Double-Blind, Randomized Clinical Trial of 1% Buffered vs.

2% Unbuffered Lidocaine Injections in Children

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Problem: Receiving local anesthetic injections is uncomfortable for children, and the risk of adverse events limits the local anesthetic dosage that can be safely administered to young children based on body weight.

Goal / Purpose: Assess the self-reported pain experience during Inferior Alveolar Nerve (IAN) blocks with buffered 1% lidocaine with 1/100k epinephrine (EPI) as compared to the unbuffered 2% lidocaine with 1/100k EPI and assess clinical efficacy of buffered 1% lidocaine with 1/100k EPI as compared to the unbuffered 2% lidocaine with 1/100k EPI routinely used in dental and oral surgical procedures.

Background:

Pain control is of paramount importance for procedure success and patient management in pediatric dentistry. Although adjuncts exist to aid in pain management during procedures including distraction, anxiolytic medications, and sedative drugs, the primary tool remains local anesthesia. Unfortunately, injecting local anesthetic can be a particularly anxiety-producing procedure for patients of all ages, especially young children (1,2). Minimizing pain during the administration of local anesthetic must be a goal of all dentists and other clinicians.

Based on discovery of the anesthetic effects followed by the invention of the hypodermic syringe at the end of the 19th century, cocaine was rapidly adopted as a means of blocking painful sensory impulses during surgical procedures (3). The discovery of procaine early in the 20th century led to this newer drug replacing cocaine avoiding the potential addictive properties of the latter. Products of the late 20th century, lidocaine and its derivatives—mepivacaine, bupivacaine, and articaine—are widely used today with invasive procedures in both medicine and dentistry (4). Innovation continues allowing clinicians wider use of local anesthetics in the head and neck region. Recently, local anesthetics have been administered in vehicles such as liposomes to produce longer term sensory nerve blockade, reducing the need for analgesic drugs post-procedures, chiefly opioids, to reduce pain (5). New options for improving local anesthetic effectiveness continue to emerge with a better understanding of their pharmacology (6).

The addition of a vasopressor, usually epinephrine, to lidocaine and other injected local anesthetics serves to prolong the anesthetic effect by reducing blood flow to the anatomic area and the diffusion of the drug away from the anatomic site of injection.

To prolong the shelf life of the vasopressor, the drug combination must be formulated with a low pH, approximately pH 3.5 for lidocaine with 1/100k EPI. When injected, the low pH causes the “sting” felt by patients on injection. Buffering local anesthetics just prior to use can produce positive outcomes including less “sting” on injection, faster onset of the drug, and possibly added drug potency i.e., providing the same positive clinical effect at lower dosage (7-11).

Since more of the unionized form of the drug is available to penetrate the targeted nerve membrane, buffering the local anesthetic makes the drug more potent in less time because the pH of the injected solution is closer to the pKa of the drug itself, approximately 8.0 for the most commonly used local anesthetics. The buffered drug injected at a neutral pH reduces the time-lag required for buffering by tissue fluid while retaining the desired qualities of the vasopressor. The clinical outcome is a more rapid onset of the local anesthetic (10,11). The ability to potentially decrease the dose of local anesthetic drug while maintaining an equal effect has important implications for pediatric dentistry, as children may be at greater risk for toxicity related to such drugs (12).

Phero et al reported lower peak blood lidocaine levels in healthy young adult subjects, and a tendency to less pain on injection comparing mandibular nerve block with buffered 2% lidocaine with 1/100k EPI, compared to the unbuffered drugs (13).

Warren et al reported in healthy young adult subjects significantly lower pain on injection and no difference in duration of pulpal anesthesia tested with cold and EPT on mandibular 1st molar and canine comparing mandibular nerve block with 1% buffered and 2% unbuffered lidocaine both with 1/100k EPI (14).

In children, few studies explore the outcomes after buffering local anesthetics for intraoral injections. Chopra et al. found there to be no reduction in pain on injection or reduction in time to onset of anesthesia for IAN block using buffered 2% lidocaine in comparison to unbuffered lidocaine in children ages 6-12 (15). They did not sample blood levels following injection, nor did they test for pulpal anesthesia, instead relying on subjective measures of soft tissue anesthesia alone (15). Results are similar to those of Fatovich and Jacobs who reported that buffered lidocaine does not reduce pain on infiltration in children or adults for simple lacerations being treated in an emergency room setting (16). However, children did not report their own pain experience, and caregivers reported what they believed the child's level of pain was (16).

Given the recently reported results in adults and lack of studies in children, this study is designed to explore the effect of pain on injection, time to onset, duration of action, and blood lidocaine levels following intraoral injections of buffered local anesthetic in patients 10-12 years of age.

Rational:
Because more of the unionized form of the local anesthetic is available to affect the nerve membrane immediately after buffering it is possible buffered 1% lidocaine may be as effective as unbuffered 2% lidocaine in pediatric patients, allowing procedures in more than one quadrant of the mouth without reaching maximum drug dosages based on body weight. In addition, reducing pain on injection is an important goal for all dentists, particularly when treating pediatric patients who may be having their first dental experience.

Specific Aims:

1. To assess pain experience on injection during an IAN block with unbuffered 2% Lidocaine compared to buffered 1% lidocaine, both with 1/100k EPI.

2. To assess time to onset following the administration of an IAN block with unbuffered 2% Lidocaine compared to buffered 1% lidocaine, both with 1/100k EPI.

3. To assess duration of pulpal anesthesia at the mandibular first permanent molar following administration of an IAN block with unbuffered 2% Lidocaine compared to buffered 1% lidocaine, both with 1/100k EPI.

4. To assess blood lidocaine levels 15 minutes following the administration of an IAN block with unbuffered 2% Lidocaine compared to buffered 1% lidocaine, both with 1/100k EPI.

5. To assess time recovery, lip no longer numb, following the administration of an IAN block with unbuffered 2% Lidocaine compared to buffered 1% lidocaine, both with 1/100k EPI.

Null Hypotheses:

No differences exist in anesthetic effectiveness for pulpal anesthesia after intraoral IAN block between buffered 1% lidocaine with 1/100k EPI as compared to unbuffered 2% lidocaine with 1/100k EPI.

No differences exist in peak blood lidocaine levels, pain on injection, time to lip numbness, and duration of anesthesia between the two drug formulations.

Subjects / Methods

Inclusion Criteria

Age 10-12 years
ASA I or II
Body Weight: the IQR 33-60Kg for subject ages
English-speaking
Willingness to participate in two sessions
No history of adverse reaction to dental anesthetic
Have bilateral, disease/symptom-free mandibular first molars present

Exclusion Criteria

Allergy to lidocaine class of anesthetic drugs
Local anesthetic drug use in past week
Current symptomatic teeth or oral mucosa
ASA III or above

Methods: Blinded, Randomized Clinical Design

Target enrollment 24 subjects

The number of subjects is within budget which is limited. Based on data from studies of young, healthy adult subjects, N=24 each, we anticipate enrolling 24 healthy Peds subjects will be adequate producing similar clinically important outcomes.

Recruit subjects with IRB approved caregiver consent at UNC, along with assent from subjects
Subjects will serve as their own controls in a cross-over AB/BA study design which is uniform within sequences, uniform within periods, and balanced
Sample size justification: A primary interest is estimation of effect size from pilot study. 24 subjects should be sufficient to provide data to assess whether a larger study is warranted and provide estimates for sample size calculation for larger studies.
Vital signs recorded: 10 min before lidocaine injection, just prior to blood draw, 30min later after blood draw, and pre D/C.

Randomized subjects to be injected orally for mandibular block (inferior alveolar, lingual, buccal nerves) alternatively with 3cc of buffered 1% lidocaine (30mg) with 1/100k EPI and 3cc unbuffered of 2% lidocaine (60mg) with 1/100k EPI. Added volume of 0.3cc 8.4% sodium bicarbonate of buffered drugs.

SAS will be used to create randomization schedules: The randomization will be performed first to type of drug given with a balanced randomization (half subjects buffered; half to unbuffered). In week One each subject would receive anesthetic to block the inferior alveolar N, lingual N, buccal N; Halstead techniques. At least a week later, longer than the elimination half-life of the drug lidocaine (1.5-2hr), injections would involve the alternate local anesthetic combination.

One of two faculty in the Department of Pediatric Dentistry at UNC School of Dentistry will administer the drugs in the Pediatric Dentistry clinic. The same clinician will administer injection to same subjects at both visits. Clinicians and subjects masked to injected drugs.

A clinician assigned to each subject's clinical station will record:

- Response to pain on injection self-reported on 10pt Likert scale anchored; 1 = "no pain" and 10 = "worst pain imaginable."
- Response in minutes from time of injection to lower lip numb.
- Response, Yes/No, to cold test (Endo ice) on ipsilateral mandibular permanent 1st molar before injection and after drug injection at 30 min intervals thru 120 min.
- Response in minutes to time lower lip no longer numb. If a sensory deficit, "lower lip numb," exists longer than 24 hours a clinical follow-up will be mandated and appropriate treatment instituted. Adverse events will be reported to the UNC IRB.

Ms. Marsh RN will apply topical LMX4 to the antecubital fossa of the upper extremity and draw 10cc venous blood 15 minutes after local anesthetic drug injection.

Dr. Macdonald's lab: Blood assayed for serum lidocaine levels with a Sciex TripleTOF liquid chromatography- mass spectrometry (LC-MS) equipped with a C18 Hypersil (10mm x 2.1mm, 3.0µm) using methods previously described by Bo and others (17).

Outcome Variables:

Response to pain on injection
Timed Assessment for Clinical Signs: when subjects' lower lips numb and no longer numb
Yes/No for pulpal anesthesia
Peak blood lidocaine levels (15 min. post injection).

Predictor / Explanatory Variables:

The alternate local anesthetic combination.

Confounding Variables:

Though subjects' response to pain on injection and response to cold testing will be recorded as numerical values, the responses are subjective. Cross-over design may minimize this variable.

IAN block is a more complex procedure than field block in skin. Having an experienced clinician administer the drugs should minimize this variable.

Period Effect may exist for all subjective responses, but no Period Effect was detected in three comparable studies in young adults, N=24 each.

Data Management:

Data will be managed by Dr Phillip's staff. Data collection forms and questionnaires for clinical data will be developed to use Teleform for direct scanning input into an ACCESS database. Similar forms have been used in previous studies. Coded hardcopy case report forms will be kept in a locked office. These forms will contain only initials, not names, of participants. Coded electronic data and linkage files will be kept in separate files on the UNC-CH SOD secure server. These files are password protected.

The data transfer from Teleform to ACCESS to SAS is no more likely to produce error transmissions than that from Redcap to SAS since the transfers from both systems are all done electronically. Teleform is a HP software package that is capable of creating a CRF, similar to the functionality of Redcap, except that Teleform is paper based while Redcap is electronically based. Both systems require entry by hand of data recorded or measured. With Teleform once a CRF has been published, an access database is automatically produced by the Teleform software with a database and data dictionary. Once the paper form is completed, it is scanned through a scanner and the data verified by a human operator. The likelihood of an error in entry is no greater with Teleform than with Redcap and double entry can be used with either if required . The advantage of Redcap is that logical and quality control checks can be programed in the CRF program. With Teleform, logical and quality control checks are implemented in SAS.

Statistical Analyses:

Analyses for this project will be conducted by the Biostatistics Liaison program: Dr. Ceib Phillip, MPH, PhD is the School of Dentistry faculty and Dr. John Preisser, PhD is the Department of Biostatistics faculty. Pooja Saha is the current PhD level Graduate Research Assistant.

Crossover study designs are appropriate for pharmaceutical drug comparisons given that this design eliminates the between patient variation. In addition, this design is appropriate for this project given that drug comparisons are considered only with respect to the elimination of symptoms. Although a carry-over effect can be a major problem in a cross-over design, in this study, the washout period of two weeks far exceeds six times the half-life of lidocaine. For this reason, the period by treatment interaction will not be included in the analysis and will not be tested.

An adequate model from Grizzle (Grizzle, 1965) is $y_{ijk} = \mu + b_{ij} + \pi_k + \phi_i + \lambda_l, + e_{ijk}$ j = 1,2,…, n_i; i = 1,2; k = 1,2; l, l' = 1, 2 (1)

where μ is a general mean, b_{ij} is the random effect for the j-th patient within the i-th sequence, π_k is the effect of the k-th period, ϕ_i is the direct effect of the l-th drug, λ_l, is the residual effect of the l'-th drug, and e_{ijk} reflects random error in the measurement of the response. When the b_{ij} and the e_{ijk} are each normally distributed as $N(0, \sigma_b^2)$ and $N(0, \sigma_e^2)$, respectively, and are mutually independent, Grizzle discusses tests of hypotheses pertaining to the direct effects, residual effects, and period effects (Grizzle, 1965).

From (1), the sum off the two observations on the same patient is given by

$$y_{ij1} + y_{ij2} = 2(\mu + b_{ij}) + (\pi_1 + \pi_2) + (\phi_1 + \phi_2) + \lambda_i + e_{ij1} + e_{ij2} \qquad (2)$$

where λ_i represents the residual effect of the i-th drug in the sequence ii'. Hence the sum of the two observations can be used for the test of the hypothesis of no residual effects ($H_{0\lambda}: \lambda_1 = \lambda_2$).

If there are no residual effects in the above test, then the differences between the two observations on the same patient reduce to $y_{ij1} - y_{ij2} = (\pi_1 - \pi_2) + (-1)^{i+1}(\phi_1 - \phi_2) + (e_{ij1} - e_{ij2})$ (3)

where $(-1)^{i+1} = 1$ for the sequence AB and $(-1)^{i+1} = -1$ for the sequence BA. Hence the difference between the two observations on the same patient can be used for the test of the hypothesis of no direct effects $(H_{0\phi}: \phi_1 = \phi_2)$.

Grizzle, JE, The two-period change-over design and its use in clinical trials. Biometrics, 1965 (21), 461-480.

The model above has been implemented in the Proc TTEST Crossover procedure in Sas V9.3. We will not include the IGNOREPERIOD option in the first run to assess whether a period effect is present. If no period effect is statistically significant, then the analysis will be rerun with the IGNOREPERIOD option providing a paired analysis on the drug 1, drug2 response value pairs, regardless of the treatment sequence.

If an outcome is not normally distributed, then a Wilcoxon rank sum test can be used to assess whether a period effect is present by comparing the difference of the first period and -1 times the difference of the second period. The assessment of treatment effect can also be done using a Wilcoxon rank sum test to compare the differences of the two periods for both sequences pooled over periods.

Simpson P et al “Cross Crossover Studies off Your List”. (http://www2.sas.com/proceedings/sugi24/Posters/p221-24.pdf)

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