Efficacy of Local Anesthetics in Clinical Dentistry

A Systematic Review and Meta-analysis

By

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DEDICATION

To Carol, for all of the love, support, and understanding.

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LIST OF ABBREVIATIONS

EPT	Electronic Pulp Tester
VAS	Visual Analog Scale
PABA	Para-aminobenzoic Acid
TSL	Tooth Sensitivity Level
IP	Irreversible Pulpitis
IANB	Inferior Alveolar Nerve Block
GG	Gow Gates Technique
AK	Akinosi Technique
AMSA	Anterior Middle Superior Alveolar
PASA	Palatal Anterior Superior Alveolar
IO	Intra-osseous Technique
PDL	Periodontal Ligament Technique

Journal Abbreviations

JOE / J Endod	Journal of Endodontics
OOO / Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics
Quintessence	Quintessence International
Anesth Prog	Anesthesia Progress
Ped Dent	Pediatric Dentistry
J Dent Child	Journal of Dentistry for Children
Aus Dent J	Australian Dental Journal
JADA / J Amer Dent Assoc	Journal of the American Dental Association
IEJ / Int Endod J	International Endodontic Journal
Gen Dent	General Densistry
JOMS	Journal of Oral and Maxillofacial Surgery
J Clin Ped Dent	Journal of Clinical Pediatric Dentistry
Dent Traumatol	Dental Traumatology
J Col Dent A	Journal of the Colorado Dental Association
J Pain Symptom Manag	Journal of Pain and Symptom Management
Br Dent J	British Dental Journal
J Study Alc	Journal of Studies on Alcohol and Drugs
J Canadian Dent Assoc	Journal of the Canadian Dental Association
J Dent Res	Journal of Dental Research
Int J Oral Surg	International Journal of Oral Surgery

CHAPTER 1 - INTRODUCTION

Local anesthesia has been defined as a loss of sensation in an area of the body caused by a depression of excitation in nerve endings or an inhibition of the conduction process in peripheral nerves (Covino & Vassallo 1976). Local anesthetic solutions have been utilized in clinical dentistry to alleviate or eliminate pain associated with invasive procedures as early as the 19th century (Malamed 2004). An important requirement prior to initiating endodontic or operative dental treatment is the ability to achieve and maintain profound anesthesia. Local anesthetics are correctly considered to be the most important drugs used in clinical dentistry. Unlike the majority of other anesthetic drugs, which act as central nervous system depressants, local anesthetics prevent nociceptive impulses from reaching the central nervous system by blocking the progress of an action potential. A local anesthetic binds to sodium channel receptors on the axonal membrane, the permeability to sodium ions is lost and nerve conduction is interrupted (Malamed 2004).

Dentists currently have a variety of anesthetic solutions at their disposal, with the major difference being their expected duration of clinical anesthesia (**Table 1.1**). Although these solutions are considered to be generally effective in providing a pain free oral environment for dental treatment, local anesthetic failure remains a common problem in certain instances. Clinicians have constantly sought an anesthetic solution that may improve success rates that have been demonstrated to be well below one-hundred percent, particularly in

the posterior mandible (Robertson et al. 2007, Claffey et al. 2004, P. Mikesell et al. 2005, Donaldson et al. 1987).

DURATION	SOLUTION	TRADE NAME	Infiltration (pulpal)	Nerve Block (pulpal)	Soft tissue duration	Mgs per cartridge
Short Duration- Plain	Lidocaine HCl 2%	Xylocaine	5 m	Not indicated	2 h	36
	Mepivacaine HCl 3%	Carbocaine, Isocaine, Polocaine, Scandanest	20-30 m	45-65 m	2-3 h	54
	Prilocaine HCl 4%	Citanest Plain	10-15 m	45-65 m	3-4 h	72
Normal Duration- with vasoconstrictor	Articaine HCl 4% w/ epi 1:100,000	Septocaine, Articadent, Zorcaine	60-75 m	Up to 120 m	3-5 h	68
	Articaine HCl 4% w/ epi 1:200,000	Septocaine, Articadent	60 -75m	Up to 120 m	3-5 h	68
	Lidocaine HCl 2% w/ epi 1:50,000	Lidocaine, Xylocaine, Lignospan Standard, Octocaine 50	55-65 m	80-90 m	3-5 h	36
	Lidocaine HCl 2% w/ epi 1:100,000	Lidocaine, Xylocaine, Lignospan Standard, Octocaine 100	55-65 m	80-90 m	3-5 h	36
	Mepivicaine HCl 2% w/ levo 1:20,000	Carbocaine, Isocaine 2%, Polocaine, Scandanest 2%	40-60 m	60-90 m	3-5 h	36
	Prilocaine HCl 4% w/ wpi 1:200,000	Citanest Forte	35-45 m	50-70 m	3-6 h	72
Long Duration	Bupivacaine HCl 0.5% w/ epi 1:200,000	Marcaine, Vivacaine, Bupivacaine	Up to 7 h	Up to 7 h	Up to 12 h	9

epi = epinephrine, levo = levonordefrin

TABLE 1.1. AVAILABLE LOCAL ANESTHETIC SOLUTIONS FOR USE IN CLINICAL DENTISTRY

In the U.S., lidocaine has been the most widely used anesthetic solution for sometime (Malamed et al. 2000). Since it became clinically available in 1948 it has been associated with efficacy and a low incidence of side effects (Malamed 2004). These attributes have been confirmed through clinical use and research making it the "gold standard" to which all new local anesthetic solutions are compared (Malamed 2004). The recent U.S. Food and Drug Administration approval of articaine (NDA # 20-971) and the possibility that it will provide increased efficacy has already caused this drug to be a popular choice in place of lidocaine among clinicians especially endodontists who commonly treat inflamed teeth. This solution made up approximately 25% of total sales of dental anesthetics in the U.S. in 2007, second only to lidocaine at 54% (Pogrel 2007).

Articaine was approved by the FDA for use in the U.S. in April 2000 but has been available in Germany and other European nations since 1969, and is currently the most widely used solution there (Malamed et al. 2000). In the U.S. the formulation is marketed under the trade names Septocaine™ (Septodont, France) and Articadent™ (Novocol Pharmaceutical of Canada, Inc) and is available as a 4% solution with 1:100,000 or 1:200,000 epinephrine. Articaine contains a thiophene ring instead of a benzene ring found in lidocaine and other amide local anesthetics, which allows the molecule to diffuse more readily through the nerve membrane due to increased lipid solubility. A second molecular difference is the extra ester linkage incorporated into the articaine molecule which results in hydrolysis of articaine by plasma esterases. Ninety to ninety-five percent of articaine is metabolized by plasma esterases, with the remainder being broken down in the liver (Oertel et al. 1997). The solution's plasma half-life can be as low as 20 minutes (Oertel et al. 1997). Articaine is

excreted mainly by the kidneys. From an epidural dose 2 to 5% is excreted unchanged; 40 to 70% is excreted as articainic acid and 4 to 15 % as articainic acid glucuronide (Vree et al. 1988).

The recommended maximum dose of articaine is 500 mg similar to that advised for lidocaine (Malamed 2004). Adverse reactions to articaine are characteristic of those associated with other amide-type anesthetics (Malamed et al. 2000). For a healthy adult weighing 70 kg, this maximum dose equates to seven 1.8 mL carpules of 4% articaine, or 13 of 2% lidocaine (Oertel et al. 1997). As with other amide local anesthetics, articaine is capable of producing methemoglobinemia. However, this has thus far been observed only with epidural anesthesia (Vree et al. 1988).

Anesthetic Efficacy:

The success of mandibular block anesthesia has traditionally been determined by the presence of a feeling of “lip numbness” (Malamed 2004). It was thought that if soft tissue anesthesia was present, indicated by a lack of mucosal responsiveness to a sharp instrument, pulpal anesthesia would also be adequate. However, a number of studies have now clarified that successful pulpal anesthesia is not guaranteed when signs of soft tissue anesthesia are present (Hannan et al. 1999, Certosimo & Archer 1996). An investigation utilizing ultrasound to accurately locate the inferior alveolar neurovascular bundle found success rates ranged from 38% to 92%, although every patient did experience subjective lip anesthesia (Hannan et al. 1999).

Due to the unreliability of correlating soft tissue anesthesia with true pulpal anesthesia, a more objective method of measurement would be preferred. The electric pulp tester (EPT) has long been used to evaluate the sensibility of the dental pulp (Cooley et al. 1984). This device stimulates A-delta fibers, normally indicating neural transmission and presence of innervation (Närhi et al. 1979). An EPT reading of "80" on the device most commonly used (Analytic Technologies Corp, Redmond, WA) indicates profound pulpal anesthesia (Dreven et al. 1987, Certosimo & Archer 1996). EPT readings of less than 80 have been correlated with pain during operative procedures in asymptomatic teeth (Certosimo & Archer 1996). Currently, most investigations interested in determining pulpal anesthesia utilize the EPT method. Successful anesthesia is commonly defined as the percentage of subjects who achieve two consecutive "80" readings on the EPT within 15 minutes of anesthesia administration, and continuously sustain this lack of responsiveness for some defined period (Evans et al. 2008, Corbett et al. 2008). These criteria help remove some of the subjectivity in assessing pulpal anesthesia, although the evaluation still relies on a patient's response. The behavior of the patient and the responses given by control teeth also should require careful consideration (Lin & Chandler 2008). Using the EPT as a more objective means of determining pulpal anesthesia has been useful in improving the clarity of research outcomes in the area of local anesthesia in dentistry.

Evaluating the efficacy of local anesthetics is more uncertain in symptomatic teeth. Effectively anesthetizing a tooth that contains an acutely inflamed pulp is often difficult. Success rates for traditional anesthesia methods drop to unacceptable levels (Claffey et al. 2004, Srinivasan et al. 2009). Using

the EPT to determine the efficacy of pulpal anesthesia is unreliable. The absence of a response to EPT may not guarantee profound pulpal anesthesia (Dreven et al. 1987, Hsiao-Wu et al. 2007). Several explanations for the failure of anesthetic solutions in such patients are present in the literature. Nerves in inflamed tissues have reduced excitability thresholds (Byers et al. 1990). It has also been noted that certain classes of sodium channels are resistant to the action of local anesthetics. A class of tetrodotoxin-resistant sodium channels (Na v 1.8 and 1.9) have been shown to be resistant to the measures of local anesthetics (Roy & Narahashi 1992). These channels are up-regulated during inflammation, and are thought to contribute to instances of orofacial hyperalgesia (Morgan & Gebhart 2008). Additionally, pulps that have been diagnosed with irreversible pulpitis may have an increased expression of sodium channels (Malamed 2004). These findings help explain why dental patients who present with pain from pulpal disease may have be difficult to anesthetize.

Clinical studies of various designs have investigated the efficacy of local anesthetic solutions in clinical dentistry. The conclusions of several recent clinical studies suggest that articaine may be more effective than lidocaine. One prospective, randomized, double-blind study reported that the use of 4% articaine with 1:100,000 epinephrine resulted in a higher success rate and faster onset of anesthesia than 2% lidocaine with 1:100,000 epinephrine (Robertson et al. 2007). A similar study supported articaine's superiority to lidocaine when used in a buccal infiltration technique (Kanaa, et al. 2006).

Other clinical evidence has indicated that articaine may *not* outperform lidocaine. Controlled comparisons of mandibular block anesthesia have failed to show any difference between articaine and lidocaine solutions. Unacceptable rates of success for both articaine and lidocaine when used for mandibular block

injections have been demonstrated for patients who had been diagnosed with irreversible pulpitis (24 and 23 % success rates, respectively) (Claffey et al. 2004). Other studies have also concluded that there were no significant differences between articaine and lidocaine solutions when used for inferior alveolar nerve blocks (P. Mikesell et al. 2005). The lack of consensus can be reached in regard to the clinical efficacy of articaine anesthetic solutions supports the need for a thorough review of available clinical data, and the formulation of recommendations regarding the appropriate use of local anesthetics in clinical dentistry.

Maxillary infiltration has a higher rate of success than mandibular anesthesia. Using a volume of 3.6 mL or less and various anesthetic formulations, pulpal anesthetic success has ranged from 64% to 100% for maxillary infiltrations (Vähätalo et al. 1993, Donaldson et al. 1987, Costa et al. 2005).

When focusing on the maxilla, clinical trials have repeatedly failed to show that articaine is superior to lidocaine or prilocaine in obtaining pulpal anesthesia with a maxillary infiltration (Donaldson et al. 1987, Vähätalo et al. 1993). Yet other studies contradict these findings. It has been reported that the use of articaine resulted in a longer duration of anesthesia in maxillary infiltrations than lidocaine (Costa et al. 2005). To add to the ambiguity one randomized, double-blind clinical study demonstrated a higher rate anesthetic success for articaine when compared with lidocaine in maxillary infiltration of the lateral incisor, but not the first molar (Evans et al. 2008). This lack of a clear conclusion provides a strong rationale for conducting a systematic review.of the available literature.

Clinicians' conclusions regarding their preference of local anesthetics are also influenced by lower levels of evidence, such as expert opinions. Malamed, a well-known scientist who routinely lectures on the topic of local anesthesia in dentistry, submitted the first articaine study originating in the U.S. to the Journal of the American Dental Association in 2000. This report stated that the newly FDA approved solution of articaine would provide improved local anesthetic activity (Malamed et al. 2000). The study reported superior qualities including more success in achieving anesthesia, the ability to achieve more rapid and profound anesthesia, the success of buccal infiltration in the maxilla to achieve palatal anesthesia, and the success of mandibular infiltration to replace inferior alveolar block anesthesia (Malamed et al. 2000).

Other opinions have contributed to a belief in the superior efficacy of articaine. In a 2001 a report from Clinical Research Associates, a majority of 94 dentist surveyed stated that articaine's effects were more profound than other routinely used anesthetic solutions (Christensen 2001). Many clinicians who have adopted the use of articaine agreed that its use seemed to offer an increased profoundness of anesthesia compared to other solutions. However, the evidence associated with this survey is merely anecdotal.

Anesthetic Safety:

The use of local anesthetics in dentistry has historically been accompanied by a very low risk of complications, although current evidence suggests that with some specific solutions the risk may be increased. Several retrospective studies state that the fear of increased risk of paresthesia with articaine is warranted. In an investigation of 52 incidences of paresthesia in

Denmark, Hillerup and Jensen reported that 54% of the nerve injuries were associated with the use of articaine (Hillerup & Jensen 2006). The authors concluded that "during the two-year period mentioned, articaine produced a more than 20-fold higher incidence of injection injury when applied for mandibular block anesthesia". A retrospective analysis of paresthesia after local anesthetic administration for non-surgical dental procedures over a 20 year period also revealed a higher than expected frequency of paresthesia with articaine (Haas & Lennon 1995). An even more recent retrospective review of reported paresthesias from 1999 to 2008 reported that higher concentration solutions such as articaine were associated with significantly greater frequencies of such complications (Gaffen & Haas 2009).

Contradictory data suggest that articaine is just as safe as other anesthetic solutions. Malamed stated that "there is absolutely no scientific evidence available to support the claim that articaine is associated with a greater incidence of paresthesia than other local anesthetics" (Malamed 2007). Additionally, Clinical Research Associates released two reports of paresthesia in 13,000 patient treatments with articaine (Christensen 2001). A review of Septodont's FDA application indicated that there were 21 paresthesias in 882 patient treatments (2.4%), a frequency similar to that reported for lidocaine. A 2007 study by Pogrel reported that lidocaine was used in 35% of cases in which there was permanent nerve injury and articaine in 30% of the cases (Pogrel 2007).

The belief among practitioners that articaine has improved efficacy when compared with other solutions has reached a near consensus level (Overman 2007). The concern over an increased risk of paresthesia with the use of

articaine for mandibular block anesthesia is nearly as common (Wynn et al. 2003, Dower 2003).

There is still a very active dialogue among dentists regarding articaine's safety, which can be seen on web-based discussion forums such as www.dentaltown.com, and in frequent letters to the journals of numerous local and national dental associations (Malamed 2007, Dower 2007). Searching for the word "paresthesia" on Dentaltown's online message board results in 544 original discussion forums on the topic (www.towniecentral.com/MessageBoard/Search). Empirical evidence indicates that some local anesthetics including articaine, have a significantly higher rate of paresthesia associated with their use than others. A February 2003 issue of *Dentistry Today* contained an article that recommended that articaine not be used for mandibular block anesthesia, and that informed consent should be obtained if articaine is to be used for such injections (Dower 2003).

Allergenicity is also a concern with local anesthetic solution in dentistry. Historically, the most common ester-type anesthetics such as novocaine and procaine have been removed from the U.S. market because of occurrences of allergic reactions. Local anesthetic solutions defined as 'esters' are derivatives of para-aminobenzoic acid (PABA), and hydrolysis liberates a moiety that may be immunogenic (Becker & Reed 2006). Articaine and lidocaine are classified as amide local anesthetics because of the linkage between their lipid-soluble rings and terminal amines. However, concern with the presence of PABA-related compounds in articaine local anesthetic solutions caused scrutiny by the FDA. Only after the U.S. composition was altered to not contain PABA-related compounds was articaine approved for therapeutic use in the U.S, despite its availability in Europe and Canada.

Evidence-Based Research:

With such apparently divergent data on the safety and efficacy of using articaine as a local anesthetic solution it is not surprising that a wide range of opinions exists among dentists regarding the appropriateness of its use in clinical practice. Evidence-based practice seeks to assess the quality of evidence relevant to the risks and benefits of treatments. The Centre for Evidence-Based Medicine defines “evidence-based medicine” as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett et al. 1996). In instances where the level of evidence supporting the use of a therapy appears unclear, techniques such as a systematic review of the literature should be applied to better clarify recommendations for clinical practice.

Systematic reviews can condense many studies into valid and unbiased summaries of the best available evidence for a specific clinical problem (Carr 2002). This type of overview should benefit clinicians who have difficulty staying current as the literature greatly expands. Systematic reviews of the existing literature can provide an objective summary of the best available evidence that can help dentists and their patients make informed choices (Needleman 2002). By using explicit and transparent methods to perform a thorough literature search, systematic reviews are inherently less biased, more reliable, and more valid than narrative reviews (Carr 2002). During the past 14 years, clinically relevant systematic reviews have been published with increasing frequency (Bader & Ismail 2004). As the number of systematic reviews continues to grow,

dentistry will become better informed about the foundation of scientific evidence that directs evidence-based clinical practice (Bader & Ismail 2004).

Systematic reviews do however have some limitations. The quality of the underlying studies, the consistency of results across studies and the precision of the pooled data can considerably affect the strength of inference obtained (Torabinejad & Bahjri 2005). Clinical practitioners need to recognize these inherent limitations, understand the results, and apply them judiciously to patient care.

A systematic review may be even more valuable when partnered with a meta-analysis of the collected data. Meta-analysis is the statistical pooling of data across studies to generate pooled estimates of effects (Manchikanti et al. 2009). Benefits of meta-analysis include the ability to improve the power of small studies to answer questions, and can also help detect biases and deficiencies in the design, analysis, and interpretation of research (Ioannidis 2008). These methods can highlight needed improvements in the quality of the data needed for optimal evidence-based clinical practice. In this way, meta-analysis can be a useful tool in planning new clinical trial in areas where the evidence is sparse.

Because of the rather contradictory data regarding both the efficacy and safety of using articaine for local anesthesia, the **objective** of the present review is to evaluate the available information and provide reliable evidence regarding the use of articaine in the context of current local anesthetic solutions used in dentistry. All clinical trials regarding the use of local anesthetics in dentistry that meet the developed inclusion criteria will be analyzed. Clinical recommendations on the use of the various formulations will also be generated.

Specific Aims:

(1) To systematically review available evidence on the efficacy of local anesthetic solutions used for local anesthesia in clinical dentistry.

(2) To compare the outcomes, benefits, and harms of using the available anesthetic solutions to provide pulpal anesthesia required for dental treatment.

(3) To statistically analyze available data via meta-analytic approaches to determine the odds ratios of achieving anesthetic success of articaine versus lidocaine.

CHAPTER 2 - OVERVIEW OF EXISTING LITERATURE

As previously mentioned, there has been no clear consensus on which local anesthetic solutions should be expected to provide the highest rate of success. Numerous publications have discussed topics regarding local anesthesia in clinical dentistry. In searching the Medline database for the previous twenty years, a total of 65 review articles are present that cover such subject matter. However, only one article adhered to the methods of a systematic review. This study investigated the effects of epinephrine in combination with local anesthetic solutions on dental patients that were previously diagnosed with hypertension (Bader et al. 2002). Another focused literature search aimed to compare the anesthetic efficacy of articaine and lidocaine, although it cannot be defined as a systematic review (Wells & Beckett 2008). The remainder of the review papers could potentially contain bias, and must be classified as expert opinions, or a Level 5 source of evidence according to Sackett and colleagues (Sackett et al. 1996).

Five of the reviews describe the use of local anesthetic solutions for the purpose of anesthesia during surgical procedures (Krohner 2003), including considerations for patients that are pregnant (Crowley 2007), obese (Todd 2005), children (Meechan & Welbury 1993), and those undergoing orthognathic surgery (Weaver 1992). Four articles cover topics that could be classified under the discipline of periodontics (Wilson et al. 2008, Kumar & Leblebicioglu 2007) Overman 2007, Higgins 1999). An additional four reviews discuss local

anesthetic use in pediatric populations (Ram & Peretz 2002, Saxen et al. 1999) Giovannitti 1995, Cheatham & Primosch 1991), and two specifically cover anesthetic considerations for patients in need of endodontic treatment (Saxen & C. W. Newton 1999, Haas 1997).

Topical anesthetic compounds are exclusively described in two publications (Kravitz 2007, Meechan 2002) and one reviews the basic biology and pharmacology of local anesthetic solutions (Subramaniam & Tennant 2005). The possibility of adverse events and complications following the administration of local anesthetics in dentistry are detailed in a total of seven articles (Haas 2006, Smith & Lung 2006, Finder & Moore 2002, Chen 1998, Haas 1998, Meechan & Rood 1997, Dower 2003). Various techniques and anatomical considerations are described in eleven publications (Dower & Barniv 2004, Blanton & Roda 1995, Blanton & Jeske 2003, Meechan 2002, McKissock & Meyer 2000, R Brown 1999, Kretzschmar & Peters 1997, Yap & Ong 1996, van der Bijl 1995, Gross 1991, Donkor et al. 1990). The remaining twenty-nine papers discuss various general matters of local anesthetic use in clinical dentistry (Jeske & Blanton 2006, Brown & Rhodus 2005, Ramacciato & Meechan 2005, Yagiela 2004, Blanton & Jeske 2003, Budenz 2003, Blanton & Jeske 2003, Hawkins & Moore 2002, Haas 2002, Wong 2001, Friedman 2000, Meechan 2000, Potocnik & Bajrović 1999, Leyman et al. 1999, Estafan 1998, Blanton & Jeske 2003, Brown 1994, Blanton & Jeske 2003, Blanton & Roda 1995, Roda & Blanton 1994, Malamed 1993, Hersh 1993, Anderson & Reagan 1993, Sisk 1992, MacKenzie & Young 1993, Ayoub & Coleman 1992, Malamed et al. 1992, Sisk 1992, Yagiela 1991, Moore 1990).

CONCLUSION:

No previous publication has systematically reviewed the existing literature to summarize the current best evidence regarding the success rates of local anesthetic solutions in dentistry.

CHAPTER 3 - SYSTEMATIC REVIEW METHODS

PICO Framework

The PICO (Patient Population, Intervention, Comparison, and Outcomes) process is a technique used in evidence-based medicine to frame and answer a clinical question. It has been stated that a trend towards higher precision of search results when a PICO template was used, thus improving the relevancy of search results (Schardt et al. 2007).

Defining the Scope of the Question

The questions addressed by a systematic review may be both broad or narrow in scope, both of which have advantages and disadvantages. Adopting a broad scope may allow for a more comprehensive summary of the evidence, provide the ability to assess generalizability of findings across different implementations of the intervention or types of participants. However, searching, data collection, analysis, and writing may require more resources, and interpretation may be difficult if a high degree of heterogeneity is present. A narrow scope has the advantage of manageability for the review team and improved clarity of objections, although evidence may be sparse and findings may not be generalizable.

In practice, a systematic review may start with a broad scope, and be divided up into narrower reviews as evidence accumulates and the originally review

becomes unwieldy. This investigation took this approach, as the original question hoped to achieve a broad point of comparison among all local anesthetic solution. As evidence was gathered and a high level of heterogeneity identified, a more narrow focus was adopted for practical and logistical reasons.

In this investigation, the original research question was of a broad scope. The *Population* under consideration being all patients receiving dental treatments in a clinical setting. The *Intervention* included all types of local anesthetic solutions approved for dental therapeutic use. The *Outcome* was the achievement of profound anesthesia of the dental pulp. As the question was narrowed, the addition of the *Comparison* component of the PICO question specifically aimed to compare the anesthetic success associated with lidocaine versus articaine (**Table 3.1**). Data identified from the focus of this narrow based question were the basis for the meta-analysis.

Criteria	Definition
Population Characteristics	Ages were confined to adult patients (age > 18 years. Treatment-based trials were limited to procedures impacting pulpal tissues, such as endodontic therapy, dental restorations, and prosthetic tooth preparation. Treatments potentially affecting periodontal, oral mucosal, or osseous tissues were excluded, including periodontal treatments, extraction of teeth, and implant procedures. Trials in medically compromised patients were excluded.
Intervention Characteristics	Studies included trials involving maxillary and mandibular infiltration and block anesthesia. Trials evaluating supplemental anesthetic techniques such as intraosseous, intraligamentary, or intrapulpal routes were excluded.
Comparison Characteristics	Studies that directly compared similar doses of local anesthetic solutions of articaine hydrochloride and lidocaine hydrochloride, combined with epinephrine as a vasoconstrictor, were included. If vasoconstrictor was not used in combination with the respective local anesthetic formulations, the associated trial was excluded.

Outcome Characteristic	Included trials reported outcome measures as below: anesthesia success defined as none or mild pain measured using standard or modified VAS during clinical instrumentation or measured by no response by the tooth to maximal stimulation (80 μA) on two or more consecutive tests with EPT.

Table 3.1 – Criteria for selecting studies in the meta-analysis

Final Question Format

The PICO framework was used to formulate the following questions for a systematic review of the existing literature:

- *BROAD SCOPE*: In patients receiving dental treatments, which local anesthetic solution provides the highest percentage of successful anesthesia for various clinical situations?
- *NARROW SCOPE*: In adult patients receiving operative or endodontic treatments, does using an articaine solution for local anesthesia compared to lidocaine provide superior pulpal anesthetic efficacy?

Defining Inclusion/Exclusion Criteria

Studies were considered relevant to this analysis if they included specific defined characteristics. Initially, the broad scope question was employed to focus the literature searching process. The following characteristics were considered during the study selection process:

Population - Included trials were limited to human, adult subjects. An initial review of the methodologies of trials involving pediatric poplulations revealed a wide variety of outcome measurement devices that made analysis impractical (**Table 3.2**). Comparison of these outcomes to those of trials utilizing the EPT or

VAS protocols was not possible; thus studies solely involving children and adolescents were excluded.

TABLE 3.2

LOCAL ANESTHETIC TRIALS WITH A PEDIATRIC POPULATION:

Author, Year	Publication	Methods	Subjects	Evaluation Scale	Conclusions
73- Ashkenazi, 2006	Pediatric Dentistry	Compared infiltrative and intrasulcular (computer delivered) methods for 1° max molars.	N=178	Face picture scale; CHEOPS	No ss diff in anesthetic effectiveness or associated pain of injection.
81- Klein, 2005	J Dent Child	Compared standard infiltrations to a P-ASA block (computer delivered).	N=21	ADBC behavior code	No ss diff in quality of anesthesia between the 2 groups.
83- Ashkenazi, 2005	J Am Dent Assoc	Evaluated a computerized delivery system for intrasulcular anesthesia in 1° molars.	N=193	Face picture scale; CHEOPS	CDS-IS is effective for anesthetizing 1° molars.
87- Oztas, 2005	Quintessence	Compared IAN with a traditional syringe to PDL injection with a computerized device (WAND).	N=25	Eland color scale	Pain scores during treatment were sig higher for the WAND.
111- Naidu, 2004	Anesth Prog	To compore dental pain control of infiltration/intrapapillary injection to the IAN/LB block in children.	N=101	Color Analog Scale	No ss diff in pain control effectiveness between the 2 methods.
162- Munshi, 2001	J Clin Ped Dent	To evaluate efficacy of anesthesia and pt preference using the needle-less jet syringe.	N=100	Faces pain scale; Lickert scale	This method was completely successful, and there was a ss diff in preference toward the instrument.
167- Munshi, 2000	J Clin Ped Dent	To evaluate the effectiveness of electronic dental anesthesia in dental procedures for pediatric patients.	N=40	Eland color scale; Lickert scale	Administration of EDA was perceived to be significantly comfortable by both the clinician and patients, and was perceived to be clinically effective.
175- Nakai, 2000	J Amer Dent Assoc	The authors observed patients in 17 pediatric dental practices and described characteristis and factors related to effectiveness.	N=361	Sounds, Eyes, and motor scale; Frankl	The data suggest that painful treatment is relatively frequent, with 82% of providers having instances of ineffective pain control.
219- Sharaf, 1997	J Dent Child	To compare the effectiveness of mand infiltration and mandibular block anesthesia for dental procedures in pediatric pts.	N=80	Sounds, eyes, and motor scale	Infiltration anesthesia was effective in providing good anesthesia, although not for pulp treatment of mand 2nd 1° molars.
238- Oulis, 1996	Pediatric Dent	To compare the effectiveness of mand infiltration to mandibular block anesthesia in children.	N=89	Frankl Behavior Rating Scale	Infiltration was less effective than block for pulpotomy and extraction.

Timeline - To keep the investigation relevant to contemporary solutions and administration techniques trials published before1970 were excluded. This allowed for a near 40-year range of data for a comprehensive summary of the topic.

Language - The initial group of included studies was limited to those published in the English language. Throughout the study identification and selection process, it was identified that publications in English directly comparing articaine and lidocaine were sparse, likely because the delay in FDA approval of

articaine for use within the U.S. Thus, for the meta-analysis portion, the language limitation was removed, and publications in all languages were included for inclusion.

Study Characteristics - Included studies within this review were limited to randomized controlled trials (RCTs). Quality of randomization and appropriateness of experimental controls were discussed among the research team, and studies were defined as RCTs when consensus was reached.

Assessments of Anesthetic Success - Publications were included in they defined anesthetic success as "none" or "mild" pain measured using a standard or modified VAS during clinical instrumentation. If there was no instrumentation, success was measured by no response by the tooth to maximal stimulation with EPT or Bofors Pulp Tester.

Study Selection Process

Literature Search

The Medical Subject Heading (MeSH) database, the National Library of Medicine's controlled vocabulary indexing system, was used to search terms that would be related to this study. The principle areas of interest were the location of dental articles, those concerned with the discipline of endodontics, and publications detailing the anesthetic solutions of interest. An example of MeSh terms that were utilized in this investigation and the number of identified publications is illustrated in **Figure 3.1**.

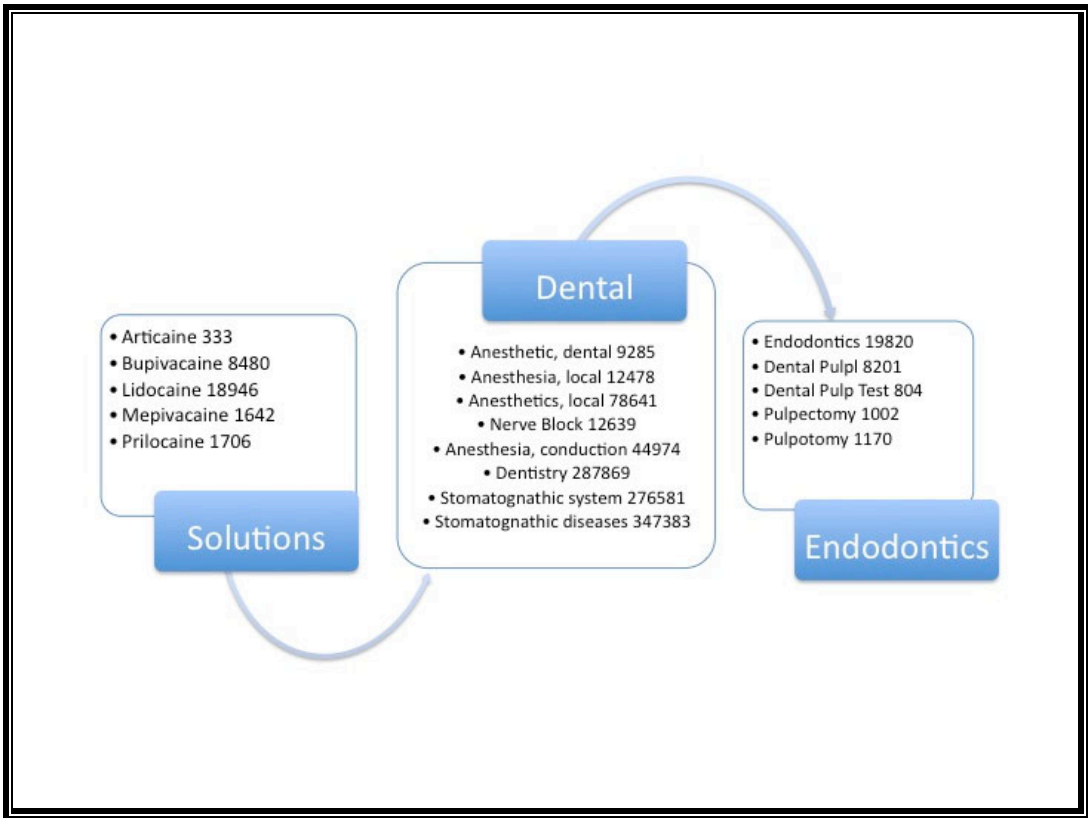


FIGURE 3.1 MeSH terms identified for search strategy

To identify publications that included the variety of local anesthetic solutions commonly used in clinical dentistry, all potential names and labels of each solution was recognized (**Appendix III**).

Multiple electronic databases were used to locate and recover publications relevant to this investigation (**Appendix IV**). Using PubMed, the National Library of Medicine's text-based search and retrieval system for biomedical literature, a search through June 2009 was executed. A similar search strategy was used for Embase (Excerpta Medica Database, Elsevier).

To validate the focus of each search strategy, five known articles of interest were confirmed to be contained within the results of each database search. These seminal articles were as follows:

Evans et al. 2008, Robertson et al. 2007, Kanaa et al. 2006, Nusstein et al. 2005, Claffey et al. 2004

Both the MEDLINE and Embase search strategies contained all five seminal articles, and their focus was deemed appropriate for this investigation.

Hand-Searching

In addition to publications located by this electronic search strategy attempts to enrich the available references were made. Hand searches were made by reviewing the reference lists of relevant articles and clinical trials and the tables of content of the journals containing most of the included studies for the last two years.

A total of 32 individual journals produced the 119 articles that were selected for full-text appraisal. It was calculated that 80% of these articles were contained in the following list of publications:

1. *Journal of Endodontics*
2. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*
3. *Anesthesia Progress*
4. *Journal of the American Dental Association*
5. *International Endodontic Journal*
6. *Dental Traumatology*
7. *Quintessence International*

The tables of content of these seven journals was reviewed for a period of two years. No additional trials were located that could potentially contribute data to this review.

Recommendations of experts in the field of local anesthesia in dentistry were considered. Articles were suggested by Prof. A. H. Jeske DMD, Department of Restorative Dentistry and Biomaterials, University of Texas Dental Branch–Houston. Dr. Jeske is noted as a prolific writer on the topic of pain

control in dentistry, including local anesthesia, and has authored or co-authored a total of sixty articles. Additionally, studies for consideration were offered in conversations with Professor A. Reader DDS MS, director of the Ohio State University's Advanced Endodontics Program, who has published more than fifty trials on the topic of local anesthesia in dentistry throughout the past decade. All expert recommendations were included within the results of the original database searches, which also served to validate focus of the search strategies.

Selection Procedures

Electronic searching produced 734 publications when combining the main areas of interest. When this set was limited to articles published in English, and those involving human subjects only, 422 articles remained to review at the title-only level (**Figure 3.2**). Lists of these publication titles were reviewed without knowledge of author or journal of origin in order to remove any known or subconscious bias of the reviewer. Titles that were obviously of non-dental origin were removed, and any questionable titles were included at this stage for further review. Abstracts were then gathered and reviewed and any publications that were inappropriate for this investigation were excluded. Again, if the abstract did not contain enough detail to determine the quality or methods of a specific trial, it was included for more detailed review. Following the exclusions made at the abstract level, a total of 119 publications remained as potential articles of interest.

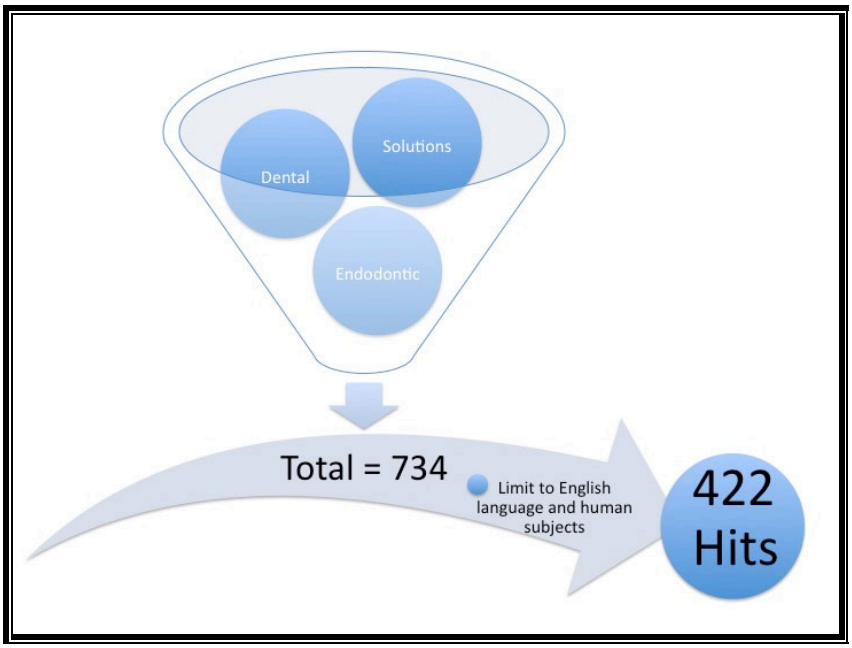


FIGURE 3.2: Results of Electronic Database Searching

Full text copies of the 119 articles that were identified by title and abstract search were obtained for critical appraisal. A pilot study was conducted to calibrate the two independent researchers regarding their decisions of inclusion or exclusion. For a sample of 5 articles, two observers independently appraised each publication, and a third reviewer served to arbitrate the reports. Consensus was reached, and the independent reviewers were considered calibrated.

This process was repeated with three additional random sets of five articles each (N=15). The first author reviewed each article, noting the specific methods of each trial and whether each trial met the defined inclusion criteria and this process was also undertaken by the independent reviewer. All decisions were reviewed by a third member of the review team and compared for reliability. Any disagreements were then resolved by means of discussion and consensus between the three reviewers was reached. After this process of calibration, the first reader continued the review of the remaining articles. Before finalizing the

exclusion list, the review team discussed each excluded study and resolved any remaining discrepancies. The process resulted in the final list of excluded studies (**Table 3.3**).

The first group of exclusions were ten studies that included only children and adolescents as their subjects (**Table 3.2**). An additional ten trials were excluded because their assessment of pulpal anesthesia was either completely absent, unacceptable, or poorly described. A total of eleven articles could be eliminated because they were case series reports of various techniques or solutions without control groups. Nine of the trials were excluded because subjects were not randomly allocated into groups. Two publications were retrospective in nature and one was an observational study that did not properly assess pulpal anesthesia. In addition to these groups of exclusions there were other reasons for exclusion. One article described an intra-osseous method of anesthesia and did not include any clinical data. One well-designed trial evaluated the efficacy of electronically induced dental anesthesia but did not include any local anesthetic solutions and was thus excluded. One trial was excluded on the basis that diagnosis, administration of the anesthetic and evaluation was performed by a single, un-blinded examiner. Two trials were excluded as the trials were halted because of complications associated with the experimental groups. See **Table 3.3** for the detailed list of excluded trials and the corresponding reasons for exclusion.

Before finalizing the list of excluded publications, the review team discussed each excluded study and resolved any remaining uncertainties regarding the articles status. After arriving at consensus among the team of investigators, a total of 71 original articles were deemed to have met the criteria for inclusion into the review (**Table 3.4, Appendix V**).

Quality Assessment

Attention was paid to the quality of methodology of included trials, and indicators of quality were recorded on the abstraction form. These included proper randomized allocation of subjects to their respective study groups as well as blinding of subjects and evaluators. Clinical trials were considered randomized if random sequences were generated by random numbers or tables, a tossed coin, or any other random sequence generation. If just the terms randomized or randomly allocated were used with no detailed information on the exact method, the trial was deemed 'unclear' as regards to the randomization, and clarification was sought by attempted contact from the original authors. Allocation was considered concealed if measures of allocation concealment were described, such as the use of opaque, sealed and sequentially numbered envelopes, or if anesthetic cartridges were indistinguishable, and sequentially numbered. The examiners of each trial were deemed to be properly blinded if the outcome assessor could not know to which group the participants had been randomized. Reporting of adverse events was recorded as being present if reported, or noted as 'not mentioned' if no description of side effects was included in the results. The "Intent to treat" was considered adequate because treatment effects were observed and evaluated on the same day of intervention. For the trials that employed a cross-over design, it was noted that no losses occurred, and outcome data was available for all randomized subjects. Thus, all participants were included in these trials, and should be considered as an "intent to treat" analysis. Analysis appropriateness was assessed (**Appendix II**), and funding sources for included trials were reviewed to evaluate the existence funding bias.

Data Abstraction Process

An initial data abstraction form was designed and served as a unified framework to record the research design parameters including information pertaining to the quality of the study. This form allotted space for both categorical and quantitative entries, depending on the particular item of interest. (**Appedndix VI**)

A pilot study was conducted to observe agreement between two independent researchers and to test the utility of the abstraction form. For five randomly selected articles, two observers independently abstracted data using the form, and a third party of the research team reviewed and arbitrated the reports. Minor adjustments were made to the data abstraction form as deemed necessary, and any disagreements were resolved.

Following the pilot and confirmation of complete observer agreement, the full-text version of each study was reviewed, and data was extracted using the revised data abstraction form. Again, a third party member served to arbitrate any disagreement among the abstracted data. Once consensus was achieved, the data were prepared for analysis.

The data recorded in the abstraction form included both information regarding the quality of the included trials, as well as their outcomes. Determination of proper randomization and blinding, as previously described, was noted on the form. Details of the study population included the sample size, mean age of participants, as well as age range. The goal of anesthesia was identified, being either an evaluation of an anesthetic solution on the pulpal innervation of teeth tested, or of soft-tissue being instrumented. The goal of anesthesia was labeled as ‘pulpal’ or ‘surgical’, respectively. Site of administered

anesthesia was noted as buccal or lingual if an infiltration was employed. If block anesthesia was being investigated, the specific technique used was noted, as were other supplemental techniques. Anesthesia of the maxilla or mandible was recorded. The specific intervention was qualitatively (type of anesthetic solution) and quantitatively (mg dose of administered anesthetic) described. Dichotomous data described the outcomes as either "anesthetic success" or "anesthetic failure" (**Appendix VII –Glossary of Terms**).

Meta-Analysis

Because the evidence comparing lidocaine to articaine was sparse, the language restriction was modified prior to final data analysis. Because articaine has been in use in both Europe and Canada for several decades, the English-language restriction was removed in an attempt to find meaningful data that may have been published in an alternative language. This additional searching revealed six potential publications for inclusion into the meta-analysis, and the full-text versions were obtained, translated, and appraised. Four articles were originally published in German language (Winther 1972, Khoury et al. 1991, Ruprecht & Knoll-Köhler 1991, Szabó et al. 1988). The publication by Khoury et al. was excluded because its methods did not meet the inclusion criteria for assessment of pulpal anesthesia. The publication by Szabo et al. was also excluded, as it included data on duration and diffusion of anesthesia, but no designation of anesthetic success. One article was located from a Croatian-language publication (Amsel & Katanec 1986), but was excluded because there was no randomization of subjects in the trial. And finally, one Russian publication (Anisimova et al. 1997) was excluded on the basis that there was an absence of randomization and the evaluator was unblinded to the interventions.

For the meta-analysis portion, two independent evaluators and a third-party arbitrator served as the review team, and reached complete agreement for the abstracted data. Data for meta-analytic comparisons were obtained from the arbitrated abstracted data.

Statistical analysis of the extracted outcomes data was conducted using the RevMan software (Review Manager Version 5.0, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Mantel–Haenszel odds ratios were calculated to describe the overall estimated treatment effects of licocaine versus articaine across the multiple quantitative scientific studies. This was done for an overall broad comparison of all direct comparisons of lidocaine and articaine, and then repeated to select data for the techniques of infiltration and block anesthesia separately. Forest plots from this data were constructed to illustrate the estimated treatment effects graphically. The Q statistic value was calculated according to the method of Cochrane to test for heterogeneity among the reported results of the studies. A funnel plot of the included trials was created to depict the possibility of publication bias.

TABLE 3.3: FINAL LIST OF EXCLUDED PUBLICATIONS

AUTHOR, YEAR	JOURNAL	REASON FOR EXCLUSION
Willett, 2008	JOE	Study halted due to complications.
Sixou, 2008	OOO	Subjects were children and adolescents.
Remmers, 2008	JOE	Diagnosis, injection, and evaluation was performed by a single, unblinded operator.
Dabarakis, 2007	Quintessence	Randomization was not present.
McCartney, 2007	OOO	Retrospective study investigating pain of needle insertion, no pulpal assessment.
Dabarakis, 2006	Anesth Prog	No randomization, testing effect of temperature.
Bigby, 2006	JOE	Case series of supplemental io anesthesia.
Lai, 2006	OOO	No preoperative assessment of pulpal status.
Ashkenazi, 2006	Ped Dent	Subjects were children and adolescents, and non-randomized.
Klein, 2005	J Dent Child	Subjects were children from 3-5 years old.
Modaresi, 2005	Aus Dent J	Non-randomized case series.
Ashkenazi, 2005	JADA	Subjects were children and adolescents, and non-randomized.
Mellor, 2006	IEJ	The study was discontinued due to complications associated with the experimental group.
Oztas, 2005	Quintessence	Subjects were children from 6-10 years old.
Nusstein, 2005	JOE	Case series of supplemental anesthesia.
Naidu, 2004	Anesth Prog	Subjects were children from 5-8 years old.
Nusstein, 2003	JOE	Case series of supplemental anesthesia.
Fukayama, 2003	Quintessence	Case series of injections using The Wand.
Nusstein, 2002	Gen Dent	Randomization was not present, retrospective analysis of experimental data.
Ernberg, 2002	JOMS	Randomization was not present.
Munshi, 2001	J Clin Ped Dent	Case-series of a needle-less technique for children subjects.
Gallatin, 2000	JOE	No evaluation of pulpal anesthesia.
Munshi, 2000	J Clin Ped Dent	Case series of the use of electronic dental anesthesia in a pediatric population.
Nakai, 2000	JADA	Observational study, not a clinical trial.
Goodell, 2000	OOO	No evaluation of pulpal anesthesia.
Kramp, 1999	Anesth Prog	No evaluation of pulpal anesthesia, just pain associated with injection.
Parente, 1998	JOE	Case series of supplemental anesthesia.
Nusstein, 1998	JOE	Case series of supplementa anesthesia.
Uckan, 1998	OOO	No randomization present.
Reisman, 1997	OOO	Case series of supplemental anesthesia.
Sharaf, 1997	J Dent Child	Subjects were children from 3-9 years old.

Rakusin, 1986	IEJ	No randomization present.
Oulis, 1996	Ped Dent	Subjects were children from 3-9 years old.
Odor, 1994	Dent Traum	No assessment of pulpal anesthesia.
Odor, 1994	Dent Traum	No assessment of pulpal anesthesia.
Kaufman, 1994	OOO	Randomization was not present.
Pitt Ford, 1993	Dent Traum	Randomization was not present.
Gerschman 1991	Anesht Prog	Evaluated electronic dental anesthesia.
White, 1988	JOE	Controls groups not present.
D'Souza 1987	JADA	Evaluated postinjection discomfort.
Eriksen, 1986	Dent Traum	Injection type was arbitrarily chosen, without randomization.
Dunsky, 1984	JOE	Poor assessment of pulpal anesthesia.
Smith, 1983	JADA	Case-series of supplemental anesthesia.
Moore, 1983	OOO	Poor assessment of pulpal anesthesia.
Walton, 1981	JADA	Case-series of supplemental anesthesia.
Pearce, 1976	J Col Dent A	Not a clinical trial.
Birchfield, 1975	JOE	Randomization was not present.
Chilton, 1971	JADA	No assessment of pulpal anesthesia.

TABLE 3.4 - Characteristics of Included Studies – Randomized Controlled Trials

Author, Year	Publication	Methods	Sample	Eval Scale	Conclusions
Tortamano, 2009	J Endod	Compared articaine and lidocaine during pulpectomy in patients with IP* mandibular posterior teeth, subsequent to IAN* block.	N=40	EPT, VAS	For patients reporting none or mild pain during pulpectomy, the success rate of articaine (65%) was higher than that of lidocaine (45%). However, differences were not statistically significant.
Srinivasan, 2009	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared articaine and lidocaine when delivered via buccal infiltration for maxillary posterior teeth diagnosed with IP.	N=40	VAS	Success rate for articaine were 100% for both first molar and first premolar, and for the lidocaine solution, 30% in first premolar, and 80% in first molar. There was a highly significant difference.
Goldberg 2008	J Endod	Subjects each received conventional IAN, GG*, or AK* with a standard volume of lidocaine.	N=40	EPT	There was no statistically significant difference among the techniques. Conventional IAN had a faster onset of pulpal anesthesia.
Lindmemann 2008	J Endod	Compared the effect of sublingual triazolam prior to IAN administration of a standard volume of lidocaine in patients with IP.	N=58	VAS	The success rate was 43% for IAN block following triazolam, and 57% with placebo; no significant difference was present between groups.
Haase, 2008	J Amer Dent Assoc	Compared articaine and lidocaine by mandibular first molar buccal infiltration, after initial IAN block was given with articaine.	N=73	EPT	Articaine resulted in a significantly higher success rate (88%) than did lidocaine (71%), when given via buccal infiltration following an IAN block of articaine.
Brunetto 2008	Anesth Prog	Compared 3 volumes of lidocaine (0.6, 0.9, 1.2mL) for infiltration anesthesia of the maxillary canine.	N=25	EPT	The greater volume (1.2mL) resulted in greater success, faster onset, and longest duration.
Sherman, 2008	J Endod	Compared articaine and lidocaine in patients with IP in either maxillary or mandibular posterior teeth.	N=40	VAS	Overall anesthetic success was 87.5% in both arches. Articaine was as effective, but not statistically superior to lidocaine.
Corbett, 2008	J Endod	Compared articaine given by means of buccal or buccal and lingual infiltration to IAN block of lidocaine.	N=31	EPT	Efficacy of articaine when given by infiltration was not statistically significantly different than using lidocaine via IAN* block for mandibular 1st molars.
Evans, 2008	J Endod	Compared articaine with lidocaine in maxillary infiltrations of 1st molars and lateral incisors.	N=80	EPT	In maxillary lateral incisors, articaine exhibited a significantly higher success rate (88%) when compared with lidocaine (62%). Differences were not significant for 1st molars (78% vs. 73%).

Jensen 2008	J Endod	Evaluated the anesthetic efficacy of a repeated IO injection (X-tip) following a primary IO of lidocaine for the mandibular 1st molar.	N=55	EPT	The primary injection resulted in 100% anesthetic success, and the repeated IO injection provided an additional 15 minutes of pulpal anesthesia.
Mikesell 2008	J Endod	Compared the efficacy of two volumes (1.8 and 3.6mL) for maxillary buccal infiltration of lateral incisors, 1st premolars, and molars	N=31	EPT	The two doses resulted in similar onset and success rate (97-100%). The larger dose did not result in a statistically longer duration of anesthesia.
Tempestini 2008	JOMFS	Evaluated the duration effect of mepivacaine when hyaluronidase or placebo was injected 40 minutes after the beginning of pulpal anesthesia for bilateral IAN blocks.	N=40	EPT	The duration of pulpal anesthesia from IAN block of mepivacaine was significantly increased when hyaluronidase was subsequently administered.
Jung 2008	J Endod	Compared buccal infiltrations and IAN blocks for a standard volume (1.7mL) of articaine in mandibular 1st molars.	N=35	EPT	Success rates of buccal infiltration (54%) and IAN block (43%) were not found to be statistically significant. Onset of the infiltration was significantly faster.
Whitworth 2007	J Endod	Evaluated the influence of injection speed (60s vs. 15s) on the effectiveness of the mental nerve block of 2.0mL of lidocaine.	N=38	EPT	Speed of injection had no significant influence on anesthetic success or duration of anesthesia for individual teeth: bicuspid success was 79% for slow administration vs. 84% for rapid administration.
Robertson, 2007	J Amer Dent Assoc	Compared articaine and lidocaine when given via buccal infiltration in mandibular posterior teeth, testing from first premolar to second molar.	N=60	EPT	Lidocaine resulted in anesthetic success ranging from 45-67%, while articaine resulted in a range of 75-92%. Articaine did result in a significantly higher success rate for mandibular buccal infiltrations.
Foster 2007	Anesth Prog	Using a crossover design, the efficacy of buccal or lingual mandibular infiltration of 1.8mL lidocaine following a primary IAN block of 3.6mL lidocaine.	N=49	EPT	There was no significant difference in success with the IAN block when an additional buccal or lingual infiltration was given.
Gross 2007	J Endod	Compared a standard volume (1.8mL) of bupivacaine and lidocaine in maxillary infiltrations of lateral incisors and 1st molars.	N=65	EPT	Bupivacaine had a slower onset for the 1st molar, and a significantly lower success rate for the lateral incisor. (78 vs. 90%)
Rosenberg 2007	J Endod	Compared articaine and lidocaine buccal infiltrations in mandibular posterior teeth with IP* that required	N=48	VAS	The mean % change in VAS score was 70 and 65% for articaine and lidocaine, respectively, demonstrating no significant difference.

		supplemental anesthesia.			
Elsharrawy 2006	J Pain Symptom Manage	Compared supplemental 0.02mg fentanyl vs. 8mg mepivacaine delivered intraligamentary following 1.8mL infiltrations of mepivacaine for maxillary 1st molars with IP*.	N=40	5 point scale	The fentanyl group reported a highly significant decrease in pain intensity when compared to the mepivacaine group during the different stages of endodontic procedures.
Tofoli 2007	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Groups of women either using or not using contraceptives, and men were given a buccal infiltration of 1.8mL of lidocaine to evaluate the influence of gender and the menstrual cycle.	N=30	EPT	Although women showed a lower pain threshold, the phases of the menstrual cycle and the use of oral contraceptives did not affect injection discomfort or local anesthetic efficacy and duration.
Ianiro 2007	J Endod	Compared preoperative administration of acetaminophen (1g) or a combination of acetaminophen (1g) and ibuprofen (600mg) vs. placebo for effectiveness of IAN block of 3.6mL lidocaine in teeth with IP*.	N=40	VAS	Success was 71% for the acetaminophen group, 76% for the combination group, and 46% for the placebo group, resulting in no significant difference. However, a trend of increased success in the medication groups was noted.
Bigby 2007	J Endod	Compared the efficacy of lidocaine 1.8mL to lidocaine 1.8mL plus meperidine (36mg) for IAN blocks in patients with IP* of posterior teeth.	N=48	VAS	Success rates were severely low: 26% for lidocaine and 12% for lidocaine with meperidine, with no significant difference among the groups.
Steinkruger 2006	J Amer Dent Assoc	Compared the significance of needle bevel orientation when giving IAN block of 2.2mL lidocaine.	N=51	EPT	There was no significant difference in regards to anesthetic success between the two groups.
Kanaa 2006	J Endod	Evaluated the efficacy and discomfort of IAN blocks using 2.0mL of lidocaine when comparing speed of injection (15 vs. 60s).	N=38	EPT	Slow IAN block was more comfortable than rapid administration, and produced more episodes of no response to EPT.
Meechan 2006	Int Endod J	Compared the efficacy of buccal and buccal plus lingual infiltrations of 1.8mL lidocaine for mandibular 1st molars.	N=31	EPT	The two methods of infiltration anesthesia did not differ in their efficacy, both providing low rates of success (<40%).
Modaresi 2006	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared the efficacy of placebo, ibuprofen, and acetaminophen-codeine premedication therapy on the depth of anesthesia for mandibular posterior teeth with IP.	N=60	TSL	Significantly lower tooth sensitivity levels were observed after intervention in acetaminophen-codeine and ibuprofen groups, which was more significant in the ibuprofen group.
Kanaa, 2006	J Endod	Compared articaine and lidocaine in mandibular buccal infiltrations of 1st	N=31	EPT	Success rates were 65% for articaine, and 39% for lidocaine, resulting in

		molars.			significantly more chance for anesthetic success with articaine.
Branco 2006	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared bupivacaine and levobupivacaine when 1.8mL was given via IAN block.	N=30	EPT	Success rates of the two solutions ranged from 70 to 80%, and no significant differences were noted.
Volpato 2005	Anesth Prog	Compared the anesthetic efficacy when 1.8mL of two bupivacaine solutions (racemic bupivacaine vs. levobupivacaine/dextrobupivacaine) were given via IAN block.	N=22	EPT	There was no difference in incidence of failure, onset, or duration of anesthesia between the two solutions.
Fernandez 2005	J Endod	Compared bupivacaine vs. lidocaine when 1.8mL was given via IAN block, using a crossover design.	N=39	EPT	Anesthetic success was significantly higher for all teeth except the 1st molar with the lidocaine solution. Bupivacaine provided significantly longer pulpal anesthesia.
Costa 2005	Quintessence	Compared 1.8mL of articaine and lidocaine for infiltration of maxillary posterior teeth.	N=20	EPT	There was no significant difference between the success rates of articaine and lidocaine. Articaine did produce significantly shorter onset and longer duration of anesthesia.
Mikesell, 2005	J Endod	Compared articaine and lidocaine when administered via IAN* block, testing molars, premolars, and incisors.	N=57	EPT	Lidocaine resulted in anesthetic success ranging from 2-48%, while articaine resulted in a range of 4-54%. There was no significant difference between the articaine and lidocaine solutions.
Berlin, 2005	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared 1.4mL of articaine and lidocaine when administered via computer-controlled intraligamentary injections in mandibular posterior teeth.	N=51	EPT	Success rates were 74% for lidocaine and 86% for articaine solutions. There was no significant difference between the two solutions.
Lee 2004	Anesth Prog	Compared the efficacy of the AMSA block using a computer-assisted system vs. a conventional syringe to deliver 1.4mL lidocaine.	N=40	EPT	For all teeth, except the central incisor, the use of the computer-assisted system was significantly more likely to result in pulpal anesthesia than the conventional syringe, although success rates were low (35-58%).
Burns 2004	J Amer Dent Assoc	Compared the efficacy of 1.4mL of lidocaine or mepivacaine using a computer-assisted system to administer the PASA block.	N=40	EPT	Except for the left canine, the lidocaine solution was more likely to result in successful anesthesia than mepivacaine, although success rates were low (32-58 vs. 22-38%).
Claffey, 2004	J Endod	Compared articaine and lidocaine when administered via IAN	N=72	VAS	The success rate of lidocaine (23%) and articaine (24%) revealed no significant

		block in patients experiencing IP* in mandibular posterior teeth.			difference. Neither solution resulted in an acceptable rate of success for patients with IP.
Oliveira 2004	Br Dent J	Compared articaine to lidocaine (2.15mL of each) for buccal and lingual infiltration of maxillary canines.	N=20	EPT	Although articaine resulted in faster onset and longer duration of anesthesia, differences were not significant.
Tofoli 2003	Anesth Prog	Compared the anesthetic efficacy of articaine in association with 2 different concentrations of epinephrine for the IAN block.	N=20	EPT	No significant differences in success, onset or duration between the two solutions were observed.
Gallatin 2003	J Amer Dent Assoc	Compared the success rates of administering lidocaine via two types of IO deloivery (X-tip vs. Stabident) for mandibular posterior teeth.	N=41	EPT	No significant differences were observed in anesthetic success, which ranged from a low of 81% for the 2nd premolar, to a high of 95% for the 2nd molar.
Kennedy 2003	J Endod	Evaluated the significance of needle deflection on success of IAN blocks using 2.8mL of lidocaine on patients with IP*.	N=64	VAS	No significant differences were observed on success rates using a conventional IAN block when compared with a bi-directional-needle-rotation technique (50 vs. 56%)
Clark 2002	Anesth Prog	Evaluated the anesthetic efficacy of adding a buccal or lingual infiltration of 1.8mL lidocaine to an IAN block of 3.6mL lidocaine for mandibular anterior teeth.	N=40	EPT	A significant improvement in success was found with buccal infiltration of lidocaine after IAN block for the lateral incisor (40 vs. 62%).
Meechan 2002	Int Endod J	Compared the anesthetic efficacy of infiltration and intraligamentary injections of lidocaine in mandibular central incisors.	N=12	EPT	The most reliable method was a combination of labial and lingual infiltration. Intraligamentary injections were unreliable, and also more uncomfortable.
Meechan 2002	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared the efficacy of 2 concentrations of ropivacaine with lidocaine for intraligamentary anesthesia (0.36mL) for maxillary lateral incisors and mandibular 1st premolars.	N=24	EPT	Lidocaine was more successful than the ropivacaine solutions in obtaining pulpal anesthesia, and provided longer duration.
Yonchak 2001	Anesth Prog	Compared efficacy of lidocaine combined with 2 different vasoconstrictor concentrations for mandibular buccal infiltrations (1.8mL) of anterior teeth, as well as lingual infiltration.	N=80	EPT	There were no differences in the success Rates of the 3 groups, although no technique produced anesthetic success at a rate of greater than 50% for the lateral incisor.
Yonchak 2001	Oral Surg Oral Med	Evaluated anesthetic success obtained with	N=38	EPT	Success rates for the bilateral IAN block were significantly

	Oral Pathol Oral Radiol Endod	unilateral or bilateral IAN blocks using 3.6mL of lidocaine for each block.			higher for the central incisor (39 vs. 66%), lateral incisor (50 vs. 74%), and canine (68 vs. 76%) than for the unilateral block.
Ridenour 2001	Anesh Prog	Compared lidocaine to lidocaine plus hyaluronidase solution in IAN blocks.	N=30	EPT	There were no significant differences between the two solutions, but the addition of hyaluronidase resulted in an increase in postoperative pain and trismus.
Kennedy 2001	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared bupivicaine to ropivicaine with or without vasoconstrictor for the infiltration of maxillary lateral incisors.	N=40	EPT	No significant differences existed in success rates of bupivacaine and ropivicaine with or without vasoconstrictor (68, 75, and 80% respectively).
Gallatin 2000	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Evaluated the efficacy and heart rate effects of an IO injection of 1.8mL mepivacaine after an IAN block of mepivacaine.	N=48	EPT	The IO injection of 1.8mL of mepivacaine, when used to augment the IAN block, significantly increased anesthetic success for 30 minutes in the mandibular 1st molar.
Clark 1999	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared the efficacy of IAN block of 3.6mL lidocaine with or without the addition of a mylohyoid nerve block of 1.8mL lidocaine.	N=30	EPT	There were no significant increase in success with the addition of the mylohyoid nerve block to an IAN block. Mylohyoid nerve block alone resulted in low success (0-17%).
Reitz 1999	Anesth Prog	Evaluated the effect of a repeated IO (Stabident) injection (0.9mL) given 30m following a combination of IAN block (1.8mL) and IO injection (0.9mL) in mandibular posterior teeth. (All solutions were lidocaine).	N=38	EPT	The repeated IO injection did not result in greater anesthetic success, but did result in an increase in duration of pulpal anesthesia of 6-14m, although this was also not statistically significant.
Reitz 1998	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Evaluated the anesthetic efficacy of an IO injection (given distal to the 2nd premolar) of 0.9mL lidocaine to augment an IAN block in mandibular posteriors.	N=38	EPT	The supplemental IO injection significantly increased the success of pulpal anesthesia in the 2nd premolar and 1st molar in comparison with the IAN block alone.
Fiset 1997	J Stud Alc	Compared infiltrations of 1.0mL mepivacaine at the maxillary lateral incisor for both alcoholic and non-alcoholic patients.	N=44	EPT	Alcoholics did not experience significantly more anesthetic success than age-matched non-alcoholic counterparts.
VanGheluwe 1997	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Compared administering solutions of lidocaine or saline via intrapulpal delivery for supplemental anesthesia for patients with IP*.	N=35	Pain absent	Overall, 33 of 35 injections were effective, suggesting that success is not solution-dependent.
Replogle 1997	Oral Surg Oral Med	Compared a primary IO injection of lidocaine or	N=42	EPT	Lidocaine resulted in a significantly higher rate of

	Oral Pathol Oral Radiol Endod	mepivacaine in mandibular 1st molars.			success than mepivacaine (75 vs. 45%).
Dunbar 1996	J Endod	Evaluated the contribution of an IO injection (1.8mL) to the success of IAN block (1.8mL) in mandibular 1st molars. (All solutions lidocaine)	N=40	EPT	The combination of the IO injection and IAN block resulted in significantly higher success rates than the IAN block alone. (90% vs. 42%).
Childers 1996	J Endod	Evaluated the contribution of the PDL injection (0.4mL) to the success of IAN block (1.8mL) in mandibular 1st molars. (All solutions lidocaine)	N=40	EPT	Incidence of successful pulpal anesthesia was greater for the combination of injections for the 1st 23m of testing, but differences were not significant after this time point.
Coggins 1996	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Evaluated the anesthetic efficacy of the IO injection (1.8mL lidocaine) as a primary technique in maxillary and mandibular 1st molars and lateral incisors.	N=40	EPT	Anesthetic success occurred in 75% and 78% of mandibular 1st molars and lateral incisors, respectively. For maxillary 1st molars and lateral incisors, these values were 93% and 90%, respectively.
Vahatalo 1993	Anesth Prog	Compared articaine to lidocaine for maxillary lateral incisor infiltration (0.6mL).	N=20	EPT	All infiltrations resulted in successful pulpal anesthesia, with no significant difference of onset or duration of the two solutions.
Cohen 1993	J Endod	Compared lidocaine and mepivacaine when given via IAN block (1.8mL) for teeth with IP*.	N=61	Cold test	Both lidocaine and mepivacaine IAN blocks resulted in 55% success.
McLean 1993	J Endod	Compared prilocaine, mepivacaine, and lidocaine for IAN block (1.8mL).	N=30	EPT	No significant difference in onset or success were found among the solutions.
Nist 1992	J Endod	Evaluated the incisive nerve block (1.8mL) and a combination of IAN block (3.6mL) and incisive nerve blocks (all solutions lidocaine).	N=40	EPT	The incisive nerve block alone did not result in successful anesthesia in the central, lateral, of 1st and 2nd molars. The combination with IAN block was successful in the 1st and 2nd premolars, and enhanced anesthesia for laterals and 1st molars.
McLean 1992	Anesth Pain Control	Compared bupivacaine to lidocaine using the PDL injection (0.8mL).	N=24	EPT	No significant difference in success rates between lidocaine and bupivacaine was evident (38 vs. 33% respectively).
Chaney 1991	Anesth Prog	Compared 3 formulations of lidocaine (hydorchloride vs. hydrocarbonate with or without epinephrine) for IAN block (1.8mL).	N=30	EPT	Anesthetic success for the plain lidocaine hydrocarbonate solution was less than 10%. The remaining two solutions ranged in success from 37-63%, and differences were not significant.

Haas 1991	J Canadian Dent Assoc	Compared articaine to prilocaine for both maxillary and mandibular buccal infiltrations (1.5mL) of 2nd molars.	N=20	EPT	Articaine resulted in higher success rates for both arches, although differences were not statistically significant.
Haas 1990	Anesth Prog	Compared articaine to prilocaine for both maxillary and mandibular buccal infiltrations (1.5mL) of canine teeth.	N=20	EPT	The two solutions provided similar success rates for pulpal anesthesia after infiltration. (articaine 65% vs. prilocaine 50%)
Edwards 1989	J Dent Res	Evaluated the effectiveness of PDL injections (0.8mL) using lidocaine, epinephrine, or saline	N=28	EPT	Lidocaine was significantly more effective in providing pulpal anesthesia (79%), while PDL injections of saline or epinephrine provided 0% anesthesic success.
Handler 1987	J Amer Dent Assoc	Evaluated the effects of the vasoconstrictor epinephrine on the duration of pulpal anesthesia using the PDL injection (0.2mL of all 4 test solutions).	N=22	EPT	There was no statistical difference in the ability of the four solutions, including epinephrine alone, to produce anesthesia. All solutions produced anesthesia roughly 2/3 of the time.
Teplitsky 1987	J Canadian Dent Assoc	Compared bupivacaine and lidocaine for duration of pulpal and soft tissue anesthesia in the mandible and maxilla.	N=23	EPT	Results indicated an equal time of pulpal anesthesia for both agents in the maxilla, but a longer duration of pulpal anesthesia in the mandible.
Johnson 1985	Anesth Prog	Compared PDL injections (0.4mL) of etidocaine and lidocaine of maxillary canine teeth.	N=20	EPT	No significant differences in anesthetic success were noted between the two solutions.
Kaufman 1984	J Amer Dent Assoc	Four solutions (lidocaine with or without epinephrine, bupivacaine, or saline) were given via PDL injection (0.8mL) of maxillary lateral incisors.	N=10	EPT	No anesthesia was produced via the saline solution; lidocaine with epinephrine resulted in the longest pulpal anesthesia.
Petersen 1977	Int J Oral Surg	Four solutions (mepivacaine with or without epinephrine, prilocaine, and lidocaine) were given via maxillary infiltration and IAN block.	N=9	EPT	Anesthesia was produced via infiltration from 56-100%, and via IAN block from 56-90%.
Winther 1972	Scand J Dent Res	Maxillary infiltrations of 1.0mL articaine for lateral incisors were compared to the same volumes of lidocaine and mepivacaine for anesthetic efficacy.	N=39	AB Bofors Pulp Tester	Articaine compared well to the other solutions, with the 2% solution providing a frequency of anesthesia close to 100%.

*IP = irreversible pulpitis, IAN = inferior alveolar nerve block, GG = Gow Gates technique, AK = Akinosi technique, AMSA = anterior middle superior alveolar block, PASA = palatal anterior superior alveolar block, IO = intraosseous PDL= periodontal ligament, EPT = electronic pulp tester, VAS = visual analog scale, TSL = tooth sensitivity level

CHAPTER 4 - RESULTS

Heterogeneity

The 72 studies that were identified as randomized clinical trials (RCTs) Variations in methodology and quality of design were present and are presented in **Figures 4.1 – 4.4**.

Timeline

The earliest publication that met the inclusion criteria of this review was published in 1972 (Winther & Nathalang 1972). This was also the first clinical trial that reviewed the efficacy of articaine in clinical dentistry. **Figure 4.1** depicts the number of randomized, controlled trials per 5-year period. Only one trial was published in each of the initial two 5-year periods, and 33 in the final 5-year period. This trend is encouraging, as more high-level evidence is published, conclusions of this systematic review will be strengthened.

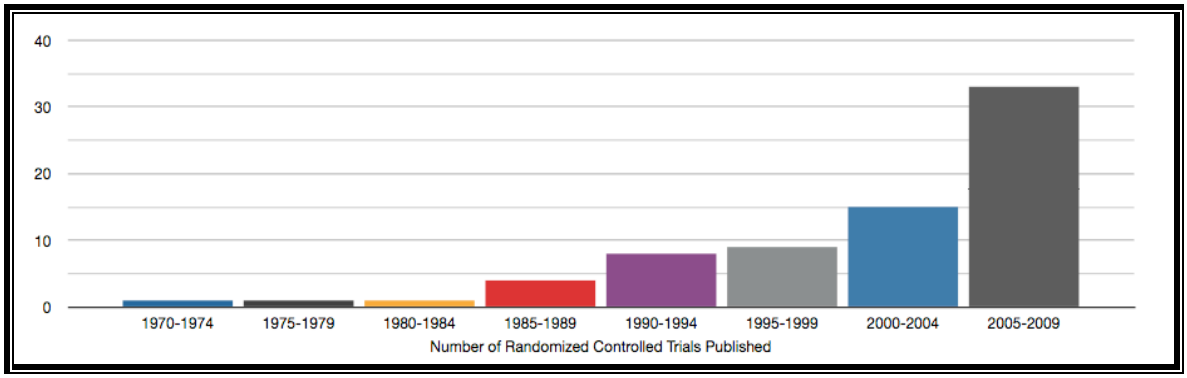


Figure 4.1 Timeline of Randomized, Controlled Trials

Geography

The United States dominated the count of investigations, in terms of country of origin of each included trial, with 45 of the 72 RCTs. Brazil, the United Kingdom, Canada, and Denmark each contributed multiple studies that were included into this investigation. And finally, a single included study was found from India (Srinivasan et al. 2009), Finland (Vähätalo et al. 1993), Egypt (Elsharrawy & Elbaghdady 2007), Korea (Jung et al. 2008), and Iran (Modaresi et al. 2006). This wide geographic distribution represents a variety of populations (**Figure 4.2**).

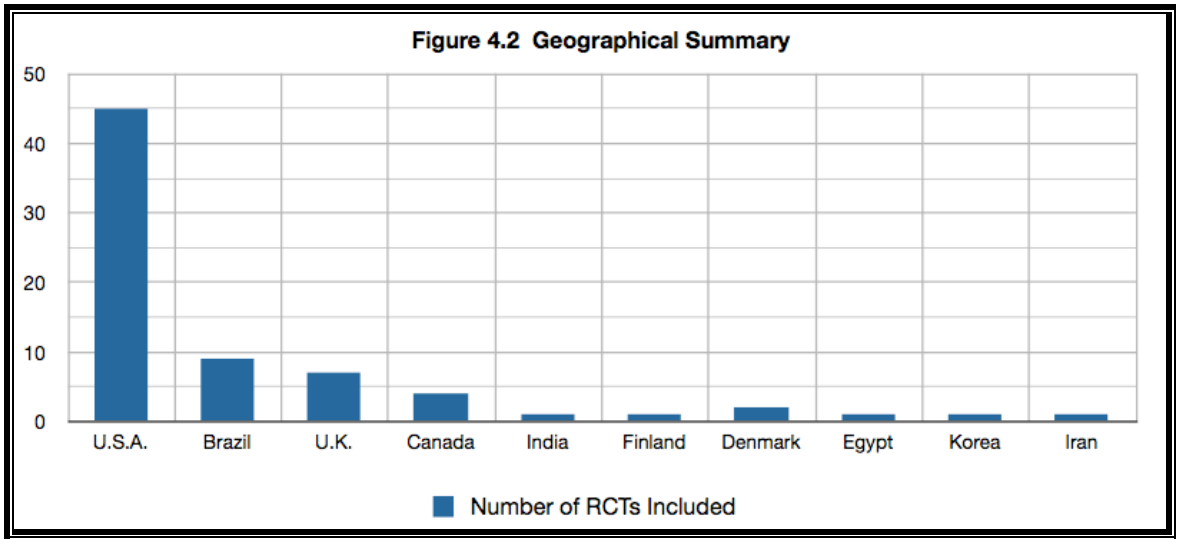


Figure 4.2 Geographical Summary of Randomized, Controlled Trials

Pulpal Status

As defined by our inclusion criteria, trials must have evaluated the condition of the dental pulp for each subject prior to anesthetic administration. Within this review, the majority of RCTs which were included evaluated the

anesthetic efficacy of the various solutions available for dentistry on teeth which contained healthy and/or uninflamed pulps. Twelve of the included RCTs investigated the effects of local anesthetic solutions on vital teeth that had been diagnosed as having irreversible pulpitis. The American Association of Endodontists includes explicit definitions of the various conditions of pulpal health, including those states that were evaluated within this review:

- *Normal pulp* – a clinical diagnostic category in which the pulp is symptom free and normally responsive to vitality testing
- *Irreversible pulpitis* – a clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is incapable of healing

The distribution of trials included in this investigation regarding the pre-operative pulpal status is exhibited in **Figure 4.3**.

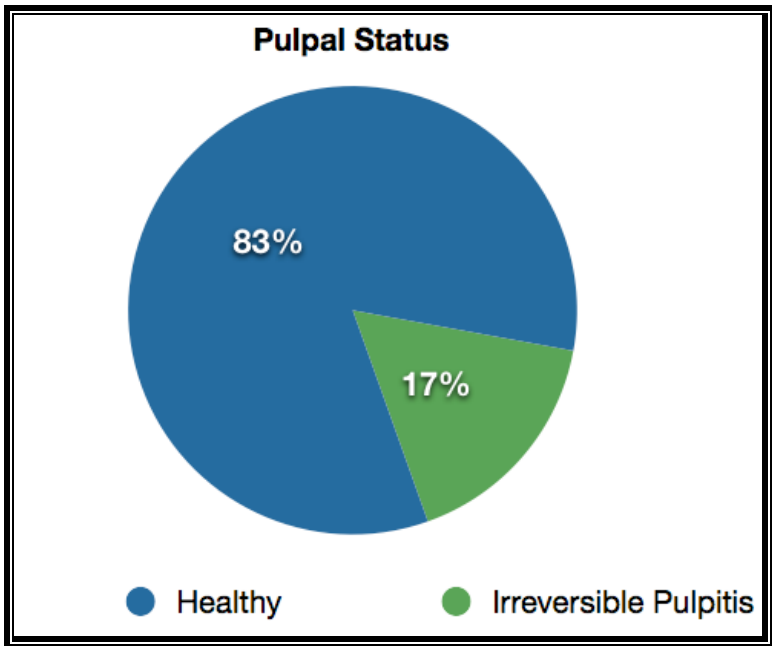


Figure 4.3 – Pre-operative Pulpal Status Identified in Included RCTs

Outcomes Measures

Two main approaches for determining anesthetic efficacy were identified, and these methods had varying definitions of successful anesthesia. The most common method was the EPT- based methodology. The EPT is an instrument that uses gradations of electric current to excite a response from the nervous tissue within the pulp. Among the trials that employed this methodology, a variety of specific protocols was identified. All of the studies recorded a baseline EPT value prior to the administration of the experimental anesthetic solution. Following the anesthetic administration, the EPT was used in cycles ranging from every 20 seconds, to longer periods of several minutes, for a predetermined duration. Timelines to completion of the trials also varied, including 30 or 60 minutes post-injection, or until the return of baseline EPT values, regardless of time. The anesthetic success rate utilizing this method was often defined as the percentage of subjects who achieved two consecutive maximal stimulations without sensation within 15 minutes of anesthesia administration, and continuously sustained this lack of responsiveness for some period.

The second approach had the patient give a pain rating using a pain-scale instrument during various clinical treatments that were considered to only impact pulpal tissues. The most common pain scale with this methodology was the visual analogue scale (VAS) but other pain-scales were also used. These psychometric response scales have been used as a measurement instrument for subjective characteristics such as dental pain and have been successfully used primarily in dentistry for patients who are symptomatic. This type of measurements requires some type of experimental dental treatment that would

be associated with pain if profound anesthesia had not been achieved. The inclusion criteria of this systematic review aimed to select trials that evaluated pulpal anesthesia only and not those that could have based success or failure on the innervation of periodontal or osseous origins. A variety of VAS instruments were seen. For example, Srinivasan quantitatively measured the pain of endodontic access on anesthetized teeth using a standard VAS ranging from 0 to 10cm, categorizing successful anesthesia as a response value of “0” or “1” (Srinivasan et al. 2009). Conversely, Mikesell et al. used a modified Heft Parker VAS ranging from 0 to 170mm, defining anesthetic success as a patient reporting a pain level <54mm, which includes the categories of mild, faint, and weak pain (Mikesell et al. 2005, Heft & Parker 1984). All varieties of VAS scales reasoned that reported pain related to anesthetic failure, and lack of reported intra-operative pain equated to anesthetic success.

Various other measurements of experimental outcome were also identified among the included publications. One trial utilized both EPT and VAS-based methods to determine successful anesthesia after local anesthetic administration (Tortamano et al. 2009). Other validated measurement scales were employed, including a 5-point scale to rate pain associated with invasive procedures (Elsharrawy & Elbaghdady 2007), and a similar pain-rating scale that evaluated tooth sensitivity levels after local anesthesia administration (Modaresi et al. 2006). One trial strictly defined anesthetic success as the patient rating “absence of pain” during a procedural-based evaluation (VanGheluwe & Walton 1997). And finally, the first two published trials within the group of included studies employed the AB Bofors Pulp Tester, which is an earlier version of the EPT (Petersen et al. 1977, Winther & Nathalang 1972). **Figure 4.4** depicts the

proportions of identified outcomes measures for the publications included in this systematic review.

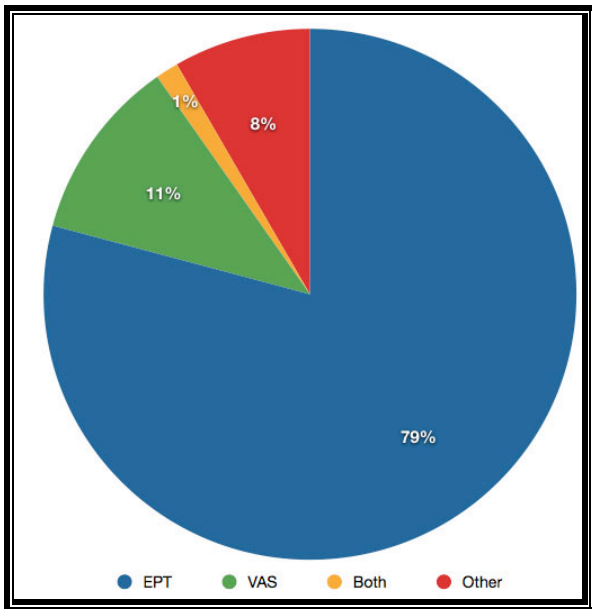


Figure 4.4 – Response Measuring Instruments Used in Included Trials

Review of Methodologies

Dentists employ multiple techniques to deliver local anesthetic solutions to desired anatomical locations to inhibit the conduction process of peripheral nerves. Researches have investigated these varying techniques, and their publications are the basis for this systematic review. The overall variety of methods of local anesthesia delivery is mirrored in the varying methodologies of the included publications **(Figure 4.5)**.

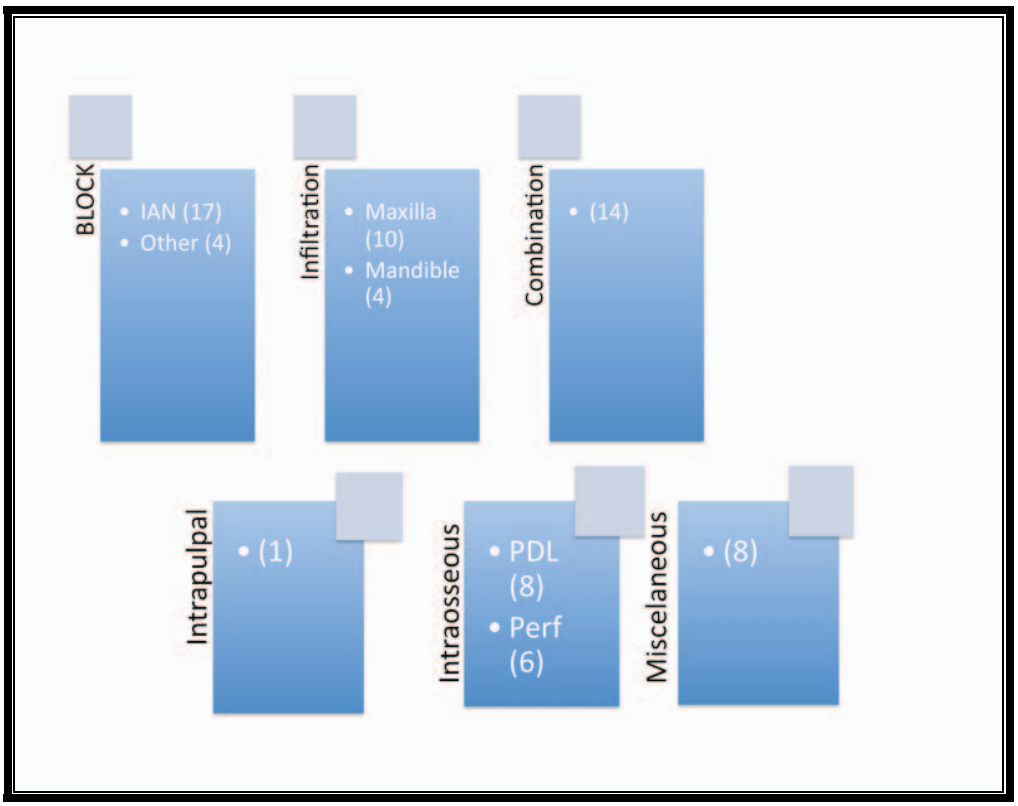
The two most common methods for delivering local anesthetic solutions in clinical dentistry are infiltration and block anesthesia (Malamed 2004). These two means are considered within this review to be the primary routes of anesthesia delivery, and included trials were categorized into respective groups

based on their techniques employed. A total of 14 RCTs included in this review investigated the efficacy of local anesthetic solutions when given via local infiltration. Block anesthesia was evaluated by a total of 21 trials. An additional 14 publications studied the combination of techniques, and were placed into a designated category separate to those that investigated infiltration or block anesthesia solely.

Supplemental techniques were the focus of several RCTs. Anesthetic delivery by direct intra-ligamentary injection or by the creation of a channel to the osseous tissues by using a perforating instrument, such as the Stabident™ or X-tip™ have been investigated. The total number of such publications that met the inclusion criteria were eight and six, respectively. One controlled trial looked at the efficacy of intra-pulpal delivery of anesthetic solutions by injecting directly within an endodontically accessed pulp (VanGheluwe & Walton 1997).

Still other investigations were identified that evaluated other aspects that could affect the efficacy of local anesthesia in clinical dentistry. These topics ranged from the impact of the female menstrual cycle (Tófoli et al. 2007), the influence of previous alcohol addiction (Fiset et al. 1997), or the degree of needle deflection when administering the anesthetic solution (Steinkruger et al. 2006). Additions of a variety of chemical compounds to local anesthetic solutions were investigated, including hyaluronidase (an enzyme which increases tissue permeability) (Tempestini Horliana et al. 2008, Ridenour et al. 2001) and fentanyl (a potent narcotic analgesic) (Elsharrawy & Elbaghdady 2007).

Pre-operative administration of oral systemic medications prior to local anesthesia delivery has also been inspected, including sedative hypnotics, and oral analgesics (Ianiro et al. 2007, Modaresi et al. 2006).



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The aim of the first analytic approach compared the estimated effects of articaine and lidocaine. The combination of studies and examination of their entire data supplied greater power to the conclusions of this analysis. Within the group of RCTs meeting inclusion criteria for this review, those publications directly comparing experimental administrations of articaine and lidocaine were identified. This sub-group originally totaled thirteen trials. As previously described, these results were further enriched with the data from two non-English language trials that met our inclusion criteria. The outcomes data of these fifteen trials was the basis of this meta-analysis.

Tests for heterogeneity indicated strong evidence of heterogeneity among the estimated treatment effects of these fifteen studies. For all studies combined, the chi-squared value associated with the test of heterogeneity was 24.12 with 12 degrees of freedom, and a p-value < 0.00001 was obtained. The Cochrane collaboration recommends using a p-value of less than 0.10, rather than the conventional cutpoint of p=0.05. A chi-squared value larger than the number of degrees of freedom, is also evidence of heterogeneity. On this basis, a random effects model of statistical analysis was employed rather than fixed effects models used when there is no evidence of heterogeneity.

Estimates of treatment differences between the two anesthetic solutions are shown in **Figure 4.6**. This comparison depicts a broad scope of comparison between these two solutions, irrespective of technique or site of administration. The overall odds ratio of articaine producing successful anesthesia compared to lidocaine is estimated at 2.3, and the results are statistically significant (the 95-percent confidence interval ranges between 1.62 and 3.26). These odds ratios are base on the pooled data of the fifteen selected studies, and is supported by 1120 experimental administrations of lidocaine, and 1175 of articaine.

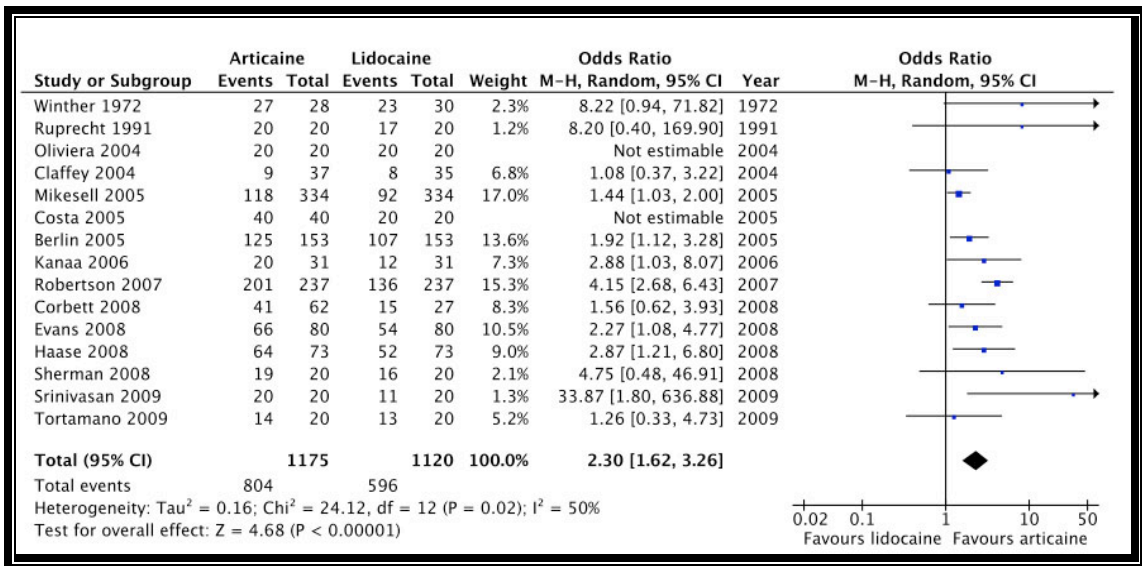
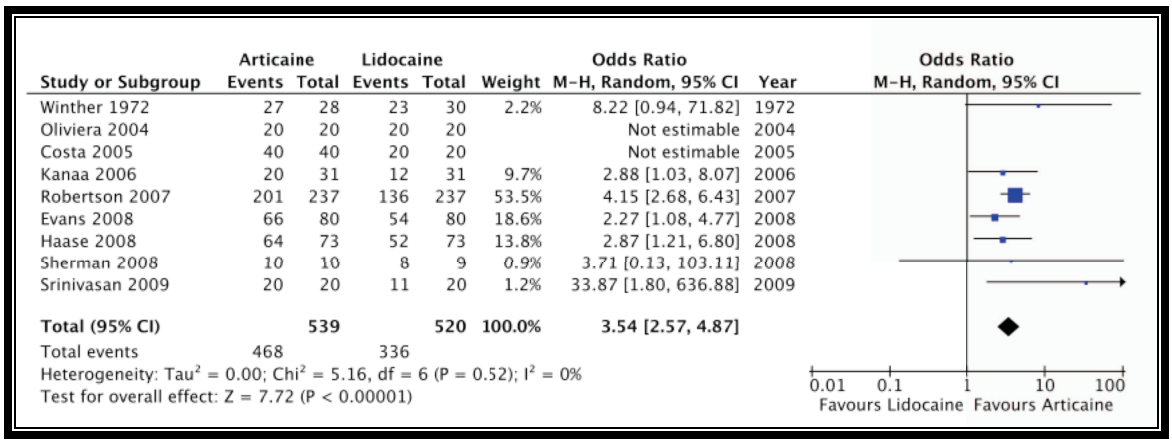
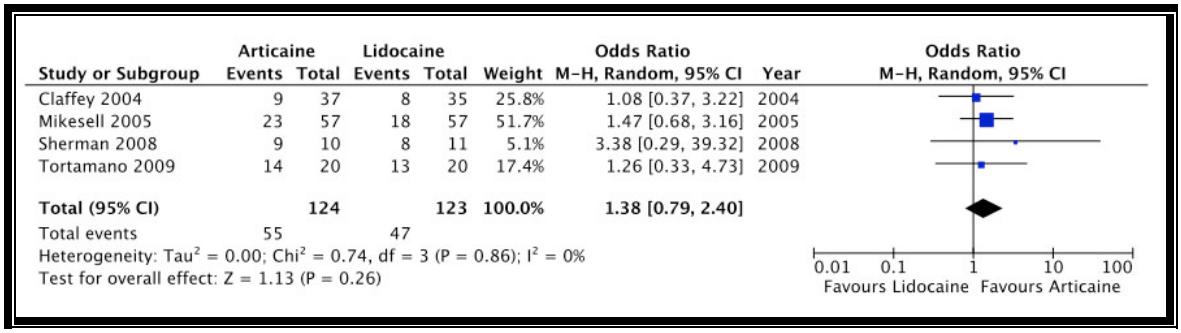


Figure 4.6 Forest Plot of Lidocaine vs. Articaine: Overall Treatment Effects

The outcomes data were further stratified into separate categories based on whether the local anesthetic solutions were administered via a block or an infiltration. These analyses also identified a trend of superiority of articaine over that of lidocaine in terms of achieving anesthetic success, although these results were not statistically significant. When infiltration anesthesia only was considered, the weighted odds ratio was 3.54 in favor of articaine (95 percent confidence interval ranged from 2.57-4.87, respectively). For clinical trials directly comparing articaine and lidocaine when administered via a block technique, articaine was modestly favored with an odds ratio of 1.38 (95 percent confidence interval ranged from 0.79 to 2.40). The relative strength of the treatment effects of lidocaine when administered by infiltration are illustrated in **Figure 4.7**, and when administered via block technique in **Figure 4.8**.





A funnel plot depicting the estimated treatment effect (odds ratio) on the horizontal axis and 'study size' (in this case standard error) on the vertical axis is seen in **Figure 4.9**. This graph is designed to check the existence of publication bias in a meta-analysis. The graph depicts 13 data points representing the included studies. Data points are not present for the data from Oliviera et al. 2004 or Costa et al. 2005 because within those trials all administrations of lidocaine and articaine resulted in anesthetic success, and thus no odds ratios were estimated. The fact that an inverse funnel pattern is not present in this funnel plot suggests that possible publication bias existed in this group.

Publication bias suggests that smaller studies showing significant results may be more likely to be published than those showing non-significant results.

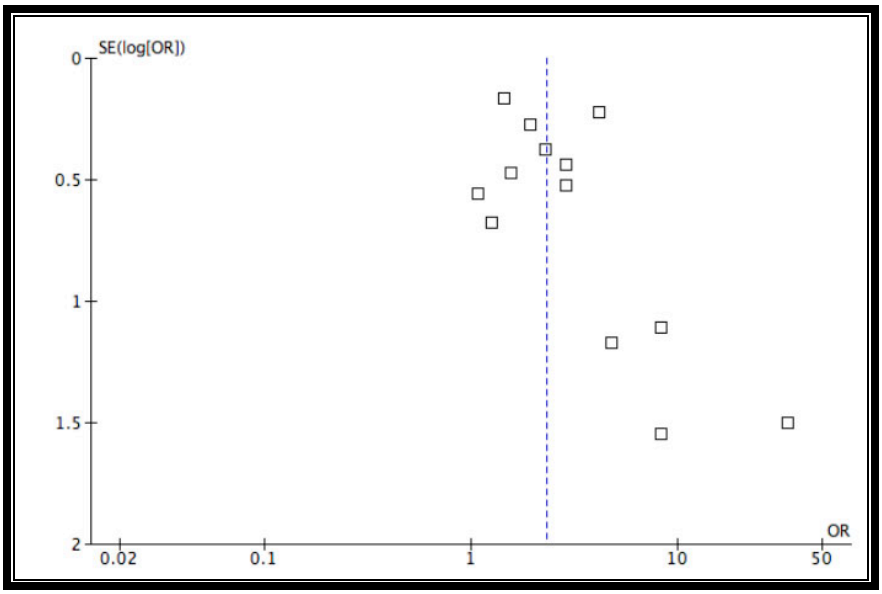


Figure 4.9 – Publication Bias - Funnel Plot

CHAPTER 5 - DISCUSSION

Reduction of Bias

The Cochrane Collaboration advises that the determination and reduction of bias be the major approach in the assessment of quality of trials within a systematic review. Within this review, quality measures were designed to reduce bias. Strategies were conducted to use modern search engines to thoroughly seek for all relevant publications. It remains possible that publication bias may affect this review as unfavorable and negative results tend to go unpublished.

Performance bias was also assumed to be eliminated by confirming the masking and calibration of subjects, operators, and evaluators among the included studies. The intention to treat analysis revealed no losses within the study designs of included trials, and has been described as being more suitable for pragmatic trials of effectiveness rather than for explanatory investigations of efficacy (Hollis & Campbell 1999). No conflicts of interest between authors and their funding sources were noted, indicating the absence of funding bias.

Evaluation of Successful Anesthesia

Traditional methods to confirm successful pulpal anesthesia in clinical dentistry may involve questioning the patient, stimulating adjacent soft-tissue, or simply commencing with treatment. A number of publications have pointed out that these approaches are less than ideal, and may not be effective for determining pulpal anesthesia. A clinical trial by Chaney et al (Chaney et al.

1991) demonstrated that although all of the subjects reported a subjective "feeling of numbness", pulpal anesthetic success was as low as 2%. They concluded that lip numbness and negative mucosal responses did not always indicate onset or guarantee successful pulpal anesthesia. Similar conclusions have accompanied a number of other clinical trials regarding dental anesthesia (Vreeland et al. 1989,McLean et al. 1993, Hinkley et al. 1991). The application of refrigerant spray has also been used to determine pulpal responsiveness (Jones et al. 2002).

The electronic pulp tester (EPT) determines anesthetic success in a more accurate and objective manner. Clinically, application of the EPT can be used to test the tooth under treatment for pulpal anesthesia prior to beginning a clinical procedure (Dreven et al. 1987, Certosimo & Archer 1996).

When using stimulus of dental pulp in an effort to determine the sensitivity of the dental pulp, various explicit definitions of success have been employed. A common way to define success when using EPT is the percentage of experimental subjects who achieve two consecutive 80 reading on the EPT within 15 minutes of local anesthetic administration, and sustain this lack of responsiveness for some predefined duration (usually 60 minutes) (Vreeland et al. 1989, McLean et al. 1993,Chaney et al. 1991,Hinkley et al. 1991, Hannan et al. 1999, Fernandez et al. 2005, Nusstein et al. 2002). Alternatively, anesthetic failure has been defined as the percentage of subjects who never achieved two consecutive maximum readings at any time during a predefined duration.

The electric pulp tester is technique sensitive (Cooley & Barkmeier 1977, Ehrmann & Millard 1973). The requirements to achieve a valid EPT outcome are: adequate stimulus, appropriate application method, and careful interpretation of results. Tests require tooth isolation and conducting media.

Explaining to patients that an electric stimulus will be applied to their tooth may be frightening, and the stimulus may sometimes be painful. Additional difficulties with this method are encountered when teeth have extensive restorations, or are wearing orthodontic bands. In these cases, the response may be caused by conduction of the current to the gingival or periodontal tissues and adjacent teeth through these conductive materials (Fulling & Andreasen 1976). Nevertheless, the EPT has been used in research applications in analgesia for many years. The first investigation to utilize the EPT for evaluating the effectiveness of local anesthetics occurred in 1947 (Bjorn 1947), and has continued to be used as an indicator of the effectiveness of local anesthesia in clinical trials to this day. This has been reflected among the included trials of this investigation.

Reporting of Clinical Trials:

This meta-analysis combined data from the publications that directly compared the two most commonly used local anesthetic solutions in the United States: lidocaine hydrochloride and articaine hydrochloride. The individual publications had a variety of outcomes and conclusions; however, the meta-analysis of their combined data revealed that a significant difference exists between these two anesthetic agents. These results favor an advantage of using the articaine hydrochloride solution for producing anesthetic success. Even within the subset of studies that were identified for the meta-analysis, numerous variations in methodologies were present. Sources of heterogeneity included specific study designs, study populations, specific teeth that were tested, injection type, and even definition of outcome. Additionally, complete standardization in reporting among the included trials was not present, leading to potentially inaccurate or incomplete reporting. The lack of standardized research

protocols has been named as a significant limitation in a number of other meta-analyses on dental topics (Keenan et al. 2005, Peng et al. 2007).

Because of the problems arising from inadequate reporting of randomized controlled trials, the CONSORT statement was developed (Altman 1996). Developed in 1993 by a group of medical journal editors, methodologists, and other researchers, the CONSORT statement is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, reducing the influence of bias on their results, and aiding their critical appraisal and interpretation (Schulz et al. 2010). A recent systematic review determined that the utilization of the CONSORT checklist does improve the reporting of randomized controlled trials (Plint et al. 2006). This report suggested that with endorsement by more journals, and greater editorial efforts to ensure that authors comply, the CONSORT statement could begin to yield the full benefits for which it was intended. It is encouraging that as time progressed, a greater proportion of the trials within this systematic review, and specifically those trials contributing to the meta-analysis, adhered to CONSORT in their reporting.

As stated, the fifteen studies that were summarized in the meta-analysis were inconsistent in methodology. This heterogeneity required critical appraisal to interpret the individual validity of each study, and whether it met the inclusion criteria standards that were specifically set to regulate the quality of studies included for the comparison.

The meta-analysis included more subjects that any single component study comparing these two local anesthetic solutions. Sackett has described the systematic review of randomized controlled trials to be the “gold

standard" for judging the effects of a treatment or intervention, stating that it is "so much more likely to inform us, and so much less likely to mislead us" (Sackett et al. 1996). In fact, the Oxford Centre for Evidence-Based Medicine touts the systematic review of randomized controlled trials as the highest level of evidence from which to base treatment decisions, recognizing that not all evidence is made accessible. Inherent to the systematic review process are efforts to reduce publication bias and retrieval bias.

Overall, the results of the meta-analysis were based on the inclusion of both male and female subjects between the ages of 18 to 60 years. Among the studies that reported the mean age of their subjects, all described a mean age of younger than 30 years. Also, the majority of subjects had reported "good" systemic health. Included studies were limited to rather young populations, most likely because many of these trials recruited students as their subjects. Incomplete reporting among the included trials regarding the age and gender of their study populations did not allow for further analysis of the influence of these variables on the likelihood of anesthetic success.

The meta-analysis compared volumes of local anesthetic solutions that were considered to be clinically reasonable. Because of the difference in concentration between articaine hydrochloride and lidocaine hydrochloride preparations available on the market, a standard volume does not equate to a standard milligram dose. One milliliter of anesthetic solution is equal to a 40 and 20 milligram dose of articaine hydrochloride and lidocaine hydrochloride, respectively. These differences may decrease the validity of comparisons of equal volume. However, none of the included trials directly compared equivalent concentrations of articaine hydrochloride and lidocaine hydrochloride. This meta-analysis reflects the comparison of these two local anesthetic solutions as they

are commonly evaluated in the literature. This means that equivalent volumes are compared, but not equivalent milligram doses. It is beyond the scope of this investigation to comment on the influence of concentration differences on the respective success rates of articaine hydrochloride and lidocaine hydrochloride. Future research designed to investigate the influence of this dose effect is needed for clarification of this difference.

The type of injection type was also a source of heterogeneity among the included studies. All types and techniques of local anesthetic administration were considered for the overall comparison of the meta-analysis, resulting in a broad point of comparison. When injection types were further stratified, the evidence more strongly supported a superiority of articaine over lidocaine with infiltration anesthesia, and weak evidence for such differences for block anesthesia. The difference between success rates between articaine and lidocaine were statistically significant when the method of administration was an infiltration, as opposed to no statistically significant difference between the two when a nerve block was given.

The strong evidence of superiority of articaine over lidocaine in administrations of infiltration anesthesia should be an evidence-based guide for clinicians. However, clinicians cannot expect an improved success rate in achieving pulpal anesthesia when substituting articaine for lidocaine when the route of administration is a local block technique. More data is needed to determine if an infiltration of articaine may enhance or even replace the IAN block. Corbett et al reported that the efficacy of articaine when administered by infiltration was not statistically different than delivering lidocaine via an IAN block for anesthetic success in mandibular 1st molars (Corbett et al. 2008). Additionally, Jung et al found that the success rates of a standard volume of

articaine was not influenced by the administration route, be it buccal infiltration or IAN block (Jung et al. 2008).

The trials that provided the basis for the meta-analysis also investigated a variety of teeth. The various types of teeth studied included incisors, canines, premolars, and molars. Again, the compilation of all of the data, regardless of selected tooth, was used for the meta-analysis. If specific tooth type had been compared individually, either the number of studies to compare would have been greatly reduced, or comparisons would have been altogether impossible. The combination of numerous tooth types in this study offers a broad point of comparison and represents the wide variety of teeth that are treated in dentistry.

Also, the meta-analysis included all pulpal diagnoses for comparisons, assuming that the pre-stated inclusion criteria of a pre-operative assessment of pulpal health status was present for each of the included trials. For the meta-analysis, the majority compared the efficacy of the two local anesthetic solutions in teeth with healthy pulps. Four of the included trials made investigations among patients who had been diagnosed with having irreversible pulpitis. This trend of having a majority of studies containing healthy, asymptomatic teeth was echoed in the overall systematic review of all local anesthetic solutions in clinical dentistry. Regarding this meta-analysis, additional well-designed and sufficiently powered trials will be needed to highlight differences in the odds ratios of healthy or diseased teeth of obtaining anesthetic success when using articaine hydrochloride versus lidocaine hydrochloride. Because both pre-operative conditions were considered for this meta-analysis, the results reflect a variety of pulpal conditions.

It was an aim of this review to determine differences in time of onset and duration of anesthesia between articaine hydrochloride and lidocaine

hydrochloride. However, because individual patient data was not available, meaningful statistical comparisons of these outcomes were not possible. Because the literature was not standardized and had variations in reporting, the influence of gender, age, injection type, tooth type, and pulpal status was not completed. Still, the main comparison of the dichotomous outcome of "success" versus "failure" was possible, and is a meaningful summary of high-level evidence for clinicians.

It was also noted that there does exist a difference in cost between the two local anesthetic solutions. Using the product catalog of Henry-Schein, a worldwide distributor of medical, dental, and veterinary products, a package of fifty carpules of articaine hydrochloride can be purchased for $38.99. When compared to purchasing the same quantity of lidocaine hydrochloride for $29.99, this results in a cost ratio articaine hydrochloride costing 1.3 times greater than lidocaine hydrochloride. This increased cost seems warranted, considering the estimation of this meta-analysis that articaine hydrochloride is 2.3 times more likely to produce anesthetic success than is lidocaine hydrochloride. The difference in cost may be considered even more negligible when considering infiltration anesthesia, where articaine was estimated to be 3.5 times more likely to provide successful anesthesia.

The likelihood of complications associated with these two local anesthetic solutions was outside the scope of this meta-analysis. However, within the subset of data which was the basis for this meta-analysis, it should be noted that no reports of paresthesia were associated with the 1175 administrations of articaine hydrochloride, or the 1120 administrations of lidocaine hydrochloride. Reported adverse events did include minor bruising or swelling in the area of the injection, although not all of the included trials stated the presence or absence of

complications. Data in the dental literature is ambiguous regarding the comparative safety of these two local anesthetic solutions. One retrospective study that reviewed over twenty years of data in Canada reported 143 cases of paresthesia following local anesthetic administration, with 49 percent being associated with articaine hydrochloride, and only 5 percent from lidocaine hydrochloride (Haas & Lennon 1995). This publication concluded that articaine hydrochloride was significantly associated with paresthesia and that lidocaine hydrochloride was not. However, this data was based on voluntary reporting from dentists, often lacking pertinent details including the size and caliber of the needle used, the injection techniques used, or the total duration of paresthesia. Additionally, the type of anesthetic used was not identified in over 30 percent of these reports, which could have shifted the conclusions of this analysis significantly (Haas & Lennon 1995). A more recent article regarding reported cases of paresthesia evaluated by the Oral and Maxillofacial Surgery Department of the University of California at San Francisco stated that 35 percent of the paresthesia involved the use of lidocaine hydrochloride, versus 30 percent being associated with articaine hydrochloride (Pogrel 2007). It was concluded that paresthesias were not significantly more likely when articaine hydrochloride was administered. The author stated that a clinician should be knowledgeable about the adverse effects and safety considerations of any local anesthetic administered.

Chapter 6 - Conclusions

Implications For Future Research:

Well-designed and properly executed randomized controlled trials provide the best evidence on the efficacy of health care interventions, while trials with inadequate methodological approaches may be associated with exaggerated treatment effects.

Further comparative trials investigating the difference in anesthetic success between articaine and lidocaine are warranted to strengthen the evidence that formed the basis for this review. Specifically, comparisons between these two solutions among older populations, as well as equivalent doses are currently absent in the dental literature. It is also suggested that a uniform pain scale be adopted to compare the efficacy of articaine and lidocaine in pediatric populations. Standardization in reporting of clinical trials of dental anesthetics should be improved, especially among the parameters of duration and onset of anesthesia. These comparisons would be of great interest to clinicians, but are not currently possible because of inconsistent or absent reporting of present clinical trials. Such randomized controlled clinical trials could expand the existing evidence regarding the superiority of articaine over lidocaine in terms of providing pulpal anesthesia.

Implications For Clinical Practice:

When comparing the newer articaine solution to the "gold standard" of lidocaine, an emerging trend was identified from the review of contemporary research. The results of these studies have often demonstrated a superior anesthetic efficacy for articaine, even though proper statistical analysis frequently reveals that such differences were not always statistically significant. This meta-analysis summarizes the unbiased direct comparison of articaine and lidocaine, and supports the argument that articaine does provide a higher rate of anesthetic success. This evidence-based review is aimed to facilitate clinicians in making informed, judicious decisions when selecting a local anesthetic solution.

Clinicians may expect a solution of articaine hydrochloride to provide a greater probability of anesthetic success than a solution of lidocaine hydrochloride, with the superiority of articaine being most significant when used during local infiltration anesthesia. Regarding the relative strength of treatment effects among the multiple quantitative studies, it can be stated that within a 95 percent confidence interval the true odds ratio of articaine hydrochloride is 1.62 to 3.26 times more likely to produce anesthetic success than lidocaine. When considering infiltration data only, the present meta-analysis estimates that articaine is 3.54 times more likely to produces anesthetic success than a similar volume of lidocaine. There is weak evidence that the use of articaine allows for a higher percentage of anesthetic success when administered via a IAN block, and thus is not recommended for substitution in place of lidocaine for block purposes.

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- Appendix I:

Commercially Available Solutions for Local Anesthesia

(Manufacturer Data)

Duration	Solution	Trade Name	Infiltration (pulpal duration)	Nerve Block (pulpal duration)	Soft tissue duration	Mgs per cartridge
Short Duration-Plain	Lidocaine HCl 2%	Xylocaine	5 min	Not indicated	2 hrs	36
	Mepivacaine HCl 3%	Carbocaine, Isocaine, Polocaine, Scandanest	20-30 min	45-65 min	2-3 hrs	54
	Prilocaine HCl 4%	Citanest Plain	10-15 min	45-65 min	3-4 hrs	72
Normal Duration-with vasoconstrictor *	Articaine HCl 4% w/ epi 1:100,000	Septocaine, Zorcaine	60-75 min	Up to 120 min	3-5 hrs	68
	Articaine HCl 4% w/ epi 1:200,000	Septocaine	60 -75min	Up to 120 min	3-5 hrs	68
	Lidocaine HCl 2% w/ epi 1:50,000	Lidocaine, Xylocaine, Lignospan Standard, Octocaine 50	55-65 min	80-90 min	3-5 hrs	36
	Lidocaine HCl 2% w/ epi 1:100,000	Lidocaine, Xylocaine, Lignospan Standard, Octocaine 100	55-65 min	80-90 min	3-5 hrs	36
	Mepivicaine HCl 2% w/ levo 1:20,000	Carbocaine, Isocaine 2%, Polocaine, Scandanest 2%	40-60 min	60-90 min	3-5 hrs	36
	Prilocaine HCl 4% w/ epi 1:200,000	Citanest Forte	35-45 min	50-70 min	3-6 hrs	72
Long Duration	Bupivacaine HCl 0.5% w/ epi 1:200,000	Marcaine, Vivacaine, Bupivacaine	Up to 7 hrs	Up to 7 hrs	Up to 12 hrs	9

*Abbreviations used: epi = epinephrine, levo = levo nordefrin

APPENDIX II:

Initial Review of Generated Studies' Methodology and Reporting

Author	Outcome Measurements/Reporting	Statistical Analysis
Sherman 2008	Modified VAS (170mm)was used before treatment: 0mm= no pain, 1-54mm = mild pain, 55-113 = moderate pain, 114+ = severe pain. Pt's contralateral canine used as a control. No response to endo ice on experimental tooth 15 min after injection indicated pulpal anesthesia. After access was completed, pts used same VAS to rate discomfort.	X2 comparisons. Regression analysis of pulpitis pain before tx compared to pain after tx by using Spearman rank correlation test. P<.05
Corbett 2008	Investigator of anesthetic efficacy was blinded to the infiltration method. Pulpal anesthesia was determined by using an EPT. Tooth was tested 2x before injection, and then every 2 min after injection for 30 min. Successful anesthesia was no response to maximum stimulation on two or more consecutive measurements. Duration measured until more than 2 responses at less than maximum stimulation. Injection discomfort for each injection rated on a VAS (100mm) scale.	Pearson X2, Fisher's exact test, McNemar test, and Student's T test, performed using a statistical analysis package. P<.05
Sixou 2008	Used Articaine 4% with epinephrine 1:200,000 Efficacy was scored as 0 when the anesthesia did not allow the treatment to be completed, 1 when the treatment was completed with no pain or sensitivity, 2 when the treatment was completed despite mild sensitivity, and 3 when the assessment could not be performed.	X2 test, P<.05
Gregorio 2008	Crossover study, Articaine used for one 3rd molar removal, and then Bupivicaine used at least 1 mo later for the ipsilateral tooth (same surgeon). The parameters evaluated were: Total anesthetic volume used, onset (soft tissue), quality of anesthesia (based on 3 point scale), difficulty of surgery (based on 3 point scale), duration of the surgery (1st incision to last suture), duration of analgesia (time at end of surgery and the first ingestion of piroxicam for pain), duration of anesthesia on soft tissues, subjective pain evaluation on a VAS scale (100mm)	Paired t test, ANOVA, followed by Tukey's test for multiple comparisons. Nonparametric measures, were analyzed by Wilcoxon (for repetitive measures) of Mann-Whitney (for independent measures). P<.05
Evans 2008	Before injections, the experimental tooth was tested 3x with the EPT for baseline. Heft-Parker VAS (170mm) used to rate each phase of the injection. No pain=0mm, mild= 0-54, moderate= 55-114, severe= 114+. After 1 min, EPT reading taken for the experimental tooth and the contralateral canine, continuing in 3 minute cycles for 60 min. Success = 2 consecutive non responses to maximum output.	Group comparisons with exact McNemar test. Between-group comparisons using ANOVA w/ a Tukey-Kramer multiple comparison test. P< .05.

Appendix III:

Electronic Search Strategy development-

Lidocaine

PubChem Compound: CID: 3676
IUPAC: 2-diethylamino-N-(2,6dimethylphenyl)acetamide
Entry Terms:

* 2-2EtN-2MePhAcN
* 2 2EtN 2MePhAcN
* Lignocaine
* 2-(Diethylamino)-N-(2,6-Dimethylphenyl)Acetamide
* Lidocaine Carbonate (2:1)
* Lidocaine Carbonate
* Carbonate, Lidocaine
* Lidocaine Hydrocarbonate
* Hydrocarbonate, Lidocaine
* Lidocaine Hydrochloride
* Hydrochloride, Lidocaine
* Lidocaine Monohydrochloride
* Monohydrochloride, Lidocaine
* Lidocaine Monoacetate
* Monoacetate, Lidocaine
* Xyloneural
* Lidocaine Sulfate (1:1)
* Octocaine
* Xylesthesin
* Xylocaine
* Xylocaine CO2
* Xylocitin
* Dalcaine
* Lidocaine Monohydrochloride, Monohydrate
* Monohydrate Lidocaine Monohydrochloride

MeSH Categories:

Chemicals and Drugs Category
Organic Chemicals
Amides
Anilides
Acetanilides
Lidocaine

Mepivacaine

PubChem Compound; CID: 4062
IUPAC: N-(2,6-dimethylphenyl)-1-methylpiperidine-2-carboxamide
Entry Terms:
* Isocaine
* Novocol Brand of Mepivacaine Hydrochloride
* Isogaine
* Clarben Brand of Mepivacaine Hydrochloride
* Meaverin
* Aventis Brand of Mepivacaine Hydrochloride
* Mecain
* curasan Brand of Mepivacaine Hydrochloride
* Scandonest
* Dentsply Brand of Mepivacaine Hydrochloride
* Mepivacain-Injektopas
* Mepivacain Injektopas
* Pascoe Brand of Mepivacaine Hydrochloride
* Mepivacaina Braun
* Braun, Mepivacaina
* Braun Brand of Mepivicaine Hydrochloride
* Mepivacaine Hydrochloride
* Hydrochloride, Mepivacaine
* Mepivacaine Monohydrochloride
* Monohydrochloride, Mepivacaine
* Mepivastesin
* 3M Brand of Mepivacaine Hydrochloride
* Scandinibsa
* Inibsa Brand of Mepivacaine Hydrochloride
* Carbocaine
* Abbott Brand of Mepivacaine Hydrochloride
* AstraZeneca Brand of Mepivacaine Hydrochloride
* Scandicain
* Sanofi Brand of Mepivacaine Hydrochloride
* Carbocaïne
* Astra Brand of Mepivacaine Hydrochloride
* Scandicaine
* Polocaine
* Mepihexal
* Hexal Brand of Mepivacaine Hydrochloride

MeSH Categories:
Chemicals and Drugs Category
Heterocyclic Compounds
Heterocyclic Compounds, 1-Ring
Piperidines
Mepivacaine

Prilocaine

Year Introduced: 1968 (1967)
PubChem Compound; CID 4906
IUPAC: N-(2-methylphenyl)-2-propylaminopropanamide
Entry Terms:
* Propitocaine
* Citanest
* Inibsa Brand of Prilocaine Hydrochloride
* Xylonest
* Astra Brand of Prilocaine Hydrochloride
* Prilocaine Hydrochloride
* Delvet Brand of Prilocaine Hydrochloride
* Parnell Brand of Prilocaine Hydrochloride
* Citanest Octapressin

Previous Indexing: Anesthetics, Local (1966)

MeSH Categories:
Chemicals and Drugs Category
Organic Chemicals
Amides
Anilides
Prilocaine

Articaine

Year Introduced: 1991 (1979)
PubChem Compound; CID 32170
IUPAC: methyl 4-methyl-3-(2-propylaminopropanoylamino)thiophene-2-carboxylate
Entry Terms:
* Carticain
* Articain
* Articaine
* Carticaine Hydrochloride
* Hydrochloride, Carticaine
* Hoe-40045
* Hoe 40045
* Hoe40045
* Hoe-045
* Hoe 045
* Septocaine
* Hoe045
* Ultracaine
* Hoechst Brand of Carticaine Hydrochloride

Previous Indexing: Thiophenes (1966-1978)

MeSH Categories:
Chemicals and Drugs Category
Organic Chemicals
Sulfur Compounds
Thiophenes
Carticaine

Bupivacaine

Year Introduced: 1973 (1971)
PubChem Compound: 2474
IUPAC: 1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide
Entry Terms:
* 1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide
* Bupivacain-RPR
* Bupivacain RPR
* Aventis Brand of Bupivacaine Hydrochloride
* Bupivacaina Braun
* Braun, Bupivacaina
* Braun Brand of Bupivacaine Hydrochloride
* Bupivacaine Anhydrous
* Anhydrous, Bupivacaine
* Svedocain Sin Vasoconstr
* Inibsa Brand of Bupivacaine Hydrochloride
* Bupivacaine Hydrochloride
* Hydrochloride, Bupivacaine
* Bupivacaine Monohydrochloride, Monohydrate
* Buvacaina
* Pisa Brand of Bupivacaine Hydrochloride
* Dolanaest
* Strathmann Brand of Bupivacaine Hydrochloride
* Sensorcaine
* Astra Brand of Bupivacaine Hydrochloride
* Marcaine
* Carbostesin
* Marcain
* Abbott Brand of Bupivacaine Hydrochloride
* AstraZeneca Brand of Bupivacaine Hydrochloride
* Bupivacain Janapharm
* Janapharm, Bupivacain
* Jenapharm Brand of Bupivacaine Hydrochloride
* Bupivacaine Carbonate
* Carbonate, Bupivacaine

Previous Indexing: Anesthetics, Local (1966-70)

MeSH Categories:
Chemicals and Drugs Category
Organic Chemicals
Amides
Anilides
Bupivicaine

Appendix IV:

Electronic Search Strategies-

Database: Ovid MEDLINE(R) <1950 to May Week 5 2009>

Search Strategy (Line-by-Line Version):

---

1 exp Anesthesia, Dental/ (9373)
2 exp Anesthesia, Local/ (12671)
3 exp Anesthetics, Local/ (78730)
4 exp Nerve Block/ (12474)
5 exp Anesthesia, Conduction/ (45033)
6 ((local or infiltration or conduction or block) adj (anesthe: or anaesthe:)).mp. (26226)
7 exp Dentistry/ (288524)
8 exp Stomatognathic system/ (276423)
9 exp Stomatognathic diseases/ (347974)
10 or/7-9 (656226)
11 or/2-5 (109061)
12 11 and 10 (5616)
13 1 or 12 (11864)
14 exp Carticaine/ (263)
15 septocaine.mp. (1)
16 ultracaine.mp. (41)
17 articain$2.mp. (183)
18 carticain$2.mp. (294)
19 (hoe-40045 or hoe40045 or "hoe 40045" or hoe-045 or hoe045 or "hoe 045").mp. (6)
20 23964-57-0.rn. (263)
21 "methyl 4-methyl-3-(2-propylaminopropanoylamino)thiophene-2-carboxylate".mp. (0)
22 14 or 15 or 16 or 17 or 18 (323)
23 Thiophenes/ (6945)
24 22 or 23 (7209)
25 exp Bupivacaine/ (8400)
26 bupivacain$5.mp. (10330)
27 svedocain$2.mp. (0)
28 dolanaest.mp. (0)
29 sensorcain$2.mp. (10)
30 marcain$2.mp. (320)
31 carbostesin.mp. (23)
32 2180-92-9.rn. (8400)
33 "1-butyl-n-(2,6-dimethylphenyl)-2-piperidinecarboxamide".mp. (0)
34 or/25-32 (10432)
35 exp Lidocaine/ (19034)
36 lidocain$2.mp. (22997)
37 lignocaine.mp. (2261)
38 octocaine.mp. (2)
39 xylesthesin.mp. (0)
40 xylocain$5.mp. (941)
41 dalcaine.mp. (0)
42 xylocitin.mp. (10)
43 xyloneural.mp. (3)
44 ("2-2etn-2mephacn" or "2 2etn 2mephacn").mp. (0)

45 "2-(diethylamino)-n-(2,6-dimethylphenyl)acetamide".mp. (2)
46 137-58-6.rn. (19034)
47 or/35-46 (23841)
48 exp Mepivacaine/ (1661)
49 mepivacain$2.mp. (2107)
50 isocain$2.mp. (1)
51 meaverin.mp. (2)
52 mecain.mp. (0)
53 scandonest.mp. (3)
54 mepivastesin.mp. (0)
55 scandinibsa.mp. (0)
56 carbocain$2.mp. (109)
57 scandicain$2.mp. (31)
58 polocain$2.mp. (7)
59 mepihexal.mp. (0)
60 isogain$2.mp. (0)
61 "N-(2,6-dimethylphenyl)-1-methyl-2-Piperidinecarboxamide".mp. (0)
62 "N-(2,6-dimethylphenyl)-1-methyl-2-carboxamide".mp. (0)
63 96-88-8.rn. (1661)
64 or/48-63 (2156)
65 exp Prilocaine/ (1692)
66 prilocain$2.mp. (1955)
67 propitocain$2.mp. (11)
68 citanest.mp. (119)
69 xylonest.mp. (17)
70 "N-(2-methylphenyl)-2-(propylamino)-Propanamide".mp. (0)
71 721-50-6.rn. (1692)
72 or/65-71 (2009)
73 or/13,24,34,47,64,72 (51038)
74 exp Endodontics/ (20525)
75 exp Dental Pulp Diseases/ (7854)
76 exp Periapical Diseases/ (5330)
77 exp "Root Canal Filling Materials"/ (5154)
78 Dental Pulp Test/ (821)
79 Dental Pulp/ (8377)
80 Dental Pulp Cavity/ (5108)
81 or/74-80 (36956)
82 "root canal".mp. (18594)
83 apicectom:.mp. (200)
84 apicoectom:.mp. (1354)
85 (dead adj3 (teeth or tooth)).mp. (29)
86 (dental adj3 pulp:).mp. (18570)
87 endodont:.mp. (10745)
88 endont:.mp. (15)
89 endosonic.mp. (56)
90 ((lateral or vertical) adj condensation).mp. (586)
91 ((non-vital or nonvital) adj3 (teeth or tooth)).mp. (1081)
92 obtura.mp. (77)
93 obturation.mp. (4623)
94 obturate.mp. (78)
95 (pulp adj3 (capping or therap: or extirpation:)).mp. (1993)
96 (pulp adj (canal$1 or chamber$1)).mp. (1106)
97 pulpectomy.mp. (1032)
98 pulpotomy.mp. (1181)
99 replantation.mp. (6368)
100 ("root" adj end adj5 fill:).mp. (264)
101 ((silver or gutta) adj3 (percha or balata)).mp. (2486)
102 (silver adj (cone$1 or point$1)).mp. (129)
103 thermafil.mp. (143)
104 trans-polyisoprene.mp. (8)

105 transpolyisoprene.mp. (1)
106 ultrafil.mp. (41)
107 (periradicular or radicular or periapical or apical).mp. (53250)
108 exp tooth/ (56413)
109 exp tooth components/ (45905)
110 107 and (108 or 109) (6093)
111 or/82-106,110 (43553)
112 or/81,111 (46231)
113 *Apicoectomy/ (647)
114 *Dental Implantation, Endosseous, Endodontic/ (289)
115 *Retrograde Obturation/ (546)
116 *Tooth Replantation/ (1078)
117 or/113-116 (2408)
118 112 not 117 (43823)
119 73 and 118 (735)
120 limit 119 to (english language and humans) (422)
121 from 120 keep 1-418 (422)
122 from 121 keep 1-418 (422)

Prose Version

(((exp Anesthesia, Dental/ OR exp Anesthesia, Local/ OR exp Anesthetics, Local/ OR exp Nerve Block/ OR exp Anesthesia, Conduction/) OR (((local or infiltration or conduction or block) adj (anesthe: or anaesthe:)).mp. AND (exp Dentistry/ OR exp Stomatognathic system/ OR exp Stomatognathic diseases/))) OR (exp Carticaine/ OR septocaine.mp. OR ultracaine.mp. OR articain$2.mp. OR carticain$2.mp. OR (hoe-40045 or hoe40045 or "hoe 40045" or hoe-045 or hoe045 or "hoe 045").mp. OR 23964-57-0.rn. OR "methyl 4-methyl-3-(2-propylaminopropanoylamino)thiophene-2-carboxylate".mp.) OR Thiophenes/ OR (exp Bupivacaine/ OR bupivacain$5.mp. OR svedocain$2.mp. OR dolanaest.mp. OR sensorcain$2.mp. OR marcain$2.mp. OR carbostesin.mp. OR 2180-92-9.rn.) OR (exp Lidocaine/ OR lidocain$2.mp. OR lignocaine.mp. OR octocaine.mp. OR xylesthesin.mp. OR xylocain$5.mp. OR dalcaine.mp. OR xylocitin.mp. OR xyloneural.mp. OR ("2-2etn-2mephacn" or "2 2etn 2mephacn").mp. OR "2-(diethylamino)-n-(2,6-dimethylphenyl)acetamide".mp. OR 137-58-6.rn.) OR (exp Mepivacaine/ OR mepivacain$2.mp. OR isocain$2.mp. OR meaverin.mp. OR mecain.mp. OR scandonest.mp. OR mepivastesin.mp. OR scandinibsa.mp. OR carbocain$2.mp. OR scandicain$2.mp. OR polocain$2.mp. OR mepihexal.mp. OR isogain$2.mp. OR "N-(2,6-dimethylphenyl)-1-methyl-2-Piperidinecarboxamide".mp. OR "N-(2,6-dimethylphenyl)-1-methyl-2-carboxamide".mp. OR 96-88-8.rn.) OR

(exp Prilocaine/ OR prilocain$2.mp. OR propitocain$2.mp. OR citanest.mp. OR xylonest.mp. OR "N-(2-methylphenyl)-2-(propylamino)-Propanamide".mp. OR 721-50-6.rn.) AND ((exp Endodontics/ OR exp Dental Pulp Diseases/ OR exp Periapical Diseases/ OR exp "Root Canal Filling Materials"/ OR Dental Pulp Test/ OR Dental Pulp/ OR Dental Pulp Cavity/) OR (("root canal".mp. OR apicectom:.mp. OR apicoectom:.mp. OR (dead adj3 (teeth or tooth)).mp. OR (dental adj3 pulp:).mp. OR endodont:.mp. OR endont:.mp. OR endosonic.mp. OR ((lateral or vertical) adj condensation).mp. OR ((non-vital or nonvital) adj3 (teeth or tooth)).mp. OR obtura.mp. OR obturation.mp. OR obturate.mp. OR (pulp adj3 (capping or therap: or extirpation:)).mp. OR (pulp adj (canal$1 or chamber$1)).mp. OR pulpectomy.mp. OR pulpotomy.mp. OR replantation.mp. OR ("root" adj end adj5 fill:).mp. OR ((silver or gutta) adj3 (percha or balata)).mp. OR (silver adj (cone$1 or point$1)).mp. OR thermafil.mp. OR trans-polyisoprene.mp. OR transpolyisoprene.mp. OR ultrafil.mp.) OR ((periradicular or radicular or periapical or apical).mp. AND (exp tooth/ OR exp tooth components/))) NOT (*Apicoectomy/ OR *Dental Implantation, Endosseous, Endodontic/ OR *Retrograde Obturation/ OR *Tooth Replantation/))) limit 1 to (english language and humans)

Database - Embase:

Search Strategy

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3. septocaine (26)
6. ‘articaine’/exp OR articaine (614)
7. ‘carticaine’/exp OR carticaine (608)
8. ‘ultracaine’/exp OR ultracaine (604)
11. ‘thiophene derivative’/de (4,308)
12. #11 OR #8 OR #7 OR #6 OR #3 (4,914)
14. ‘dentistry’/exp (86,832)
16. ‘mouth’/exp OR mouth (618,775)
17. #16 OR #14 (669,577)
18. #17 AND #12 (174)

Appendix V:

Workflow of Trial Identification and Selection-

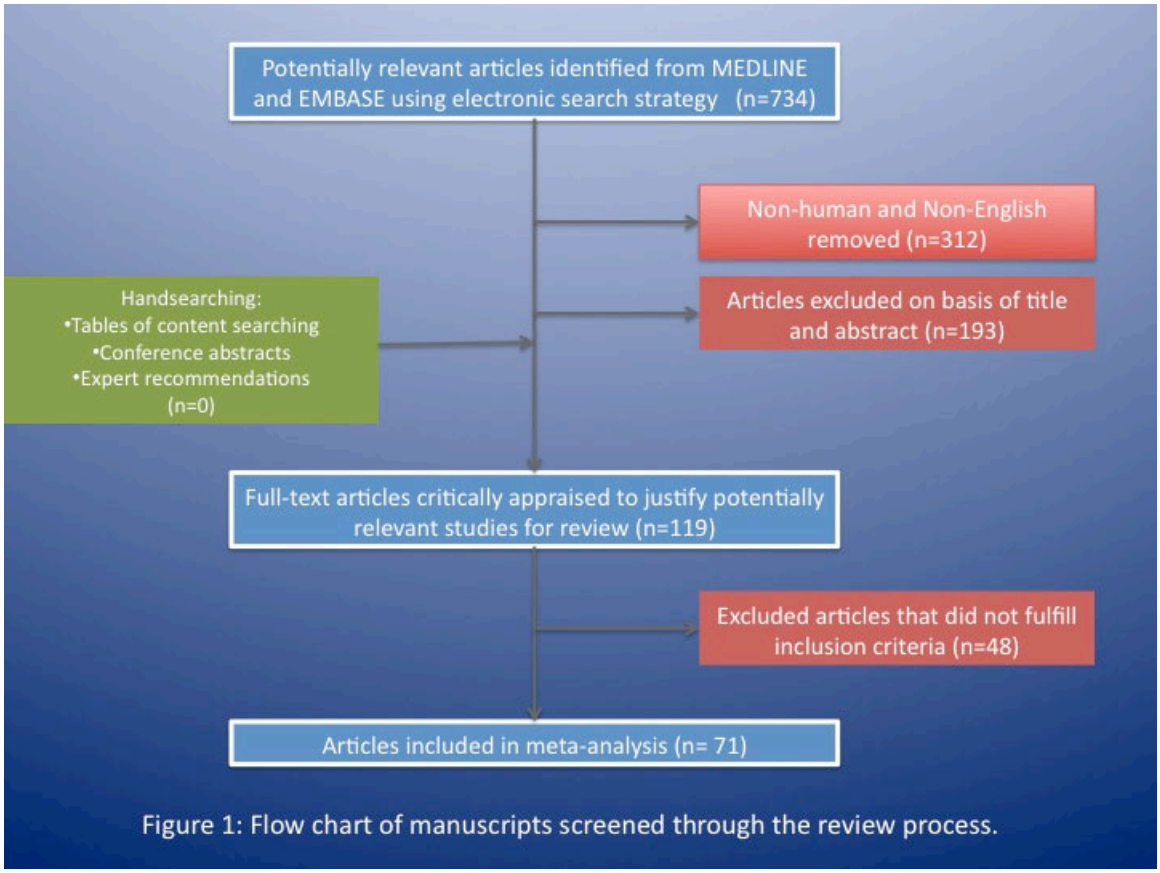

Figure 1: Flow chart of manuscripts screened through the review process.

Appendix VI:

Data Abstraction Form -

1. Author	2.Year	3. Study Design		4. Participants		5. Goal	6. Site and Technique			7. Specific Intervention		8. Design Notes	9.Inclusion
		a. Blinidng	b. Randomization	a. Number	b. Age		a. Infiltration	b. Block	c. Intraosseous	a. Solution/ Dose	b. Groups		
		s/d/n	y/n	#	#	p/s	b/l/mx/mn	s/gg/ak/o	io/pdl	L/M/P/A/B	#		y/n

1. Chief Author
2. Year of Publication
3. a.) s = single, d = double , n = none b.) y = yes, n = no
4. Number of participants, and age range or mean, if stated
5. Referring to the studies goal to test pulpal anesthesia, or only surgical (soft tissue) p = pulpal, s = surgical
6. a.) Infiltration anesthesia given: b = buccal, l = lingual ; also: mx = maxillary, mn = mandiubular;
   b,) Block anesthesia given: s = standard inferior alveolar nerve block, gg = Gow/Gates, ak = Akinosi, o = other
   c.) Intraosseous anesthesia given: io = intraosseous method of delivery using a perforator (Stabident, X-Tip, etc…); pdl = intraligamentary mode of delivery
7. Specific anesthetic solutions that were compared or given, in mg dose a.) L = lidocaine, M = mepivacaine, P = prilocaine, A = articaine, B = bupivacaine
8. Design Notes: a brief description of the study design, what was being looked at specifically
9. Does the trial meet basic inclusion criteria

Appendix VII:

-Glossary of Terms

Anesthetic Success	None or mild pain measured using standard or modified VAS during clinical instrumentation or measured by no response by the tooth to maximal stimulation (80 μA) on two or more consecutive tests with EPT.
Anesthetic Failure	A rating of greater than mild pain measured using a standard or modified VAS during clinical instrumentation or measured by never achieving a 'non-response' to maximal stimulation to EPT stimulation.
Normal Dental Pulp	A clinical diagnostic category in which the pulp is symptom free and normally responsive to vitality testing
Irreversible Pulpitis	A clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is incapable of healing
Analgesia	Absence of sensibility to pain, designating particularly the relief of pain without loss of consciousness
Anesthesia	The loss of feeling or sensation as a result of an anesthetic agent to permit diagnostic and treatment procedures
Paresthesia	A sensation such as burning, prickling, or partial numbness caused by neural injury

Appendix VIII

Pulpal Anesthetic Efficacy of Articaine versus Lidocaine in Dentistry: A Meta-Analysis

Brandt RG, Anderson PF, McDonald NJ, Sohn W, Peters MC

Manuscript in review (JADA)