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Reversing the effects of 2% Lidocaine: A randomized controlled clinical trial

Pierre-Luc Michaud[a,*], Brittany Flood[b], Martha Smith Brillant[c]

[a] Department of Dental Clinical Sciences, Faculty of Dentistry, Dalhousie University, 5981 University Ave, PO BOX 15000, Halifax, NS, B3H 4R2, Canada
[b] Faculty of Dentistry, Dalhousie University, Halifax, NS, Canada
[c] Division of Research Affairs, Faculty of Dentistry, Dalhousie University, Halifax, NS, Canada

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ABSTRACT

Objectives: Prolonged soft tissue anesthesia following a dental appointment is a complaint that is frequently reported by patients. Soft tissue anesthesia generally exceeds the duration of pulpal anesthesia by a few hours. This can lead to difficulties with smiling, drinking, speaking and lip/cheek biting following dental appointments. Phentolamine Mesylate (PM) is a pharmacological agent capable of reducing the duration of soft tissue anesthesia following dental treatments. Many clinical trials supporting its efficacy have used sham injections compared to injections with PM. The present study aims to evaluate the effect of PM on the duration of soft tissue anesthesia compared to a control injection of saline water.

Methods: This randomized controlled trial recruited 40 participants above 18 years of age. Following an inferior alveolar nerve block using 1.8 ml of Lidocaine 2%, 1:100 000 epinephrine, participants were randomized into one of 2 groups. The test group received an injection of 0.4 mg PM (OraVerse). Participants in the control group received an injection of sterile saline water. Participants were trained in self-assessing their anesthesia, which they did until return to normal sensation.

Results: Thirty-six participants completed the study. PM significantly reduced the duration of soft tissue anesthesia in the lower lip (104 vs 170 min, p = .001), and tongue (83 vs 134 min, p = .004) compared to the control injection. No serious adverse events were encountered. The only adverse events observed were post-operative pain and discomfort.

Conclusions: Phentolamine Mesylate hastens the return to normal soft tissue sensation and function by approximately one hour compared to a control injection of water.

Clinical significance: Phentolamine Mesylate can be considered a safe and effective way of reducing the duration of soft tissue anesthesia following a dental appointment.

This controlled clinical trial is registered at the National Institutes of Health (ClinicalTrials.gov) #NCT02861378.

1. Introduction

Local anesthesia is an important part of outpatient dentistry. On average, dentists use 1800 cartridges of local anesthetic per year [1]. In the United States, it is estimated that 300 million cartridges of local anesthetic are used yearly [2]. Lidocaine is the most commonly used dental anesthetic [3]. When using Lidocaine, although pulpal anesthesia is maintained for an average of 60 min, soft tissue anesthesia persists much longer and usually lasts between 180 and 300 min [2]. Conversely, the average dental appointment is only 51 min long [4,5]. Therefore, many patients experience persistent lip, cheek and tongue numbness for 2 or more hours following their dental appointment. This could result in discomfort, as well as difficulties eating, drinking and speaking. While anesthetized, patients are also at risk of self-injury by inadvertently biting their soft tissues. This risk is especially significant in the pediatric dental population for which the incidence of soft tissue injury following dental local anesthesia is 13% [6,7].

While ongoing soft tissue anesthesia may be beneficial when surgical procedures are done, it has no benefit in restorative dentistry when only tooth structure is altered. The discomfort and risks associated with undesirable long-lasting soft tissue anesthesia have been acknowledged for a long time and various alternative anesthesia and reversal techniques have been evaluated. In the 1980's transcutaneous electrical nerve stimulation (TENS) was evaluated for the purpose of inducing intra-oral local anesthesia as an alternative to injections [6]. This method did not produce reliable results and was therefore considered not clinically relevant. However, another electrical nerve stimulation technique known as Electronic Dental Anesthesia (EDA) was

* Corresponding author.
E-mail address: PL.Michaud@Dal.ca (P.-L. Michaud).

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shown to reduce soft tissue anesthesia following anesthetic injections by two probable mechanisms: vasodilation and skeletal muscle contraction [6]. Nevertheless, the technique fell out of favor because its efficacy was not consistent, and it was difficult to place the electrodes intraorally [6]. In more recent years it has been suggested that Phentolamine Mesylate (PM) may be a reliable way of reducing the duration of soft tissue anesthesia in dentistry. PM is a nonselective competitive alpha-adrenergic antagonist, which has been shown to reduce vasoconstriction and to ultimately lead to vasodilation [6,8]. Phentolamine Mesylate has been used in the United States since 1952 for reversal of accidental extravasation of catecholamines during intravenous administration, prevention of hypertensive episodes, treatment of norepinephrine-related dermal necrosis, and for the diagnosis of pheochromocytoma [6,9–12].

An injectable dental formulation of the drug (OraVerse, Septodont, Lancaster PA) was approved in 2008 by the U.S. Food and Drug Administration (FDA) as a reversal agent for intra-oral local anesthesia and has been sold in the United States since February 2009 [13,14]. OraVerse has also been approved for use in Canada since September 2014 [15]. OraVerse is packaged in a standard dental carpule and contains 0.4 mg of Phentolamine Mesylate in 1.7 ml of saline water. It is indicated for use following the completion of the traumatic portion of dental appointments in the same volume, site and injection technique as the local anesthetic previously deposited [8,11]. Due to the vasodilation that will occur in the area following its use, it is postulated that its mechanism of action is an increase in blood flow removing the anesthetizing agent from the area [6,8,11].

Several clinical trials have evaluated the efficacy of PM on adults and children. These studies generally observed a statistically significant reduction in the duration of soft tissue anesthesia for participants receiving injections of PM compared to controls. In the adult population, the reduction in the duration of soft tissue anesthesia for the maxillary lip and cheek has been found to be between 60 and 88 min, while for the mandibular lip the reduction was between 47 and 105 min [10,16–18]. In children, a median reduction in recovery time of approximately 100 min was found for the lower lip [19,20]. Results from these studies have shown that PM is efficacious and well tolerated in both adults and children. Local and systemic toxicity were evaluated histologically in beagle dogs and clinical trials have been conducted to assess the safety of PM on both adults and children [10,12,16,19,21]. No serious adverse events were reported. On the contrary, it was found that there was a significant reduction in the incidence of self-induced soft tissue trauma in the pediatric population when using PM to reverse anesthesia [20].

According to existing literature, PM is therefore safe and effective at reducing the duration of soft tissue anesthesia. However, one major flaw in the design of most of these studies is their lack of a true control injection. Except for one study, all other published investigations used a sham injection as the control. Only one study, conducted by the drug manufacturer, used a control injection. However, the protocol and control injectable used were not reported in detail [16]. Also, in this study, different treatments were done, different quantities of anesthetic were used, and different amounts of time passed between the anesthetic injection and the injection of PM or control, but these factors were not used as covariates in the statistical model. Currently, no published study has compared the outcome of an injection of 0.4 mg Phentolamine Mesylate to a control injection of saline water, while standardizing treatments and controlling for time between the anesthetic and reversal or control injections. A control injection using sterile physiologic water would help differentiate whether PM is the main reason for reduced perceived soft tissue anesthesia, or if other factors such as placebo effect or an increase in water volume at the site are contributory. Therefore, there is a need for a controlled clinical trial comparing the difference in the duration of soft tissue anesthesia following an injection of PM to a control injection of sterile physiologic water.

The objective of this study was therefore to compare the time to return of normal soft tissue sensation and function for participants receiving an inferior alveolar nerve block (IANB) using Lidocaine 2%, 1:100,000 epinephrine followed by an injection with either 0.4 mg Phentolamine Mesylate or normal saline (control). The null hypothesis was that no difference would be present between both groups.

2. Materials & methods

Dentistry and dental hygiene students being trained in dental anesthesia at the Dalhousie University Faculty of Dentistry were invited to participate in this randomized placebo-controlled trial. The study was approved by the Dalhousie Research Ethics Board (#2015-3515) and registered at the National Institutes of Health (#NCT02861378). All participants were 18 years of age or older and were capable of providing informed consent. Exclusion criteria included any medical history contraindicating the use of epinephrine, use of opioid or opioid-like analgesic intake in the 24 h preceding the clinical trial and pregnancy. The researchers, participants, clinician and statistician were all blinded to the group allocation.

The study took place between November 2015 and January 2016. Forty participants were enrolled in the study by BF. Each received an inferior alveolar nerve block using 1.8 ml of 2% Lidocaine with 1:100,000 epinephrine. Any participants who did not achieve profound anesthesia were withdrawn from the study prior to randomization. Following confirmation of anesthesia 38 participants were randomized to either the PM or control group by BF using 40 numbered opaque envelopes. These envelopes contained the letter ‘A’ or ‘B’ and were prepared by MB. To design these envelopes, a computerized random number generator was used to generate 7 randomly permuted blocks, with a block size of 6. Within each block, an equal number of subjects were allocated to the two treatment groups (‘A’ or ‘B’). These referred to either PM group or Control group, but this information was withheld until the statistical analyses were completed. Unlabeled 3 ml disposable syringes (BD Luer-Lok) with a 25-gauge needle (BD PrecisionGlide) were used to perform all injections of PM and saline. To maintain study blinding, the clinic nurse (who possessed the randomization key) preprepared the syringes and labeled them ‘A’ and ‘B’. The prepared syringes contained 1.7 ml of either 0.4 mg PM in saline water (OraVerse) or normal sterile saline. One person (BF) performed all injections of PM or sterile saline. The PM or control solutions were injected in the same site as the initial injection over a period of 1 min. The time elapsed between the first (anesthetic) and second (PM or control) injections was recorded. Other than the injections of Lidocaine and PM or saline, no dental treatments were done in these participants.

Prior to receiving any injections, participants were trained in self-assessment of soft tissue anesthesia using finger palpation and tapping with comparison with the non-anesthetized side. Participants self-evaluated the time to return to normal sensation and function at 10-minute intervals using a questionnaire.

A sample size of 17 individuals per group was needed to detect a large effect size ($f^2 = 0.5$) with an alpha error of 0.05 and a power of 80%. The target sample size was increased to 20 per group to compensate for potential drop-outs and failures to reach profound anesthesia. The primary outcome measures were the time to return to normal sensation in the lip and tongue as well as normal speaking, drinking and smiling. An ANCOVA model was used to compare the time needed for return to normal sensation and function between treatment groups while controlling for the time between the injection of the anesthetic solution and the injection of PM or control. A secondary outcome measure was the occurrence of any adverse events. Pearson Chi-Square analysis was used to compare the rate of adverse events between the intervention and control groups. All statistics were conducted before the randomization code was revealed.