SHORT COMMUNICATION

Fibrin glue in managing intractable gingival bleeding in patients with inherited bleeding disorders—a quasi-experimental pilot study

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Abstract

This study presents the clinical outcomes of using in-house prepared fibrin glue for controlling gingival bleeding in patients with inherited bleeding disorders (IBD). The objective of the study was to assess the reduction in transfusion days and improvement in compliance for dental evaluation over a one-year period in a low-to-middle-income country. The quasi-experimental pilot study included 40 IBD patients with gingival bleeding. These were divided into two groups: Group A received fibrin glue (n=20), while Group B did not (n=20). The study compared outcome metrics, including the number of treatment days and blood components transfused, using non-parametric tests with a significance threshold of $p<0.05$. Results showed that Group A required fewer blood components (n=154) as compared to Group B (n=204) ($p<0.001$). Patients in Group A with Glanzmann thrombasthenia (GT) had a shorter treatment duration (one day) than those in group B (three days) ($p<0.01$). In conclusion, the application of fibrin glue effectively managed intractable gingival bleeding in IBD patients.

Keywords: Fibrin glue, Inherited blood coagulation disorders, Dental care; blood component transfusion, Oral health.

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Introduction

Proper oral hygiene is essential in patients with inherited bleeding disorders (IBD) to prevent persistent gingival bleeding.[1] Neglecting oral care can lead to gum bleeding and progress to irreversible periodontitis. Patients with IBD may avoid brushing their teeth due to the risk of bleeding and plaque formation, resulting in recurrent and severe bleeding that may require iron supplementation or blood transfusion.[1] This cycle gets worse as patients continue to neglect oral hygiene. Moreover, IBD patients often delay seeking dental treatment due to a lack of specialised care for their condition.

Pakistan, a South Asian country, faces challenges in providing haemophilia treatment due to limited haemophilia treatment centres (HTCs) and resources. Mucocutaneous bleeding, including gingival bleeding, is a common issue in IBD patients in Pakistan,[2] often requiring blood transfusions. As prophylaxis therapy is not widely available, on-demand therapy, cost-effective local haemostatic agents like Tranexamic acid, and blood transfusions are the primary approaches for managing acute bleeding episodes.

Fibrin glue, a locally prepared topical biological adhesive, using cryoprecipitate, bovine thrombin, and calcium, has shown promise in controlling bleeding after procedures such as circumcision and dental extractions.[3] This study aims to evaluate the clinical outcomes of fibrin glue application in managing intractable gingival bleeding in IBD patients in a resource-limited setting.

Patients/Methods and Results

This quasi-experimental pilot study was conducted from May 2, 2019, to May 2, 2020. at Fatimid Foundation Karachi center (FFK), a 12 bedded not-for-profit HTC, that catered to 729 IBD patients. Forty patients with IBD and intractable gingival bleeding lasting up to seven days were included in the study after obtaining informed consent, regardless of age and gender. Patients with anaemia (haemoglobin <8.0 g/L) received red cell transfusions before being included. The patients were consecutively selected by purposive sampling technique and non-randomly divided into two groups: Group A (n=20) received fibrin glue application, while Group B (n=20) did not. Patients with gingival bleeding following dental procedures were excluded. Each patient was assessed at FFK on alternate days for one week and then referred to Baqai Medical University for dental management. The follow-up duration was one year, with visits to the outpatient clinic every two months.

Baseline clinical assessments were performed using an in-

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Table-1: Baseline clinical and demographic details (n=40)

Demographics	Group A (Fibrin Glue applied) n=20	Group B (Fibrin Glue not applied) n=20	Total n=40	p-value
Gender (n, %)				
Males	13 (65.0)	11(55.0)	24 (60)	>0.05
Females	7 (35.0)	9 (45.0)	16 (40)	
Age (median, min-max, years)	21.5 (10-33)	24.5 (5-35)	22 (5-35)	>0.05
Education (n, %)				
Never been to school	12 (60)	0	12 (30)	<0.001***
High school or lower	6 (30)	20 (100)	26 (65)	
College or incomplete university	2 (10)	0	2 (5)	
ISTH-BAT Score (n, %)				
2	0	1 (5)	1 (2.5)	>0.05
3	0	1 (5)	1 (2.5)	
4	20 (100)	18 (90)	38 (95)	
Diagnosis (n, %)				
GT	11 (55)	5 (25)	16 (40)	>0.05
VWD†	6 (30)	9 (45)	15 (37.5)	
HA‡	3 (15)	6 (30)	9 (22.5)	
Haemoglobin (median, min-max, g/l)	78 (38-130)	100 (26-164)	89 g/L (26-164)	<0.001***
Red cell transfusion at initial presentation (n,%)	11 (55)	4 (20)	15 (37.5)	<0.05*
Ferritin level (median, min-max, µg/l)§	16.2 (7.8-62)	15.9 (3-192)	13.6 µg/L (3.1-191.6)	>0.05
Iron Deficiency Anaemia (n,%)§	13 (93)	6 (60)	19 (79)	>0.05
Gingival Bleeding Pattern				
Age at the first episode (n, %)				
<1 year	1 (5)	8 (40)	9 (22.5)	<0.05*
1-5 years	13 (65)	10 (50)	23 (57.5)	
6-12 years	6 (30)	2 (10)	8 (20)	
Duration of bleeding at presentation (median, min-max, days)	2 (1-6)	1 (1-3)	1 (1-6)	>0.05
Bleeding at rest (n, %)	18 (90)	19 (95)	37 (92.5)	>0.05
Duration of bleed (n, %)				
1-10 minutes	-	3 (15)	3 (7.5)	>0.05
>10 minutes	20 (100)	17 (85)	37 (92.5)	
Interval between episodes (median, min-max, days)¶	16 (3-1350)	23 (8-275)	-	<0.001***
Bleeding during tooth brushing (n,%)	7 (35)	15 (75)	22 (55)	<0.05*
No. of times treatment received for gingival bleed per annum (n, %)				
>10	19 (95)	15 (75)	34 (85)	>0.05
6-10	-	3 (15)	3 (7.5)	
3-5	1 (5)	2 (10)	3 (7.5)	
Eating Pattern				
Daily snacking between meals (n, %)	4 (20)	8 (40)	12 (30)	0.05
Daily consumption of soft drinks (n, %)	11 (55)	6 (30)	17 (42.5)	>0.05
Cleaning Pattern				
Daily cleaning of teeth (n, %)				
Soft toothbrush	-	4 (20)	4 (10)	<0.01**
Fingertips	20 (100)	16 (80)	36 (90)	

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Tooth cleaning frequency (n, %)				
Irregular	-	6 (30)	6 (15)	<0.05*
Daily	20 (100)	14 (70)	34 (85)	
Cleaning despite bleeding (n, %)	20 (100)	20 (100)	40 (100)	-
Fear of tooth brushing (n, %)	9 (45)	12 (60)	21 (52.5)	>0.05
Dental History				
Last dental visit (n, %)				
Never	6 (30)	17 (85)	23 (57.5)	0.001***
> 1 year	2 (10)	-	2 (5)	
< 1 year	12 (60)	3 (15)	15 (37.5)	
Reason for the last dental visit (n, %)				
Bleeding	13 (65)	-	13 (32.5)	
Follow-up treatment	1 (5)	2 (10)	3 (7.5)	-
Dental pain	-	1 (5)	1 (2.5)	

GT: Glanzmann Thrombasthenia; VWD: Von Willebrand Disease; HA: Haemophilia A, ISTH-BAT: International Society of Thrombosis and Haemostasis Bleeding Assessment Tool. Mild HA: factor VIII level >5%, Moderate HA: factor VIII level 1-5%, Severe HA: factor VIII level <1%

† Group A; Type 1 VWD: n=2(33%), type 3 VWD: n=4(66%) and Group B; Type 1 VWD: n=1 (11%), Type 3 VWD: n=8 (89%).

‡ Group A: mild HA n= 2(66%), moderate HA: n=1 (33%); Group B: mild HA n=3 (50%), severe HA: n=3 (50%).

§ Ferritin levels were available for n=14 (70%) patients in group A and n=10 (50%) patients in group B.

¶ Duration between existing and previous oral bleeding episode.

^ Fluoridated toothpaste was used.

Table-2: Transfusion Details and Oral Bleeding/Dental Evaluation Outcomes in Patients with and without Fibrin Glue Application (n=40).

Characteristics	**Group A (Intervention) n=20**	**Group B (Control) n=20**	**p-value**
No. transfusion days (median, min-max, days)	2 (1-3)	2.5 (1-4)	<0.001***
HA	2 (1-3)	2 (1-3)	>0.05
VWD	2.5 (1-3)	2 (1-3)	<0.05*
GT	1 (1-3)	3 (2-4)	<0.01**
Consumption of blood components (no. of units; n, %)	154	204	<0.001***
Red cells			
Platelets	13	8	>0.05
Cryoprecipitate	32	48	<0.01**
Fresh frozen plasma	85	148	<0.001***
	24	0	<0.001***
Compliance for dental evaluation (n, %)	8 (40)	6 (30)	>0.05
Patients with persistent oral bleeding despite intervention (n, %)†	4 (20)	6 (30)	>0.05
Number of patients with recurrence of oral bleeding (n, %)†	8 (40)	13 (65)	>0.05
Interval between existing and next episode of oral bleed (median, min-max, days)‡	64 (11-291)	23 (8-275)	<0.001***
Patients who underwent dental evaluation (n, %)	8 (40)	*6 (30)*	>0.05
HA	2 (25)	3 (50)	
VWD	2 (25)	1 (17)	
GT	4 (50)	2 (33)	

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Findings of dental evaluation (n, %)	8 (40)	6 (30)	-
Poor oral hygiene	8 (100)	6 (100)	-
Bleeding	5 (63)	4 (67)	>0.05
Gingivitis	8 (100)	5 (83)	>0.05
Localised	*0*	*1 (20)*	-
Generalised	*8 (100)*	*4 (80)*	-
Caries	1 (13)	5 (63)	<0.05*
Plaque	8 (100)	6 (100)	-
Broken roots	1 (13)	3 (50)	>0.05
Periodontitis	0	1 (17)	>0.05
Calculus	0	4 (67)	<0.05*
Treatment (n, %)	*8 (40)*	*6 (30)*	-
OHI¥	8 (100)	6 (100)	-
Filling	1 (13)	5 (83)	>0.05
Ultrasonic Scaling	8 (100)	6 (100)	-
Tooth extraction	3 (38)	3 (50)	>0.05
Antibiotics	8 (100)	5 (83)	>0.05
Antiseptic mouth wash	8 (100)	6 (100)	-

house questionnaire, and the severity of oral cavity bleeding was assessed using the International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) at the initial visit (Table 1).[4] Patients with iron deficiency anaemia (IDA) with serum ferritin level <50 µg/L, were treated with oral ferrous sulfate (3–6 mg/kg/day in three divided doses).

An in-house fibrin glue preparation method was used, combining 5ml group-specific cryoprecipitate in one syringe and 1.5ml thrombin (100 U/mL, 5ml vial, Dade, Siemens, measurable range of fibrinogen 0.89-2.8 g/L), with 3.5ml calcium chloride (15ml vial, 0.025mol/L, Siemens) in another syringe. Both syringes were joined by a tape and fibrin glue was sprayed simultaneously at the site of bleeding on the gingival mucosa. The formation of the glue marked the endpoint. Blood transfusion and/or factor concentrates was administered, if necessary, during the seven-day assessment period. Both the groups received Chlorhexidine mouthwash and oral Tranexamic acid (20–50mg/kg/day in three divided doses). Antibiotics (Amoxicillin 500mg and Metronidazole 200mg, three times a day for seven days) were prescribed by the dentist if required.[5]

Several outcome measures were evaluated (Table 2) and the data was analysed using SPSS V.23.0. Normality was checked using the Shapiro-Walk test. Continuous variables were expressed as median (min-max), categorical variables as frequency/percentage. Comparative analysis utilised Wilcoxon/McNemar's tests ($p<0.05$).

Table 1 presents the baseline clinical and demographic details of patients in Groups A and B. Group A had a higher prevalence of Glanzmann thrombasthenia (GT) compared to Von Willebrand Disease (VWD) in group B [11 (45%) vs 9 (55%)]. As shown in Table 2, patients with GT in Group A experienced a significant reduction in the number of transfusion days compared to Group B (1 vs 3 days, $p <0.01$). However, no significant difference was observed in patients with HA (2 vs 2 days, $p >0.05$). In contrast, patients with VWD in Group A had a higher number of transfusion days compared to group B (2.5 vs 2 days, $p <0.05$). Group B had a significantly higher utilisation of blood components compared to Group A (204 vs 154 units, $p <0.001$), particularly platelets (48 vs 32 units, $p <0.01$) and cryoprecipitate (CP) (148 vs 85 units, $p <0.001$). Although not statistically significant, compliance for dental evaluation was slightly higher in Group A as compared to Group B [8 (40%) vs 6 (30%) $p >0.05$]. Group A also exhibited a significantly delayed recurrence of gingival bleeding as compared to Group B (64 vs 23 days, $p <0.001$).

Discussion

The study demonstrated that fibrin glue application can effectively reduce blood component consumption and improve patient compliance with dental evaluations. Patients with platelet function defects, like GT, had a higher prevalence of gingival bleeding compared to Western populations where haemophilia is more prevalent. Fear of bleeding during tooth brushing and lack of dental evaluation were significant challenges in

our patient cohort, leading them to use ineffective methods like using fingertips to clean their teeth.

Both the study groups had poor oral hygiene and dental plaque due to factors such as consuming soft drinks (17, 85%) and frequent snacking (12, 60%), leading to increased risk of dental caries. Inadequate oral hygiene practices, including ineffective tooth cleaning, lack of dental floss use, and infrequent dental evaluations, contributed to the development of dental plaque and caries. The prevalence of dental caries,[6] gingivitis, and periodontitis in IBD patients, as cited in previous studies, aligns with the findings of the current study.[7] A significant portion of patients (23, 58%) experienced their initial gingival bleeding between the age of one and five years, potentially linked to teeth eruption or inadequate oral hygiene guidance during IBD diagnosis. Additionally, 13 (76%) patients attributed gingival bleeding as the primary reason for their last dental visit, in contrast to dental pain being the primary cause in high-income nations.[8]

The findings of the current study emphasise the importance of primary prevention in managing oral diseases, particularly during childhood when sugary food and drink consumption is highest. Fibrin glue application improved compliance with dental evaluations and reduced the recurrence of bleeding episodes, potentially by addressing underlying oral pathology. Combining fibrin glue, Tranexamic acid, and blood components may be beneficial for controlling gingival bleeding in IBD patients, similar to haemophilia cases.

The study has limitations, such as a small sample size and a potential selection bias due to non-comparability between the two groups. Group A had a higher number of GT patients, which may have influenced the outcomes. Additionally, calculus and caries were more prevalent in Group B and these may have been possible confounders, but their significance in excessive bleeding was insignificant ($p > 0.05$). Gingivitis was equally prevalent in both the groups, indicating that the risk of oral bleeding remained the same. Furthermore, patients' unanimous dislike of the taste of fibrin glue led to a lack of consent for its application in subsequent gingival bleeding episodes. Alternative approaches like diode laser coagulation or oral splints with Tranexamic acid may address these concerns.[9] Despite being easily accessible, cost-effective, and effective in achieving haemostasis, fibrin glue has a higher tendency to dissolve when exposed to salivary enzymes. In contrast, the use of home-made oral splints made from impressions using putty and a soft splint containing Tranexamic acid creates a protective barrier that shields the bleeding gum from the breakdown caused by salivary fibrinolysis.[10]

Conclusion

In conclusion, although fibrin glue application has shown benefits in managing IBD patients with gingival bleeding, larger-scale studies with randomised control trials are necessary to validate our preliminary findings.

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Abbreviations:
Inherited Bleeding Disorders (IBD)
Low-To-Middle-Income Country (LMIC)
Glanzmann's thrombasthenia (GT)
Von Willebrand Disease (VWD)
Haemophilia A (HA)
Iron Deficiency Anaemia (IDA)
Cryoprecipitate (CP)
Haemophilia Treatment Centres (HTCs)
Fatimid Foundation Karachi Centre (FFK)
International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT)

References

1. Kumar M, Pai KM, Kurien A, Vineetha R. Oral hygiene and dentition status in children and adults with haemophilia: A case-control study. Spec Care Dentist. 2018;38:391-4. doi: 10.1111/scd.12324.
2. Hussain S, Baloch S, Parvin A, Najmuddin A, Musheer F, Junaid M, et al. Inherited Bleeding Disorders-Experience of a Not-for-Profit Organisation in Pakistan. Clin Appl Thromb Haemost. 2018;24:1241-8. doi: 10.1177/1076029618781033.
3. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Haemophilia, 3rd edition. Haemophilia. 2020; 26:1-158. doi: 10.1111/hae.14046.
4. Ambika PL, Basu D, Nair SC, Kar R. Utility of International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) in Patients with Inherited Bleeding Disorders: A Cross-Sectional Study from Southern India. Indian J Haematol Blood Transfus. 2022; 38:122-31. doi: 10.1007/s12288-021-01435-8.
5. Francis J, Hughes KGS,Turner W, Shahdad S, Nohl F. Clinical Problem Solving in Periodontology and Implantology 1st ed.

Taylor A, Francis J. Hughes KGS, Turner W, Shahdad S, Nohl F, eds. China: Churchill Livingstone Elsevier, 2013; pp-194.

6. Ellakany P, Madi M, Fouda SM, Ibrahim M, AlHumaid J. The Effect of Parental Education and Socio-economic Status on Dental Caries among Saudi Children. Int J Environ Res Public Health. 2021; 18. doi: 10.3390/ijerph182211862.
7. Czajkowska S, Rupa-Matysek J, Gil L, Surdacka A. Assessment of Oral Health and Healthy Habits in Adult Patients with Congenital Haemophilia. Eur J Dent. 2023; 17:161-72. doi: 10.1055/s-0042-1743156.
8. Yazicioglu I, Deveci C, Ciftci V, Antmen B, Dogan MC. Parent's report on oral health-related quality of life of children with haemophilia. Haemophilia. 2019; 25:229-35. doi: 10.1111/hae.13678.
9. Ngoc VTN, Van Nga TD, Chu DT, Anh LQ. Pulpotomy management using laser diode in paediatric patient with severe haemophilia A under general anaesthesia—A case report. Spec Care Dentist. 2018; 38:155-9. doi: 10.1111/scd.12279.
10. Bhavyaa R, Vignesh KC, Muthu MS, Haridoss S, Abirami S. Glanzmann Thrombasthenia: Use of the Soft Splint with Tranexamic Acid Paste to Reduce Spontaneous Oral Bleeding. Int J Clin Pediatr Dent. 2021; 14:580-5. doi: 10.5005/jp-journals-10005-1973.

Author's Contributions

SH and BM: Concept and design.

SH, BM, SAAZ and SS: Data analysis and interpretation.