Research Article

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The Evaluation of Fibrin Sealants and Tissue Adhesives in Oral Surgery Among Patients with Bleeding Disorders

Kanama Bozukluğu Olan Hastalarda Fibrin Sealant ve Doku Yapıştırıcılarının Oral Cerrahi Uygulamalarda Kullanımının Değerlendirilmesi

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Abstract

Objective: The aim of this study was to evaluate the efficiency of two local hemostatic agents administered with a preoperative dose of replacement therapy in patients with bleeding disorders undergoing oral surgery.

Material and Methods: The study included 21 patients that were randomly divided into 3 groups. Patients in Group 1 (n = 7) received preoperative replacement therapy and postoperative fibrin sealant applied to the surgical site. Patients in Group 2 (n = 7) received preoperative replacement therapy and postoperative tissue adhesive applied to the surgical site. Patients in Group 3 (n = 7) were given replacement therapy pre- and postoperatively.

Results: Postoperative bleeding was not observed in 17 of the 21 patients, including 5 in Group 1 (71.42%), 6 in Group 2 (85.71%), and 6 in Group 3 (85.71%). Hemorrhagic complications occurred in only 4 of the 21 patients.

Conclusion: The use of fibrin sealant and tissue adhesive was beneficial, as they reduced the level of factor concentrates used for replacement therapy and resulted in rapid hemostasis at the surgical site, facilitating the ability to perform serial surgical procedures concurrently.

Key Words: Fibrin sealants, Tissue adhesive, Tooth extraction, Hemophilia, Bleeding disorders

Özet

Amaç: Bu çalışmanın amacı kanama bozukluğu olan hastalarda, oral cerrahi girişimlerde replasman tedavisinin yalnızca preoperatif dozu uygulanarak cerrahi alana lokal doku yapıştırıcı veya fibrin sealant uygulamasının hemostaz üzerindeki etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Kanama bozukluğu olan 21 hasta randomize olarak üç farklı gruba ayrılmıştır. Grup 1'deki hastalara (n=7) preoperatif replasman tedavisi ile fibrin sealant uygulanmıştır. Grup 2'deki hastalara (n=7) preoperatif

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replasman tedavisi ile doku yapıştırıcısı uygulanmıştır. Grup 3'deki hastalara preoperatif ve postoperatif replasman tedavisi uygulanmıştır.

Bulgular: Grup 1'de beş hasta (%71,42), Grup 2'de altı hasta (%85,71) ve Grup 3'de altı hasta (%85,71) olmak üzere toplam 17 hastada hiçbir postoperatif komplikasyon gözlenmemiştir. Bütün gruplardan olmak üzere sadece dört hastada hemorajik komplikasyon gözlenmiştir.

Sonuç: Bu klinik çalışmanın sonuçlarına dayanarak, fibrin sealant ve doku yapıştırıcılarının oral cerrahi işlemlerde uygulanmasının replasman tedavisinde kullanılan faktör konsantresi miktarının azaltılması ve operasyon alanında hemostaz sağlanarak aynı anda çok sayıda işlemin yapılabilmesine olanak vermesi açısından faydalı olduğu görüşündeyiz.

Anahtar Sözcükler: Fibrin sealant, Doku yapıştırıcısı, Diş çekimi, Hemofili, Kanama bozukluğu

Introduction

Patients with bleeding disorders that require oral surgery due to hemorrhage have a high risk of prolonged or excessive bleeding. Multiple transfusions and prolonged hospitalization associated with oral surgery had previously been a necessity for this group of patients. Subsequently, the introduction of clotting factor concentrates and antifibrinolytic agents has facilitated the use of oral surgical procedures in patients with bleeding disorders [1]. Thus, various unconventional methods are used in patients with bleeding disorders, particularly the application of fibrin sealants and tissue adhesives, as adjunctive treatment or in some cases primary treatment.

Fibrin sealants contain fibrinogen, factor XIII, thrombin, and aprotinin. Following application to the tooth extraction site, thrombin converts fibrinogen to an unstable fibrin clot and aprotinin prevents clot degradation [2,3]. Traditionally, fibrin sealants are used as tissue adhesive and hemostatic agent, as well as in new and creative ways, such as for cellular growth stimulation in tissue engineering [4,5].

Ethyl-2 cyanoacrylate, a rapid polymerizable liquid monomer, is a synthetic tissue adhesive for topical use. Upon application, liquid monomer formulation polymerizes instantly into a thin flexible polymer film that adheres strongly to oral tissues [6,7]; however, the mechanism by which cyanoacrylate glue generates hemostasis is unclear. The hypothesis is that the ester forms a microfilm that causes mechanical blockage that slows blood flow, providing a surface agent to activate the clotting cascade [8]. There is evidence that the film forms a porous mass that is invaded by blood with subsequent clotting within the pores of the adhesive. As such, the rationale behind the use of ethyl-2 cyanoacrylate is to hold the opposing wound edges together while also functioning as a wound dressing that enhances clot formation or as a clot stabilizer [9]. The clinical features and benefits can be altered by adding different side chains [10]. As with fibrin sealants, tissue adhesives are widely used for oral and general surgical interventions, such as root canal treatment and embolotherapy for complex cerebral and extracerebral vascular anomalies [11].

The aim of the present study was to evaluate the hemostatic efficacy of a fibrin sealant and a tissue adhesive, with only preoperative administration of replacement therapy in patients with bleeding disorders undergoing oral surgery.

Material and Methods

The study included 21 patients with bleeding disorders who were referred for dental assessment. In all, 15 patients had Hemophilia A (5 had the severe type, 7 had the moderate type, and 3 had the mild type), 1 patient had Hemophilia B, and 5 patients had von Willebrand disease (vWD). The male:female ratio was 3.2:1 and mean age was 22.28 years (range: 6-40 years). Each patient underwent an initial consultation to establish a dental treatment plan. Severe dental caries, dental abscess, and prolonged retention of deciduous teeth were the indications for tooth extraction. Surgical intervention included tooth extraction, subgingival scaling, and frenectomy. Informed consent was obtained from each patient or their parents.

The patients were randomly divided into 3 groups, regardless of their disease type and severity. The replacement therapy procedure was carried out in collaboration with the Department of Pediatric Hematology-Oncology (Table 1). Group 1 (n=7) received preoperative replacement therapy and postoperative fibrin sealant applied to the surgical site. Group 2 (n=7) received preoperative replacement therapy and postoperative tissue adhesive applied to the surgical site. Postoperative replacement therapy would not be given unless hemostasis was achieved in Groups 1 and 2. Group 3 (n=7) received the total dose of replacement therapy pre- and postoperatively. Oral surgical procedures were performed with minimal trauma to surrounding tissues. The distribution of patients according to

Table 1: Protocol for Hemostasis

	Severe Hemophilia A/B	Mild, moderate hemophilia A/B and vWD	Other (FX, XI, and XIII deficiency
12h before +Day 5/7	Tranexamic acid 25-40mg·kg^{-1}·d^{-1} (t.i.d.or q.i.d.)		
2h before	FVIII: 25 U kg^{-1} F IX: 40 U kg^{-1}	FVIII and vWD: 20 U kg^{-1} F IX: 40 U kg^{-1}	FFP*
Day 1	FVIII and vWD: 20 U kg^{-1} F IX: 40 U kg^{-1}		DDAVP: 0.3 µg·kg^{-1}·dose (twice)
Day 2	FVIII: 20 U kg^{-1} F IX: 40 U kg^{-1}	DDAVP: 0.3 µg·kg^{-1}·dose (twice)	
Day 3	FVIII: 15 U kg^{-1} F IX: 30 U kg^{-1}		

Table 2: General Patient Characteristics and Dental Interventions Performed with Preoperative Replacement Therapy and Local Fibrin Sealant Application (Group 1)

Case	Gender	Age (years)	Disease	Dental interventions (number of teeth)	Complications
1	F	26	von Willebrand disease	Subgingival scaling and dental extraction (3.8)	(+)
2	F	17	von Willebrand disease	Dental extraction (1.6)	(–)
3	M	31	Hemophilia A (moderate form)	Dental extraction (1.6, 2.5, 3.6, 4.6)	(–)
4	M	11	Hemophilia A (severe form)	Dental extraction (5.4, 5.5, 3.6)	(–)
5	M	14	Hemophilia A (severe form)	Dental extraction (2.6)	(+)
6	M	21	Hemophilia A (moderate form)	Dental extraction (1.4,4.4)	(–)
7	M	29	Hemophilia A (mild form)	Dental extractions (3.5,4.5)	(–)

hematologic disease and oral surgical procedure is given in Tables 2, 3 and 4. Subgingival scaling was performed in two patients who had spontaneous gingival bleeding due to mild gingivitis. Frenectomy of the inferior labial frenulum was performed in 1 patient due to diastema between the incisors.

Deciduous and permanent teeth (except for the permanent mandibular molar) were extracted after administration of articaine HCl (40 mg mL^{-1}) and epinephrine HCl (0.006 mg mL^{-1}) (Ultracaine DS, Aventis), either locally or intraligamentally. Extraction of permanent mandibular molar was performed with the inferior alveolar nerve block. Teeth were extracted with minimal trauma to surrounding tissues. The socket was curetted and the extraction cavity was filled with 14x7x7 mm gelatin sponges (Gelatamp, Roeko, Germany) in all patients. Fibrin seal-

Table 3: General Patient Characteristics and Dental Interventions Performed with Preoperative Replacement Therapy and Local tissue Adhesive Application in Group 2

Case	Gender	Age (years)	Disease	Dental interventions (number of teeth)	Complications
1	M	6	Hemophilia A (severe form)	Dental extraction (7.4, 7.5, 8.1)	(–)
2	M	28	Hemophilia A (severe form)	Dental extraction (1.6, 1.4, 2.4, 2.7, 4.4, 4.5, 4.6)	(+) at the needle penetration site
3	M	24	Hemophilia A (mild form)	Dental extraction (1.8, 4.8)	(-)
4	M	12	Hemophilia A (moderate form)	Dental extraction (7.5,8.5)	(–)
5	F	18	von Willebrand disease	Dental extraction (4.5)	(–)
6	F	40	von Willebrand disease	Dental extraction (2.8)	(–)
7	M	15	Hemophilia A (moderate form)	Dental extraction (7.5,3.6)	(–)

Table 4: General Patient Characteristics and Dental Interventions Performed with Pre-and Postoperative Replacement Therapy in Group 3

Case	Gender	Age (years)	Disease	Dental interventions (number of teeth)	Complications
1	M	7	Hemophilia A (moderate form)	Frenectomy and dental extraction (7.1,7.2,8.1,8.2)	(–)
2	M	17	Hemophilia A (mild form)	Subgingival scaling and dental extraction (4.6)	(–)
3	M	26	Hemophilia B	Dental extraction (3.7)	(–)
4	F	22	von Willebrand disease	Dental extraction (1.5)	(–)
5	M	29	Hemophilia A (severe form)	Dental extraction (1.6,2.6)	(+)
6	M	35	Hemophilia A (moderate form)	Dental extraction (1.3)	(–)
7	M	40	Hemophilia A (moderate form)	Dental extraction (4.2,4.4)	(–)

ant 0.5 mL (Tisseel™ Kit, Eczacıbaşı, Baxter, Turkey) was used for patients in Group 1 and tissue adhesive (0.3 ml/cc in tubes of 3g) (Epiglu® Meyer-Haake, Germany) was used for patients in Group 2. Patients in Group 3 were not administered additional local therapy. All patients were monitored until the cessation of bleeding at the surgical site and were informed about postoperative care.

Results

Patient demographics, surgical procedures, and post-operative outcomes are summarized in Tables 2, 3 and 4. A total of 21 patients with bleeding disorders underwent oral surgery for tooth extraction (44 teeth including 12 deciduous and 32 permanent), subgingival scaling (n=2),

Figure 1: Application of fibrin sealant for gingival hemorrhage in Case 1 in Group 1.

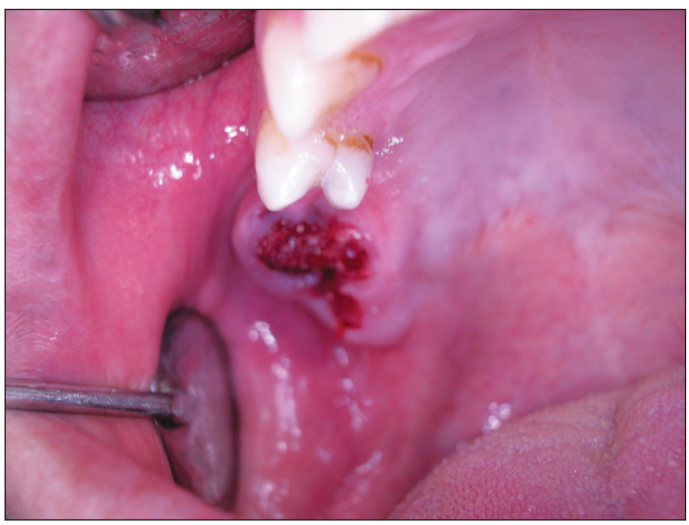

Figure 2: Application of tissue adhesive in the extraction socket in Case 2 in Group 2.

and frenectomy (n=1). Postoperative hemostasis was achieved in 17 patients, with a success rate of 71.4% (n = 5) in Group 1, 85.7% (n=6) in Group 2, and 85.7% in Group 3 (n=6).

Hemorrhagic complications occurred in only four of the 21 patients. In Group 1; Case 1 (vWD) had undergone a single tooth extraction and subgingival scaling, and Case 5 (severe Hemophilia A) had one tooth extraction. To achieve hemostasis in these patients additional replacement therapy was given postoperatively. In Group 2 Case 2 (severe Hemophilia A) had 6 teeth extracted and postoperative hemorrhage occurred only at the site of needle penetration in the palatal mucosa. Tissue adhesive was applied once again and the bleeding ceased. In Group 3 mild postoperative bleeding was observed in Case 5 (severe Hemophilia A) following extraction of two teeth; complete clotting was achieved with local administration of tranexamic acid.

Discussion

The present study demonstrated the outcome of the use of fibrin sealant and tissue adhesive, with the addition of only preoperative replacement therapy to control hemorrhage in patients with bleeding disorders undergoing oral surgery. To the best of our knowledge this is the first such study, and therefore the results could not be compared to those of other studies. Hemorrhagic complications occurred in only 4 of 21 patients, of which one had vWD, two had Hemophilia A, and one had Hemophilia B. It is interesting to note that one of these patients (Case 2 from Group 2 [Hemophilia A]) had bleeding at the site of needle penetration, but not in the extraction cavity. In Group 2 preoperative replacement therapy and local application of tissue adhesive resulted in a 100% success rate. Additional postoperative replacement therapy was given to patients in Groups 1 and 2 that had postoperative bleeding despite local application of fibrin sealant or tissue adhesive. Based on the results of the present study we conclude that local application of fibrin sealant or tissue adhesive, together with preoperative replacement therapy is a reliable and efficacious procedure in patients with bleeding disorders undergoing oral surgery. In addition, the observed reduction in blood loss during and after oral surgery facilitates multiple surgical procedures during a single session of replacement therapy, providing economical and rapid patient rehabilitation.

Currently available treatment options for achieving hemostasis in patients with bleeding disorders are primarily factor replacement therapy, release of endogenous factor stores, and clot stabilization [9,12]. Factor replacement therapy is the golden standard treatment for hemophilia; however, its high cost is a major disadvantage, and as such recent research has focused on local hemostatic agents, such as fibrin sealants and tissue adhesives. Satisfactory hemorrhage control with the use of these materials has been reported [12,13]. The primary benefits of these hemostatic agents are a life-saving reduction in hemorrhage caused by trauma, a reduction in factor dependency, a reduction in the cost of treatment, and rapid control of hemorrhage, which reduces patient anxiety related to uncontrollable bleeding [13]. Other features of these agents regarding availability, application, safety and complication are sum-

Table 5: Comparison of Fibrin Sealants and Tissue Adhesives

	Fibrin Sealants	Tissue Adhesives
Cost	–	+
Readily available	–	+
Reduction in patient's stress	+	+
Resolution in saliva	+	–
Viral transmission risk	+	–
Provides hemostasis without replacement therapy	+	–
Difficulty in application in moist regions	–	–
Exothermic reaction heat	–	+
Inhibitor occurrence	+	–
Residual monomer occurrence	–	+

marized in Table 5 with a comparison to each other indicating superiority.

Suturing plays an important role in controlling hemorrhage, especially in patients with bleeding disorders undergoing tooth extraction. It has been suggested that when suturing is not performed (e.g. in children, as sometimes suturing is impossible due to a flat socket) saliva, due its potent fibrinolytic activity, dissolves and washes fibrin sealant away from the socket within a short time. Tongue movements also contribute to the mechanical removal of a clot from the socket [14]. A celluloid splint, as Suwannuraks suggested may prevent the tongue from scratching the inside of the socket, therefore the clot would be safe beneath the layer of the fibrin sealant [14]. On the other hand, cyanoacrylate functions well in a moist environment. Because moist environment does not interfere with the firm structure of the material, following application of tissue adhesives the enviroment need not be completely dry. Moreover, ethyl-2 cyanoacrylate—a monomer in liquid form—polymerizes in an exothermic reaction when in contact with a fluid medium, thereby forming a bond that strongly holds together the opposing edges of a wound [15]. Adhesion is achieved via attraction between the molecules of an adhesives and tissue surfaces [8]. These properties represent an advantage over fibrin sealants. Utilization of tissue adhesive functions as suturing does in providing hemostasis. Additionally, tissue adhesives with their inert feature show no resolution in saliva. These advantages were observed in the present study in Group 2, which received Epiglue® Meyer-Haake tissue adhesive; saturation and complications were not observed. Nevertheless, application in highly moist surfaces is challenging because the material sets quickly when it contacts with excess liquid that is comprised of blood and/or saliva.

Fibrin sealants are derived from plasma and therefore carry a similar risk of viral transmission as other similar plasma products; however, Kavaklı reported that during the last 20 years, no commercial fibrin sealant product has been reported to be responsible for viral transmission, as the result of modern viral inactivation procedures [16]. Nevertheless, it is well known that a viral infection cannot be detected during the initial incubation period of an infectious disease—a time period during which a donor is unaware of infection and laboratory serological assays are not able to detect the presence of a virus. As such, non-autologous fibrin sealants can carry a potential risk for viral transmission and homemade autologous fibrin sealants appear to be a good treatment choice; however, they are more expensive than other types of fibrin sealants. On the other hand, tissue adhesives are not associated with the risk of microbial transmission, as they are synthetic, and they exhibit bacteriostatic activity on wound surfaces and are less expensive than fibrin sealant products.

Based on the limited available data, tissue adhesives appear to have several advantages. However, their potential for forming exothermic heat during polymerization and residual monomer appears as a serious disadvantage. As the polymerization chain which occurs during the recurrent or thick applications becomes longer, the risk of exothermic heat increases.

In terms of cost-effectiveness, the treatment protocol in Group 2 was the best, due to the lower price of tissue adhesive (as compared tot fibrin sealant) and the lower dose of factor replacement. Patients in Groups 1 and 2 received only one dose of preoperative replacement therapy (in patients with severe and moderate-mild Hemophilia A: 25 U kg^{-1} and 20 U kg^{-1} of FVIII, respectively; in those with Hemophilia B: 40 U kg^{-1} of FVIX); however, patients in Group 3 also received postoperative replacement therapy on postoperative d 1-3—a total of 55 U kg^{-1} for each patient with Hemophilia A and 110 U kg^{-1} for those with Hemophilia B. As clotting factor concentrates are costly components of hemostatic therapy in patients with bleeding disorders, a reduction in their use will directly reduce the cost of therapy. In the UK it has been estimated that in terms of medication alone the cost per bleeding episode in a child of 20 kg varies from £54 to £493, and that for

an adult varies from £90 to £822.50, depending on the severity of the bleeding, and the purity, type, and quantity of FVIII used [17]. Thus, financial concerns has forced the researchers to study on ancillary therapies such as developing new techniques or hemostasis protocols that may provide an opportunity to define what would be closer to optimal replacement therapy by using lower doses.

Our experience as oral surgeons indicates that there is an increased risk of hemorrhage triggered by the intense vascularization of oral tissues and iatrogenic trauma during oral surgical procedures; therefore, oral care providers that treat patients with bleeding disorders should be aware of all the measures for controlling bleeding and the principles of atraumatic surgery. The goal is "key hole" surgery and minimal interference with the attached gingiva around the teeth and periosteum, so as to minimize postoperative bleeding [19]. Choice of anesthesia is also an important issue. With the use of appropriate replacement treatment regional anesthesia can be used; however, infiltration anesthesia is safer than other methods. In addition, considering the direct relationship between emotional factors such as dental anxiety, fear of bleeding and increased fibrinolysis, which can complicate postoperative healing in patients with bleeding disorders [1], dentists should perform various methods to alleviate patient stress prior to surgery. Patients with bleeding disorders would greatly benefit from dental educational programs presented by oral care providers.

The present study has some limitations, including a small patient population and groups consisting of patients with various types of bleeding disorders. As the results of this study are considered to be preliminary, additional research with larger patient populations and different study designs is necessary to further investigate and compare the efficacy of various local hemostatic agents in patients with bleeding disorders undergoing oral surgery.

Conclusion

Utilization of fibrin sealant or tissue adhesive, with only preoperative administration of replacement therapy in patients with bleeding disorders undergoing oral surgical procedures safely provided rapid hemostasis at the surgical site and facilitated performance of serial surgical procedures concurrently.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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