The Effect of Topical Epinephrine on Cardiovascular Outcomes in Children Receiving Prefabricated Zirconia Crowns: A Randomized Controlled Trial

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Abstract

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Pediatric Dentistry

Purpose: Topical racemic epinephrine has been used widely in dentistry to achieve rapid hemostasis. However, no well-designed clinical trials have assessed the cardiovascular effects of topical epinephrine on gingival tissue in a pediatric population. The purpose of this study was to determine if topical application of racemic epinephrine pellets affects heart rate, blood pressure, and mean arterial pressure in children receiving dental care under general anesthesia. The hemostatic effect of the pellets was also assessed.

Methods: Otherwise healthy pediatric patients between the ages of 2 to 9 years who had carious lesions requiring prefabricated zirconia crowns on both primary maxillary first molars were recruited into a split-mouth randomized controlled pilot study. For the purpose of randomization, each patient's oral cavity was divided into left and right sections. We first randomized the control to the right side of the mouth and this was maintained for all participants. The second

randomization step determined the sequence by which the treatment was applied, determining whether control or intervention treatment was done first. Under general anesthesia, teeth were prepared for zirconia crowns. After preparation in the control treatment, two saline saturated pellets were applied directly to gingival tissue for 1 minute with gauze pressure. For the intervention treatment, two racemic epinephrine pellets were applied in a similar manner as the control treatment. Heart rate and blood pressure measurements were recorded at baseline and at 1-minute intervals for 5 minutes after placement. The adequacy of hemostasis was determined during the 1-minute intervals subjectively by the operating dentist as “adequate” or “inadequate”.

Results: Comparison within the control group showed a statistically significant decrease in baseline heart rate over the 5-minute observation period, with no significant changes in diastolic blood pressure and mean arterial pressure. Comparison within the intervention group showed a statistically significant decrease in heart rate, diastolic and systolic blood pressure and mean arterial pressure over 5 minutes. There was a statistically significant difference between control and intervention baseline and 5-minute post-intervention mean diastolic blood pressure (-11.1% vs. -3.9%, $p<0.01$) and mean arterial pressure (-8.1% vs. 2.1%, $p<0.01$). There was no significant difference between mean heart rate (-4.1% vs. 2.9% $p=1.13$) and systolic blood pressure (-2.7% vs. -3.1%, $p=0.50$) for the control and intervention groups. All 13 of the intervention-treated teeth reached adequate hemostasis after an average of 2.2 ± 1.1 min. Meanwhile, only 5 out of the 13 control-treated teeth reached adequate hemostasis over the 5-minute observation, and it was achieved after 4.2 ± 0.8 min. The difference was statistically significant ($P<0.01$).

Conclusion: This pilot randomized controlled trial showed no statistical difference in mean heart rate and systolic blood pressure and a statistically significant decrease in mean diastolic blood

pressure and mean arterial pressure when using racemic epinephrine hydrochloride pellets compared to saline pellets. The clinical effects of the cardiovascular measures, however, were similar between the two interventions. Additionally, hemostasis was reached more predictably and in a shorter time period using racemic epinephrine hydrochloride pellets.

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Dr. Mir Sohail Fazeli for his excellence as a knowledgeable researcher and his guidance throughout. As well as Dr. Yvonne Lin and Dr. JoAnna Scott for their feedback, direction and assistance.

To the patients and families of the Center for Pediatric Dentistry who participated in the study we conducted, thank you for your patience, time and readiness to participate in our study.

DEDICATION

I would like to dedicate this thesis to the pediatric patients who motivated me to pursue further education in pediatric dentistry and strive for excellence.

This thesis is also dedicated to my husband, Adel for his love and continuous encouragement, to my caring and supportive parents, Nina and Ali and my two amazing brothers, Mir Farhang and Mir Sohail, who have always been an inspiration with their pursuit of being lifelong learners. Finally, I dedicate this to my son, Leonardo, who has brought a new joy and meaning to our lives.

Chapter 1. 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.

  Hypothesis: 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.

  Hypothesis: We hypothesized that the use of topical racemic epinephrine would reduce clotting time around the gingival tissue, resulting in more rapid hemostasis.

Chapter 2. MATERIALS AND METHODS

2.1 SUBJECTS

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.

2.2 STUDY DESIGN AND PROCEDURES

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.

2.3 DATA COLLECTION

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.

2.4 DATA ANALYSIS

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.

Chapter 3. RESULTS

3.1 DEMOGRAPHIC CHARACTERISTICS

The final sample included total of 13 patients (54% males, 46% females), age range of 2.7-7.8 years old with mean age 4.7 years (SD:1.6) and weight of 18.2 kg (SD:4.2). All patients had either ASA I (n = 10) or ASA II (n = 3) classification. All participants had Medicaid insurance.

3.2 CARDIOVASCULAR OUTCOMES

Comparison of cardiovascular measurements within the control group revealed a statistically significant decrease from baseline to 5 minutes for HR (91.5 ± 18.2 vs 88.5 ± 16.2 bpm, p = 0.04) and SBP (89.0 ± 6.4 vs 86.1± 5.6 mmHg, p = 0.047); however, no significant change was noted in DBP (37.8 ± 7.8 vs 35.8 ± 5.8 mmHg, p = 0.13) or MAP (54.8 ± 7.2 vs 53.2 ± 4.5 mmHg, p = 0.28). There was not a significant trend over time for any of these variables (Table 1).

Comparison of cardiovascular measurements within the intervention group revealed a statistically significant decrease from baseline to 5 minutes for all measurements, including HR (93.4 ± 15.1 vs 89.6 ± 15.5 bpm, p = 0.01), SBP (91.4 ± 6.2 vs 88.8 ± 4.7 mmHg, p = 0.02), DBP (41.3 ± 7.7 vs 36.1 ± 5.2 mmHg, p = 0.01) and MAP (58.2 ± 5.6 vs 53.2 ± 4.5 mmHg, p = 0.01) ; however, there was not a significant trend over time in any of these variables (Table 2).

Baseline values recorded prior to pellet application for all cardiovascular measurements were comparable between the intervention and control treatments: HR (93.4 vs 91.5 bpm), SBP (91.4 vs 89 mmHg), DBP (41.3 vs 37.8 mmHg) and MAP (58.2 vs 54.8 mmHg). However, both control and intervention treatment groups did not show any significant change in all cardiovascular measurements from baseline to 5 minutes (Tables 1 and 2).

There was a statistically significant difference between mean percent change in DBP and MAP from baseline to 5 minutes post-intervention, showing a larger decrease in mean DBP (-11.1% vs -3.9%, $p<0.01$) and MAP (-8.1% vs. -2.1%, $p<0.01$) in the intervention group compared with controls (Table 3).

3.3 HEMOSTATIC OUTCOMES

All 13 intervention teeth reached adequate hemostasis after an average of 2.2 ± 1.1 min. Meanwhile, only 5 of the 13 control teeth reached adequate hemostasis (McNemar's Exact $p=0.01$) over the 5-minute observation period, and it was achieved after average of 4.2 ± 0.8 min. This difference was statistically significant ($p = <0.01$). When comparing the five patients who reached hemostasis for both the intervention and control, there was a statistically significant difference in time to hemostasis (1.6 vs 4.2 minutes, $p = 0.01$).

Eight of the 13 control teeth did not reach adequate hemostasis by minute 5. In these cases, hemostasis was achieved by injection of lidocaine 2% 1/100,000 epinephrine and direct pressure with gauze prior to crown cementation.

Chapter 4. DISCUSSION

The purpose of this pilot study was to determine the efficacy and safety of topical racemic epinephrine pellets used to obtain hemostasis following zirconia crown preparation in pediatric patients. The results demonstrated a small but statistically significant *decrease* in all cardiovascular parameters after application of the racemic epinephrine pellets. This finding indicates that, compared to placebo, topical application of two concentrated epinephrine pellets does not pose risk of increased BP, SBP, DBP or MAP in healthy children treated under controlled GA conditions.

Systemic administration of epinephrine can be expected to result in an increase of all studied cardiovascular parameters. In this pilot study however, we saw the opposite effect over the course of each 5-minute observation period. This is not surprising, as vital signs were recorded after tooth preparation was completed, during the observation period no additional clinically stimulating procedures were performed, and patients were maintained via continuous infusion of anesthesia medications.

Comparison of vital signs between intervention and control treatment demonstrated a statistically significant difference between diastolic blood pressure and mean arterial pressure when comparing the mean percentage change between baseline and 5-minute interval; however this was not clinically significant and did not lead to any change in clinical management of the patients. Mean percentage changes also showed negative values demonstrating all cardiovascular variables decreasing in value from baseline to 5 minutes. (Table 3) It appears that when applied directly to gingival tissues, the cardiovascular effects of racemic epinephrine hydrochloride pellets (HemeRx, Racellet#3, Sprig Oral health technologies, Inc. Loomis, CA) are negligible. However, there was a significant difference between tissues treated with epinephrine pellets and those that

were treated with saline pellets. Hemostasis was achieved in all cases when epinephrine pellets were used, in an average of 2.2 minutes. In contrast, fewer than half of the sites treated with saline achieved hemostasis within 5 minutes, and when adequate hemostasis was achieved it occurred after an average of 2 minutes more waiting time.

Prefabricated pediatric zirconia crowns are still a relatively recent addition to the materials available for restorative pediatric dentistry. While there remains limited scientific evidence regarding their performance, recent research findings indicate that prefabricated zirconia crowns are not only aesthetically superior but may also provide a more durable alternatives to stainless-steel crowns (SSC) for primary molars. [25] When compared with SSCs, plaque accumulation is lower and gingival health is better. [26] Disadvantages of the restoration include reduced mechanical retention when compared with SSC or bonded composite, which may result in failure due to loss of the restoration. The preparation design is also more aggressive, which may result in necrosis and pulp-related failures.[27] While no restorative treatment is perfect, prefabricated zirconia crowns do represent a highly durable and esthetic treatment option for primary teeth. As the market for esthetic pediatric restorative options grows, the need for safe and effective methods for obtaining hemostasis may also increase. The results of this pilot study indicate that administration of topical epinephrine pellets appears to be a safe and effective option for achieving hemostasis prior to zirconia crown cementation in healthy children. However, we recommend completion of larger studies before the of study's conclusions can be generalized.

4. 1 STRENGTHS AND LIMITATIONS OF THE STUDY

The split-mouth single-blinded study design was a major strength of this pilot study. By conducting a split-mouth randomized controlled pilot study, we were able to perform within patient comparison rather than between-patient comparisons. Thus, the error variance of the

experiment was reduced, thereby obtaining a more powerful statistical test. However, the single-blinded study design was also a limitation, as the dentist was aware of the treatment being using due to the color difference of epinephrine and saline pellets. This contributes to potential performance bias for the personnel and detection bias for outcome assessment.

Another major strength of this pilot study was that all the patients were studied under GA, administered via a continuous intravenous infusion and inhaled anesthetic agents. General anesthesia eliminated changes in vital signs that may be the result of the patient's agitation or behavior. This method of anesthesia resulted in perfect behavioral compliance and the ability to detect even very minor alterations in patient vital signs. While GA conveyed a number of advantages to this study design, it did allow completion of all restorative procedures without use of injected local anesthesia. In a clinical scenario with patients who are not anesthetized, local anesthesia containing epinephrine would be used. This would potentially decrease time to achieve adequate hemostasis in both the control and intervention condition.

Another limitation of this pilot study was the small sample size. This limits the generalizability of the results of the study and may lead to potential sampling bias. The investigators recognize this as a potential cause for concern and suggest that the results be interpreted with caution and methods of this study be used in a larger clinical trial in the future.

Chapter 5. CONCLUSIONS

In this pilot randomized controlled trial racemic epinephrine hydrochloride pellets and saline pellets showed similar decreases in heart rate and systolic blood pressure. Use of racemic epinephrine pellets was associated with a significantly greater decrease in mean diastolic blood pressure and mean arterial pressure compared with saline pellets. The clinical effects of the cardiovascular measures, however, were similar between the two interventions. In addition, hemostasis was achieved more predictably and in a shorter time period using racemic epinephrine hydrochloride pellets than with saline pellets.

5.1 CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Table 1: Mean cardiovascular measurements at baseline and 1-minute to 5-minute intervals for the Control treatment

Cardiovascular parameters	Baseline	1 min.	2 min.	3 min.	4 min.	5 min.	t test (baseline to 5 min)	ANOVA (baseline to 5 min)
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	p-value	p-value
ΔHR (bpm)	91.5(18.2)	89.8(16.3)	89.0(15.5)	88.8(16.1)	88.7(16.5)	88.5(16.2)	0.04	0.99
ΔSBP (mmHg)	89.0(6.4)	87.1(5.7)	88.5(4.9)	85.9(7.9)	88.3(4.8)	86.1(5.6)	0.047	0.68
ΔDBP (mmHg)	37.8(7.8)	36.5(6.5)	36.9(8.2)	35.8(6.9)	35.2(6.8)	35.8(5.8)	0.13	0.95
ΔMAP (mmHg)	54.8 (7.2)	54.4(6.4)	53.9(6.4)	51.5(5.5)	53.1(6.0)	53.2(4.5)	0.28	0.79

Values reported as mean ± standard deviation.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation.
HR = heart rate; DBP = diastolic blood pressure; SBP = systolic blood pressure; MAP = mean arterial pressure.

Table 2: Mean cardiovascular measurements at baseline and 1-minute to 5-minute intervals for the Intervention treatment

Cardiovascular parameters	Baseline	1 min.	2 min.	3 min.	4 min.	5 min.	t test (baseline to 5 min)	ANOVA (baseline to 5 min)
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	p-value	p-value
ΔHR (bpm)	93.4(15.1)	90.5(14.5)	90.8(15.1)	90.1(14.9)	89.5(15.9)	89.6(15.5)	0.01	0.99
ΔSBP (mmHg)	91.4(6.2)	89.7(7.0)	89.8(6.8)	87.9(8.4)	88.9(6.1)	88.8(4.7)	0.02	0.84
ΔDBP (mmHg)	41.3(7.7)	37.8(4.9)	37.4(4.9)	37.4(5.0)	36.4(5.5)	36.1(5.2)	0.01	0.22
ΔMAP (mmHg)	58.2(5.6)	54.6(4.6)	55.6(4.4)	55.6(5.0)	54.2(4.1)	53.2(4.5)	0.01	0.14

Values reported as mean ± standard deviation.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation.
HR = heart rate; DBP = diastolic blood pressure; SBP = systolic blood pressure; MAP = mean arterial pressure.

Table 3: Mean percentage change comparison of cardiovascular parameters between Control and Intervention treatments.

Cardiovascular parameters	**Control**	**Intervention**	
	Mean (SD)	**Mean (SD)**	**p-value***
Heart Rate (%)	-2.9(4.2)	-4.1(4.3)	0.13
Systolic Blood Pressure (%)	-3.1(5.1)	-2.7(3.6)	0.50
Diastolic Blood Pressure (%)	-3.9(8.8)	-11.1(12.0)	<0.01
Mean Arterial Pressure (%)	-2.1(9.0)	-8.1(8.4)	<0.01

bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation. HR = heart rate; DBP = diastolic blood pressure; SBP = systolic blood pressure; MAP = mean arterial pressure.

*Calculated using a paired t-test.

Figure 1: Participant flow in single blinded, split-mouth randomized controlled pilot study

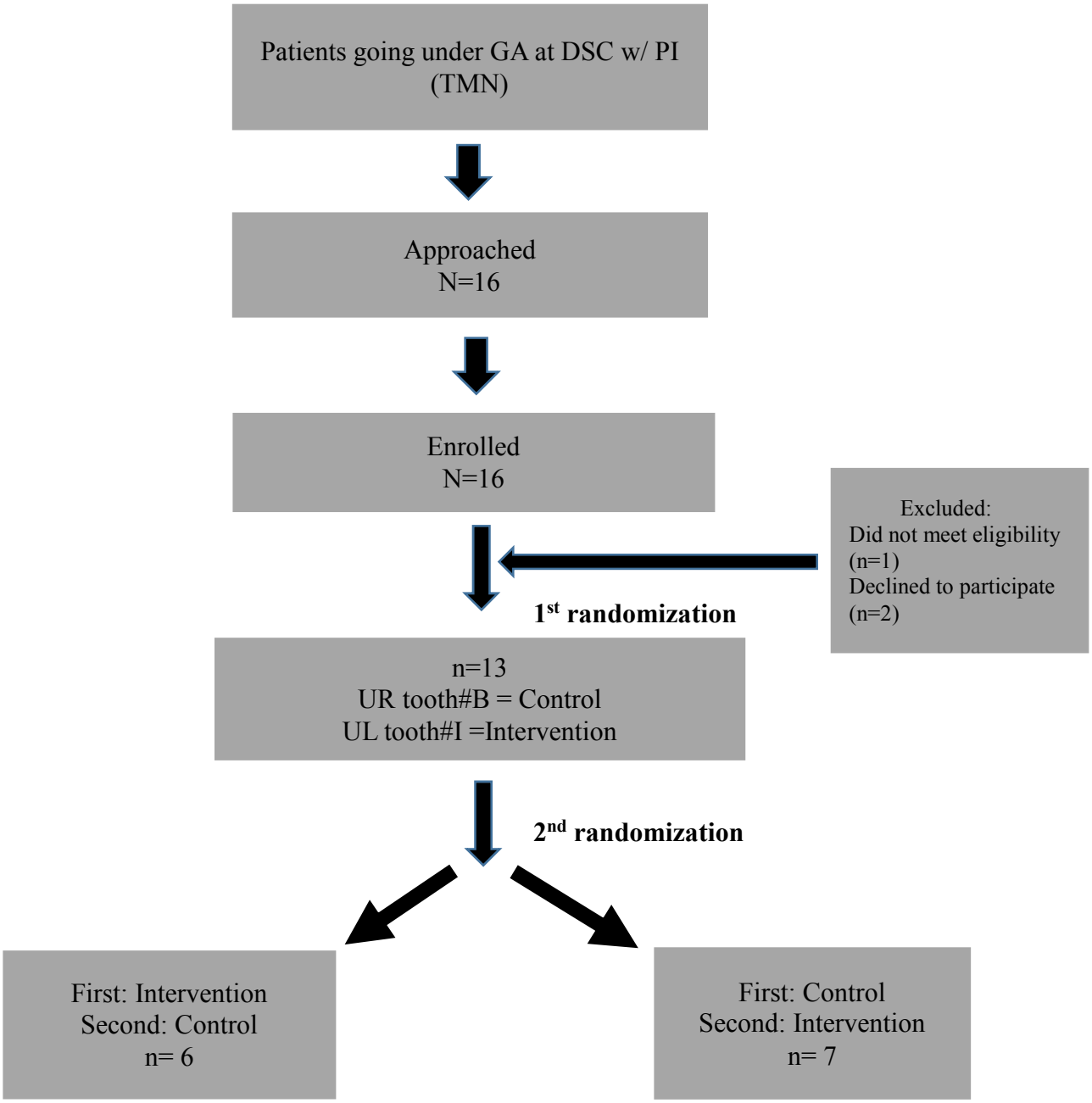


Figure 2:
Inadequate hemostasis of tooth#I:

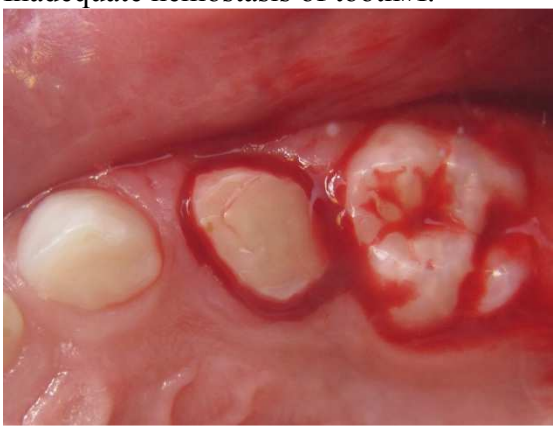


Figure 3:
Adequate hemostasis of tooth#I:

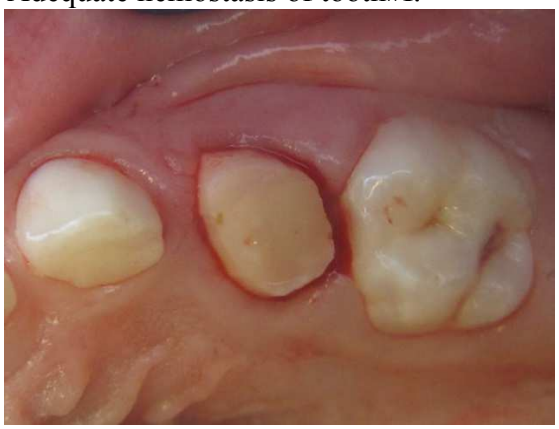
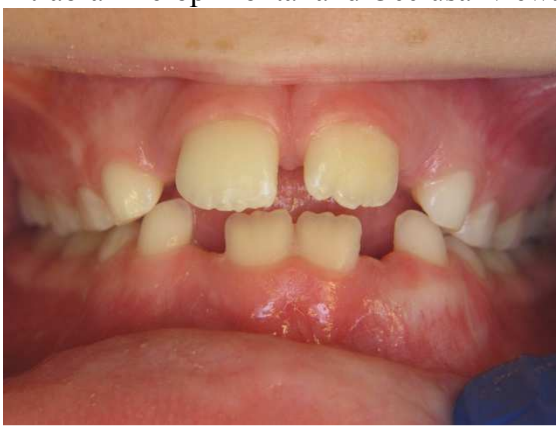
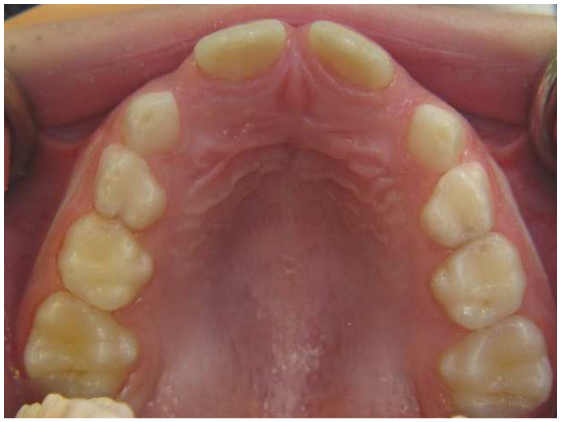
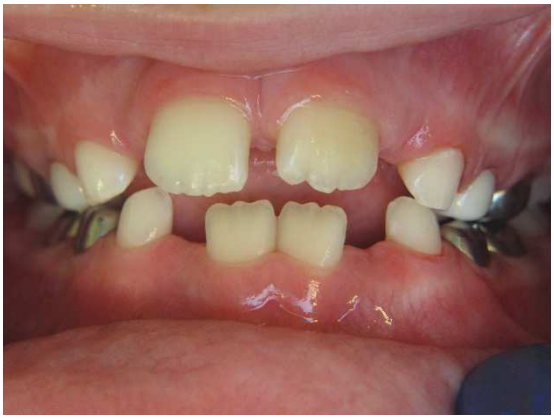


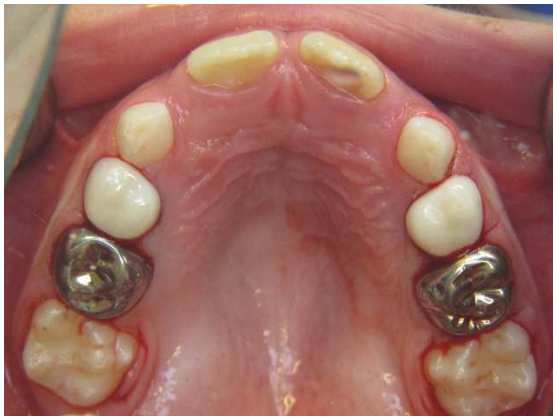
Figure 4:
Intraoral Pre-op Frontal and Occlusal view:





Intraoral Post-op Frontal and Occlusal view:





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