IN BRIEF

- This pilot study is small and lacks the power to recommend changes in clinical practice. A larger multi-centre study may be the solution.
- The results from this study promise the possibility of reducing the need of using factor replacement therapy on a minor traumatic procedure in people with haemophilia.
- It gives the patients more freedom in determining their own treatment; reserve factor for more severe bleeding situations; thus
- avoiding the disadvantages of factor replacement therapy (high cost, development factor antibodies and risks of blood product contamination).

Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using tranexamic acid mouthwash

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Aims To compare the effectiveness of tranexamic acid mouthwash (TAMW) in controlling gingival haemorrhage after dental scaling with that of using factor replacement therapy (FRT) prior to dental scaling in people with haemophilia.

Design Double-blind cross-over randomised control trial.

Setting Dedicated hospital dental practice for patients with inherited bleeding disorders.

Method Sixteen patients with haemophilia who required dental scaling participated in this pilot study. The experimental treatment regime (ETR) involved transfusing each patient with saline before scaling both quadrants on one side of the mouth followed by oral rinsing with TAMW four times daily for up to eight days. The control regime (CR) involved giving each patient FRT before scaling the opposite side of the mouth followed by use of a placebo TAMW. Each patient underwent both treatments in a randomised sequence. Both the operator and the patients were unaware of which were the ETR and CR episodes. On both occasions the patient kept a log book of the rinsing regime and any post-operative bleeding. Additionally, a structured post-treatment telephone interview was conducted to assess the effectiveness and the patient acceptability of the ETR.

Results Thirteen patients completed the study. No statistically significant difference was found in gingival bleeding and mouthwashing frequencies between the ETR and the CR ($p > 0.05$). Five patients reported no gingival bleeding with either the ETR or the CR. No patient, using either regime, required extra FRT due to gingival haemorrhage. All subjects found the ETR acceptable and easy and reported feeling safe in using TAMW alone to control gingival bleeding after dental scaling.

Conclusion TAMW use after dental scaling was as effective as using FRT beforehand in controlling gingival haemorrhage for people with haemophilia.

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Haemophilia is an inherited disorder of blood clotting with an incidence of 1 in 5,000 male births.[1] There are two types – haemophilia A characterised by a deficiency of clotting factor VIII (F VIII), and haemophilia B characterised by a deficiency of clotting factor IX (F IX). Haemophilia A is the more common type, accounting for approximately 85% of all cases of haemophilia.[2] Despite a deficit of different clotting factors, types A and B have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Specific factor assays are required to distinguish the two.[1]

The frequency and severity of bleeding experienced by a person with haemophilia depends mainly on their plasma levels of F VIII or the F IX activity. The lower the factor levels are, the more severe the condition (Table 1). An individual with haemophilia does not bleed more profusely or faster than normal – simply for longer.[3] The main treatment options currently available to control bleeding are: factor replacement therapy; release of endogenous factor stores; and clot stabilisation.[4]

Factor replacement therapy (FRT) is the main mode of treatment for both haemophilia A and haemophilia B. The missing factor is given intravenously by the person with haemophilia, parents or experienced staff at hospitals.[3] It is either prescribed regularly two or three times a week on a prophylactic basis to prevent bleeds, or it is administered on-demand as soon as a bleed starts. In many bleeding situations, FRT is the only effective treatment for people with

Table 1 Classification of haemophilia[1]

% of F VIII or IX*	Degree of haemophilia	Characteristics
1% or less	Severe	Frequent spontaneous bleeds. Coagulation screening tests always abnormal.
>1 - 5%	Moderate	Few spontaneous bleeds. Bleeding after minor trauma. Prolonged partial thromboplastin time.
>5 - 30%**	Mild	Bleed only after trauma or surgery. Coagulation screen tests may be low normal.
>30 - 50%**	Very Mild	May or may not bleed abnormally after major trauma or surgery. Coagulation screen tests often normal.

*The activity of clotting factors is expressed in terms of units, defined as the activity present in 1ml of fresh plasma from normal donors. The concentration of all clotting factors in native plasma is thus 1U/ml or 100U/dl or 100% activity.
**About one third of people with haemophilia have levels between 15% and 50%.

haemophilia. The development of recombinant factor replacement therapy (rFRT) has reduced the risk of blood borne infection. Whilst it has been postulated that recombinant F VIII might cause the formation of more inhibitors than plasma F VIII products, there is no evidence to support this concern and recombinent F VIII is the recommended treatment for haemophilia A.[5] The main disadvantage is its high cost. It has been estimated that for medication alone, the cost per bleeding episode for 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 amount of F VIII used.[6]

Release of endogenous F VIII stores from endothelial cells to the blood stream[7] can be stimulated by the use of the hormone desmopressin (DDAVP). DDAVP can be used to increase plasma concentrations of F VIII in people with mild to moderate haemophilia A for a short time.[8] However, patients repeatedly treated with DDAVP can become less responsive, probably because stores are exhausted,[9] thus, limiting its use in the management of haemophilia.

Clot stabilisation can be used to facilitate haemostasis and is achieved through the use of synthetic amino acid derivatives of lysine that have antifibrinolytic activity.[10] One such product is tranexamic acid [4-(aminomethyl) cyclohexanecarboxylic acid]. It works by binding reversibly to plasminogen (preventing it from forming plasmin) and preventing plasminogen binding to fibrin, thereby, halting fibrinolysis (Figure 1). Tranexamic acid (TA) has been used in conjunction with other haemostatic measures to control bleeding in various medical and surgical situations including oral bleeding in congenital and acquired coagulation disorders.[12] It has some role in controlling haemorrhage in haemophilia.

Sindet-Pedersen has demonstrated that TA produces therapeutic saliva concentrations by mouthrinsing with 10 ml of 5% TA aqueous solution.[14] TA in conjunction with FRT, in a non-blind study, has been shown to provide effective haemorrhage control after subgingival dental scaling in people with haemophilia.[15]

The dental needs of people with haemophilia are high. A recent study of people with inherited bleeding disorders attending a dental service established specifically for their care showed that 50% of people required scaling and polishing, 74% required restorative treatment, 30% needed extractions and 10% needed partial dentures. This outstanding dental treatment need was mainly due to anxiety related to dental treatment and focused on haemorrhage management.[13]

AIM

As there is no randomised control study on the effectiveness of using TA mouthwash (TAMW) alone for haemorrhage control in people with haemophilia after dental scaling, the aims of this study were to:

a. Compare the effectiveness of TAMW, to control haemorrhage after dental scaling, with that of FRT prior to dental scaling using a double-blind cross-over randomised control trial.

b. Gauge patient acceptability of the use of TAMW alone.

METHOD

Design

This pilot study was a double-blind cross-over randomised controlled trial. The patients underwent both the experimental and control treatment regimes in turn with at least a two-week interval, and the sequence was determined by a random table provided by the statistician, thus accounting for the cross-over and randomisation characteristics of this study. The procedures for the two dental appointments were similar except that opposite sides of the mouth were scaled and different medications used on each of the two appointments. During the study period, neither the patients nor the hygienist knew which regime the patients were receiving in order to achieve the effect of double-blindness. The staff of the Haemophilia Reference Centre at St. Thomas' Hospital, London and the researcher (AL), however, were not blinded in this study in case of emergencies.

Sample selection

Potential subjects were identified from the Haemophilia Reference Centre database. Patients were contacted and those fulfilling the non-dental inclusion criteria (Table 2) of the study were invited to participate. Once informed consent had been obtained, they underwent a thorough dental examination including a six point periodontal pocket charting and recording of any sites that bled on probing. Those participants who fulfilled the dental inclusion criteria were assigned identification numbers, to facilitate the organisation of the double blind trial, and given two dental appointments at least two weeks apart.

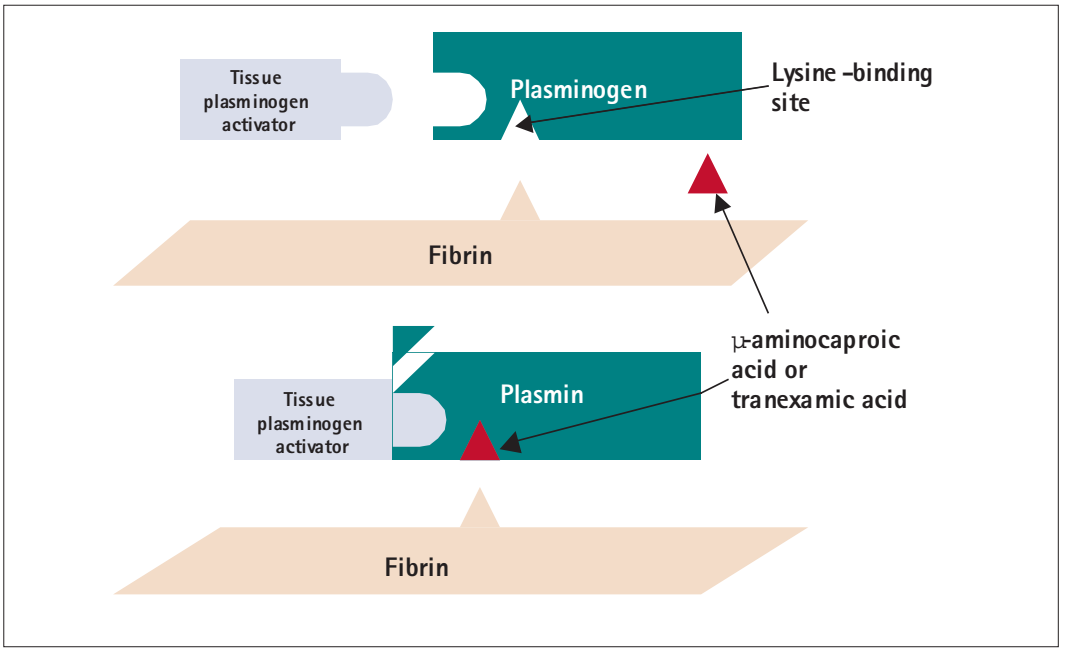

Fig 1 Antifibrinolytic effect of tranexamic acid[11]

Table 2 Study inclusion / exclusion criteria

Non-dental inclusion criteria	Dental inclusion criteria
1. Haemophilia A or B	1. Requires a dental scaling
2. Aged 16 or over	2. < 3 teeth difference between the left & right sides of mouth
3. Platelet counts >50 x 10^9/L	3. CPITN score of 2 or 3
4. No history of:	
i. allergy to tranexamic mouthwash	
ii. deep vein thrombosis	
iii. renal impairment	
iv. cardiac pacemaker	
Non-dental exclusion criteria	**Dental exclusion criteria**
1. Receiving ongoing prophylactic replacement therapy	1. Does not require a dental scaling
2. History of acquired disturbances of colour vision	2. > 3 teeth difference between the left & right sides of mouth
3. Taken aspirin or NSAI in the week prior to/during the study period	3. CPITN score of < 2

Ethical approval

Ethical approval was granted from the Guy's and St Thomas' Research Ethics Committee in July 2000, following changes to the patient information sheet and log book.

Drug licensing exemption

Tranexamic acid is not covered for use as a mouthwash by the existing pharmaceutical licence in the UK. Exemption was sought and obtained from the Medicines Control Agency of the Department of Health for this experimental use.

Experimental treatment regime (ETR)

The ETR involved patients receiving placebo factor concentrate (0.9% normal saline) by intravenous transfusion (administered by the nurses at the Haemophilia Centre) no more than one hour prior to dental treatment. The scaling of both upper and lower quadrants of one side of the mouth was carried out by a dental hygienist. As indicated in the dental inclusion criteria (Table 2), all the patients had a CPITN of either 2 or 3, the gingival pockets scaled were between 3mm and 5mm deep. The hygienist was blinded in the study and she was instructed to treat the patients as if they had FRT prior to both scaling appointments. She was allowed to choose the most appropriate method to perform the scaling, but she was obliged to use the same method for the same patient. The study participant was given three 100 ml bottles of active 5% TAMW (Table 3) for home use – sufficient for eight days. The subject was instructed to visually check for gingival bleeding four times per day, once after each of the three main meals and once before going to bed. If bleeding was noted, 10 ml of the mouthwash was to be held in the mouth for 2 minutes and then expectorated. Patient bleeding and mouthwash-use data was recorded in a log book (Figure 2) supplied by the researcher. The patients determined how often and for how many days they needed to use the mouthwash.

Table 3 Composition of active 5% tranexamic acid mouthwash

Tranexamic acid	500 g
Methyl hydroxybenzote (Nipagin M)*	15 g
Propyl hydroxybenzoate (Nipasol M)*	1.5 g
Distilled water (cold)	10 L

* Preservatives.

Table 4 Composition of placebo mouthwash

Methyl hydroxybenzoate (Nipagin M)	15 g
Propyl hydroxybenzoate (Nipasol M)	1.5 g
Distilled water (cold)	10 L

Prepared by the Pharmacy Department, St Thomas' Hospital, London

Control treatment regime (CTR)

For the CTR, the patient was transfused pre-operatively with active factor concentrate according to their type of haemophilia (ie F VIII for patients with haemophilia A and F IX for patients with haemophilia B) rather than with saline. Upper and lower quadrants of the other side of the mouth were scaled by the hygienist and the subject was given three 100 ml bottles of placebo mouthwash (Table 4) for post-operative use. The instructions for inspection for bleeding, mouthwash use and data recording were the same as for the ETR.

Safety measures

In the interests of safety and emergencies, there was a mechanism in place so that patients could find out from either the Haemophilia Reference Centre or from the researcher (AL) which regime they had been given. Additionally, patients were informed that they could receive factor replacement therapy at any time during the study if they thought the mouthwash was ineffective or if bleeding occurred in other parts of their bodies. Also, patients were at liberty to withdraw from the study at any point.

Day 1

		Yes	No	Forgotten
Morning	Did you find bleeding gums?	☐	☐	☐
	Did you use the mouthwash?	☐	☐	☐
Noon	Did you find bleeding gums?	☐	☐	☐
	Did you use the mouthwash?	☐	☐	☐
Evening	Did you find bleeding gums?	☐	☐	☐
	Did you use the mouthwash?	☐	☐	☐
Bedtime	Did you find bleeding gums?	☐	☐	☐
	Did you use the mouthwash?	☐	☐	☐

Fig 2 Log book sample page

Collection of patient log books

The patients were provided with a log book after each phase of the study. They were requested to return their log books to the researcher in the self-addressed envelopes provided once their data recording was completed. Subjects who had not returned log books by two weeks after their last dental scaling appointment were reminded by phone to do so.

Telephone interviews

Structured telephone interviews (Fig. 3) were carried out by one researcher (AL) to record the subjects' experiences after each dental scaling appointment and to assess the effectiveness and the patient acceptability of the ETR.

Data analysis

The data were collated and presented as absolute numbers and percentages. They were analysed using SPSS for Windows Release 10.0.1, Stata Release 7 and StatXact 3. The differences in the oral conditions between the patients' left and right hand sides of the mouth and the differences between the experimental and control treatment regimes were both analysed using the Wilcoxon signed rank test with test significance predetermined at 0.05.

RESULTS

Patient demography

All 16 participants in this study were male. The data of three subjects were excluded from the analysis – one person required FRT for an elbow bleed during the study and two others failed to return their log books despite reminders. Thirteen people (81%) completed the study. Their mean age was 37.8 years with a range from 18 to 68. Eleven of them had haemophilia A and 2 had haemophilia B. Among the haemophilia A patients, one had mild haemophilia, 3 had moderate and 7 had severe haemophilia. The 2 haemophilia B patients both had severe haemophilia.

The information obtained from both haemophilia A and B patients was grouped together by their severity in this study.

Periodontal conditions

The percentages of the number of pockets > 3 mm between the left and right hand sides of the mouth were compared for each patient and then calculated among all the study participants using the Wilcoxon signed rank test. The difference was not statistically significant ($p = 0.56$). Similarly, the percentages of bleeding sites on probing pre-operatively were compared for each patient. Adopting the Wilcoxon signed rank test, these differences were compared among all subjects and no significant differences were found ($p = 0.06$).

Post-scaling haemorrhage

Five out of the 13 subjects (38.5%) who completed the study reported no gingival bleeding with either the experimental or the control treatment regimes.

No patients required extra factor replacement therapy due to gingival haemorrhage with either the experimental or the control treatment conditions. Data analysis showed no significant difference for reported gingival bleeding between the ETR and the CTR ($p = 0.57$, Wilcoxon signed-rank test with test significance predetermined at 0.05).

Use of mouthwash

Data related to the use of mouthwash was analysed using the Wilcoxon signed-rank test with test significance predetermined at 0.05. No significant differences were found for mouthwash use between the ETR and the CTR for the number of times the mouthwash was used to control bleeding ($p = 0.51$); the number of times the mouthwash was electively not used when bleeding occurred ($p = 0.32$); and the number of times the mouthwash was used despite no bleeding ($p = 0.62$). Additionally, no statistically significant differences were found between the ETR and CTR for the overall use of the mouthwash.

Patient assessment of acceptability of the ETR

A structured telephone interview was used to establish the patients' experiences after each dental scaling appointment and to gauge acceptability of the ETR. After matching the random table with the patients' responses, it was found that there was a statistically significant preference towards the ETR over the CTR ($p = 0.04$ using Pearson Chi-square test for independence with test significance predetermined at $p = 0.05$). Subjects were unable to accurately assess which treatment regime had been used, and only one person felt that his 'guesstimate' of which regime he had undergone influenced his use of the mouthwash. Additionally, all patients found the mouthwash easy to use and 12 subjects (92%) found its taste acceptable. One person found the taste of both the active and placebo mouthwashes unacceptably salty.

Patient assessment of safety of the ETR

One hundred per cent of participants reported that they would feel safe receiving dental scaling when only using tranexamic acid mouthwash afterwards to control gingival bleeding. Five patients (38.5%) felt that it was not safe to use nothing to control gingival bleeding after dental scaling. The remaining eight patients thought it was safe to do so.

1. Of the two scaling appointments, which one do you prefer?

   Appointment 1 **Appointment 2** **No difference**

2. On which occasion did you think you had the factor cover before the scaling appointment?

   Appointment 1 **Appointment 2** **Uncertain**

3. Did it influence your behaviour of using the mouthwash?

   Yes **No** **Uncertain**

4. Did you think the mouthwash was easy to use?

   Yes **No**

5. Did you think the taste of the mouthwash acceptable?

   Yes **No**

6. Would you feel safe having a dental scaling *without factor cover* in advance and by using *just the tranexamic acid mouthwash* afterwards?

   Yes **No** **Uncertain**

7. Would you feel safe having a dental scaling with *neither the factor cover* in advance *nor the tranexamic acid mouthwash* afterwards?

   Yes **No** **Uncertain**

Fig 3 Structured telephone interview

DISCUSSION

Study design

This study is, to the authors' knowledge, the first double-blind randomised controlled trial on the effectiveness of TAMW in controlling gingival haemorrhage after dental scaling in people with haemophilia. The finding, that the use of TAMW after dental scaling is as effective in controlling gingival bleeding as using FRT before dental scaling, is encouraging.

However, it is difficult to overlook the fact that the number of participants in this study is small (n = 13) and some statistics provided results that are difficult to interpret. For example, although it was found that among all subjects there was no significant difference ($p = 0.06$) in the percentages of bleeding sites on probing pre-operatively between the left and the right sides of each patient, the p-value is too close to the predetermined value 0.05.

The rigorous study design and the appropriate data analysis go someway to compensate for the small sample size. Consideration of appropriate data analysis for this size sample led to the use of non-parametric inference. This is a computationally intensive type of analysis based on permutation techniques such that data are repeatedly rearranged and the appropriate test statistic recalculated to produce an exact sampling distribution and reduce the likelihood of chance results.

Difficulty in recruitment

The difficulty in recruiting subjects to the study was due to a combination of factors. They included: the distance some people have to travel to the Haemophilia Reference Centre (up to 200 miles round trip); mobility problems as a consequence of haemarthrosis; the desire to limit the number of episodes of haemostatic cover and thus a preference for full mouth scaling in one visit rather than in two; and a reticence to receive 'unnecessary' FRT because of the fear of contracting viral or other infections. This latter fear was inflamed by a front page, newspaper article (reporting that NHS patients were treated with blood products from a man who died of vCJD) that appeared on a day when patients were being recruited to the study.[16]

The problem of recruitment to future studies could be overcome by recognising the difficulties and by using a multi-centred approach.

Use of FRT

Until now FRT has remained the main method of controlling haemorrhage in people with haemophilia A and B.[19] Its use is not without concern. Not only is it very costly,[6] but also its use (both as plasma and recombinant factor concentrates) has been associated with the formation of inhibitors.[20] This is a serious complication that compromises haemostatic management as the inhibitors render the factor concentrates ineffective. The development of inhibitors can occur at any time but the more often FRT is used the more likely they are to develop.[20] Additionally, the transmission of blood borne viruses (including HIV, Hepatitis A, B, C, G, parvovirus) has been associated with FRT.[21] At present a small risk of plasma concentrates transmitting blood borne viruses still exists.[5] Also, the production of factor concentrates is not constant due to the complex procedures involved. For example, from early 2001 there has been a worldwide shortage of recombinant F VIII because Bayer suspended their product with the discovery of bacterial contamination in the production process.[22] Thus the attraction of finding alternative methods of haemorrhage control is evident.

Barriers to dental care

The documented barriers to dental care,[13,23] and the consequent unmet treatment needs,[13] experienced by people with inherited bleeding disorders (IBD) such as haemophilia are multifactorial. Anxiety related to dental treatment, *per se*, and to haemostatic management, in particular, are major factors.[13,23] The concern of people with IBD that dentists may not have the knowledge and experience to provide their treatment safely[23] acts as a deterrent to seeking care that, when they do attend, is compounded by dentists' lack of confidence in providing invasive treatment.[23,24] The use of TAMW in preference to FRT transfers the responsibility for haemostatic management from the dentist to the patient. In so doing it provides the individual with control and removes/reduces any anxiety about the operator's understanding of the haemophilia management.

A further difficulty associated with FRT is that Factor VIII cover has a comparatively short half-life (around 2 hours) necessitating dental treatment to begin immediately following its administration.[13] This poses a problem for those people who do not administer their own prophylactic factor and who have to travel from the centre of administration to the dental surgery. The use of TAMW in preference to FRT allows this barrier to be overcome.

Interestingly, five of the thirteen participants (38.5%) in the current study reported no post-operative bleeding with either the experimental or the control regimes suggesting that a proportion of patients with haemophilia may not require any medication at all to control gingival bleeding after dental scaling. This makes TAMW ideal in that it can be used as needed post-operatively.

Feeling of safety

All the patients in the current study related that they would feel safe using the TAMW regime alone following dental scaling in the future. However, this feeling cannot be detached from the environment in which the treatment was delivered. All treatment was provided in a dedicated dental unit for patients with IBD on the same site as the patients' HRC and overseen by a dentist experienced in the dental management of patients with IBD. A previous study[23] found that, despite the increased autonomy associated with self-administration of factor replacement, adults with IBD made little use of the general dental practitioner service and preferred to receive dental treatment in a hospital environment where they felt more secure.

The current study has demonstrated that TAMW used post-operatively is an effective regime for controlling gingival haemorrhage following dental scaling. The work of Forbes *et al.*[17] and Sindet-Pedersen and Stenbjerg[18] suggests that the use of TAMW post-operatively, rather than FRT pre-operatively, may also be suitable for haemostatic control following tooth extraction. However, it is important to remember that haemophilia can still be a life threatening condition and any haemostatic regime used for dental treatment that is not general practice should only be employed with the agreement and close support of the individual's haemophilia reference centre.

CONCLUSION

As the number of participants was small causing difficulties in interpreting some of the statistics, the authors cannot recommend a change in clinical practice based on the results of this study. However, this pilot study has shown that the use of tranexamic acid mouthwash after dental scaling is well tolerated by patients and is as effective as using factor replacement therapy before dental scaling in controlling gingival bleeding for people with haemophilia. By adopting this treatment, it avoids the disadvantages of factor replacement therapy (high cost, development of factor antibodies, and risk of blood product contamination). The authors thus recommend further studies in this area with a multi-centred approach to overcome recruitment problems.

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1 Berry E, Hilgartner M, Mariani G, Sultan Y, Members of the Advisory Board, World Federation of Hemophilia; Jones P (Ed); Kasper C and Peake I (Reviewers). Haemophilia: *Facts for health care professionals.* WHO. (WHO/HGN/WFH/EM/96.4) 1996.
2 Walter J, High K. Haemophilias. *Encyclopedia of life sciences.* Nature Publishing Group. www.els.net 2001 [accessed on 4 July 2001].
3 Cowe A, Fuller S. *Introduction to Haemophilia.* 1999; www.haemophilia.org.uk/booklets.html [accessed on 23 May 2001].
4 Cahill M R, Colvin B T. Haemophilia. *Postgrad Med J* 1997; **73:** 201-206.
5 Anthony D, Milne R. *On-demand recombinant factor VIII for people with haemophilia A.* Report to the Development and Evaluation Committee. 1997; 71.
6 United Kingdom Haemophilia Centre Directors Organisation Executive Committee. Guidelines on therapeutic products to treat Haemophilia and other hereditary coagulation disorders. *Haemophilia* 1997; **3:** 63-77.
7 Mannucci P M. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first twenty years. Haemophilia. 2000; **6(Suppl. 1):** 60 - 67.
8 Mannucci P M, Aberg M, Nilsson I M and Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. *Br J Haematol* 1975; **30:** 81-90.
9 Mannucci P M, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with hemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP). *Br J Haematol* 1992; **82:** 87.
10 Andersson I, Nilsson I M, Nilehn J E, Hedner U, Granstrand B, Melander B. Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. *Scand J Haematol* 1965; **2:** 230-247.
11 Astedt B. Clinical pharmacology of tranexamic acid. *Scand J Gastroenterol* 1987; **22 (suppl 137):** 22-25.
12 Mannucci P M. Hemostatic drugs. *N Engl J Med* 1998; **339:** 245-253.
13 Fiske J, McGeoch R J, Savidge G F, Smith M P. The treatment needs of adults with inherited bleeding disorders. *J Disabil Oral Health* 2002; **3:** 59-61.
14 Sindet-Pedersen S. Distribution of tranexamic acid to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. *J Clin Pharmacol* 1987; **27:** 1005–1008.
15 Sindet-Pedersen S, Stenbjerg S and Ingerslev J. Control of gingival hemorrhage in hemophilic patients by inhibition of fibrinolysis with tranexamic acid. *J Perio Res* 1998; **23:** 72-74.
16 Race to find patients at risk of CJD. *The Times.* 30th January 2001; pp 1, 8.
17 Forbes C D, Barr R D, Reid G *et al.* Tranexamic acid in control of haemorrhage after dental extraction in haemophilia and Christmas disease. *Br Med J* 1972; **2:** 311-313.
18 Sindet-Pedersen S, Stenbjerg S. Effect of local antifibrinolytic treatment with tranexamic acid in hemophiliacs undergoing oral surgery. *J Oral Maxillofac Surg* 1986; **44:** 703-707.
19 Minor P D. Are recombinant products really infection risk free? *Haemophilia* 2001; **7:** 114-116.
20 Ehrenforth S, Kreuz W, Scharrer I, Linde R, Funk M, Güngör T, Krackhardt B, Kornhuber B. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; **339:** 594-598.
21 Jarvis L M, Davidson F, Hanley J P, Yap P L, Ludlam C A, Simmonds P. Infection with hepatitis G virus among recipients of plasma products. *Lancet* 1996; **348:** 1352-1355.
22 World Federation of Hemophilia. *Factor VIII product shortage.* Information Update (23 April 2001). www.wfh.org [accessed on 15 June 2001].
23 Fiske J, Pitt Ford H E, Savidge G F, Smith M P. The expressed dental needs of patients attending a Haemophilia Reference Centre. *J Disabil Oral Health* 2000; **1:** 20-25.
24 Roberts R E, McCory O F, Glasser J H *et al.* Dental care for handicapped children re-examined: II Dimensions of dental practice. *J Public Health Dentistry* 1978; **38:** 136-147.