A Randomized Controlled Trial: Absorbable Hemostatic Pack Effect on Bleeding Time Following Extraction of Primary Maxillary Incisors

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in Dentistry in the Graduate School of The Ohio State University

By

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Abstract

Purpose: To compare pressure only versus hemostatic pack application into the socket for hemostasis after extraction of maxillary primary incisors in healthy children. To determine if hemostasis is associated with age, sex, heart rate, blood pressure, timing of administered ketorolac, type of isolation, root status, presence of periapical pathology, or parent reported pre-operative pain post extraction in the general anesthesia setting.

Methods: The study was designed as a prospective, randomized, controlled, split-mouth trial. Healthy children ages one to seven years old requiring extraction of at least two primary maxillary incisors under general anesthesia were included in this study. Extraction sites were randomly assigned to receive pressure only or hemostatic pack. Post-operative bleeding was rated on a scale of zero to three at two, ten, and 15 minutes.

Results: After calibration, Light's Kappa score was 0.873 for inter-rater reliability of the 11 participating dentists. Data was collected for 50 teeth (25 subjects). Ratings were significantly lower for sockets receiving the hemostatic plug at two minutes and 15 minutes. No significant difference was observed at 10 minutes. Time-of-extraction heart rate showed significant effect on bleeding ratings at 10 minutes only. For every one unit increase in time-of-extraction heart rate, the odds of having worse bleeding increases by nine percent. Other variables including age, gender, tooth pain before extraction, parulis,

stabilization device, discoloration, amount of tooth resorption, and periapical radiolucency had no association with bleeding time.

Conclusions:

1. Placing a hemostatic pack in a maxillary primary incisor sockets reduced bleeding at two minutes and 15 minutes post-extraction but not at 10 minutes, compared to a control.
2. From a clinical standpoint, placing a hemostatic pack does not control bleeding well enough to immediately complete moisture sensitive procedures such as composite restorations.
3. Future studies should explore other modalities of non-pharmacological hemostasis such as gauze pressure.

Dedication

Thank you to the faculty, residents, and staff at Nationwide Children's Hospital dental surgery center for their support and dedication to improving the oral health of children.

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Chapter 1. Introduction

Tooth extraction is a common procedure performed for children under general anesthesia and comes with risks of morbidity including post-operative bleeding.[1] Bleeding secondary to extractions performed late in the procedure may delay patient discharge from the operating room (**OR**) to the recovery unit. If extractions are performed early in the procedure, bleeding may interfere with moisture-sensitive restorative procedures including composite restorations and zirconia crowns prolonging anesthesia time subsequently increasing costs and risk. Moisture-sensitive procedures for more esthetic outcomes are being performed more frequently in the OR. Zimmerman[2] found that parental concerns about materials in decreasing order were esthetics, cost, toxicity, and durability. Forty-Three percent of pediatric dentists follow parental preferences, even when that action is contrary to their initial clinical judgement.[2]

Blood loss secondary to extractions in healthy children during general anesthesia can vary based on patient factors, number of teeth extracted, root surface area of the teeth extracted, and surgical technique. Henderson concluded total blood loss ranged from 2.5-57mL in a group of 50 children aged three to five years requiring up to extraction of the entire upper arch together with the lower molars.[3]

In the surgical recovery unit, break-through bleeding from tooth extractions may attenuate recovery and/or necessitate post-general anesthesia hemostatic treatment,

including return to the OR in severe cases. Bridgman et al found 71% of children aged five to 15 years were bleeding during the immediate post-treatment phase, and 37% were still bleeding on the trip home.[4] Hu et al found 23% of healthy children one to eight years of age experienced bleeding one hour postoperatively.[5]

Primary hemostasis is initially achieved by vasoconstriction of the blood vessels and platelet pack formation, while secondary hemostasis is formation and stabilization of the fibrin clot.[6] Dentists may use absorbable hemostatic packs, sutures, local anesthetic with a vasoconstrictor (LA), or local pressure application to control postoperative bleeding.[7] Alternative measures include topically-administered haemocoagulase or irradiation with blue-violet light LEDs (light-emitting diode).[8, 9] All of these methods aim to increase the stability of the fibrin clot. Many absorbable hemostatic packs are available on the market. Gelfoam® (Pfizer, Kalamazoo, MI) is a water-insoluble, off-white, non-elastic, porous, pliable product prepared from purified porcine skin gelatin granules and water for injection. Surgifoam® (Ethicon, Somerville, NJ) is a sterile, water-insoluble, malleable, porcine gelatin absorbable sponge. Surgicel® (Ethicon, Neuchatel, Switzerland), an absorbable hemostat composed of oxidized regenerated cellulose, and BenaCel® (Unicare Biomedical, Laguna Hills, CA), a dental dressing made of biocompatible oxidized cellulose with no chemical additives, are alternatives which contain no animal byproducts.

Hemostatic packs, sutures, and LA contribute to material costs, potential risk of an allergic reaction, and complications such as sutures dislodging and hemostatic packs extruding from the socket. Rare allergic reactions to animal products in absorbable

hemostatic packs have been reported. In one case, a pediatric dentist placed Gelfoam® with sutures after extractions, and the patient developed periorbital and lip edema and puffy hands within 2 minutes.[11] Another case report revealed elevated levels of tryptase, total IgE, porcine, and bovine gelatin-specific IgE after the placement of Gelfoam®.[12] A third case example reported that a child developed an anaphylactic reaction to the gelatin component of thrombin-soaked Gelfoam® during spinal cord surgery. A few months prior, the patient had experienced generalized hives, lip swelling, and abdominal pain 20 minutes after ingesting canned pork with a gelatinous glaze.[13] In recent years, cases of immediate-type allergic reaction caused by gelatin present in vaccines or in the recombinant human erythropoietin have been reported in which specific IgE to gelatin was found in the sera of patients. Possible delayed-type hypersensitivity to gelatin was observed in one case following hernia surgery.[14] Some parents may object to hemostatic packs containing animal products due to religious or ethical beliefs and consent should be obtained prior to placement.[10]

There have been various studies comparing hemostatic packs in populations with bleeding disorders. Petersen et al.[15] compared a gelatin sponge to oxidized regenerated cellulose after surgical extraction of maxillary third molars. There was no difference between groups in swelling or bleeding, but patients experienced more pain in sites where materials had been packed versus the control site with no packing. Bajkin et al. compared different local hemostatic modalities including suturing, placing gelatin sponges, or no intervention in patient receiving long-term oral anticoagulant therapies. In most cases, for patients with an International Normalized Ratio equal to or less than 3.0 requiring

extraction of one or two teeth, postoperative bleeding could be controlled with local pressure and no alteration of anticoagulant dose.[16] Blinder et al. also studied patients treated with oral anticoagulant drugs after dental extractions by comparing gelatin sponge + sutures, gelatin sponge, sutures and tranexamic acid mouthwash, and gelatin sponge, sutures, and fibrin glue. They concluded dental extractions can be performed without interruption of oral anticoagulants, and local hemostasis with gelatin sponges and sutures is sufficient.[17] Finally, a systematic review evaluated the clinical outcomes of topical hemocoagulase compared with placebo in extraction socket sites of adults and found that topical hemocoagulase led to a significant differences in bleeding stoppage time, pain, swelling, wound healing, and other postoperative complications.[18]

To our knowledge, no one has investigated effectiveness of applying an absorbable hemostatic pack after extraction of maxillary primary incisors in healthy children. The aim of this study was to compare post-extraction bleeding time after inserting a hemostatic pack versus no intervention after extraction of maxillary primary incisors in healthy children. Our secondary objective was to identify variables that may be associated with bleeding time.

Chapter 2. Methods

This prospective, randomized, controlled, split-mouth trial was approved by the Institutional Review Board (#589) at Nationwide Children's Hospital. Eligible subjects were patients scheduled for general anesthesia in a dental ambulatory surgery center from January through March, 2020. Inclusion criteria were patients with American Society of Anesthesiologists Class 1 status[19], age of 1-7 years, and planned treatment of at least 2 maxillary primary incisor extractions. Exclusion criteria were extractions of teeth that required gingival reflection or elevation, or complete extrusion of the hemostatic pack any time during the study. A sample size of 220 teeth would give the study power of 0.80.

Consent was obtained from each child's legal parent or guardian. Each patient was randomly assigned to one of two study groups which dictated the socket to receive the hemostatic pack (BenaCel®), the experimental group, and the socket to have no intervention for hemostasis, the control group (Table 1). BenaCel® (in 5mmx7mm standardized packs) was selected for its availability on the market as well as its non-porcine contents. Tooth extractions were performed using a straight #1 forceps only and no LA was used for any patient. Blood pressure, heart rate, and time of extraction was recorded and subsequent dental treatment for the patient was provided without alteration of the dentist's routine process.

Set A		
Teeth extracted	Hemostatic Pack	Control
E,F (both centrals)	E	F
D,G (both laterals)	D	G
One lateral and one central	Lateral	Central
One lateral and both centrals	Lateral	R central
Two laterals and one central	R lateral	Central
All four incisors	D	F
Set B		
Teeth extracted	Hemostatic Pack	Control
E,F (both centrals)	F	E
D,G (both laterals)	G	D
One lateral and one central	Central	Lateral
One lateral and both centrals	R central	Lateral
Two laterals and one central	Central	R lateral

Table 1. Randomization Assignments

At 2 minutes, 10 minutes, and 15 minutes post-extraction, bleeding was scored according to a scale developed for this study (Figure 1). The dentist gently wiped the palate with a moist gauze to remove existing blood and observed the socket for 3 seconds prior to rating each socket. The stabilization device used during the subsequent treatment was noted (Isovac®, Zyris, Inc, Santa Barbara, CA, Molt mouth prop, E-prop^{TM} mouth prop, or none). At 15 minutes, dentists noted if any portion of the hemostatic pack was extruding beyond the plane of the socket for the experimental group. The pack was left in place regardless of its position in the socket but was not replaced if completely lost. Raters included seven pediatric dental faculty and four residents. Calibration on the bleeding scale was performed prior to and during the data collection period.

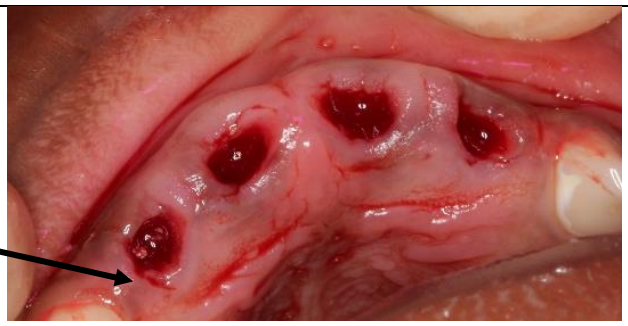
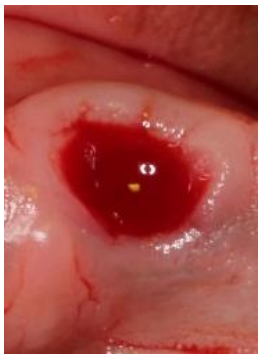
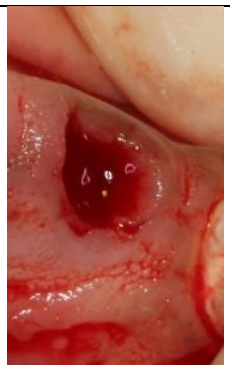
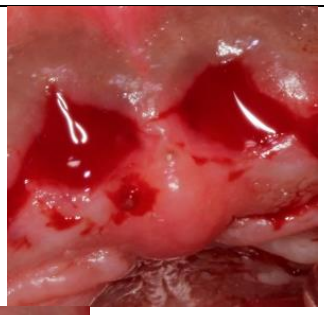
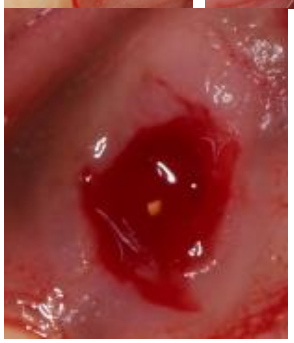
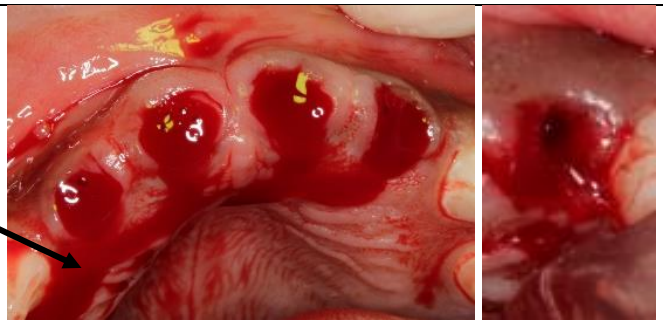
0	**No active bleeding/fully clotted** -No oozing or changes within 3 seconds. Blood clot has formed. -Blood may remain in natural gingival grooves.	
1	**Active bleeding which fills the socket, but no oozing outside of the socket onto the alveolar ridge.** -The margins of the socket are easily traceable. -Blood fills socket but is not clotted.	 
2	**Active bleeding which is oozing outside of the socket, but limited to immediate alveolar ridg**e. -The margins of the socket are not easily traceable.	  

Figure 1. A continued figure. Scale of Post-Operative Bleeding

Figure 1 Continued

3	**Active bleeding which is oozing outside of the socket, over the alveolar ridge into the working field.**	

Other data and tooth characteristics recorded included patient age, sex, presence of pre-operative pain in the maxillary anterior region, history of non-steroidal anti-inflammatory drug (NSAID) use, and baseline blood pressure and heart rate (taken after anesthesia induction, but prior to throat pack placement by the dentist). An occlusal radiograph with the bisecting angle technique was exposed prior to treatment. One investigator (S.M.) reviewed all occlusal radiographs, recorded evidence of radiographic pathology, and rated root resorption according to a scale developed by Fanning (Figure 2).[20] The time of patient discharge to the recovery unit, and interventions required due to bleeding in the recovery unit were recorded. Ketolorac, an NSAID, was not administered during the 15-minute data collection period for any patient, and no dentist intervention due to bleeding was required in the recovery unit for either group.

Stage	Original Designation	Designation for this study	Frequency
Root intact	Res 0	0	20
Root shows blunting or rounding at apex	Res_i	1	19
Root resorbed 1/4	$Res_{1/4}$	2	4
Root resorbed 1/3	$Res_{1/3}$	3	3
Root resorbed 1/2	$Res_{1/2}$	4	3
Root resorbed 2/3	$Res_{2/3}$	5	0
Root resorbed 3/4	$Res_{3/4}$	6	0
Root entirely resorbed	Res_c	7	1

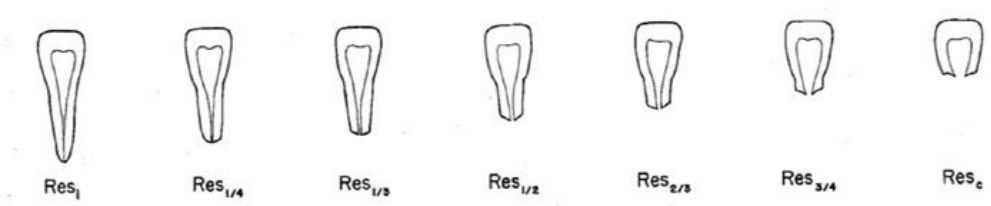


Figure 2. Root Resorption Stages, modified from Fanning[20]

Data analysis was performed using R statistical software (version 3.6.2). Light's Kappa score was used to assess the inter-rater reliability of dentists on scoring post-extraction bleeding. Descriptive statistics (frequency, percentage, mean and standard deviation) were generated for demographic information, tooth characteristics, and vital signs. To examine whether post-extraction bleeding differs between the experimental and control groups, we generated a two-way table of bleeding scores by group, and three stacked column charts (one for each time point). To adjust for potential confounders in the association between post-extraction bleeding in the two groups, we developed three multivariate ordinal logistic regression models (one for each time point). The adjusted potential confounders were age, gender, post-extraction heart rate, tooth pain before extraction, parulis, stabilization device used, discoloration, amount of tooth resorption,

and periapical radiolucency. A P-value of less than 0.05 was considered statistically significant.

Chapter 3. Results

After calibration, Light's Kappa score was 0.873 (Z score of 0.00173 and p-value of 0.999) for inter-rater reliability of the 11 participating dentists indicating a strong level of agreement.

Data was collected for 50 teeth (25 subjects). In one patient two teeth, were excluded after enrollment due to the complete extrusion of the hemostatic pack from the socket during the 15 minute rating period, and a second patient because the tooth broke during the extraction. Of the 25 remaining patients, 52% (n=13) were female and 48% (n=12) male, and median age was four years with a range of two to seven years. Pre-operatively, 84% of patients (n=21) reported no pain associated with the primary maxillary incisors and no patients were given NSAIDs within 24 hours of the procedure. None of the teeth had associated swelling, four percent (n=2) had a parulis, and six percent (n=3) had discoloration consistent with previous trauma. Based on radiographic findings, 40% of the teeth had no radiographic resorption (n=20), 38% had blunting of the apex (n=19), eight percent (n=4) had one-quarter root resorption, six percent (n=3) had one-third root resorption, six percent (n=3) had one-half root resorption, no teeth had two-third or three-quarter root resorption, and two percent (n=1) the root entirely resorbed. Twenty-two percent (n=11) had a periapical radiolucency. Time-of-extraction vital signs were higher than baseline, with mean systolic and diastolic blood pressure of

9± 9.4 and 3.8± 11.7 points higher, respectively, and mean heart rate of 14.4 ± 16.2 beats per minute higher.

Stabilization devices used by the dentists were 64% Isovac® (n=16), eight percent E-prop bite block (n=2), eight percent molt mouth prop (n=2), 12% none (n=3), and eight percent not recorded (n=2). At 15 minutes post-extraction, the hemostatic pack was extruded out of the socket in 14% (n=7) of cases. The mean time from extraction to operating room discharge was 42 ± 12 minutes.

The bleeding ratings during the study period are shown in Table 2. Ratings were significantly lower for sockets receiving the hemostatic pack at 2 minutes (OR = 0.19, 95% CI 0.05-0.66, p=0.010) and 15 minutes (OR = 0.24, 95% CI 0.06-0.87, p=0.03) (Figure 3, Table 3). No significant difference was observed at 10 minutes (OR=0.44, 95% CI 0.14-1.35, p=0.16). Time-of-extraction heart rate showed significant effect on bleeding ratings at 10 minutes only. For every one unit increase in time-of-extraction heart rate, the odds of having worse bleeding increases by nine percent (OR 1.09, 95% CI 1.03-1.15, p=.006). In the ordinal logistic regression models, other variables including age, gender, tooth pain before extraction, parulis, stabilization device, discoloration, amount of tooth resorption, and periapical radiolucency had no association with bleeding time.

	Control		Hemostatic Pack		Total
2 min					
0	0	0%	1	4%	1
1	3	12%	10	40%	13
2	10	40%	7	28%	17
3	12	48%	7	28%	19
10 min					
0	7	28%	8	32%	15
1	6	24%	10	40%	16
2	7	28%	5	20%	12
3	5	20%	2	8%	7
15 min					
0	12	48%	17	68%	29
1	4	16%	4	16%	8
2	4	16%	4	16%	8
3	5	20%	0	0%	5
Total	**25**	**100%**	**25**	**100%**	**50**

Table 2. Distribution of Bleeding Ratings during Study Period

2 minutes	**Odds Ratio**	**95% Confidence Interval**	**P-value**
Control	Reference		
Hemostatic Pack	0.19	(0.05, 0.66)	0.010
10 minutes			
Control	Reference		
Hemostatic Pack	0.44	(0.14, 1.35)	0.16
Post Heart Rate	1.09	(1.03, 1.15)	0.006
15 minutes			
Control	Reference		
Hemostatic Pack	0.24	(0.06, 0.87)	0.03

Table 3. Association between Group and Outcome (Ordinal Logistic Regression)

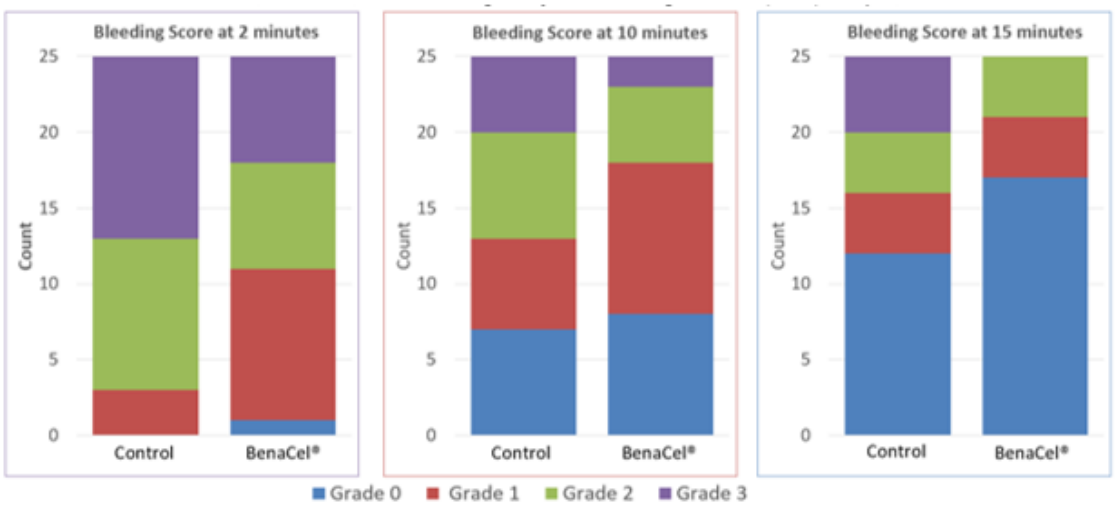


Figure 3. Stacked counts of teeth with different bleeding scores by group at 2 min, 10 min, 15 min post-extraction

Chapter 4. Discussion

Dentists must consider the risks and benefits of introducing a foreign material into a patient's body. Some hemostatic packs contain gelatin which introduces an additional risk of potential allergic reaction.[11,12,13,14] Food products including gelatin-containing gum or candies and some vaccines containing porcine or bovine gelatin could be the source of initial exposure.[21] This highlights the importance of obtaining a through medical history, including the details of previous allergic reactions. This also necessitates that dentists choose materials wisely and are cognizant of religious or cultural restrictions on the use of certain animal products. Adding additional products to a procedure also introduces considerations such as cost, time, and staff training.

Only one hemostatic pack brand (Benacel®) was tested in this study and the findings cannot be extrapolated to other products. While this study demonstrates a hemostatic pack significantly reduces bleeding at 2 minutes and 15 minutes post-extraction, but not at 10 minutes, we are unsure if this reduction is clinically significant. Less than half (40%) of hemostatic pack sockets and 12% of control sockets received a grade 0 or 1 at 2 minutes, signifying active bleeding but confined in the socket. Grade 1 bleeding is active but still confined to the socket. It is easily disturbed with tissue manipulation as a clot is not fully formed and attempting a moisture sensitive procedure, such as a composite restoration, within 2 minutes after hemostatic pack placement would still be challenging without additional hemostatic methods or wait time. It is difficult to

extrapolate these bleeding results to the outpatient setting because extractions are typically performed with local anesthetic containing a vasoconstrictor.

At 10 minutes post-extraction no significant difference in bleeding present between the experimental and control groups and the distribution of bleeding scores was somewhat even. Again, attempting to complete a moisture sensitive procedure 10 minutes after extractions on adjacent teeth would be unpredictable regardless of hemostatic pack placement. Finally, at 15 minutes post-extraction hemostatic pack placement significantly reduced bleeding. According to the BenaCel® manufacturer's information, the dressing forms a gelatinous scaffold and adheres to the wound site to facilitate the development of a stable blood clot prevents dry socket formation.[22] Although alveolar osteitis after extraction of primary maxillary incisors is not a concern, it seems the product does stabilize the blood clot making it less prone to bleeding with manipulation of tissues when continuing to work in other areas of the mouth. However, 48% of control sockets at 15 minutes also achieved complete blood clot formation with no bleeding (grade 0).

Upon discharge to the surgical recovery unit, it is beneficial from an anesthesia perspective to have adequate hemostasis (Grades 0 and 1). In this study, the average time from extraction to the recovery unit was 42 ± 12 minutes, suggesting the dentists did not perform extractions at the end of the procedure. When considering hemostasis for discharge purposes, placing a hemostatic pack is unlikely to have clinical significance if extractions are completed earlier in the procedure, as occurred in our study. There may be a benefit, however, to placing a hemostatic pack if the extractions are completed near the end of the procedure.

Time-of-extraction heart rate showed a statistically significant effect on bleeding at 10 minutes. For every one unit (beats per minute) increase in time-of-extraction heart rate, the odds of having increased bleeding increases by nine percent. Comparing a HR of 100 to 110 at time of extraction is 90% likely to have worse bleeding. However, at two and 15 minutes time-of-extraction heart rate had no statistical effect on bleeding. A possible explanation of this finding comes from examining how bleeding was graded. At two minutes, 72% (36 out of 50) sockets achieved a grade two or three on the bleeding scale due to the short amount of time after the extraction. Regardless of heart rate, it is reasonable to expect more bleeding immediately after an extraction versus 10 or 15 minutes later. At 15 minutes, the same concept can be applied only assuming it is reasonable to expect little bleeding near the end of healthy patient's physiologic bleeding time. At 15 minutes, 74% (37 out of 50) had achieved a grade zero or one on the bleeding scale. Thus, only at 10 minutes did time-of-extraction blood pressure become significant.

After discharge, the responsibility of managing a child's morbidities such as post-operative bleeding falls on the caretaker. The hemostatic pack was extruded in 28% (7 out of 25) sockets at the end of the 15 minute study period. Parents should be advised hemostatic packs can extrude or fall out after discharge. Sometimes bleeding may temporary increase if this happens or the pack is pulled out by the child. This may cause concern for some parents leading to additional after-hours parent phone calls.

The study has several strengths. Intra-rater reliability (kappa= 0.873) showed a strong level of agreement.[23] The split-mouth design allowed each patient to serve as his own control. The study was also intended to be pragmatic in nature and provide results

useful for clinical environments. The general anesthesia protocol was not modified for the study and dentists used their preferred stabilization device, 64% of whom used Isovac® (Figure 4). After tooth extraction, the dentist continued working in other quadrants, likely manipulating the tissues close to the extraction sites, influencing results but also imitating “real world” scenarios versus a strict, controlled 15-minute post-extraction reporting period where no manipulation of the oral tissues occurred.

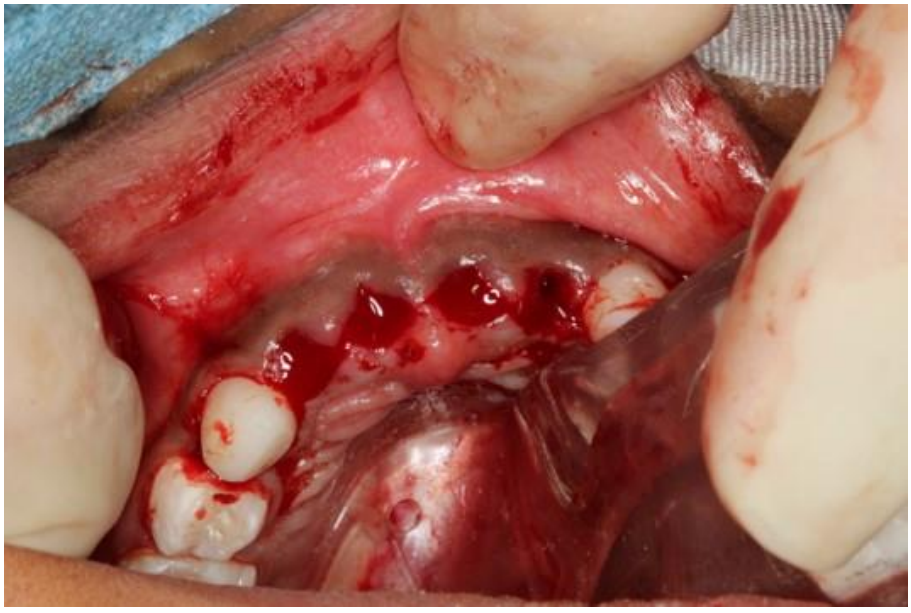


Figure 4. Isovac® positioning post-extraction

The study also has some limitations, including sample size. An ideal sample size for a study power of 0.80 is 220 teeth, but time and clinical constraints precluded data collection from this large sample size. In addition, some variables such as parulis, discoloration, and radiographic periapical radiolucency were present in small numbers possibly affecting bleeding. Other limitations surround the non-controlled clinical environment. Dentists did not use a standard template for radiographs, enabling variation

in angling. Even so, overlap of the primary tooth apex by the permanent successor made it difficult to determine intact versus blunted roots on the resorption scale. The resorption scale also does not account for lateral resorption, so the rater modified the scale to account for percentage of root resorbed. However, there was no significance of root resorption related to bleeding. It is also difficult to quantify amount of bleeding in real time. In our research, no bleeding scale relevant to tooth sockets existed so we had to create our own (Figure 1). This scale remains invalidated.

This study laid the foundation for further clinical studies regarding post-extraction hemostasis in healthy children. Future directions include continuation of data collection to acquire a larger sample size, or modifying study design in order to include posterior teeth. Future studies can also examine continuous gauze pressure. In this study, a moist gauze was applied immediately following extraction only to remove excessive blood. Some practitioners' routine procedure following extractions under general anesthesia includes placing and maintaining pressure on a moist gauze over the extraction sites until hemostasis is obtained. This method may achieve different hemostatic results. One study concluded 94-96% of single and multiple tooth extractions stop bleeding in 10 minutes with pressure applied by the patient biting on gauze, although this study included local anesthetic and patients 15 years and older.[15] Keeping continuous gauze pressure, whether kept in place by a molt mouth prop or a rubber dam, was not universal in our department and we chose not to modify clinical technique or preference for this study.

Chapter 5. Conclusions

1. Placing a hemostatic pack in a maxillary primary incisor sockets reduced bleeding at two minutes and 15 minutes post-extraction but not at 10 minutes, compared to a control.
2. From a clinical standpoint, placing a hemostatic pack does not control bleeding well enough to immediately complete moisture sensitive procedures such as composite restorations.
3. Future studies should explore other modalities of non-pharmacological hemostasis such as gauze pressure

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