Efficacy of tranexamic acid mouthwash as an alternative for factor replacement in gingival bleeding during dental scaling in cases of hemophilia: A randomized clinical trial

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Abstract

Objective: The objective of the following study is to evaluate freshly prepared tranexamic acid mouth wash (FTAMW) as an alternative to factor replacement therapy (FRT) in controlling gingival bleeding in hemophiliacs during dental scaling. **Materials and Methods:** Experimental treatment regime (ETR) involved saline transfusion followed by FTAMW and the control treatment regime (CTR) involved FRT followed by placebo mouthwash. A total of 22 hemophiliacs randomly received dental scaling under either CTR or ETR at two different visits, following a split mouth design. They were instructed to use the rendered mouthwash 4 times a day for 5 days and record the mouthwash usage and bleeding episodes in a logbook. The difference in the bleeding episodes was analyzed using Chi-square test with the level of significance predetermined at 0.05. **Results:** Totally 19 patients completed the study. Seven patients reported no bleeding either in ETR or CTR; five patients noticed bleeding in CTR, but not in ETR. Three patients noticed bleeding in ETR, but not in CTR. Patients reported ease in usage and cost-effectiveness of ETR. **Conclusion:** FTAMW was found to be an effective alternative to FRT in controlling gingival hemorrhage in hemophiliacs during dental scaling.

Keywords: Dental scaling, factor replacement, hemophilia, tranexamic acid

Introduction

In India, more than 65,000 people are estimated to live with hemophilia[1] out of which only 12,500 are identified as per the records of hemophilia federation of India, 2011. Hemophilia is a class of inherited bleeding disorders characterized by a lifelong defect in the clotting mechanism and can be categorized as hemophilia A and B, when there is a deficiency of factor VIII and IX respectively (both inherited as X linked recessive). It can further be subdivided conventionally into mild (6-50 IU/dl), moderate (1-5 IU/dl) or severe (<1 IU/dl) depending on the level of factor activity.[2] Another autosomally dominant inherited bleeding disorder that is closely related to hemophilia is von Willebrand disease (vWD) characterized by qualitative or quantitative abnormalities of von Willebrand factor (vWF) leading to impaired platelet aggregation and adhesion to vascular walls, thus resulting in a bleeding tendency.[3]

Importance of maintaining the dental and periodontal health in persons with inherited bleeding disorders has been reported by many with suggestions to expand the preventive measures and educational programs.[4-7] Though widely discussed, these hemophiliacs often face problems in acquiring the primary care. The options available in the existing literature to control bleeding during primary dental care are, factor replacement therapy (FRT), release of endogenous factor stores and clot stabilization by antifibrinolytic agents,[8-12] with FRT being the main mode of treatment. The development of recombinant FRT has minimized the risk of blood borne infections, but, the major disadvantage reported is the formation of antibodies or inhibitors;[12] even cost of therapy is high ranging from Indian Rupees (INR or `) 6000 to 20,000, depending on the severity of the bleeding, purity, type and amount of factor used. Thus, preventive dental care with alternatives to FRT will always be safe; one such alternative is desmopressin (1-deamino-8-d-arginine vasopressin [DDAVP]),[13] that can release endogenous factor VIII from endothelial cells to the blood stream and can increase the plasma concentration in mild to moderate hemophiliacs for a short time.[14] However, the problem with this is, patients who are repeatedly treated with DDAVP become less amenable due to exhaustion of endogenous stores, thus, limiting its use.[15] Another alternative to FRT is the synthetic amino acid derivatives of lysine such as tranexamic acid (TA) [4-(aminomethyl) cyclohexanecarboxylic acid] which has antifibrinolytic activity and works by binding reversibly

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Access this article online	
Quick Response Code:	Website: www.contempclindent.org
	DOI: 10.4103/0976-237X.128663

to plasminogen (preventing it from forming plasmin), preventing plasminogen binding to fibrin and facilitating clot stabilization.[16] TA (5% aqueous solution) has been depicted to produce therapeutic saliva concentrations when used as a mouth rinse[17] and when used in conjunction with FRT has been proved to be effective in controlling hemorrhage after subgingival scaling.[18]

As a step forward, tranexamic acid mouth wash has been proved in another study to be as effective as FRT on its own in hemophiliacs undergoing dental scaling;[19] however, authors have prepared the mouth wash using active ingredient TA and preservatives for usage over a period of time. However, in Indian scenario, getting drug licensing is a major hurdle to freely use this mouthwash for hemophiliacs undergoing dental scaling and also the efficacy of TA is doubtful when stored for a long time. Hence, the present study was conducted to evaluate the efficacy of a freshly prepared tranexamic acid mouth wash (FTAMW) from commercially available TA tablets in controlling gingival hemorrhage in hemophiliacs during dental scaling and compare it with FRT.

Materials and Methods

Ethical approval was obtained from the Institutional Ethical Committee. Permission from the hemophilia society and consent from the patients/legal guardians were obtained.

Trial design and participants

This was an explanatory, non-inferiority, double-blinded, randomized clinical trial with a split-mouth design. Eligible participants were those with inherited bleeding disorders who fulfilled the inclusion criteria adopted from Lee *et al*.[19] with minor modifications [Table 1]. The study was conducted over a period of about 40 days from 18th November 2012 to 28th December 2012; screening of the patients was carried out at the hemophilia society, while the dental procedures were performed at a private dental clinic.

Interventions

Experimental treatment regimen

Coin toss randomization was used to select either right or left side of the mouth for the ETR. All the patients received an intravenous infusion of 0.9% normal saline (as placebo) in a syringe blinded with an opaque obscuring sleeve and after half an hour underwent ultrasonic scaling procedure on the selected side. Subsequently, for home use the participants were provided with 20 unlabeled packets each containing 500 mg of TA tablet (Trapic®, Sun Pharmaceutical Ind. Ltd., IGC, Samba, J and K, India) that was crushed into powder, 200 ml distilled water, a measuring cup and a log book [Table 2]. The participants were instructed to check for gingival bleeding in a portable mirror; and irrespective of bleeding, use freshly prepared mouth wash by dissolving one packet of powder in 10 ml of distilled water (5% TA mouth wash) in the cup provided, 4 times a day (morning, afternoon, evening and night) for 5 days by holding the solution in the mouth for 2 min and then to expectorate. They were expected to record gingival bleeding episodes, area of bleeding in the quadrants and usage of mouth wash in the log book provided and to return books to the researcher during the second session.

Control treatment regimen

After 2 weeks, the same set of participants received intravenous transfusion of required factor concentrate in a syringe blinded with an opaque obscuring sleeve, as per the dosage calculated from the formula,[10] to raise factor concentration around 20-25% (depending on the type of bleeding disorder). After half an hour all the participants underwent ultrasonic scaling for the remaining side of the mouth and were again provided with 20 unlabeled packets of 450 mg of starch each (as placebo), 200 ml distilled water, a measuring cup and a log book. The participants were instructed to check for gingival bleeding, use freshly prepared mouth wash by dissolving one packet of powder in 10 ml of distilled water in the cup provided 4 times a day for 5 days, to record the same in the log book and return them to the researcher by post.

Interview

After disclosing both the regimens to the participants, a structured telephone interview, adopted from Lee *et al*.[19] with minor modifications [Table 3] was conducted to assess the opinions, effectiveness and acceptability of both the treatment regimens.

Table 1: Inclusion and exclusion criteria

Non-dental inclusion criteria	Dental inclusion criteria
Hemophilia A or B or vWD Platelet count >50×10^9/L No history of Allergy to tranexamic acid medication Deep vein thrombosis Renal impairment Cardiac pacemaker	Require dental scaling <3 teeth difference between the right and left side of mouth CPITN score of 2 or 3 >75% of contralateral teeth with matching CPITN score
Non-dental exclusion criteria	**Dental exclusion criteria**
Receiving ongoing prophylactic replacement therapy History of acquired disturbances of color vision Taken NSAIDs in the week prior to/during the study period	Presence of primary teeth

CPITN: Community periodontal index treatment needs; NSAIDs: Non-steroidal anti-inflammatory drugs; vWD: von Willebrand disease

Table 2: Log book sample

	Morning	Noon	Evening	Night
Did you find bleeding gums	Yes/no/not noticed	Yes/no/not noticed	Yes/no/not noticed	Yes/no/not noticed
Location of bleeding				
Did you use mouth wash	Yes/no/ forgotten	Yes/no/ forgotten	Yes/no/ forgotten	Yes/no/ forgotten

Table 3: Structured telephone interview

Of the two scaling appointments, which one do you prefer?
Appointment 1
Appointment 2
No difference
Did you think the FTAMW was easy to use?
Yes
No
Did you think the taste of the FTAMW was acceptable?
Yes
No
Would you feel safe having a dental scaling without factor cover in advance and by using just the FTAMW afterwards?
Yes
No
Uncertain
Would you feel safe to have a dental scaling with neither the factor cover in advance nor the FTAMW afterwards?
Yes
No
Uncertain

FTAMW: Freshly prepared tranexamic acid mouth wash

Emergency measures

It was a double-blinded study where in the participant and the researcher (KRG) performing the scaling procedure were blinded to the treatment regime. However, before starting the study all the participants were instructed that, they can withdraw at any point of time and if required, receive factor replacement when the bleeding was uncontrollable or for bleeding in other parts of the body. Concerned authority in the hemophilia center and one of the researchers (SN) were open for the regimens to take care of any emergencies.

Primary and secondary outcome measures

The difference in post scaling bleeding of the right and left sides of the mouth was considered as the primary outcome; whereas the usage of mouth wash and patient assessment of acceptability of the ETR were considered as the secondary outcome measures.

Sample size determination

To determine the sample size a pilot study was conducted on 5 hemophilic patients (3 hemophilia A and 2 hemophilia B patients), in whom 6 bleeding episodes during ETR and 8 during CTR were noticed in the post-operative period of 5 days which gave a risk ratio/effect size of 0.75. With the level of significance set at 0.05 and a power of 80%, considering post scaling bleeding as the primary outcome measure and the prevalence of the inherited bleeding, disorders a minimum sample size of 15 was necessary.

Statistical methods

The intercooled STATA version 9.2 (StataCorp LP, TX, United States) was used for statistically analyzing the data. The statistical difference in the periodontal condition (community periodontal index treatment needs [CPITN] scores) of the right and left sides was determined using Mann-Whitney *U*-test; the differences between the ETR and CTR (reported cases of bleeding and usage of mouthwash) were analyzed using Chi-square with the test significance predetermined at 0.05.

Results

Recruitment and randomization of the participants is shown in Figure 1.

Out of 22 participants, 20 were male and two female with the mean age of 23.63 (13.2-53.6) years. Nineteen (86.4%) completed the study of which 12 were with hemophilia A (3 severe and 9 moderate) and 7 hemophilia B (3 severe, 3 moderate and 1 mild). The difference in the CPITN scores between right and left halves were not statistically significant ($P = 0.84$). The procedures could not be completed on three, all of whom with vWD, two with uncontrolled bleeding requiring factor replacement and one withdrew from the study.

Of the 19 participants who completed the study, seven reported no bleeding in either the experimental or CTRs whereas four reported bleeding in both. Bleeding only in CTR was reported by five and only in ETR by three, but there was no requirement of extra factor replacement with either of the regimens [Table 4]. The difference between the reported cases of bleeding in CTR and ETR was not significant statistically ($P = 0.63$). There was no difference even with the data segregated into hemophilia A ($P = 0.8$) and B ($P = 0.25$); or moderate ($P = 0.35$) and severe ($P = 0.71$). The total frequency of bleeding episodes in all patients for 5 days in ETR and CTR were 23 and 29 times respectively, which gave a risk ratio/effect size of 0.75. No significant difference was found with the frequency of the mouthwash used for either of the regimens ($P = 0.33$) and with respect to type and severity of hemophilia.

All the 19 participants responded for the telephone interview and felt that FTAMW was easy and safe to use and expressed that the taste was acceptable though slightly bitter. They were not willing to undergo scaling with neither the factor coverage nor FTAMW.

Discussion

Effect of tranexamic acid mouth wash (TAMW) in controlling post-operative bleeding after oral surgical procedures in hemophiliacs was first tested which proved it to be a good supplement to FRT.[19,20] The effectiveness of this mouthwash

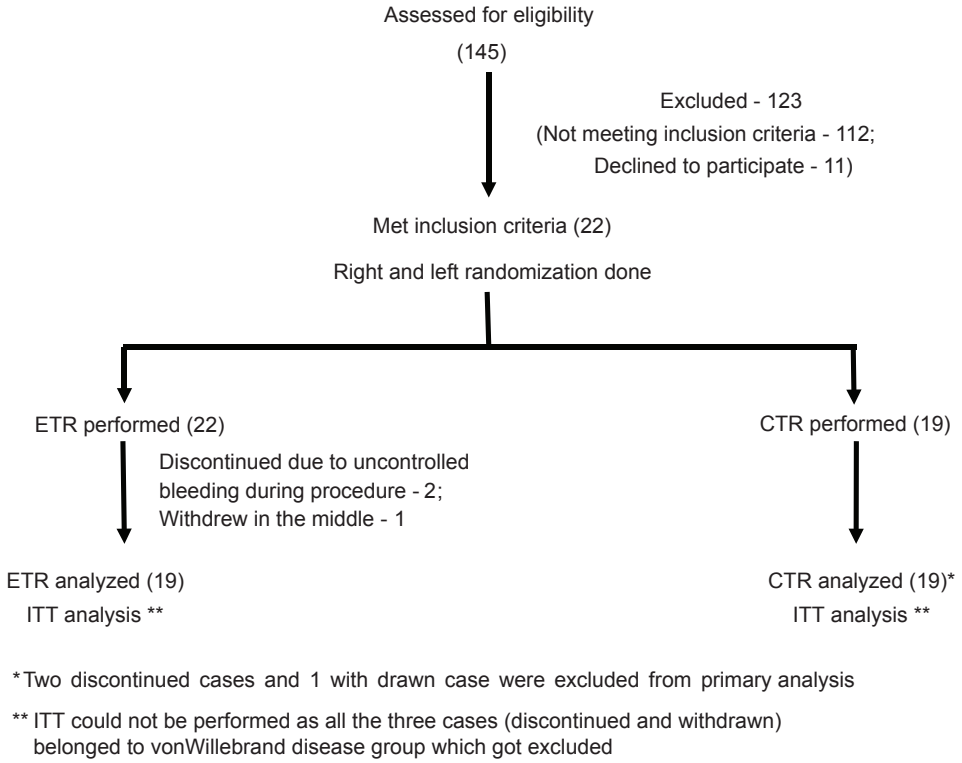

Figure 1: Recruitment and randomization of the participants

Table 4: Reported number of participants with bleeding in control and experimental regimes

Type	Bleeding only in CTR	Bleeding only in ETR	Bleeding in both CTR and ETR	No bleeding in either
Hemophilia A (12)	5	0	3	4
Hemophilia B (7)	0	3	1	3
Total (19)	5	3	4	7
Mild (1)	-	-	-	1
Moderate (12)	4	1	2	5
Severe (6)	1	2	2	1

CTR: Control treatment regime; ETR: Experimental treatment regime

as a replacement for the FRT in controlling hemorrhage after scaling was then tested in a pilot study, which proved it to be equally effective[19] and the present study is a second randomized clinical trial testing the same. Ultrasonic scaling was preferred in the present study for all patients as it is a proven fact that the bleeding will be less with minimal tissue trauma when compared to hand scaling.[21]

Among the three vWD deficient participants, two, undergoing dental scaling under ETR in their first visit, had uncontrollable bleeding that could not be stopped with either pressure application and astringent or FTAMW; eventually needed infusion of factor injection followed by full mouth scaling. They were then instructed to use FTAMW, similar to other participants and no further bleeding was noted in their post-operative period. Even in the pilot study, we could not recruit vWD patients; hence, the results of the present study cannot be generalized for this group of patients.

In hemophilics A and B, irrespective of the regime, bleeding if reported was noticed from the buccal posterior gingival surfaces on brushing which can be due to comparatively maximum amount of calculus accumulation that increases the inflammation of the gingival tissues in these areas. Spontaneous bleeding was noticed from the lingual gingival surfaces of the lower jaw which can be due to movement of the tongue that dislodges the early clot formed. Bleeding during CTR was first noticed in the 2nd and 3rd day after scaling which can be correlated with the half-life of factors, whereas during ETR it was on the first day of scaling. However, neither of the regimens required additional factor replacement. Thus, this study supports the use of FTAMW for hemophiliacs during their scaling procedures. Recruitment problems leading to less number of participants and bleeding noted only 4 times in a day are the major limitations of the present study.

As TAMW is proved to be successful in decreasing the hemorrhage during scaling, it can be combined with the most common form of topical treatment that involves the use of chlorhexidine gluconate gel or mouth wash with the intention of decreasing the gingival inflammation prior to

scaling which in turn decreases bleeding from periodontal tissues. It is also important to educate the hemophiliacs about the cyclic pattern of deterioration of their periodontal health as they will often be less enthusiastic to brush their teeth because of concerns about bleeding.

However, it is important to remember that hemophilia is always a medical emergency and bleeding can occur at any time; no treatment should be carried out without prior planning. Any hemostatic regimen used for dental treatment should be in agreement with the individual's hemophilia reference center.

Conclusion

Within the limitation of our study, the usage of FTAMW was found to be an effective alternative to FRT in controlling gingival hemorrhage for people with hemophilia undergoing dental scaling, with advantages such as low cost, no risk of development of antibodies and blood product contamination. Further studies are needed in this area to affirm the use of FTAMW in clinical practice.

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How to cite this article: Nuvvula S, Gaddam KR, Kamatham R. Efficacy of tranexamic acid mouthwash as an alternative for factor replacement in gingival bleeding during dental scaling in cases of hemophilia: A randomized clinical trial. Contemp Clin Dent 2014;5:49-53.

Source of Support: Nil. **Conflict of Interest:** None declared.