Cardiovascular Effects of Racemic Epinephrine Pellets Used in Pediatric Restorative Dentistry Under General Anesthesia

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INTRODUCTION

Dental caries is the most common chronic disease of childhood.[1] According to the American Academy of Pediatric Dentistry, it is estimated that 5% of children under the age of 6 experience severe early childhood caries, an additional 15% roughly 1.5 million US children experience lesser levels of ECC, a condition that may necessitate restorative dental treatment. [2,3,4] Prefabricated crowns are the treatment of choice for children with rampant caries involving large or multiple surface lesions or developmental defects.[5] In such situations, crowns reinforce the tooth and provide increased durability and longevity over intracoronal restorations such as fillings. Crowns also reduce the chance of recurrent caries. [5]

In routine clinical practice, preformed metal crowns, also known as stainless steel crowns (SSC) are frequently indicated due to their durability, relatively low cost, and minimal technique sensitivity.[5] They are adapted to the prepared tooth and cemented with a biocompatible luting agent.[6,7,8,9] According to American Academy of Pediatric Dentistry[5], use of SSCs should be considered in patients at high risk for caries, whose cooperation is affected by age, behavior or medical history. Such patients frequently receive treatment under sedation or general anesthesia.

Although SSCs are highly effective, esthetics can be a concern for parents.[10] Prefabricated zirconia crowns provide an esthetic solution and are now available for both primary incisors and molars. Zirconium dioxide (zirconia) is a crystalline solid that has strength similar to metals while its color is similar to that of teeth. According to a recent randomized controlled trial, both stainless steel and zirconia crowns proved to be an excellent choice for posterior full coverage restoration of primary teeth.[11] However, zirconia crowns have shown to have better performance with regards to esthetics, gingival response and plaque retention.[4,11,12,13]

The process of preparing the tooth for a prefabricated zirconia crown requires a circumferential subgingival preparation. Prefabricated zirconia crown preparations include occlusal reduction of 1-2 mm followed by supragingival reduction of 0.5-1.25 mm circumferentially. Once prepared, caries is removed, and the preparation is reduced 1-2 mm subgingivally to create a feather edge margin. Tissue irritation and bleeding is inherent in this process. If hemostasis is inadequate when the crown is cemented, blood contamination will affect the integrity of the tooth-cement-crown interface. Zirconia crowns are also translucent, and blood incorporated into the cement may cause visible discoloration, resulting in poor esthetics.

Hemostasis can be achieved by allowing the tissues to clot naturally using direct pressure with gauze. However, in clinical settings, it is not always possible or desirable to wait for extended periods of time. Thus, clinicians have relied upon topical or injected vasoconstrictors such as epinephrine to facilitate rapid hemostasis. Epinephrine is a powerful stimulator of both alpha and beta-adrenergic receptors, eliciting different effects depending on the tissue involved. Alpha-adrenergic receptors predominate in tissues such as oral mucosa and periodontium where epinephrine causes vasoconstriction of blood vessels.[14] Beta 1 receptors, predominantly located in the heart, can increase heart rate and contraction force. Beta 2 receptors are predominately located in the lungs and skeletal muscle. Activation can cause bronchodilation in lungs, vasodilation of skeletal muscle and increased cardiac output. In medical and dental surgical practice, dilute formulations of injectable epinephrine are used to provide local hemostasis; however, when injected, they may raise serum epinephrine levels and increase potential for cardiopulmonary side effects.[12] In contrast, topical epinephrine causes local vasoconstriction of the contacted mucosa, resulting in decreased systemic absorption. Administration of topical epinephrine has been shown

to result in elevation of serum concentrations 140-times less than injections of even dilute epinephrine preparations.[15,16]

Topical epinephrine has been used widely in medicine and dentistry to achieve rapid hemostasis. Studies by Korkmaz et al and Gunaratane et al showed no significant hypertensive episodes and no hemodynamic parameter changes associated with placement of 1:1000 topical epinephrine.[17,18] However, others have reported topical epinephrine sensitivity on only small portion of patients. These studies showed that topical epinephrine may induce significant hemodynamic changes in only a subset of patients which included the ones with preexisting cardiovascular diseases.[19,20]

A literature review of prior studies investigating the effects of topical racemic epinephrine showed its effectiveness to decrease intraoperative bleeding. Degerliyurt K. et al. showed practical use of topical epinephrine without safety concerns for sinus surgery.[15,21,22] Vickers et al. studied the cardiovascular effects of topical epinephrine pellets and 20% ferric sulfate in endodontic surgery. They found that neither agent had any statistically significant cardiovascular effects. However, subjectively, epinephrine pellets showed better hemostasis outcome than 20% ferric sulfate.[23]

Complications associated with use of topical epinephrine are extremely rare, and changes in cardiovascular outcomes have not been shown to be statistically significant.[15,23,24] To the best of our knowledge, no well-designed clinical trials have been conducted to assess the cardiovascular effects of topical epinephrine on gingival tissue in a pediatric population.

The overarching purpose of this split-mouth randomized pilot study was to determine the efficacy and safety of receiving treatment with topical racemic epinephrine compared to placebo, measured by cardiovascular and hemostasis outcomes. Specifically, the primary objective of this

study was to determine if the use of racemic epinephrine has any effect on heart rate, blood pressure, or cardiac rhythm in children receiving dental care under general anesthesia. We hypothesized that the use of topical racemic epinephrine would be associated with no significant change on heart rate, blood pressure, or mean arterial pressure in children receiving dental care under general anesthesia compared to patients receiving a placebo.

The secondary objective of this study was to determine if the use of racemic epinephrine has any effect on hemostasis, as measured subjectively by the dentist performing the procedure. We hypothesized that the use of topical racemic epinephrine would reduce clotting time around the gingival tissue, resulting in more rapid hemostasis.

METHODS

The study was approved by the Institutional Review Board at the University of Washington (STUDY00006670). Participants and their parents/legal guardian were recruited from a pool of patients who were scheduled to receive comprehensive dental care under general anesthesia (GA) at the University of Washington Center for Pediatric Dentistry. Families were approached regarding study participation the day of the initial dental surgery consultation or were contacted by phone at least 2 days prior to their scheduled dental surgery appointment. Consent was obtained the day of the surgery. Inclusion criteria included American Academy of Anesthesiologists physical status classification (ASA) I or II, English speaking, and having caries lesions requiring prefabricated crowns on both primary maxillary first molars, teeth #B and I.

Subjects were excluded from the study if the parents or guardians were not able to communicate with the study coordinator in English or the patient had severe systemic illness (ASA III or greater), cardiac arrhythmia, cardiovascular disease, diabetes, thyroid disease and/or prescribed anti-arrhythmic, antihypertensive, or ionotropic medications. Subjects were also

excluded if they required pulpotomy or pulpectomy treatment on the primary maxillary first molars.

This was a single blinded, split-mouth randomized controlled pilot study. We recruited patients from June 2019 until November 2019. Sixteen children met inclusion criteria and were approached for participation. Three patients were excluded from the study: One patient did not meet the inclusion criteria after new radiographs were taken under GA and two caregivers declined to participate in the study on the day of surgery (Figure 1).

Randomization was performed in two stages. Using Stata 14.2 (StataCorp, College Station, TX) statistical software we first randomized whether the control treatment would be applied to the primary right or left maxillary first molar. The first randomization resulted in assignment of the right side of the mouth for the control treatment. This assignment was maintained for all participants. The second randomization step determined the treatment sequence; whether control or intervention treatment was done first. A randomization list was created and placed into a password protected Excel file prior to the start of the study. The order in which the patient received the intervention (either first or second) was randomly assigned to each patient using the randomization list.

The main objective of this method was to have each patient serve as their own control and ensure randomization of the timing (first or second) of the experimental condition. Parents were not present during the procedure, and patients were unconscious and therefore blinded to the intervention. The treating dentist and study personnel were not blinded.

Each patient's weight and medical history was updated on the day of surgery. All patients fasted for at least eight hours prior to the procedure. They were transferred to the operating room and received mask inhalation induction (8% sevoflurane and 50-70% N2O/O2). Monitoring

equipment was applied after the patient was anesthetized, and it was maintained in place throughout the course of the procedure. Vital sign measurements included capnography, oxygen-saturated hemoglobin percentage (SpO2), heart rate (HR) in beats per minute (bpm), and cardiac rhythm-which was continuously recorded from a 5-lead electrocardiogram (ECG). The systolic blood pressures (SBP) and diastolic blood pressures (DBP) were measured in millimeters of mercury (mmHg) via standard automatic noninvasive arterial cuff on the ankle or upper arm.

All baseline vitals were recorded and peripheral intravenous (IV) access was obtained. Patients then received 1to 2mg/kg of propofol, Decadron 4 to 6mg total and 0.5 mg/kg of ketorolac via IV, followed by direct laryngoscopy and nasotracheal intubation. Anesthesia was maintained throughout the procedure with a continuous IV infusion of propofol (50-100 mcg/kg/min), Remifentanil infusion (0.05-0.1 mcg/kg/min), and inhaled nitrous oxide/oxygen (30-70%).

After successful intubation, necessary radiographs were taken, a throat pack was placed, followed by cleaning, dental examination and treatment planning. Next, the maxillary first primary molar that was randomized to be completed first was prepared to receive a zirconia crown. To reduce pressure stimulation, no dental isolation (e.g. rubber dam) was used during any of the study procedures. After preparation, an appropriately sized zirconia crown was fit, and baseline heart rate and blood pressure were recorded. Next, two saline or intervention pellets were stretched and applied directly around the gingival tissue of the prepared tooth covering the tooth circumference. Control pellets were prepared by soaking in 0.9% sodium chloride (physiological saline) whereas intervention pellets were obtained directly from the manufacturer, containing an average of 0.55 mg (0.42 to 0.68 mg/pellet) of racemic epinephrine hydrochloride per pellet (HemeRx, Racellet#3, Sprig Oral Health Technologies, Inc. Loomis, CA). Pellets were maintained in position for one

minute with gauze pressure based on manufacturer's recommendation. After pellet removal, any residual coagulum was removed using suction or moistened gauze.

Cardiovascular outcomes including patient's systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and mean arterial pressure (MAP) were recorded via standard automatic noninvasive arterial cuff immediately before pellet placement (baseline) and again at 1, 2, 3, 4 and 5 minutes after placement.

The adequacy of hemostasis was determined subjectively by the operating dentist/principal investigator (TMN), as "adequate" or "inadequate" at baseline and again at 1, 2, 3, 4 and 5 minutes after placement. Adequate hemostasis was defined as cessation of blood flow from gingival tissue. Inadequate hemostasis was defined as continued blow flow from gingival tissue, with blood contamination of the prepared tooth. Figures 2 and 3 demonstrate examples of adequate vs. inadequate hemostasis. Figure 4 demonstrates pre and post-op intraoral photos of maxillary arch of one of the patients.

Following study procedures, the remainder of each patient's dental care was completed, including application of rubber dam isolation, sealants, composite restorations, pulpotomies, stainless-steel crowns and extractions. All patients were discharged on the same day after adequate recovery and observation time.

Data was analyzed using Stata SE version 14.2 (College Station, TX) software. Descriptive statistics are reported as mean and standard deviation. Paired t-test and one-way repeated analysis of variance (ANOVA) were used for comparison of cardiovascular outcomes within controls (Table 1) and within interventions (Table 2). A paired t-test with equal variance was used for comparing control and intervention cardiovascular values as well as time to hemostasis adequacy (Table 3). McNemar's Exact test was used to compare whether a patient reached adequate

hemostasis in the intervention and control sides. A p-value < 0.05 was considered to be statistically significant.