

Safer circumcision in patients with haemophilia: the use of fibrin glue for local haemostasis

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Objective To evaluate the efficacy and the reduced costs of factor concentrates in circumcision by using fibrin glue in patients with haemophilia.

Patients and methods Eleven patients with haemophilia (age range 6–14 years, 10 with haemophilia A, one with haemophilia B) were circumcised using fibrin glue for local haemostasis and to reduce the duration of clotting factor replacement after surgery. Circumcision was carried out under general anaesthesia; the prepuce was incised circumferentially and excised using the Gomco clamp technique. Haemophiliac patients were divided into two groups: in group 1 (four patients, three with haemophilia A and one with haemophilia B) the factor levels were assessed every 8 h and bolus injections of factor repeated during the first 4 days after surgery; in group 2, the seven remaining haemophilia A patients received a postoperative bolus injection and ≈ 4 U/kg

per hour of factor substitution for the first 2 days after surgery by continuous infusion. Eleven other patients with haemophilia A underwent circumcision using same surgical procedure but were given only factor substitution without fibrin glue, and served as a control group (group 3).

Results None of the patients had significant bleeding or complications. The total costs were significantly reduced, to \$8898 per patient in group 1 and \$4866 per patient in group 2, when compared with \$12875 per patient in group 3 (both $P < 0.05$).

Conclusion Fibrin glue is a useful treatment for circumcision in patients with haemophilia; it lessens the need for factor substitution after circumcision and thus reduces the high cost of treatment.

Keywords Haemorrhagic disease, haemophilia, fibrin glue, circumcision

Introduction

Patients with haemophilia have a high risk of excessive and prolonged haemorrhage after all surgical procedures. Enhancement of haemostasis at the site of the wound diminishes the risk of postoperative bleeding and reduces or eliminates the need for systemic factor replacement therapy [1–3].

Circumcision is a traditional and religious ceremony in Turkey, as in other Muslim countries, and in Jewish culture. In Muslim societies, circumcision is 'the first step toward being a man and masculinity' and a sign of becoming a member of society [1,4]. In the past, circumcision was fatal for infants with severe haemophilia. With the discovery of plasma cryoprecipitate that contains a high factor VIII concentration, and later with the production of commercial viral-inactivated factor concentrates, surgical procedures in patients with haemophilia became a therapeutic reality [2,3,5].

Fibrin glue is a topical biological adhesive, the effect

of which imitates the final stages of coagulation. It is composed of purified, virus-inactivated human fibrinogen, human thrombin, and sometimes added components such as virus-inactivated human factor XIII and bovine aprotinin [2,3,5–8] (Fig. 1).

In this study we evaluated the efficacy and cost reduction of factor concentrates in circumcision by using fibrin glue in 11 patients with severe or moderate haemophilia.

Patients and methods

Eleven patients with haemophilia (aged 6–14 years, 10 with haemophilia A and one with haemophilia B) were circumcised using fibrin glue for local haemostasis and to reduce the duration of clotting factor replacement after surgery (Table 1). Commercial heat-treated two-component fibrin glue (Tisseel-Kit, Immuno AG, Vienna, Austria) was used in all patients; all were hospitalized for preoperative preparation. A bolus dose of factor concentrate was injected preoperatively to achieve a factor level activity in plasma of at least half of normal

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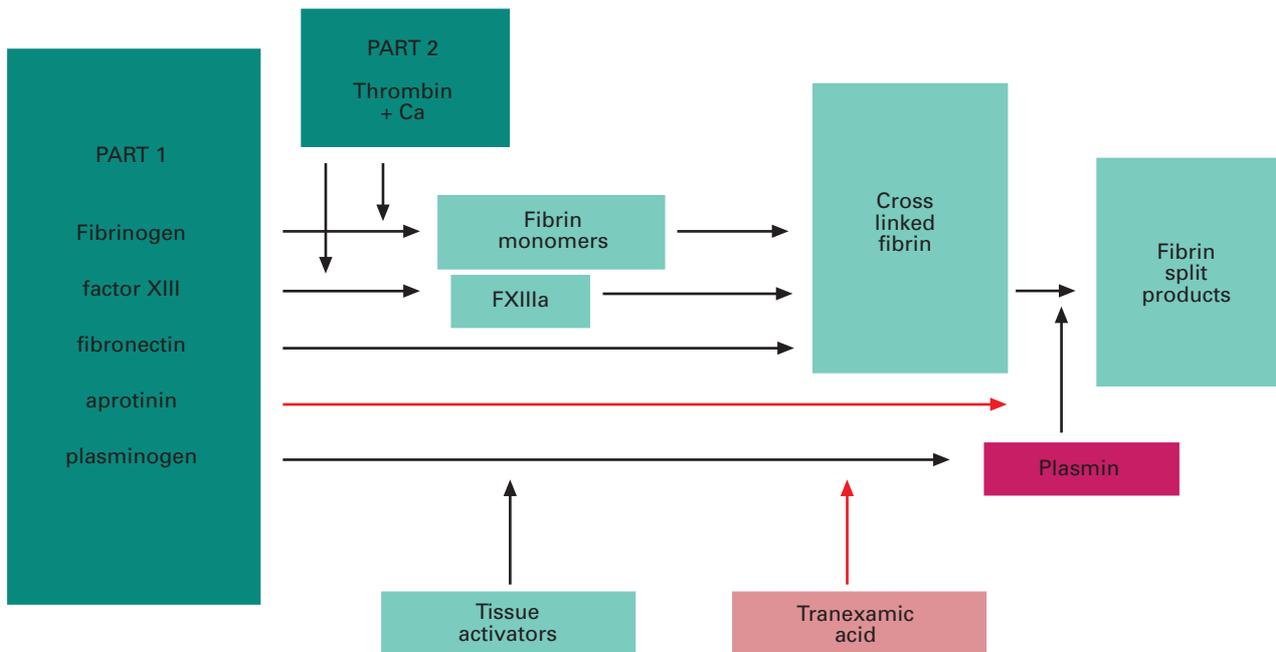


Fig. 1. Local haemostasis with fibrin glue and its biological components. After mixing the two components, fibrinogen is transformed to fibrin monomers. Thrombin transforms factor XIII to factor XIIIa. Factor XIIIa crosslinks the fibrin monomers to a polymer, so its resistance to fibrinolytic degradation is increased. In the course of wound healing, plasminogen activators derived from the tissue activate the plasminogen present to plasmin. Fibrinolytic activity eventually produces soluble fibrin products. This process is retarded by aprotinin (protease inhibitor) in concentrate. Also, tranexamic acid (not included in the glue) inhibits fibrinolytic activity and helps to prevent fibrinolysis. Thus wounds heal without haemorrhaging.

Table 1 Original factor levels in the patients

Patient no.	Original factor VIII level (%)		
	Group 1	Group 2	Group 3
1	0.5	5.6	1.1
2	1.9	1.6	1.5
3	2.1	2.9	2
4	1 (F a IX)*	1.7	15
5		1	1
6		2	1
7		5	2
8			5
9			1
10			1
11			1

*Haemophilia B patient.

levels in these patients. Circumcision was carried out under general anaesthesia. The prepuce was incised circumferentially and excised using the Gomco clamp technique. Major bleeding vessels on the shaft were fulgurated or tied and then 1 mL of fibrin glue was applied onto the denuded area through a 22 G needle. The skin edges were then approximated with 4/0 inter-

rupted catgut sutures and the incision covered again with the fibrin glue. The wound was covered with a gauze dressing. Soon after surgery the factor levels were assessed and a bolus dose of concentrate injected in all haemophiliac patients.

The haemophiliac patients were divided into two groups: group 1 comprised four patients (three with haemophilia A and one with haemophilia B) and group 2 the seven remaining haemophilia A patients. For patients with haemophilia A, intermediate-purity factor concentrates (Nordiate, Novo Nordisk, Denmark; Koate-HP, Bayer, USA; and Factor 8Y, BPL, UK) were used. In those with haemophilia B, high-purity factor IX concentrate (Replene, BPL, UK) was used. The replacement therapy was aimed at maintaining a factor level of >50% normal. In group 1, factor levels were assessed every 8 h and bolus injections repeated during the first 4 days after surgery. In the group 2, after a postoperative bolus injection, ≈4 U/kg per hour of factor substitution was administered for the first 2 days after surgery by continuous infusion. All the patients received oral tranexamic acid (50 mg/kg per day; three times daily) for 7 days and their wound covers were dampened locally three times daily with tranexamic acid. The dressing was removed 2 days after the operation.

Eleven other patients with haemophilia A were circumcised using the same surgical procedure but were given only factor substitution with no fibrin glue and served as the control group (group 3); they received no inhibitor. Intermediate factor concentrates, Koate-HP and Nordiate, were used in these patients, together with tranexamic acid for 7 days. Factor substitution was administered for 8 days after the operation to achieve and maintain a factor activity level of at >50% in plasma.

Results

There was no significant bleeding or wound infection after surgery in any group. Only one patient had minimal bleeding 12 days after surgery, because of erection, and this problem was resolved with an injection of factor concentrate. The total costs were significantly less in group 1 and 2 than in group 3 (both $P < 0.05$; Table 2). The cost difference between groups 1 and 2 was also significant and the duration of hospitalization was halved in group 2.

Discussion

Fibrin glue stimulates the normal clotting process and is subsequently resorbed by normal tissue enzyme systems, with no foreign-body reactions or extensive fibrosis. Fibrin glue is available in Europe and Canada as a haemostatic agent, and it has been used for many years for fixing skin grafts [2,8]. The utility of the sealant as a potent haemostatic agent in the control of bleeding is well documented in the fields of plastic, cardiovascular and thoracic surgery, neurosurgery, otorhinolaryngology, orthopaedic surgery and dental care in patients with either normal or abnormal haemostasis. Local use

of fibrin glue is a safe and cost-effective method for treating patients with haemorrhagic disease, especially for dental extractions and oral surgery. It has also been shown to be useful in the circumcision of haemophilic patients [1–3,9].

Various compositions of fibrin glue have been described, and this has implications for the effects of the sealant. In the USA, the fibrinogen component in the 'home-made' glues is derived from single-donor, heterologous plasma or autologous cryoprecipitate. The emergency use of autologous fresh plasma or platelet-rich plasma, obtained intraoperatively, has also been described. In Europe, commercial multidonor fibrinogen concentrates are the main source. The products differ in the contents of fibrinogen, factor XIII, plasminogen and mode of viral inactivation [2,3].

It was recently reported that the risk of viral transmission can be further reduced by using plasma from a single donor ('home-made' fibrin glue) or using current viral inactivation procedures, e.g. the solvent/detergent method. A combination of inactivation steps to further increase viral safety is preferable, and recently u.v. radiation, ultrafiltration, heat treatment or both the last two have been added to the solvent/detergent step. Inhibitor formation has also been reported after using fibrin glue. Thrombin preparations produced by most manufacturers also contain bovine factor V; antibodies against multiple epitopes of factor V or thrombin have been detected by ELISA. *In vivo*, antibodies to bovine factor V can cross-react with human factor V, producing an immune complex that is cleared from the circulation. The resulting deficiency of factor V can be sufficiently severe to produce a bleeding diathesis. Antibodies that cross-react with human thrombin can promote thrombosis by impairing the inhibition of thrombin by antithrombin III [2,3,5,8]. We follow our patients periodically to assess viral transmission and inhibitor formation, but prefer to use human thrombin preparations.

In Turkey, children with haemophilia (and their parents) may have an inferiority complex because the boys are unable to be circumcised. Before using fibrin glue, we continued factor substitution for 7–8 days after circumcision. The cost of circumcision was significantly reduced after introducing the present method when compared with other patients not treated with fibrin glue, as described previously in four patients [1]. The present study extended the results to seven patients with haemophilia and two with other congenital haemorrhagic disease (one with factor V deficiency and one with Glanzman's disease). We now use only 2 days of factor substitution by continuous infusion to maintain steady factor levels in patients also treated using locally applied fibrin glue. Although some authors report that satisfactory local haemostasis was obtained using fibrin

Table 2 The cost of blood products for circumcision with or without fibrin glue in patients with haemophilia

Variable	Group		
	1	2	3
Age (years)	6–14	7–11	8–17
Duration of substitution/case (days)	4	2	8
Mean weight (kg)	26.5	26.3	28.5
Total cost* (\$)			
Per case	8898†	4866†	12 874
Per kg per case	366†	180†	472

*Total cost only contains factor concentrates and fibrin glue; hospitalization and operation costs are excluded. † $P < 0.05$ compared with factor group 3.

glue in some haemophilic patients with no factor replacement for circumcision, we recommend that factor replacement should be used for at least 2 days after surgery to achieve normal haemostasis and wound healing [2,3,9]. Thus fibrin glue significantly reduces the requirement for factor replacement and as a result the cost of treatment and duration of hospitalization is halved.

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