Spring 5-18-2017

Do Buffered Local Anesthetics Provide More Successful Anesthesia Over Non-Buffered Solutions in Patients Requiring Dental Therapy? – A Systematic Review & Meta-Analysis.

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Abstract
Background:

The pH of commercially available local anesthetics (LAs) is purposefully low (pH 3–4). Decreasing the pH extends the shelf life of the solution and prevents its early oxidation. However, a low pH may produce a burning sensation on the injection site, a slower onset of anesthesia, and a decrease in its clinical efficacy. Buffering of local anesthetics (alkalinization) by adding sodium bicarbonate has been suggested to achieve better pain control, reduce the pain of injection and produce a faster onset of local anesthetics. The aim of this review is to utilize a systematic review to collate evidence on the use of buffering agents with local anesthetics and its effect on causing profound pulpal anesthesia in patients requiring dental therapy and its side effects.

Methods:

Electronic searches were conducted in MEDLINE, Scopus, Cochrane Library, and ClinicalTrials.gov, World Health Organization (WHO) International Trials Registry Platform, OpenGrey & Google Scholar beta. Hand searching of two books "Handbook of Local Anesthesia" & "Successful Local Anesthesia for Restorative Dentistry and Endodontics" was conducted. Also, the reference lists of all included and excluded studies were checked to identify any further trials. Weighted anesthesia success rates and 95% confidence intervals (CIs) were estimated and compared by using a random-effects model.

Results:

14,011 studies were initially identified from the search; 5 double-blind, randomized clinical trials met the inclusion criteria. For combined studies, buffered local anesthetics were more likely than non-buffered solutions to achieve successful anesthesia (odds ratio [OR], **2.29**; 95% confidence interval [CI], 1.11–4.71; P = 0.0232; I2 = 66%).

Conclusion:

This systematic review of double-blind, randomized clinical trials comparing the use of buffered and non-buffered local anesthetics in patients requiring dental therapy provides level **'A'** evidence that is based on the criteria given by the Strength of Recommendation Taxonomy (SORT). In conclusion, the present meta-analysis showed that in patients receiving dental therapy, buffered local anesthetics are more effective than non-buffered solutions when used for mandibular or maxillary anesthesia. Buffering local anesthetics has **2.29** times greater likelihood of achieving successful anesthesia.

Degree Type
Thesis

Degree Name
MSOB (Master of Science in Oral Biology)

Do buffered local anesthetics provide more successful anesthesia over non-buffered solutions in patients requiring dental therapy? – A systematic review & Meta-analysis.

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Keywords: Buffering, Buffered, Sodium Bicarbonate, Alkalinization, Adjusting pH, Local anesthesia, Dentistry, Systematic review.

B A C K G R O U N D: Local anesthetics (LAs) form the backbone of pain control techniques in dentistry. They are the most utilized drugs in dentistry. The site of action of local anesthetics is believed to be the nerve membrane. In nerve cells, action potentials are created by the influx of sodium ions from the surrounding tissues. These action potentials result in the conduction of nerve impulses that produce sensations, including pain. Local anesthetics prevent the conduction of impulses by decreasing the permeability of nerve membranes to sodium ions. By impeding the influx of sodium ions into the neuron, local anesthetics block the conduction of impulses, prevent excitation along a neural pathway, and give rise to anesthesia (Malamed, 2013).

Two ionic forms of the local anesthesia exist in equilibrium within an anesthetic cartridge: RN (the uncharged, deionized, 'active' free base form of the drug which is lipid soluble) and RNH+ (the 'charged' or ionized cationic form, which is not lipid soluble); only the lipid soluble de-ionized form can cross the nerve membrane. Once within the nerve, the RN picks up a H+ with the resultant RNH+ entering a Na+ channel to block nerve conduction. Only after the body buffers the pH of the anesthetic solution closer toward the physiologic range (7.35 – 7.45) does the anesthetic begin to take effect. The time that this transformation requires is a key factor in anesthetic latency (Malamed, 2013). Inflammation and infection represent an additional obstacle in anesthetic performance. Lower tissue pH at the site of inflammation/infection makes it extremely difficult for the typical local anesthetic injection to provide adequate pulpal anesthesia. Inflamed/infected tissue is more acidic, which makes it more difficult for the RN conversion to occur (Hargreaves & Keiser, 2002).

Description of the intervention

The pH of most local anesthetics is purposefully low (pH 3–4), because the charged acid form of the molecule is more stable and more water soluble, and thus gives a longer shelf life (Malamed, 2013). The low pH of local anesthetics may contribute to pain during the actual administration (injection) of the local anesthetic solution; a slower than desired onset of profound (pulpal) anesthesia; and less than optimal effectiveness when seeking to anaesthetize inflamed/infected teeth (Malamed, 2013; Hargreaves & Keiser, 2002).

Buffering of local anesthetics (alkalinization) has been suggested to achieve pain control (Davies, 2003) buffering will increase the dissociation rate of the local anesthetic molecule and thus increase the uncharged base form that crosses the nerve membrane to the intra-

neuronal site where it exerts its action (Gosteli et al., 1995).
The most common method for buffering of local anesthetics is with the addition of sodium bicarbonate. It is an alkalinizing agent, which is most commonly used for the treatment of metabolic acidosis.

How the intervention might work

The addition of sodium bicarbonate to local anesthetics not only will increase the pH of the solution, but will also result in the production of carbon dioxide and water (Ackerman et al., 1992). Several authors have reported on the effect of carbon dioxide on local anesthetics and anesthesia. Condouris & Shakalis (1964) in an isolated rat sciatic nerve model reported that carbon dioxide potentiated the action of local anesthetics by showing that in the presence of carbon dioxide; nerve conduction blockade was significantly greater than in its absence. Bromage et al. (1967) suggested that carbon dioxide acts by increasing the flow of local anesthetic into the nerve and demonstrated that the addition of carbon dioxide to lignocaine shortened the time to onset and spread of analgesia by 20% to 30% in epidural anesthesia. Bokesch et al. (1987) also studied the effects of carbon dioxide and concluded that its role in potentiating local anesthesia was related to either a direct effect on the nerve membrane or by indirect action on intracellular pH.
Catchlove (1973) concluded that carbon dioxide potentiates local anesthesia by three mechanisms:
1. A direct depressant effect of carbon dioxide on the axon.
2. Concentrating the local anesthetic inside the nerve trunk (ion trapping).
3. Converting the local anesthetic to the active cationic form within the nerve axoplasm by lowering its internal pH.

Why it is important to do this review

Buffering of local anesthetics is well known and accepted in medicine and many studies have shown that it reduces pain of injection (Davies, 2003; Burns et al., 2006) and increases clinical efficacy of local anesthetics (Davies, 2003; Curatolo et al., 1998). Davies (2003) reviewed the literature on buffering local anesthetics to decrease the pain of injection and found that buffering local anesthetics with sodium bicarbonate significantly reduced injection pain. Galindo (1983) used pH-adjusted local anesthetics solutions (pH 7.4) in epidurals, peripheral nerve blocks, and regional anesthesia. He found that higher pH

solutions established anesthesia of better quality. The question in dentistry has been: "do buffered local anesthetics provide an advantage over standard solutions in patients requiring dental therapy as well?"

O B J E C T I V E S: The purpose of this study was to conduct a systematic review that address the following population, intervention, comparison, outcome **(PICO) question:** In adults requiring dental therapy, what's the comparative efficacy of buffered local anesthetics compared to non-buffered (standard) solutions in achieving anesthetic success and not increasing incidence of side effects?

M E T H O D S

Criteria for considering studies for this review

Types of studies

All randomized double-blinded clinical trials (RCTs) on anesthetic success of buffered local anesthetics compared with non-buffered (standard) solutions; only parallel group RCTs are included.

Types of participants

Adults of 18 years and older of either sex, all ethnicities, settings, or socio-economic group, absence of a significant medical condition, and in need of dental therapy were the participants included in this review.

Types of interventions

The intervention compared was the use of either buffered or non-buffered (standard) local anesthetics using different delivery routes in patients requiring different dental treatments.

Types of outcome measures

Primary outcome

The primary outcome successful anesthesia that was assessed based on each study's criteria (for example, by using a Verbal Analog Scale, Visual Analogue Scale (VAS), and cold test or electric pulp tests and/or by initiating treatment procedures).

Secondary outcome

Adverse events

The number of patients presenting with adverse events, such as well-established local anesthetic toxic-reactions, skin rash, allergic reactions, or others was extracted.

Exclusion Criteria:

- Insufficient information about the definition of anesthetic success.
- Studies that don't evaluate anesthetic success.
- Dichotomous data for anesthesia outcome were unavailable.
- Crossover design randomized clinical trials (RCTs) done in healthy asymptomatic subjects.
- Patient population requiring treatment other than dental therapy.

Search methods for identification of studies

For the identification of studies included or considered for this review, a detailed search strategy was developed a for each database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

The search strategy combined the subject search with the Cochrane Highly Sensitive Search Strategy for identifying reports of RCTs (2008 revision), as published in Box 6.4.f in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The subject search used a combination of controlled vocabulary and free text-terms based on the search strategy for searching MEDLINE.

Electronic searches

The following databases were searched:

• Cochrane Central Register of Controlled Trials (CENTRAL);
• MEDLINE via PubMed (1946 to 1 November 2016);
• Scopus.

See Appendix 1 for details of all search strategies used. All databases were searched from their inception to November 2016 and no restrictions on language of publication were applied in the electronic searches.

Searching other resources

The following trials registers were searched for ongoing studies:

• World Health Organization (WHO) International Trials Registry Platform (to 1 November 2016) (www.who.int/ictrp/en/);

• U.S. National Institutes of Health Trials Registry (ClinicalTrials.gov) (to 1 November 2016).

Grey literature was searched using the following resources:

• OpenGrey (to 1 November 2016);

• Google Scholar beta (to 1 November 2016).

Two books were hand searched:

• Handbook of Local Anesthesia, 6th edition;

• Successful Local Anesthesia for Restorative Dentistry and Endodontics.

- Also, the reference lists of all included and excluded studies were checked to identify any further trials.

Selection of studies

The abstracts of studies resulting from the searches were assessed. Full text copies of all relevant and potentially relevant studies were obtained, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision were reviewed. After assessment, any duplicate publications or remaining studies that did not match the inclusion criteria were excluded from further review and the reasons for their exclusion noted in the 'Characteristics of excluded studies' table. The screening and selection process is outlined in a PRISMA flow chart 'see Figure 1'

Data extraction and management

Study details were entered into the Characteristics of included studies table (Table 2). A data extraction sheet based on the Cochrane Consumers and Communication Review Groups data extraction template (Cochrane Consumers and Communication Review Group (2015). Data extraction template. Available at: http://cccrg.cochrane.org/author-resources) was used to record data extracted from the full-text article. The data extracted from each included article was the following:

1. General information (author, year, title, journal, dental procedure)
2. Trial characteristics (sample size, type of study design, method of randomization,

allocation concealment, blinding)
3. Type of intervention (buffering agent used, anesthetics used, injection route/delivery method, pH of the solution)
4. Characteristics of trial participants (number of patients for each intervention, mean age, gender distribution)
5. Type of outcome measure (method to assess anesthesia success, definition of success).
6. Miscellaneous (conclusion and source of funding/conflict of interest)

Assessment of risk of bias in included studies

The selected trials were graded following the domain-based evaluation described in Chapter 8 of the Cochrane Handbook (http://handbook.cochrane.org).
The following domains were assessed as 'low risk' of bias, 'unclear' (i.e. uncertain risk of bias) or 'high risk' of bias.
1. Sequence generation
2. Allocation concealment
3. Blinding (of participants, personnel and outcome assessors, data analysts)
4. Incomplete outcome data
5. Selective outcome reporting
6. Other potential sources of bias
These assessments were reported in the "Risk of bias" tables for each individual study.
In addition, the overall risk of bias in each included study was categorized according to the following:
• Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
• Un-clear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear.
• High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

For dichotomous outcomes, the estimate of effect of the intervention was expressed as odds ratios (OR) together with 95% confidence intervals (CI).

Dealing with missing data

The original investigators were contacted in cases of missing data.

Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. Statistical values of 30% to 60% indicate moderate to high heterogeneity, 50% to 90% substantial heterogeneity and 75% to 100% studies has considerable heterogeneity (Higgins & Green, 2011).

Assessment of reporting biases

Assessment of reporting bias through funnel plots and formal testing (Egger, 1997) were planned if data from 10 or more studies were available.

R E S U L T S

Description of studies

See Characteristics of included studies (Table 2) and Characteristics of excluded studies (Table 3).

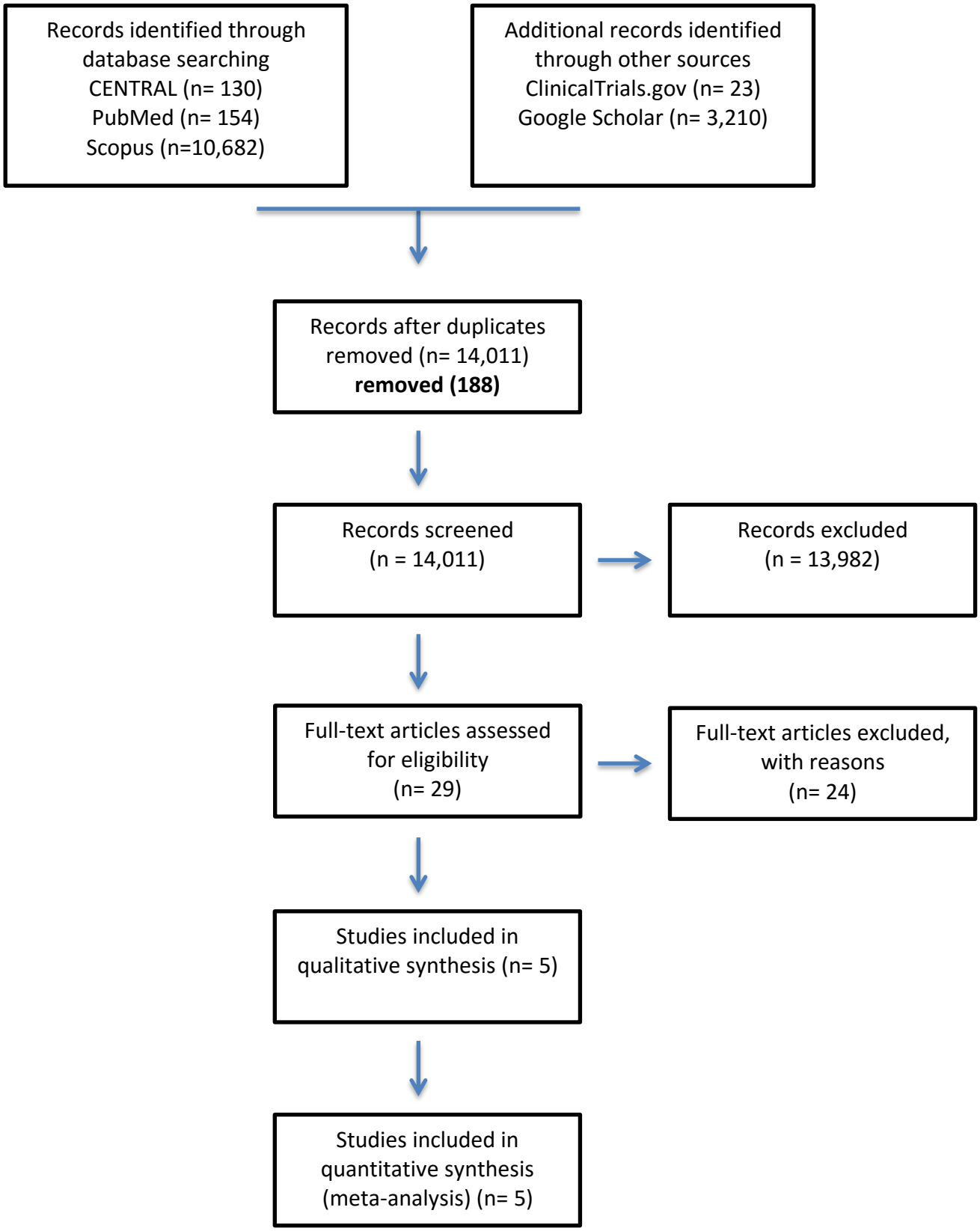
Results of the search

The electronic searches retrieved 14,011 references to studies. After examination of the titles and abstracts of these references, all of those that did not match the inclusion criteria and were clearly ineligible were eliminated. Full text copies of the remaining studies were obtained and subjected to further evaluation. Searching the grey literature through Google Scholar Beta and OpenGrey, two eligible studies could be retrieved.

The searches of the WHO International Clinical Trials Registry Platform and the ClinicalTrials.gov databases did not identify any ongoing trials.

Hand searching of two books revealed that no additional studies could be retrieved over and above those that had already been identified in the electronic search. For further details see 'Study Flow' diagram (Figure 1).

Figure 1: Study flow chart



Included studies

Five double-blind, randomized controlled trials (RCTs) satisfied the inclusion criteria (Al-Sultan et al., 2006; Gupta et al., 2014; Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015). See Characteristics of included studies table for further details (Table 2).

Characteristics of the trial settings, investigators and methods

All the studies were parallel group double-blind, randomized controlled trials which had been conducted in Iraq, India, Iran and the USA. A university or dental school was the setting in all the studies (Al-Sultan et al., 2006; Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015), except for one study, which was conducted in a private practice (Gupta et al., 2014).

Characteristics of the participants

A total of 560 participants were investigated and provided 669 teeth in the five studies. The age of the participants ranged from 18 to 64 years and included both genders. Anterior and posterior teeth, both single and multi-rooted, were investigated. In three of the included studies, the participants had a clinical diagnosis of symptomatic irreversible pulpitis requiring root canal treatment (Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015). In another study (Al-Sultan et al., 2006) participants had either failed conventional root canal treatment with large periapical radiolucency or failed endodontic surgery requiring periapical surgery/re-surgery, whereas in (Gupta et al., 2014) participants had periapical infection and teeth were indicated for extraction.

Characteristics of the interventions

There was considerable methodological heterogeneity between studies that included differences in anatomic location of teeth being anesthetized (maxilla or mandible, anterior or posterior), tooth type (molars, premolars, or anterior teeth), volume of anesthetic solution administered during the intervention (0.3 mL, 1.62 mL, 1.8 mL, 2.8 mL, 3.7 mL), volume of buffering solution administered (0.1 mL, 0.18 mL, 0.7 mL, 1.3 mL), concentration of epinephrine (1: 80,000, 1: 100,000). Anesthetic solutions were delivered via inferior alveolar nerve block (IANB), maxillary buccal infiltration (MaxBI), and supplemental mandibular buccal infiltration (SupManBI).

All studies used sodium bicarbonate as a buffering agent.

- 1.8 ml of 2% Lidocaine with 1: 80,000 epinephrine **(pH 3.5)** vs. 1.7 ml 2% Lidocaine with 1: 80,000 epinephrine + 0.1 ml of 8.4% sodium bicarbonate **(pH 7.2)** (each patient was given 3 carpules, maxillary buccal infiltration) (Al-Sultan et al., 2006).
- 3.7 ml of 2% Lidocaine with 1: 80,000 epinephrine **(pH 3.91)** vs. 3.7 ml 2% Lidocaine with 1: 80,000 epinephrine + 1.3 ml of 7.4% sodium bicarbonate **(pH 7.51)** (Maxillary buccal infiltration) (Gupta et al., 2014).
- 1.62 ml of 2% Lidocaine with 1: 80,000 epinephrine + 0.18 ml of sterile saline vs. 1.62 ml of 2% Lidocaine with 1: 80,000 epinephrine + 0.18 ml of 8.4% sodium bicarbonate (each patient was given 2 carpules, IANB) (Saatchi et al., 2015).
- 0.3 ml of 2% Lidocaine with 1: 80,000 epinephrine + 0.7 ml of sterile saline vs. 0.3 ml of 2% Lidocaine with 1: 80,000 epinephrine + 0.7 ml of 8.4% sodium bicarbonate (Mandibular buccal infiltration) (Saatchi et al., 2016).
- 2.8 ml of 4% Lidocaine with 1: 100,000 epinephrine **(pH 4.51)** vs. 2.62 ml 4% Lidocaine with 1: 100,000 epinephrine + 0.18 ml of 8.4% sodium bicarbonate **(pH 7.05)** (each patient was given 2 carpules, IANB) (Schellenberg et al., 2015).

Characteristics of the outcomes measures

All studies evaluated anesthetic success of buffered local anesthetics and controls, which is the primary outcome of this review. In three of the included studies (Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015) anesthetic success was defined as no or mild pain (≤ 54 mm on a 170-mm visual analog scale) based on Heft-Parker Visual analogue scale recordings upon access cavity preparation or initial instrumentation. In study by (Al-Sultan et al., 2006) pain grade during periapical surgery was recorded by the operator and represented the patients' pain response during the period of the operation according to the Dobb and Devier System where no or mild pain tolerated by the patient is considered as success or if the patient experienced severe pain that was intolerable and additional anesthesia was administered that was considered as failure. In Gupta et al., (2014) no pain or mild pain tolerable by patient during extraction based on Visual analogue scale (VAS) was considered as success.

Excluded studies

We excluded the majority of references, as they did not report relevant outcomes, didn't present data as dichotomous outcome, or had other characteristics that did not satisfy the inclusion criteria (see Characteristics of excluded studies, Table 3).

Risk of bias in included studies

***Allocation**

-Randomization

In four studies the random sequence generation was unclear (Al-Sultan et al., 2006; Gupta el at., 2014; Saatchi et al., 2015; Saatchi et al., 2016), only one study had an adequate randomization (Schellenberg et al., 2015).

-Allocation concealment

One study had an unclear allocation concealment (Gupta et al., 2014) but all other studies had adequate allocation concealment (Al-Sultan et al., 2006; Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015).

***Blinding**

All included studies were double blinded, and all of them had an adequate blinding of participants and personnel and of outcome assessment as well.

***Incomplete outcome data**

All studies had complete outcome data.

***Selective outcome reporting**

There was no selective reporting of outcomes in any of the studies.

***Other potential sources of bias**

There were no other potential sources of bias in any of the studies.

***Overall risk of bias**

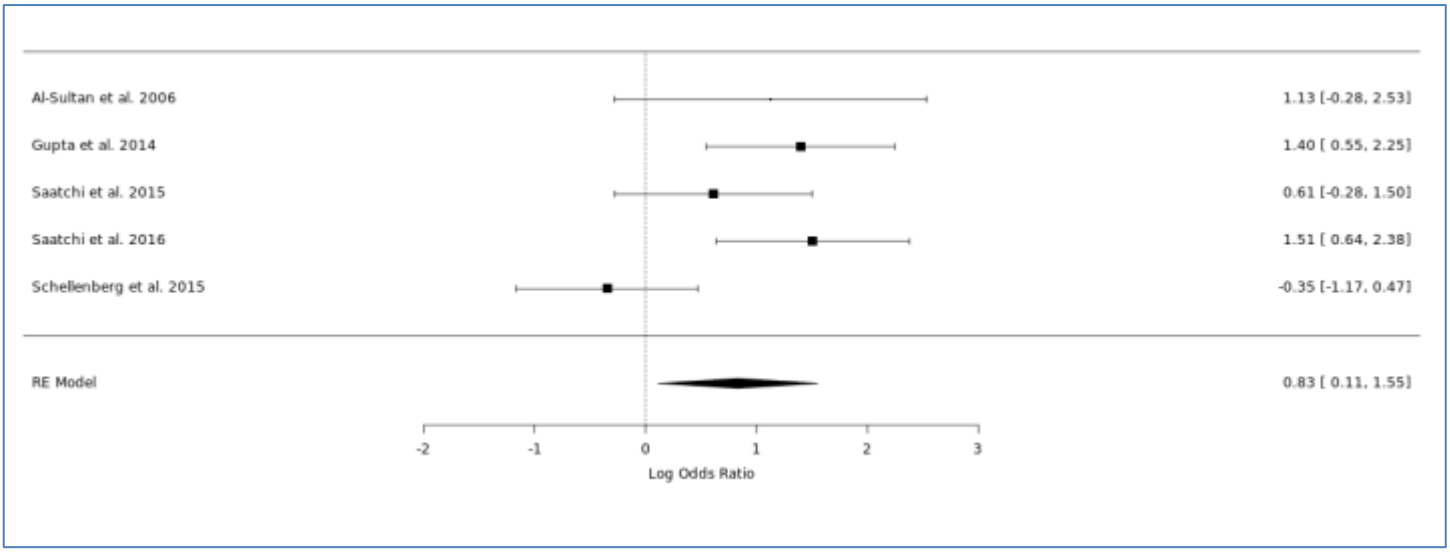
Four studies are judged to have overall unclear risk of bias (Al-sultan et al., 2006; Gupta et al., 2014; Saatchi et al., 2015; Saatchi et al., 2016), only one study (Schellenberg et al., 2015) had an overall low risk of bias.

Table 1: Risk of bias assessment:

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Al-Sultan et al. 2006	?	+	+	+	+	+	+
Gupta et al. 2014	?	?	+	+	+	+	+
Saatchi et al. 2015	?	+	+	+	+	+	+
Saatchi et al. 2016	?	+	+	+	+	+	+
Schellenberg et al. 2015	+	+	+	+	+	+	+

Study	**Selection: Random sequence generation**	**Selection: Allocation concealment**	**Performance: Blinding of participants and personnel**	**Detection: Blinding of outcome assessment**	**Attrition: Incomplete outcome data**	**Reporting: Selective reporting**	**Other biases**
Al-Sultan et al. 2006	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gupta et al. 2014	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Saatchi et al. 2015	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Saatchi et al. 2016	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schellenberg et al. 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Figure 2: Forest plot of ORs of buffered local anesthetics vs. non-buffered form: showing buffered local anesthetics to have treatment effect 2.29 times greater than non-buffered form.



Primary outcomes

Successful anesthesia

The primary outcome assessed was successful anesthesia that was based on each study's criteria. Success was defined in 3 studies (Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015) as no pain or mild/bearable pain/discomfort according to patient-reported pain scores (eg. HP-VAS) during endodontic treatment access cavity preparation and instrumentation; one study defined successful anesthesia as no pain or mild/tolerable pain during procedure (Al-Sultan et al., 2006). In study by Gupta et al., (2014) no pain or mild pain tolerable by patient during extraction based on visual analogue scale (VAS) was considered as success.

Secondary outcomes

Adverse events

Gupta et al., (2014) reported the absence of adverse events whereas the other studies made no mention.

Meta-analysis

Success rates for buffered and non-buffered local anesthetics ranged from low of 32% and 40%, respectively, to 92.5% and 80%, respectively (Table 2). For combined studies, buffered local anesthetics were more likely than non-buffered solutions to achieve successful anesthesia (odds ratio [OR], **2.29**; 95% confidence interval [CI], 1.11-4.71; P = 0.0232; I2 = 66%).

As recommended by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) section "10.4.3.1 Recommendations on testing for funnel plot asymmetry" (http://handbook.cochrane.org), tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry. As in this review we have only 5 studies included in the final meta-analysis, publication bias won't be assessed by tests due to lack of enough sample size and number of studies included to detect publication bias.

DISCUSSION

This systematic review of double-blind, randomized clinical trials (RCTs) comparing the use of buffered and non-buffered local anesthetics in patients requiring dental therapy provides level 'A' evidence that is based on the criteria given by the Strength of Recommendation Taxonomy (SORT). The main conclusion that can be drawn from this study is that there is a significant advantage to Increasing the pH (buffering) of local anesthetic solutions as it increases the quality of the anesthetic blockade.

It should be mentioned that in this review crossover design randomized clinical trials (RCTs) done in healthy asymptomatic subjects were excluded. In such situations, once local anesthetic solution is injected into the tissues, the natural process of buffering should occur rapidly. The normal pH of tissues is 7.4. A drug with a lower pH (e.g. 3.5) that is injected into tissues will be buffered by the body, and the pH of the injected solution will be slowly increased toward pH of 7.4. As this process continues, the percentage of the base in the solution steadily increases which could readily penetrates the nerve providing the desired anesthetic effect. However, cases of inflammation/infection represent an additional obstacle in anesthetic performance. The lower pH at the site of inflammation/infection makes it extremely difficult for the typical local anesthetic injection to provide adequate pulpal anesthesia. Acidic pH of the tissue reduces the amount of the base form of local anesthetic to penetrate the nerve membrane. Consequently, there is less of the ionized form within the nerve to achieve anesthesia. Hence, in this systematic review only double-blind randomized clinical trials (RCTs) were included where subjects require dental therapy for underlying inflammation/infection, instead of healthy subjects, to evaluate the effect of buffering local anesthetics in such challenging conditions.

This systematic review included several studies not previously reviewed. Three of these studies evaluated mandibular posterior teeth (Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015), and two evaluated maxillary anterior teeth (Al-Sultan et al., 2006; Gupta et al., 2014). In those two studies (Al-Sultan et al., 2006; Gupta et al., 2014) the success rate was generally higher than studies on mandibular posterior teeth included in this review, and that was not surprising as clinically, maxillary anesthesia is more easily obtained and successful than mandibular anesthesia (Kaufman et al., 1984). In maxillary anterior and posterior teeth, infiltration anesthesia results in a high incidence (90% - 95%) of

successful anesthesia. Whereas achieving successful anesthesia in mandibular teeth specially in cases of symptomatic irreversible pulpitis is challenging and more difficult (Fluery, 1990; Hargreaves et al., 2002; Quint, 1981). Reported clinical success of inferior alveolar block alone in cases of symptomatic irreversible pulpitis is between 19% to 56% which could explain lowered success rate in three studies (Saatchi et al., 2015; Saatchi et al., 2016; Schellenberg et al., 2015) included in this review.

One potential method to increase anesthetic success is to increase the injection volume of local anesthetic solution. In this review, different volumes and concentrations of local anesthetic solution were evaluated (Table 2). However, clinical studies showed that increasing the volume of 2% lidocaine (2 cartridges) does not increase the incidence of pulpal anesthesia of mandibular posterior teeth with the inferior alveolar nerve block (Nusstein et al., 2002; Vreeland et al., 1989; Yared et al., 1997).

The addition of epinephrine to local anesthetic solutions facilitates vasoconstriction, slows systemic absorption, and increases the duration and depth of local anesthetics. In this review 4 of the 5 studies used 1:80,000 epinephrine (Al-Sultan et al., 2006; Gupta et al., 2014; Saatchi et al., 2015; Saatchi et al., 2016) and one study used 4% lidocaine with 1: 100,000 epinephrine (Schellenberg et al., 2015). Dagher et al. (1997) found no significant differences in degree of anesthesia obtained by using 2% lidocaine with 1: 50,000, 1: 80,000, or 1: 100,000 concentrations of epinephrine. it is reasonable to expect that these variations in local anesthetic “volume and concentration” and epinephrine concentration would not likely have a major impact on the outcomes evaluated in this review.

In this review, two studies evaluated the effect of buffering local anesthetics in patients receiving inferior alveolar nerve block (IANB) and having symptomatic irreversible pulpitis (Saatchi et al., 2015; Schellenberg et al., 2015). Schellenberg et al., (2015) showed that increasing the pH of local anesthetic solutions didn’t improve anesthetic success of IANB in patients having symptomatic irreversible pulpitis. Their results showed that the original formulation of the 4% lidocaine with 1: 100,000 epinephrine provided 40% success, while administration of the buffered formula resulted in 32% success. Saatchi et al., (2015) found that using 3.24 mL buffered 2% lidocaine with 1: 80,000 epinephrine in patients with symptomatic irreversible pulpitis resulted in a success rate (none or mild pain during access or instrumentation) of 62% and the original formula resulted in success of 47.5%. The lower

success rate of buffered local anesthetic solution in the study by Schellenberg et al., (2015) may have been caused by population differences and lower actual amount of the injected lidocaine in the buffered formula group compared to the original one (14.4 mg lower).

In the present review only 1 of the 5 studies reported the absence of adverse events (Gupta et al., 2014) whereas the other studies made no mention of it. It is important that future clinical studies incorporate the reporting of adverse events in their methodology.

Buffering of lidocaine is most commonly performed by adding 1 ml of 8.4% sodium bicarbonate to 10 ml of local anesthetic. An 8.4% solution of sodium bicarbonate would contain 1 mEq each of sodium and bicarbonate ions per mL. The 10:1 local anesthetic to bicarbonate ratio has been shown to raise the pH to a more physiologic range (Richtsmeier & Hatcher, 1995). Buffering of local anesthetic solutions with sodium bicarbonate not only raises the pH of the solutions but also leads to production of carbon dioxide (CO2) and water as a byproduct. Catchlove, (1973) first demonstrated that CO2 in a lidocaine solution has an independent anesthetic effect and that both chemicals have similar effects on peripheral nerves. He suggested that in situations in which a solution contains both lidocaine and CO2, the CO2 may cause the more immediate form of analgesia because it diffuses rapidly through the nerve sheath and probably reaches the axon before the local anesthetic. While this initial effect may be beneficial, as a gas, however, buffered anesthetics in a glass carpule may be considered unstable. Without the timely injection of the buffered mixture, the unreleased gas may be further responsible for the recognized precipitate over time. Tissue damage from such an unstable mixture and precipitate could also be of clinical concern. No precipitation was reported in any of the studies included. All local anesthetics containing epinephrine are marketed at acidic pHs which provides chemical stability and longer shelf life. The sodium metabisulfite antioxidant which increases the shelf life of epinephrine further decreases the pH (Fyhr & Brodin, 1987). Furthermore, clinicians need to be aware that although the local anesthetic concentration in buffered solutions remains constant over time, epinephrine concentrations in buffered lidocaine solutions decrease substantially over 24 hours (Larson et al., 1991; Robinson et al., 2000). Therefore, production of prepared buffered solutions of local anesthetic in factories is not preferred.

In 2010, the Food and Drug Administration approved the Onpharma® mixing system (Onpharma Inc., www.onpharma.com) for buffering of lidocaine. The mixing system consists of three parts: the Onpharma® mixing pen, the Onpharma® cartridge connector, and the Onset® Sodium Bicarbonate Injection, 8.4% USP Neutralizing Additive Solution. This system

provides a convenient chairside mixing and delivery of buffered lidocaine and is easy to use and simple to learn. However, it has some disadvantages, the price of the unit is $450.00 with cartridge connectors $50.00 (box of 4) and sodium bicarbonate is $225.00 (box of 4 ampules) which increases the cost of a dental treatment. The sodium bicarbonate needs to be replaced once per day with the connectors replaced for every patient. Furthermore, the time required for each patient is about 1 minute to set up the assembly and less than 15 seconds to mix the solutions. Other than the expense and time required to mix solutions, this system is technique sensitive, an extra step is needed to mix the solutions and there are some concerns with infection control. Another alternative would be the preparation of double vials. The upper vial will have sodium bicarbonate as a dry substance and the lower vial the anesthetic solution so that the bicarbonate can be introduced into the local anesthetic solution at the time of injection.

Clinicians should be mindful of the limitation that this systematic review focused on the quality of the anesthetic blockade and did not evaluate other factors as the pain on injection, the duration or the post-injection discomfort when interpreting the results of the review. Moreover, the underlying heterogeneity of the included studies presents limitations. Such heterogeneity includes geographic location, sample size, number and experience of operators, amount and concentration of sodium bicarbonate added, pH of the solution and tissue, the volume of local anesthetic, the concentration of epinephrine, reproducibility of injection route, and evaluation scale used to assess pain and definition of success (VAS, HP-VAS, access cavity, pain felt during the procedure). In an effort to allow for heterogeneity issues, the meta-analysis used a random-effects model of statistical analysis, as opposed to the fixed-effects model that is used in cases with no evidence of heterogeneity.

To our best knowledge this systematic review is the first to evaluate the effect of buffering local anesthetic solutions on efficacy and success of local anesthesia in patients requiring dental therapy. Although the number of studies in this analysis was limited and heterogeneity existed, the results of this systematic review indicate that buffering of local anesthetics solutions admixture immediately prior to clinical use increase its efficacy without any side effects.

C O N C L U S I O N

In conclusion, the present meta-analysis showed that in patients requiring dental therapy, buffered local anesthetics is more effective than non-buffered solutions when used for mandibular or maxillary anesthesia. Buffering local anesthetics has **2.29** times greater likelihood of achieving successful anesthesia. Also, further comparative studies with other buffering agents and larger sample sizes are recommended.

Table 2: Characteristics of Included Studies:							
Author, year	**No. of participants**	**Operative procedure**	**Location and tooth type**	**Anesthetic delivery route**	**Interventions compared**	**Definition of successful anesthesia**	**Results for anesthetic success**
Al-Sultan et al. 2006	80	Periapical surgery	Maxillary anterior teeth	All received MaxBI	I: 2% Lidocaine with 1: 80,000 epinephrine in a 1.7 ml solution + 0.1ml 8.4% Sodium Bicarbonate, **pH 7.2** (3 carpules) C: 2% Lidocaine with 1: 80,000 epinephrine in a 1.8 ml solution, **pH 3.5** (3 carpules)	No pain or mild pain during procedure	Buffered LA = 37/40 = 92.5% Control = 32/40 = 80%
Gupta et al. 2014	200	Extraction	Maxillary teeth	All received MaxBI	I: 3.7 mL 2 % lidocaine with 1: 80,000 epinephrine + 1.3 mL 7.4 % sodium bicarbonate, **pH 7.51** C: 3.7 mL 2 % lidocaine with 1: 80,000 epinephrine, **pH 3.91**	No pain or mild pain during procedure (VAS)	Buffered LA = 92/100 = 92% Control = 74/100 = 74%
Saatchi et al. 2015	80	RCT for patients experiencing symptomatic irreversible pulpitis	Mandibular posterior teeth	All received IANB	I: 1.62 ml of 2% lidocaine with 1: 80,000 epinephrine buffered + 0.18 mL 8.4% sodium bicarbonate (2 carpules) C: 1.62 ml of 2% lidocaine with 1: 80,000 epinephrine + 0.18 mL sterile distilled water (2 carpules)	No pain or mild pain during access cavity preparation and instrumentation (HP-VAS)	Buffered LA = 25/40 = 62.5% Control = 19/40 = 47.5%
Saatchi et al. 2016	100	RCT for patients experiencing	Mandibular first molar teeth	Patients received buccal infiltration injection of	I: 0.7 mL 8.4% sodium bicarbonate with 0.3 mL 2% lidocaine containing 1: 80,000 epinephrine	No pain or mild pain during access	Buffered LA = 39/50 = 78%

		symptomatic irreversible pulpitis		either 0.7 mL 8.4% sodium bicarbonate with 0.3 mL 2% lidocaine containing 1: 80,000 epinephrine or 0.7 mL sterile distilled water with 0.3 mL 2% lidocaine containing 1: 80,000 epinephrine. After 15 minutes, all the patients received conventional IANB injection using 3.6 mL 2% lidocaine with 1: 80,000 epinephrine	or C: 0.7 mL sterile distilled water with 0.3 mL 2% lidocaine containing 1: 80,000 epinephrine	cavity preparation and instrumentation (HP-VAS)	Control = 22/50 = 44%
Schellenberg et al. 2015	100	RCT for patients experiencing symptomatic irreversible pulpitis	Mandibular posterior teeth	All received IANB	I: 2.8 mL 4% lidocaine with 1: 100,000 epinephrine buffered with 0.18 ml 8.4% sodium bicarbonate using the Onset buffering system, **pH 7.05** C: 2.62 mL 4% lidocaine with 1: 100,000 epinephrine, **pH 4.51**	No pain or mild pain during procedure (HP-VAS)	Buffered LA = 16/50 = 32% Control = 20/50 = 40%

C: Control**, I:** Intervention

Table 3: Characteristics of Excluded Studies:	
Study	**Reason for exclusion**
Agarwal et al. (2015). To evaluate the anesthetic efficacy of sodium bicarbonate buffered 2% lidocaine with 1: 100,000 epinephrine in Inferior Alveolar Nerve Blocks: A prospective, randomized, double blind study	Doesn't evaluate the anesthetic success
Al-Sultan et al. (2004). Effectiveness of pH adjusted lidocaine versus commercial lidocaine for maxillary infiltration anesthesia	Full-text article couldn't be retrieved
Auerbach et al. (2009). A Randomized, Double-blind Controlled study of Jet Lidocaine Compared to Jet Placebo for Pain Relief in Children Undergoing Needle Insertion in the Emergency Department	Doesn't meet inclusion criteria
Azizkhani et al. (2015). The effects of injections of warmed bicarbonate-buffered Lidocaine as a painkiller for patients with trauma	Patients requiring treatment other than dental therapy
Balasco et al. (2013). Buffered lidocaine for incision and drainage: A prospective, randomized double-blind study	Didn't define anesthetic success, didn't present data as dichotomous outcome
Bartfield et al. (1995). The effects of warming and buffering on pain of infiltration of lidocaine	Patients requiring treatment other than dental therapy
Bowles et al. (1995). Clinical evaluation of buffered local anesthetic	Doesn't evaluate the anesthetic success
Burns et al. (2006). Decreasing the pain of local anesthesia: a prospective, double-blind comparison of buffered, premixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy

Christoph et al. (1988). Pain reduction in local anesthetic administration through pH buffering	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy
Colaric at al. (1998). Pain reduction in lidocaine administration through buffering and warming	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy
Harreld et al. (2015). Efficacy of a buffered 4% lidocaine formulation for incision and drainage: A prospective, randomized, double-blind study	Didn't define anesthetic success, didn't present data as dichotomous outcome
Hobeichet al. (2013). A prospective, randomized, double-blind comparison of the injection pain and anesthetic onset of 2% lidocaine with 1: 100,000 epinephrine buffered with 5% and 10% sodium bicarbonate in maxillary infiltrations.	Doesn't evaluate the anesthetic success
Kashyap et al. (2011). Effect of alkalinisation of lignocaine for intraoral nerve block on pain during injection, and speed of onset of anaesthesia	Doesn't evaluate the anesthetic success
Kim et al. (2005). A clinical study of anesthetic efficacy of alkalinizing lidocaine in inferior alveolar nerve blocks.	Healthy volunteers as subjects
Lee et al. (2013). The effect of buffered lidocaine in local anesthesia: a prospective, randomized, double-blind study	Patients requiring treatment other than dental therapy
Malamed et al. (2013). Faster onset and more comfortable injection with alkalinized 2% lidocaine with epinephrine 1: 100,000.	Doesn't evaluate the anesthetic success

Matsumoto et al. (1994). Reducing the discomfort of lidocaine administration through pH buffering	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy
Momsen et al. (2000). Buffering of lignocaine-epinephrine - A simple method for less painful application of local anaesthesia	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy
Primosch et al. (1996). Pain elicited during intraoral infiltration with buffered lidocaine	Doesn't evaluate the anesthetic success
Redd et al. (1990). Towards less painful local anesthesia	Patients requiring treatment other than dental therapy
Shurtz et al. (2015). Buffered 4% articaine as a primary buccal infiltration of the mandibular first molar: A prospective, randomized, double-blind study	Healthy volunteers as subjects
Singer et al. (1995). Infiltration Pain and Local Anesthetic Effects of Buffered vs. Plain 1% Diphenhydramine	Doesn't evaluate the anesthetic success, Patients requiring treatment other than dental therapy
Shyamala et al. (2016). A Comparative Study Between Bupivacaine with Adrenaline and Carbonated Bupivacaine with Adrenaline for Surgical Removal of Impacted Mandibular Third Molar	Doesn't evaluate the anesthetic success
Whitcomb et al. (2010). A prospective, randomized, double-blind study of the anesthetic efficacy of sodium bicarbonate buffered 2% lidocaine with 1: 100,000 epinephrine in inferior alveolar nerve blocks	Healthy volunteers as subjects

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Appendix 1: Search Strategies			
PubMed Search Strategy November 1, 2016:			
Search	Query	Items found	Time
#1	Search **Buffers [MeSH]**	21056	13:25:33
#2	Search **Sodium Bicarbonate [MeSH]**	4123	13:25:45
#3	Search **Buffered**	79493	13:25:54
#4	Search **Buffering**	10940	13:26:03
#5	Search **Alkalinization**	3544	13:26:12
#6	Search **Adjusting pH**	32045	13:26:20
#7	Search **Sodium Bicarbonate**	11960	13:26:32
#8	Search **((((((Buffers [MeSH]) OR Sodium Bicarbonate [MeSH]) OR Buffered) OR Buffering) OR Alkalinization) OR Adjusting pH) OR Sodium Bicarbonate**	129715	13:27:17
#9	Search **Anesthetics, Local [MeSH]**	30129	13:27:37
#10	Search **Local anesthetics**	102586	13:27:44
#11	Search **(Anesthetics, Local [MeSH]) OR Local anesthetics**	102586	13:27:55
#12	Search **Dental pulp [MeSH]**	10909	13:28:03
#13	Search **Injections [MeSH]**	261209	13:28:10
#14	Search **Success**	215780	13:28:17
#15	Search **Pain free**	6366	13:28:25
#16	Search **((((Dental pulp [MeSH]) OR Injections [MeSH]) OR Success) OR Pain free)**	513588	13:28:56
#17	Search **randomized controlled trial [pt]**	421710	13:36:43
#18	Search **randomized [tiab]**	391428	13:36:54
#19	Search **placebo [tiab]**	179612	13:37:04
#20	Search **drug therapy [sh]**	1876818	13:37:17
#21	Search **randomly [tiab]**	260937	13:37:24
#22	Search **trial [tiab]**	445253	13:37:30
#23	Search **groups [tiab]**	1647429	13:37:38

#24	Search **((((((randomized controlled trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab]**	3870064	13:38:14
#25	Search **((((((((((Buffers [MeSH]) OR Sodium Bicarbonate [MeSH]) OR Buffered) OR Buffering) OR Alkalinization) OR Adjusting pH) OR Sodium Bicarbonate)) AND ((Anesthetics, Local [MeSH]) OR Local anesthetics)) AND (((((Dental pulp [MeSH]) OR Injections [MeSH]) OR Success) OR Pain free)) AND (((((((randomized controlled trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab])**	163	13:38:51
#26	Search **animals [mh] NOT humans [mh]**	4266417	13:39:17
#27	Search **((((((((((((Buffers [MeSH]) OR Sodium Bicarbonate [MeSH]) OR Buffered) OR Buffering) OR Alkalinization) OR Adjusting pH) OR Sodium Bicarbonate)) AND ((Anesthetics, Local [MeSH]) OR Local anesthetics)) AND (((((Dental pulp [MeSH]) OR Injections [MeSH]) OR Success) OR Pain free)) AND (((((((randomized controlled trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab])))) NOT (animals [mh] NOT humans [mh])**	154	13:52:51

Cochrane Central Register of Controlled Trials (CENTRAL) Search Strategy November 1, 2016:		
Search	Query	Items found
#1	"Sodium Bicarbonate":ti,ab,kw (Word variations have been searched)	986
#2	MeSH descriptor: [Sodium Bicarbonate] explode all trees	559
#3	buffers:ti,ab,kw (Word variations have been searched)	1808
#4	MeSH descriptor: [Buffers] explode all trees	284
#5	buffered	842
#6	buffering	377
#7	alkalinization	166
#8	adjusting PH	164
#9	**#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8**	**3019**
#10	MeSH descriptor: [Anesthetics, Local] explode all trees	6730
#11	MeSH descriptor: [Anesthesia, Local] explode all trees	1917
#12	local anesthesia	9373
#13	**#10 or #11 or #12**	**11709**
#14	MeSH descriptor: [Dental Pulp] explode all trees	268
#15	MeSH descriptor: [Injections] explode all trees	20305
#16	success	18977
#17	intraoral	677
#18	pain free	7900
#19	**#14 or #15 or #16 or #17 or #18**	**50256**
#20	randomized controlled trial	552524
#21	randomized	604020
#22	placebo	185419
#23	randomly	145697
#24	trial	703496
#25	**#20 or #21 or #22 or #23 or #24**	**786961**
#26	**#9 AND #13 AND #19 AND #25**	**131**

Scopus Search Strategy November 1, 2016:		
Search	Query	Items found
#1	"dental therapy"	487
#2	dentistry	113,639
#3	intraoral	12,050
#4	**#1 OR #2 OR #3**	**19,314,560**
#5	buffered	52,285
#6	buffering	28,306
#7	alkalinization	6,163
#8	adjusting PH	4,592
#9	"sodium bicarbonate"	12,543
#10	**#5 OR #6 OR #7 OR #8 OR #9**	**13,645,209**
#11	**"Local anesthetics"**	39,686
#12	**"Local anesthesia"**	39,624
#13	**#11 OR #12**	**3,890,333**
#14	**"dental pulp"**	24,896
#15	**injection**	1,041,097
#16	**"intraoral injection"**	63
#17	**success**	574,908
#18	pain free	7,340
#19	**#14 OR #15 OR #16 OR #17 OR #18**	6,767,240
#20	"randomized controlled trial"	571,556
#21	randomized	803,117
#22	Placebo	341,481
#23	"drug therapy"	495,700
#24	randomly	425,460
#25	trial	1,875,858
#26	groups	6,231,839
#27	**#20 or #21 or #22 or #23 or #24 or #25 or #26**	**5,851,925**

#28	#4 AND # 10 AND #13 AND #19 AND #27	10,682

World Health Organization (WHO) International Clinical Trials Registry Platform Search Strategy

Buffered AND local anesthesia
Buffering AND local anesthesia
Adjusting pH AND local anesthesia
Alkalinization AND local anesthesia
Sodium bicarbonate AND local anesthesia

US National Institutes of Health Trials Registry (ClinicalTrials.gov) Search Strategy

Buffered* AND local anesthesia*
Buffering* AND local anesthesia*
Adjusting pH* AND local anesthesia*
Alkalinization* AND local anesthesia*
Sodium bicarbonate* AND local anesthesia*

OpenGrey Search Strategy

Buffered* AND local anesthesia*
Buffering* AND local anesthesia*
Adjusting pH* AND local anesthesia*
Alkalinization* AND local anesthesia*
Sodium bicarbonate* AND local anesthesia*

Google Scholar Beta Search Strategy

Dental AND buffering AND local anesthesia AND intraoral

D E C L A R A T I O N S O F I N T E R E S T

There are no financial conflicts of interest and the review author declares that she does not have any associations with any parties who may have vested interests in the results of this review.

S O U R C E S O F S U P P O R T

Internal sources

• No sources of support supplied.