged IAN/LN paraesthesia following LA in dentistry	Direct comparison of efficacy and safety between 4% articaine and 2% lidocaine	Record incidence of nerve damage after LA in dentistry	Prolonged IAN/LN paraesthesia following LA in dentistry
Geographical origin	Maxillo Facial Dept, UCSF, USA	27 sites, 8 in the UK and 19 in the USA	USA	Maxillo Facial Dept, UCSF, USA
Study setting	Primary and secondary dental care	No stated	Voluntary reports to FDA's AERS	Primary and secondary dental care
Study funding	Not stated	"*Materials and funding*" provided by manufacturers of the LA agents	No "*disclosures*" reported by authors	Not stated
Eligible study participants	57, sex and ages not stated	1325, male and female, aged 4 – 80 years	226, male and female, 15 - 78 years	38, sex and ages not stated
LA agents used	Lidocaine, articaine, prilocaine, mepivacaine, bupivacaine	2% Lidocaine, 4% articaine,	Lidocaine, articaine, prilocaine, mepivacaine, bupivacaine	Lidocaine, articaine, prilocaine, carbocaine
Outcome reporting and recording	Examination of patient at UCSF. Details of examination not stated	Interviews and telephone calls to the patients. No further details of examination	Voluntary reports to FDA's AERS. Duration of paraesthesia noted	Examination of patient at UCSF. Details of examination not stated

Comparison made between “expected” and “observed” outcomes	Yes	No	Yes	Yes
Study period	3 years. 01/01/03 – 31/12/05	Not stated	11 years, November 1997 – August 2008	6 years, 01/01/06 – 31/12/11
Attrition bias	Not Stated	3 patients lost to follow up (0.23%)	Not stated	Not stated
Data analysis of outcomes	Narrative	Narrative	Descriptive statistical analysis	Narrative
Ethical approval	Not stated	Stated as obtained in UK and USA	Stated as obtained and approved by University of Toronto	Not stated

Table 16b: Data Extraction

Study	Design	Number of eligible participants with outcome*	Number of participants with outcome following intervention (articaine)	Number of participants with outcome following comparison (lidocaine)	Reported Outcomes
Haas & Lennon[17]	Retrospective Cohort	143*	50	5	Paraesthesia following the injection of LA in non-surgical dentsistry
Gaffen & Haas[28]	Retrospective Cohort	172*	109	23	Non-surgical paraesthesia
Hillerup & Jensen[18]	Retrospective Cohort	52*	29	10	Non-surgical IAN or LN injury following a unilateral IANB
Pogrel[26]	Retrospective Cohort	57*	17	20	Damage to IAN or LN following an IANB
Malamed, Gagnon et al[19]	Double Blind Random Controlled Trial	13	8	5	"*numbness or tingling 4 – 8 days after the procedure*"
Garisto, Gaffen et al[27]	Retrospective Cohort	226*	116	11	Oral paraesthesia following dental treatment
Pogrel[20]	Retrospective Cohort	38*	14	10	Damage to IAN or LN following an IANB

Table 17: Summary of Outcome Characteristics of Included Studies

***** In all the included studies except Malamed, Gagnon et al, agents other than articaine and lidocaine were also studied and included in the study results. The inclusion of prilocaine, mepivacaine, bupivacaine and carbocaine explains the discrepancy between the sum of the intervention (articaine) and comparison (lidocaine) participants and that of the number of eligible participants in each study.

Study	Haas & Lennon[17]	Gaffen & Haas[28]	Hillerup & Jensen[18]
Number of incidences of IAN damage with articaine	Not reported	Not reported	5
Number of incidences of LN damage with articaine	Not reported	Not reported	24
Number of incidences of IAN and/or LN damage with articaine	50 (33.6%)	109 (59.9%)	29 (54%)
Number of incidences of IAN damage with lidocaine	Not reported	Not reported	3
Number of incidences of LN damage with lidocaine	Not reported	Not reported	7
Number of incidences of IAN and/or LN damage with lidocaine	5 (3.4%)	23 (12.6%)	10 (19%)
Expected frequency of IAN and/or LN damage with articaine*****	5.3	26.5	Not reported
Observed frequency of IAN and/or LN damage with articaine	10	42	Not reported
Expected frequency of IAN and/or LN damage with lidocaine*****	3.7	23.8	Not reported
Observed frequency of IAN and/or LN damage with lidocaine	0	6	Not reported

Table 18a: Summary of Study Findings

Study	Pogrel[26]	Malamed, Gagnon et al[19]	Garisto, Gaffen et al[27]	Pogrel[20]
Number of incidences of IAN damage with articaine	Not reported	Not reported	Not reported	Not reported
Number of incidences of LN damage with articaine	Not reported	Not reported	Not reported	Not reported
Number of incidences of IAN and/or LN damage with articaine	17 (29.8%)	8 (1%)	116 (51.3%)	14 (37%)
Number of incidences of IAN damage with lidocaine	Not reported	Not reported	Not reported	Not reported
Number of incidences of LN damage with lidocaine	Not reported	Not reported	Not reported	Not reported
Number of incidences of IAN and/or LN damage with lidocaine	20 (35%)	5 (1%)	11 (4.9%)	10 (26%)
Expected frequency of IAN and/or LN damage with articaine*	Not reported	Not reported	32	Not reported
Observed frequency of IAN and/or LN damage with articaine	Not reported	Not reported	116	Not reported
Expected frequency of IAN and/or LN damage with lidocaine*	Not reported	Not reported	130	Not reported
Observed frequency of IAN and/or LN damage with lidocaine	Not reported	Not reported	10	Not reported

* Expected frequencies calculated using the “null hypothesis”.[29]

Table 18b: Summary of Study Findings