Comparative Study Of The Efficacy Of Articaine And Mepivacaine: A Double-Blind, Randomized, Clinical Trial

M Bortoluzzi, R Manfro, G Kafer, L Busetti

Citation


Abstract

Introduction: Selection of a particular agent must be taken into account for planning procedures in Dentistry. Materials and Methods: This is a double blind randomized clinical trial with paired groups to compare two commercial anesthetics solutions of mepivacaine 2% (ME) (with adrenalin 1:100.000) and articaine 4% (AR). Results: Twenty five (25) patients were randomly selected to participate. One subject was excluded due to a possibly delayed-type hypersensitivity to AR. Statistically significant differences between AR and ME VAS scores were observed in 3 minutes postinjection indicating that AR (p=0.046) reached a deepest anesthetic effect for fine sensibility and in 15 minutes postinjection 4% AR (p= 0.002) showed a greater anesthesia area. The anesthesia’s deepness was statistically significant better over the time to 4% AR (p< 0.0001) compared to 2% ME. Conclusions: The results indicated that 4% articaine was superior of 2% mepivacaine in anesthesia’s deepness mainly over the first 60 minutes.

INTRODUCTION

Local anesthetic (LA) solutions lie between the most commonly used drugs in Dentistry, however, differences in potency and pharmacokinetic parameters occur among several available LA and selection of a particular agent must take into account for planned procedure and its duration. Articaine (AR) is classified as an amide because of linkage of its intermediate chain, the thiophene ring instead of a benzene ring. A molecular difference between articaine and other amide local anesthetics is the extra ester linkage incorporated into the articaine molecule, which results in hydrolysis of articaine by plasma esterases. The result is that articaine has a half-life of only 20 minutes compared with 90 minutes for lidocaine and other amides that require hepatic clearance. Mepivacaine (ME) is an amide-type local anesthetic widely used in dentistry with a structure similar to that of bupivacaine and is primary eliminated by hepatic metabolism. Despite of claims regarding the superiority of articaine when compared with lidocaine and mepivacaine, the available literature also indicates that articaine is equally effective when statistically compared to other local anesthetics.

To our knowledge there are just 2 published papers in recent literature which compare ME and AR. Colombini et al. (2006) have compared 2% ME and 4% AR in postoperative pain after lower third molar surgical removal and Potocnik et al. (2006) have compared 3% ME and 4% AR in an animal model. The objective of this study is to compare through a double-blind clinical trial the anesthetic efficacy AR 2% and ME 2%, both with adrenalin 1:100.000. This study is the first identified in current literature which compares 2% AR an 4% ME with no pathological or surgical trauma associated.

MATERIAL AND METHODS

This is a double blind randomized clinical trial with paired groups not controlled by placebo to compare two commercial anesthetics solutions of mepivacaine 2% (with adrenalin 1:100.000) and articaine 4% (with adrenalin 1:100.000) available in the Brazilian market. Both anesthetic solutions are from the same company (Cloridrato de Mepivacaína 2% com Epinefrina 1:100.000, Mepiadre® and; Cloridrato de Articaína 4% com Epinefrina 1:100.000, Articaíne®, DFL, Rio de Janeiro, Brazil) and same pack (ME- lote 08010002; AR- lote 0709F06).

All patients were previous selected and invited to participate in this study. From that sample the subjects were randomly picked through computer based program (BioEstat, version 4.0; Belém/Pará- Brazil). The inclusion criteria applied were...
healthy patients with age between 20 and 30 years old and own a watch. The exclusion criteria were the presence of infection at the anesthesia’s site, pregnancy and any known allergy to local anesthetics or components of its formulation. The research sequence events can be viewed in figure 1.

Figure 1
Figure 1: Diagram showing the flow of the participants through each research stage.

The patients were allocated through a raffle to receive the anesthetic ME (Drug 1) or AR (Drug 2). Both, patient and operator were blind (double-blind) to which anesthetic were receiving or using. For this, in a separate room and under aseptic conditions, the commercial anesthetic solutions were transferred from the original container to disposable insulin syringes in an amount of 0.18 ml (10% of an anesthetic cartridge) (authors 1&2). All the solutions were transferred and immediately used. The remained solution in the cartridge was rejected at the end of a period of three hours. Previously of the anesthetic shot and in both occasions (Drug 1&2), the subjects were submitted to a pretest (T0) where was allowed to the patients to previous know their natural lower lip sensibility, performing touch with cotton, needle point and with deep pressure, all related with fine and deep sensibility. The tests were performed in 3 (T1) and 15 (T2) minutes after anesthesia. Blood pressure (systolic - S and; diastolic - D) and heart rate (HR) were taken at T0, T1, T2.

A perioral antisepsis with a 2% chlorhexidine gluconate solution was performed and none topical anesthetic was applied. Under aseptic conditions the anesthetic was injected at the lower lip in a controlled time between 10 to 15 seconds. All injections were performed by the same operator (author 4) and were made on the vermillion border of the lower lip in the middle sulcus (labial sulcus) and in a middle point between skin and the oral mucosa. The needle was deepened between 3 to 4 millimeters and aspiration was performed to avoid the labial blood vessels.

The exact time of the injection were wrote down using the patient’s watch as reference (cell phone). The data collector (author 3) used a chronometer and three minutes after the shot the tests started. The first postinjection test (test 1) was a little scrub over the anesthetized area with a standardized piece of cotton in the central area of the lower lip (no greater than 5 millimeters) and immediately after the patients self reported their sensibility through a Visual Analog Scale (VAS). The VAS ranged from zero (deep or total anesthesia with no sensibility) to 10 (no anesthesia or lower lip with normal sensibility). For all subsequent tests VAS were taken except for anesthesia area length (test 3) that was conducted by the operator. The second test (test 2) was performed using a needle to touch the central area of the lower lip (no greater than 5 millimeters). The third test (test 3) was performed using a needle to touch the lip in lateral direction (right and left), up to the patient report normal sensibility and at this site a dot was performed in both sides and through a flexible ruler the length (in millimeters) was taken. The fourth test (test 4) was performed using a Controlled Continuous Pressure Device (CCPD). CCPD is a simple device which produces the same continuous pressure and is capable to produce little pain in a non anesthetized lip (adapted algesimeter). This device was kept over the lip for around ten seconds (±2 seconds) then the patient report his/her VAS score. All tests were repeated after fifteen minutes.

With the patient was left a form which contains VAS to be filled up in 30 (T3), 60 (T4), 120 (T5) minutes and the final hour (FH- annotated through the patients watch) that was the exact time where the subject felt the lower lip completely normal and with no signs of residual anesthesia. The FH was converted later in minutes to obtain the period in minutes of anesthesia duration. Patients were also instructed to describe and record any problems that they experienced. After a minimum of 48 hours the second drug was applied following the same procedure.

The descriptive and inferential statistics were performed through statistical software (BioEstat, version 4.0; Belém/Pará- Brazil) with a level of significance o p ≤ .05. This research was submitted to Ethical Committee for Human Research and all patients provided written informed
consent.

RESULTS
Twenty five (25) patients were randomly selected to participate. One subject was excluded due to a possibly delayed-type hypersensitivity to AR. From the 24 remaining patients 14 were female (58.3%). The mean age of the participants was 22.6 ±2.3. No differences were found on blood pressure and heart rate between subjects when ME and AR groups where compared (Wilcoxon Signed Ranks Test) at the respective time (T0, T1 and T2).

Three minutes after anesthetic’s injection (T1), statistically significant difference between ME and AR VAS scores were observed in test 2 (Wilcoxon Signed Ranks Test, p=0.046) indicating that AR reached a deepest anesthetic effect for fine sensibility after 3 minutes. The results of VAS scores on tests 1, 2 and 4 in T1 can be viewed in table 1. At T1 the anesthesia length or area (in millimeters, test 3) also showed better results for AR (minimum 10, maximum 37, mean 16.2 ±5.4) compared with ME (minimum 6, maximum 35, mean 14.9 ±5.2), although without statistical significance.

Table 1: Mepivacaine and Articaine VAS scores compared by test 1, 2 and 4, in time 1 (T1, 3 minutes after anesthetic’s injection).

<table>
<thead>
<tr>
<th>Test 1, 2 and 4</th>
<th>Mepivacaine VAS Scores*</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (3 minutes after anesthetic's injection)</td>
<td></td>
<td>0</td>
<td>16.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.2</td>
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<td>37.5</td>
<td>18.7</td>
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<td>18.7</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
</tr>
<tr>
<td>T2 (15 minutes after anesthetic's injection)</td>
<td></td>
<td>0</td>
<td>16.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
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<td></td>
<td>10</td>
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<tr>
<td></td>
<td>0</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
<td>37.5</td>
<td>18.7</td>
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</table>

Figure 2
Mepivacaine and Articaine VAS scores were compared in T3 (30 minutes), T4 (60 minutes) and T5 (120 minutes) showing no statistically significant differences (table 4). The (minimum 6, maximum 20, mean 12.1 ±3.4). Results for anesthesia area length (test 3) in time T1 and T2 can be viewed in table 3.

Figure 3
Table 2: Mepivacaine and Articaine VAS scores compared by test 1, 2 and 4, in time (T2, 15 minutes after anesthetic’s injection).

Figure 4
Table 3: Mepivacaine and Articaine anesthesia length (millimeters) compared in time 1 (T1, 3 minutes after anesthetic’s injection) and time 2 (T2, 15 minutes after anesthetic’s injection).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mepivacaine VAS Scores</th>
<th>Articaine VAS Scores</th>
<th>Mepivacaine VAS Scores</th>
<th>Articaine VAS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (3 minutes after anesthetic's injection)</td>
<td>15</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
</tr>
<tr>
<td>T2 (15 minutes after anesthetic's injection)</td>
<td>10</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
</tr>
<tr>
<td>T3 (30 minutes after anesthetic's injection)</td>
<td>5</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
</tr>
<tr>
<td>T4 (60 minutes after anesthetic's injection)</td>
<td>0</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
</tr>
<tr>
<td>T5 (120 minutes after anesthetic's injection)</td>
<td>0</td>
<td>6.2</td>
<td>18.7</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Mepivacaine and Articaine VAS scores were compared in T3 (30 minutes), T4 (60 minutes) and T5 (120 minutes) showing no statistically significant differences (table 4). The
full recovery (in minutes) of the lip sensibility (FH) also showed no statistically significant differences (Paired Samples T Test, p=0.4) between AR (Mean 111.3 ± 26, in minutes) and ME (Mean 104.5 ± 26.7, in minutes).

**Figure 5**
Table 4: Mepivacaine and Articaine VAS scores compared in time 3 (T3- 30 minutes after anesthetic’s injection), time 4 (T4, 60 minutes after anesthetic’s injection), time 5 (T5, 120 minutes after anesthetic’s injection).

A last statistical analysis was conducted to compare the survival of anesthetic effect of AR and ME considering zero VAS score as complete anesthesia and any other value was referred as loss, through Log-Rank Test (D. Collet Method), which showed statistically significant differences between ME and AR with a better survival time to AR which kept deepest anesthesia over the time (Log-Rank Test, D. Collett Method; p< 0.0001, figure 2).

**DISCUSSION**
The first thing that should be taken into discussion is the study method. Colombini et al. (2006) already pointed that in order to investigate the therapeutic efficacy of an anesthetic drug every effort should be made to standardize the procedure. However they used a pain model after third molar surgical removal and pain is an inherently individual or psychological sensation, therefore, difficulties arise in attempting to quantify and compare different patients’ pain experiences mainly in situations linked to trauma and, for this reason we believe that pain control after surgical trauma is not a good model for anesthetics evaluation. In order to minimize surgical trauma and factors related with pain we followed a neurosensory evaluation adapted from Gregg (1993) and Hillerup & Stoltze (2007).

Clinical neurosensory testing is generally divided into two basic categories based upon the specific receptors stimulated through cutaneous contact, mechanoreceptive and nociceptive. Mechanoreceptive testing can be evaluated through light touch and brush (test 1), and nociceptive testing as pin-prick discrimination tests through sharp (test 2) and deep pressure (test 4). The goal of these neurosensory testing is to determine the deepness of nerve anesthesia based on the responsiveness of specific nerve fiber function. Tests 2 and 4 assess the free nerve endings and the small A-delta and C-fibers responsible for nociception and, test 1 assess...
myelinated afferent A-beta axons. The diffusion property of the LA was evaluated by the comprised anesthetized area measured in millimeters (test 3). We have chosen the lower lip because perioral region are among the areas with the highest density of peripheral receptors which act through the Lemniscal System and generate a highly discriminative somatic sensibility which implies in the capacity to accurately identify the quality (type), amplitude, place, and pattern of a stimulus.

Concerning to our method validation, the results here presented are similar with other published results, which indicated a superiority of AR compared with ME. Colombini et al. (2006) showed that 4% AR produced longer period of analgesic effect and a tendency for a longer period of anesthesia when compared to 2% ME. Besides of differences on the study’s methods those results are in accordance with ours, which showed that 4% AR is superior of 2% ME on nociceptive test after 3 minutes postinjection and anesthesia’s deepness mainly over the first 60 minutes postinjection. This last test took into account a dichotomized sample beginning 3 minutes (using as reference test 2) postinjection up to 120 minutes, where zero VAS score was considered as deep anesthesia (anesthesia’s survival) and any other VAS value was considered as loss (loss of anesthesia’s deepness) and 4% AR kept the deepness of anesthesia in a higher number of patients for a prolonged period time. Our study also showed that after 15 minutes postinjection the amplitude area of the anesthesia was statistically higher in 4% AR group than 2% ME group. Also these results are in accordance with Potocnik et al. (2006) results that showed that 4% AR more effectively depressed the compound action potential of the A fibers in isolated rat sural nerve than did 3% ME.

Hypersensitivity to LA has been rarely reported, but the true incidence of LA allergic reactions is unknown. A female patient of our study possibly presented a delayed-type hypersensitivity to AR solution. We were not sure that AR or other component of the solution triggered the reaction since skin tests were not performed to confirm this hypothesis. Another confounding factor regarding to the patient was the report of several other allergic conditions related with drugs, foods and cosmetics but not related with LA. At nigh of her first test (AR, through raffle) she developed a rash which began on arms and spread through the body skin which persisted for five days and responded well to oral route corticoid. This case could be an alert about patient allergy history and possible complications related with LA, mainly AR.

CONCLUSIONS
This study observed that 4% articaine was superior of 2% mepivacaine in anesthesia’s deepness mainly over the first 60 minutes postinjection.

CLINICAL SIGNIFICANCE
A proper selection of a local anesthetic is a key for success in some procedures in Dentistry, mainly those related with surgery. Between a range of anesthetic solutions and related vasoconstrictors available this study have compared and brought advantages and possible disadvantages in choosing articaine or mepivacaine for clinical use.

References
12. Mikessell P, Nusstein J, Reader A, Beck M, Weaver J. A comparison of articaine and lidocaine for inferior alveolar...
Author Information

Marcelo Carlos Bortoluzzi, DDS, PhD
Stomatology and Maxillofacial Surgery Professor, Santa Terezinha University Hospital, Oeste de Santa Catarina University (UNOESC)

Rafael Manfro, DDS, MS
Maxillofacial Surgery Professor, Santa Terezinha University Hospital, Oeste de Santa Catarina University (UNOESC)

Graciele Camile Kafer, DDS

Lara Fernanda Busetti, DDS