

FIBRINOLYTIC INHIBITORS IN THE MANAGEMENT OF BLEEDING DISORDERS

Lilian Tengborn

Centre for Thrombosis and Haemostasis
Malmö University Hospital
Malmö, Sweden

Published by the World Federation of Hemophilia (WFH)

© World Federation of Hemophilia, 2007

The WFH encourages redistribution of its publications for educational purposes by not-for-profit hemophilia organizations. In order to obtain permission to reprint, redistribute, or translate this publication, please contact the Communications Department at the address below.

This publication is accessible from the World Federation of Hemophilia's website at www.wfh.org. Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

The *Treatment of Hemophilia* series is intended to provide general information on the treatment and management of hemophilia. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side effects recognized. WFH makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or to consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this monograph.

Statements and opinions expressed here do not necessarily represent the opinions, policies, or recommendations of the World Federation of Hemophilia, its Executive Committee, or its staff.

Treatment of Hemophilia Monographs
Series Editor
Dr. Sam Schulman

Table of Contents

Introduction	1
The fibrinolytic system	1
Activation of the fibrinolytic system	1
Inhibitors in the fibrinolytic system	1
The pharmaceutical fibrinolytic inhibitors	1
Aprotinin	2
EACA and tranexamic acid	3
Clinical use	4
Gynecology	4
Bleedings in the gastrointestinal tract	5
Bleedings in nose and mouth	5
Dental surgery	6
Major surgery	7
TA as supplement to recombinant FVIIa	9
Conclusion	9
Abbreviations	9
References	10

Fibrinolytic Inhibitors in the Management of Bleeding Disorders

Lilian Tengborn

Introduction

When tissue is damaged, vessels can rupture, immediately triggering the hemostatic mechanism: vessels contract, platelet plugs form, and coagulation starts, resulting in a stable fibrin network. At the same time, the fibrinolytic system is activated. Fibrinolysis is the physiological mechanism that dissolves clots, keeps the vessels patent, and starts remoulding the damaged tissue.

Reduction of fibrinolytic activity with fibrinolytic inhibitors is important in surgery and trauma to control blood loss. Treatment with fibrinolytic inhibitors is even more strongly indicated for patients with bleeding disorders to counterbalance the decreased procoagulant state. The bleeding disorders discussed in this monograph are mainly congenital (e.g., von Willebrand disease [VWD], hemophilia A and B, and platelet dysfunctions).

The usefulness of fibrinolytic inhibitors is based on laboratory investigations demonstrating increased fibrinolytic activity in plasma, mucosa, and certain tissues; and on controlled randomized studies showing a positive effect of fibrinolytic inhibitors. Most of these studies have been carried out in patients without bleeding disorders. Patients with documented bleeding disorders are relatively rare. As a result, studies in these patients are often observational, retrospective, and rather limited in number.

Treatment with fibrinolytic inhibitors started several decades ago and the same substances are still used today. These include the naturally occurring aprotinin; the synthetic derivative of the amino acid lysine, epsilon-aminocaproic acid (EACA); and the more potent TA (AMCA). This monograph focuses on TA, which is more potent than EACA. (Tranexamic acid is hereafter abbreviated TA, though sometimes AMCA is used in the literature.) Aprotinin is only briefly discussed since it is not principally used in patients with bleeding disorders, at least not systemically.

The fibrinolytic system

Activation of the fibrinolytic system

The key reaction is the activation of the proenzyme plasminogen to the serine protease plasmin. Plasminogen binds via its lysine-binding sites (LBS) in the so-called kringle structures to specific lysines in the fibrin molecules [1]. The most important physiological activator of plasminogen is the tissue-type plasminogen activator (tPA), which has a specific affinity to fibrin. Expressed in the endothelial cells of the vessel walls, tPA is released after injury and binds to fibrin via LBS [2]. When bound to fibrin it is almost fully active [3]. This co-localization of plasminogen and tPA further facilitates fibrinolysis at the site of the fibrin clot (Figure 1). Urokinase (uPA) is another plasminogen activator, present in high concentrations in urine.

Inhibitors in the fibrinolytic system

The plasminogen activator inhibitors are PAI-1, which is synthesized in endothelial cells, adipocytes, and the liver; PAI-2, which is synthesized in placenta, monocytes, and macrophages; and PAI-3, which is identical to the protein C inhibitor and protease nexin [4]. The latter two are probably of minor importance in fibrinolysis. Deficiency of PAI-1 is a rarely diagnosed variant with increased bleeding tendency. The physiologically important inhibitor of plasmin is the liver-synthesized antiplasmin. Antiplasmin binds to LBS in plasmin but when plasmin is adsorbed to fibrin this binding is slow, thereby keeping the fibrinolytic process ongoing and localized [5]. On the other hand, if massive fibrinolysis is taking place, free plasmin will be available in circulation and it will immediately be inactivated by antiplasmin.

The pharmaceutical fibrinolytic inhibitors

The lysine derivatives EACA and TA are bound to the LBS (Figure 1) in a reversible manner, thereby reducing plasminogen's affinity for binding to fibrin. This reduces the activation of plasminogen to plasmin. Thus, the lysine derivatives interfere with

binding to the LBS. Aprotinin, for its part, inactivates free plasmin. Both aprotinin and lysine analogues reduce fibrinolysis but use different mechanisms.

Aprotinin

Aprotinin is a naturally occurring serine protease inhibitor extracted from bovine lung tissue. It is a polypeptide consisting of 58 amino acids with a molecular weight of approximately 6,500 daltons (Da). The drug binds directly to plasmin as well as other serine proteases. Its half-life is five to ten hours and it is excreted in the urine.

Side effects: Aprotinin has few side effects but may occasionally cause allergic/anaphylactic reactions [6]. Anaphylactic reactions have been reported 5% of the time if treatment is repeated within six months.

Clinical use: Route of administration is limited to intravenous injections since the drug is destroyed by oral intake. Nowadays, it is mostly used in extensive cardiac surgery and liver transplantation and, therefore, it will not be discussed further in this monograph. It should be mentioned, however, that aprotinin is used in fibrin glues.

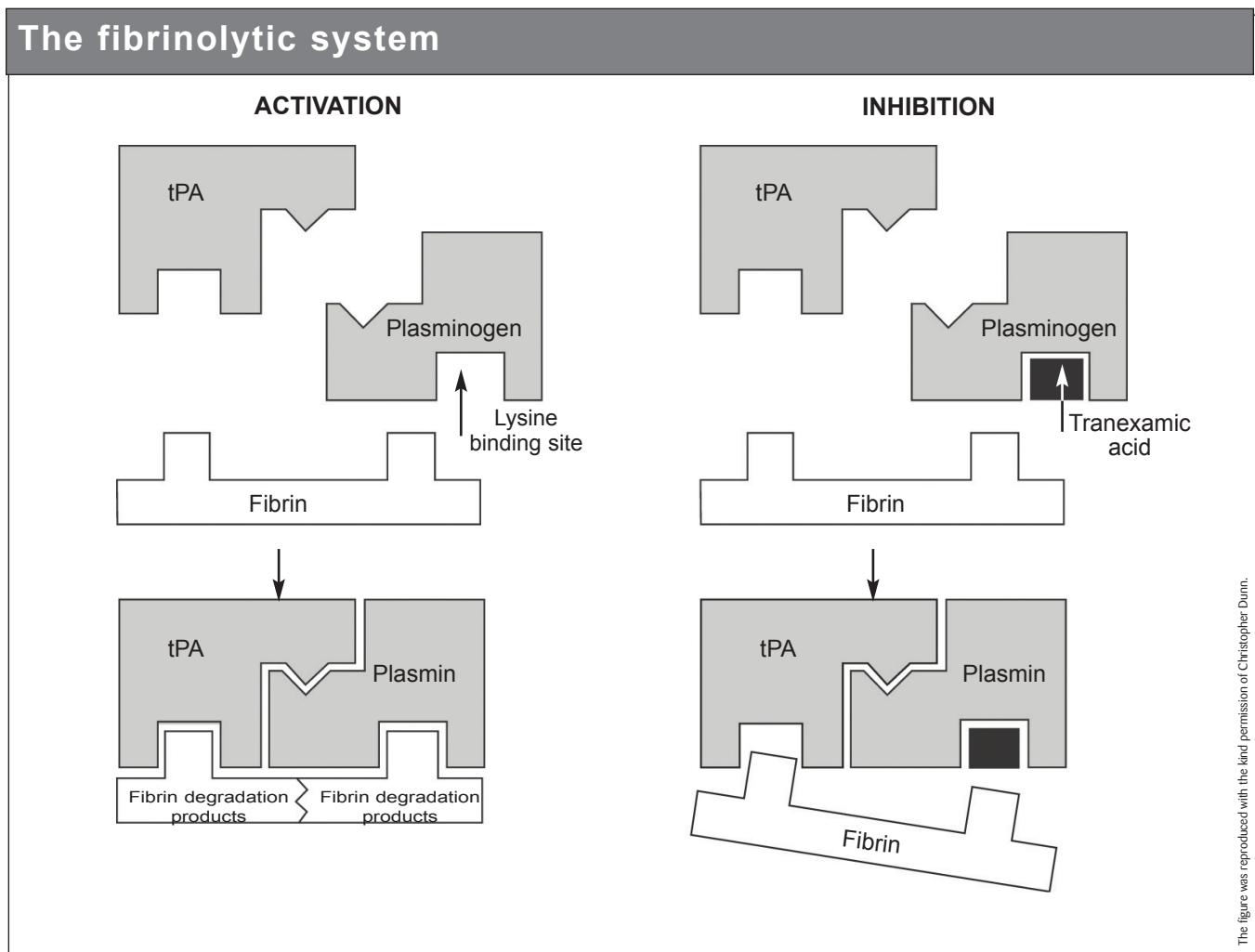


Figure 1. On the left, binding of plasminogen to fibrin occurs at a lysine-binding site. Plasminogen is converted to plasmin in the presence of tissue plasminogen activator. On the right, TA forms a reversible complex with plasminogen. Even though plasminogen is still converted to plasmin by tPA, the plasmin-TA complex is unable to bind to and digest fibrin. The mechanism of action is the same for EACA.

EACA and TA

In 1953, epsilon-aminocaproic acid (EACA), a synthetic derivative of the amino acid lysine, was shown to have a strong effect on inhibiting plasminogen. In the mid 1960s a similar agent, trans-4-(aminomethyl) cyclohexanecarboxylic acid, was found to be about 10 times more effective and has also turned out to be better tolerated than EACA [7].

EACA is a synthetic amino acid with a molecular weight of 131 Da. After a single oral dose of 5 g the peak plasma concentration is reached within 1.2 hours. It distributes throughout extra- and intravascular compartments and is excreted in the urine with a terminal elimination half-life of approximately two hours.

TA is a synthetic amino acid with a molecular weight of 157 Da. Pharmacokinetic studies in healthy individuals have shown that after intravenous administration of 10 mg per kg body weight (BW), the highest plasma concentration was reached within one hour after injection [8,9]. After the first hour, 30% of the given dosage was excreted in the urine and after 24 hours, 90% was excreted. After oral doses of 10 to 15 mg per kg BW, the maximum plasma concentration was reached within three hours [10]. Food has no influence on gastrointestinal absorption [11]. The biological half-life has been reported to be 80 minutes [6]. TA accumulates in tissues [9]. It passes through the placenta to the fetus [12] and it is present in breast milk—but in concentrations 100 times lower than in serum [10]. Moreover, TA rapidly diffuses to the joint fluid and synovial membrane [13]. In toxicological studies, no teratogenic effects were revealed [7].

Administration and dosage: EACA infusion of 4–5 g (16–20 mL) in 250 mL is administered during the first hour, followed by a continuous infusion of 1 g per hour in 50 mL of diluent until the bleeding situation has been controlled. Orally, 5 g, 10 tablets, or 20 mL syrup (25%) is administered during the first hour, followed by 1 g per hour until the bleeding situation has been controlled. These recommended dosages are for adults.

TA may be administered intravenously, orally, or topically. The intravenous dosage is generally 10 mg per kg BW, three to four times daily. Orally the dosage is

15 to 20 mg per kg BW, three to four times daily. For surgery, the first dose is given immediately before starting. However, if the first dose is administered orally, it should be given two hours before the procedure. If TA is topically administered as a mouthwash, 10 mL of a 5% aqueous solution is used, which is equal to 0.5 g if swallowed. TA is also a constituent in some types of fibrin glue.

Because TA is excreted via the kidneys, the dosage intervals should be prolonged in patients with renal insufficiency. In severe renal insufficiency, the doses should also be reduced. In macroscopic hematuria with its origin in the kidneys, TA should not be administered because of the risk that clots will be retained in the ureters and bladder.

Tolerability and side effects: EACA is generally well tolerated. Gastrointestinal (GI) side effects, such as nausea and vomiting, may occur as well as dizziness and hypotension.

TA is also generally well tolerated. The most commonly reported adverse events are GI. In a double-blind study, the total incidence of nausea, vomiting, diarrhea, and abdominal pain was 12% in those who received 1 g of TA four times daily for four days [14]. Rapid intravenous injection may cause dizziness and hypotension; therefore, it is recommended that TA not be administered faster than 100 mg per minute.

Occasionally, cases of thrombosis (cerebral thrombosis, arterial thrombosis, coronary graft occlusion) have been reported during treatment with TA, as have cases of acute renal failure [15]. However, it is uncertain that TA was the causative agent. In Japan and most of the EU, caution and supervision is recommended when administering TA to patients with a history of thromboembolism. In the U.K., TA is contraindicated in these patients [16]. However, the thrombotic disorder is multifactorial and may well occur in patients not on TA. Moreover, several randomized studies in patients undergoing cardiac surgery with coronary artery bypass grafting, as well as studies in patients undergoing total knee and hip arthroplasty, have shown no excess incidence of thrombotic events in patients receiving TA [15,17]. No thrombotic effect from TA was detected in a retrospective analysis of case records of 256 women with bleeding disorders in pregnancy, 168 of whom

underwent Caesarean section [18]. Since the early 1970s, TA has been widely used in Sweden as a first-line treatment for menorrhagia. In 238,000 patient-years of treatment, there has been no reported increase in the incidence of thromboembolic events [19]. As mentioned above, TA is widely used in Europe as well as in Canada but tablets are currently not licensed in the U.S., where TA is only available for intravenous injections.

Contraindications: EACA and TA are contraindicated in patients with renal bleeding and those being treated with the anti-inhibitor coagulant complex FEIBA. Repeated injections of EACA or TA to treat bleeding during the acute phase of disseminated intravascular consumption are also contraindicated.

Clinical use

Gynecology

Menorrhagia: Excessive menstrual bleeding or menorrhagia is a common condition in women. By definition, menorrhagia is a menstrual blood loss of at least 80 mL per cycle. The alkali hematin method described by Hallberg and Nilsson is an accurate procedure for determining blood loss [20]. In later studies, this method has been replaced by the simpler pictorial bleeding assessment chart [21].

The rationale for treating idiopathic menorrhagia with fibrinolytic inhibitors is that these women have higher plasminogen activator content in their endometrium on the first day of their periods than women who have normal blood loss [22]. Several controlled clinical trials have shown that TA taken during menstruation reduced blood loss by 34–59% compared with placebo or controls [23–28].

Heavy menstrual bleeding from menarche is an extremely common symptom in women with bleeding disorders such as VWD, platelet dysfunction, factor VII, X, and XI deficiencies, and in those carrying hemophilia A or B, according to Winikoff et al. [29]. The reported prevalence of VWD in women with menorrhagia is currently estimated to be from 5 to 20% [30]. Menorrhagia is one of the most common bleeding manifestations of VWD, reported by 60 to 95% of women with this bleeding disorder [30]. The heavy menstrual bleeds, as

expected, have a negative impact on women's day-to-day activities, as documented by Kirtava et al. in their interview study of women with VWD [31].

For patients with VWD and menorrhagia, there are no studies comparing the relative efficacy and safety of the available medical therapies. However, Demers et al. developed a consensus document on the management of inherited bleeding disorders, notably VWD, for the Society of Obstetricians and Gynecologists of Canada [32]. It was based on a Medline search of English literature on the subject published between 1975 and 2003 and recommendations from other guidelines. The review found that "an inherited bleeding disorder is not a contraindication to hormonal therapy... and non-hormonal therapies (antifibrinolytic drug TA as well as desmopressin). These therapies represent first-line treatment."

Among women with abnormal menstrual bleeding, 20 to 30% have impaired platelet function and fibrinolysis disorders that may be an additional cause of menorrhagia, as suggested in a review by Kouides [33]. In all these cases TA seems to be an appropriate approach for reducing blood loss based on the above-mentioned findings.

The recommended oral dose of TA is approximately 15 mg per kg BW every six to eight hours, generally 1 to 1.5 g three times daily from the onset of bleeding until it is arrested. In a few patients with VWD the total daily dose of 3 or 4 g was taken as a single dose. This high-dose regimen has been well tolerated; it is convenient and efficient in controlling the menorrhagia [34–36]. There are no reported serious side effects of TA, other than occasional mild GI disturbances. Subjects are encouraged to adjust the dose upward or downward themselves to find their own optimal regimen.

TA in menorrhagia for women with bleeding disorders

Oral TA: 15–20 mg per kg BW three to four times daily from the start of the menstrual period until it is arrested. The dose is increased if there is insufficient effect, or decreased if bowel-related side effects are inconvenient.

Pregnancy: Only rarely do women with congenital bleeding disorders have bleeding problems during normal pregnancies as a result of their bleeding abnormality. Even in women with a severe bleeding disease such as VWD type 3, pregnancies are generally uneventful [37]. However, in one follow-up study a higher incidence of vaginal bleedings was noticed in pregnant women with VWD and factor XI deficiency than in women with normal hemostasis, even though the miscarriage rate was not higher [38]. Although there is no evidence of teratogenicity or other side effects, either on the fetus or in the mother [18], the experts on C1 inhibitor deficiency recommend avoiding TA during pregnancy if possible [39].

Parturition: Appropriate delivery of care to women who suffer from hemostatic disorders should take place in collaboration with hemophilia treatment centres. Treatment at vaginal or Caesarean delivery should be tailored to the individual patient and include fibrinolytic inhibitors. While increased bleeding after parturition may be due to a variety of causes, it is clear that a high level of fibrinolytic activity is present. When the placenta separates, there is an abrupt loss of the plasminogen activator inhibitor PAI-2 and the uterus is extremely rich in plasminogen activators. In patients with VWD, von Willebrand factor (VWF) declines postpartum within a few weeks, as do factors VIII and IX in carriers of hemophilia A and B. This increases the risk of postpartum hemorrhage, according to Kadir and Aledort [40]. In women with VWD type 3 (the severe type), increased bleeding was observed when the affected women were treated with factor concentrate for less than three to four days after parturitions [37]. In these women, adjuvant therapy with TA may be of value. Rarely is acquired hemophilia developed post partum. In such cases TA may be used as a supplement to diminish bleedings with one important exception: if the patient is treated with activated prothrombin complex concentrates (APCC) such as FEIBA, TA is often considered to be contraindicated because of the risk of developing thrombotic complications. At the very least, it should be used with extreme caution [41].

Breastfeeding is considered safe since the concentration of TA is 100 times lower in breast milk than in serum [10].

Gynecological surgery: The cervical tissue, like uterine tissue, contains high levels of plasminogen activator, which explains the positive effect of TA in studies on conization [42,43]. Similarly, antifibrinolytic agents may be of importance in procedures like curettage and hysterectomy. This is the basis for TA/EACA treatment in patients with bleeding disorders undergoing gynecological surgery.

Bleedings in the gastrointestinal tract

The high local activity of fibrinolytic enzymes in the upper GI tract forms the basis of the rationale for antifibrinolytic treatment in GI bleedings, as demonstrated by Cox et al. [44]. Meta-analysis of six randomized, double-blind placebo-controlled studies showed that TA was associated with a 20 to 30 % reduction in the rate of rebleeding compared with no treatment, a 30 to 40 % reduction in the need for surgery, and a 40 % reduction in mortality [45].

Angiodysplasia in the gut can be another source of bleeding. Up to six per cent of patients with VWD are reported to have this disorder [46,47], which may indicate that the VWD unmasks the vessel abnormality. In treatment of these conditions— with or without VWD— TA may be a supportive agent.

TA to patients with bleeding disorders when bleeding from upper gastrointestinal tract

TA: 10 mg per kg BW three to six times daily intravenously. For erosive gastritis, 10 mg per kg BW three to four times daily is added into the nasogastric tube until the bleeding is arrested.

Bleedings in nose and mouth

The cause of nosebleeds is probably multifactorial. The fibrinolytic activity was extensively studied by Petrusin in patients with recurrent long-standing epistaxis, as well as in controls [48]. The spontaneous fibrinolytic activity in plasma was significantly higher when the patients bled, compared with some weeks later in a non-bleeding state. Likewise, the fibrinolytic activity in the nasal mucosa was significantly higher when the patients bled than one month later. A double-blind randomized study using 1 g of TA three times daily for 10 days showed that the severity, recurrence of bleeds, and number of days of hospitalization were significantly decreased for patients on TA.

Nose bleeding is very common in children and, most often, no specific cause is identified. However, bleeding disorders such as VWD, platelet dysfunction, and, more seldom, hemophilia may be present. In one study, one-third of children with recurrent epistaxis had a diagnosable coagulopathy [49]. Studies suggest that five to 10 % of children with recurrent nosebleeds may have mild, previously undiagnosed VWD [50,51]. There are two studies on antifibrinolytic agents applied topically for nosebleeds: one on EACA [52] and one on TA [53]. TA appeared to have no better effect than placebo. However, the trials seem to be too small for drawing any conclusions. Fibrin glue containing aprotinin has also been studied [54].

Oral or topical TA is recommended in patients with VWD, either alone or together with desmopressin (DDAVP) or VWF concentrate, for treatment of bleeds in the nose and oral cavity, according to guidelines from the U.K. Haemophilia Centre Doctor's Organization [55]. TA is also indicated in patients with other bleeding disorders. Bleeds from the oral cavity, such as frenulum tears and bites in the lips and cheeks, are often seen in young children and may be controlled by oral or topical TA. Jiménez-Yuste et al. advocate the use of TA alone or as a supplement to DDAVP or VWF concentrate for patients with VWD undergoing otolaryngologic surgery [56].

TA in nosebleeds to patients with bleeding disorders

A big piece of cotton wool is formed to put in the nostril. One end is dipped in oil or Vaseline mixed with a crushed TA tablet. The nose should be blown before the cotton wool is put in the nostril. TA may also be taken orally.

Dental surgery

As early as the 1960s, Björlin started studying fibrinolysis in the oral cavity [57]. He considered the local fibrinolysis in the alveoli the probable cause of bleeding after dental extraction. There are several studies on treatment with fibrinolytic inhibitors in patients with hemophilia and VWD who had dental extractions or oral surgery. The majority are descriptive analyses in which antifibrinolytic agents are

recommended alone or in combination with coagulation factor concentrates or DDAVP [58–63]. In some of the trials, a limited number of patients were randomized. Forbes et al. showed that in patients with hemophilia, treatment for five days with 1 g of TA three times daily starting two hours before surgery was associated with significantly less post-operative bleeding than in a placebo group [64]. Factor VIII or IX concentrate was given prior to surgery to achieve the same levels in the two groups. Ramström and Blombäck showed that factor concentrate requirement and days spent in hospital could be decreased if TA and antibiotics were included in the regimen [65].

The beneficial effect of local application of EACA as mouthwash was first demonstrated by Berry et al. [66]. Sindet-Pedersen advocated the addition of TA mouthwashes because, after systemic administration, TA was not detectable in saliva in healthy volunteers who had received 1 g orally as a single dose [67]. The maximum level in plasma was reached after approximately 120 minutes. On the other hand, after rinsing the mouth with 10 mL of a 5% aqueous solution for two minutes, a high concentration was achieved in the saliva, while TA was undetectable in plasma. A therapeutic concentration of TA remained in saliva for more than two hours. Patients with mild hemophilia with a factor level of at least 10 % who received TA systemically and locally (10 mL of 5% solution for two minutes four times daily) at dental surgery developed no bleeding complications even though they did not receive replacement therapy [68].

Waly showed that children with hemophilia who received replacement products prior to dental extraction plus TA mouthwash as a supplement to systemic therapy developed less post-extraction bleeding than those who did not receive TA as a local treatment [69]. In their retrospective analysis of 63 patients with VWD who had dental extraction or periodontal surgery, Federici et al. reported that with combined TA systemically, mouthwash, and irrigation at surgery, as well as fibrin glue in more extensive surgery, the need for VWF concentrate could be considerably reduced [61]. Based on their experiences with patients with hemophilia, Zanon et al. proposed a protocol for dental extraction with 20 mg of TA per kg BW and a single infusion of factor VIII or IX to achieve a peak level of about 30%

of normal factor VIII or IX prior to extraction [70]. Twenty milligrams of TA per kg BW was administered orally 8 and 16 hours later, then three times daily for the next seven days. Additionally, gauze saturated with TA was kept in place for 30 to 60 minutes after extraction.

In the protocol used by Piot et al., factor concentrate was administered to achieve a level of 50% of normal before and 24 hours after extraction (also after 12 hours in severe hemophilia A and VWD), along with TA systemically and locally as mouth rinse [71]. Rakocz et al. found that "home-made" fibrin glue with a high concentration of 10,000 Kallikrein Inhibitor Unit (KIU) of aprotinin per mL (compared with commercially available glue, generally 1,000 KIU per mL) plus "swish and swallow" rinses of TA without preventive replacement therapy was safe and cost-effective in dental extractions in patients with bleeding disorders [72]. In a placebo-controlled study, Lee et al. showed that TA mouthwash alone was as effective in controlling gingival bleeding

after dental scaling as using factor replacement beforehand in patients with hemophilia [73].

To sum up, a variety of regimens are reported in patients with hemophilia and VWD undergoing dental surgery but fibrinolytic agents are obviously the first line of treatment, alone or in combination with replacement products or DDAVP. This is already the routine according to surveyed physicians at the Hemophilia Research Society of North America [74]. Similar protocols are described by Stubbs and Lloyd in the *Australian Dental Journal* [75] and the guidelines from the U.K. mentioned above [55]. With a careful surgical procedure by an experienced dental team using available hemostatic materials such as TA and fibrin glue, factor concentrate replacement can be highly reduced. As pointed out by Schulman it is not known what minimum factor level provides a sufficient hemostatic effect in various types of interventions [76]. With its standardized procedures oral surgery is, obviously, a field where prospective studies are warranted.

TA in dental surgery or tooth extractions in patients with bleeding disorders

For dental surgery, local anesthetics with adrenaline are recommended for contraction of the vessel walls.

Oral TA: 15–20 mg per kg BW is given two hours before surgery/extraction, and then repeated three times daily for 8–10 days. Mouth rinsing with 10 mL of a 5% solution of TA for two minutes four times daily for two days may be used.

- After removal of the tooth and roots, collagen-like TissueFleece® is introduced in the sockets and careful suturing is done.
- Fibrin glue may be applied over the sutured area.
- Local compression with biting on a compress soaked in a TA solution for 60 minutes.
- Cold soft food for a couple of days.

A single infusion of FVIII or IX concentrate to achieve a peak level of 30–50% of normal is given to patients with a basal level below 10–15%.

Major surgery

Orthopedic surgery: Randomized placebo-controlled studies in patients without bleeding disorders undergoing total knee replacement have shown that administering 10 to 15 mg of TA per kg BW prior to tourniquet deflation, with or without additional doses on the day of surgery, reduced total blood loss by approximately 50% and significantly reduced the need for blood transfusion [77–79]. Meta-analysis of nine randomized controlled studies in patients undergoing total knee replacement showed that TA significantly reduced the proportion of patients requiring blood transfusion [80]. Prospective randomized controlled studies in total hip replacement [81,82] showed that a single dose of TA (10 to 15 mg per kg BW) given immediately before surgery reduced the total blood loss by about 25% in the TA groups, compared with the placebo groups. Such positive effects of TA in primary total hip replacement were also demonstrated in meta-analysis [83].

To the author's knowledge, no randomized controlled studies on the use of fibrinolytic inhibitors in major surgery have been performed on patients with bleeding disorders. Lofqvist et al published a retrospective case series of 11 patients with hemophilia (eight severe, one moderate, two mild) undergoing

hip replacement [84]. (One patient was excluded because he had bilateral arthroplasty in the same operation.) In addition to factor replacement, the patients were also given TA at six- to eight-hour intervals for seven days. The total bleeding was calculated to be 740 ± 400 mL, which is almost exactly the same as in the patients on TA in the randomized control trial for patients without hemophilia undergoing total hip replacement from the same department at the same period of time [81].

Continuous infusion of factor concentrates is often given to patients with bleeding disorders during major surgery like arthroplasty. There is evidence, albeit scientifically weak, that with continuous infusion less factor concentrate is required compared with intermittent bolus injections [76]. It is important to use antifibrinolytic agents simultaneously. Thus, in two consecutive series of patients with hemophilia B treated with the same factor concentrate in continuous infusion using essentially the same protocol for major surgery – the first one with and the second without TA – the mean blood loss was 379 and 625 mL respectively [85,76]. In a series of 27 patients undergoing total knee replacement and/or total hip replacement, Schulman et al. [86] stressed the possibility of reducing the amount of the expensive factor concentrate administered if continuous infusion were used in combination with local hemostatic and antifibrinolytic agents and could be done without any serious bleeding complications. It should also be mentioned that fibrin glue could be prepared in developing countries inexpensively [87].

Hemophilia patients with inhibitors are a particularly challenging group of patients. As previously mentioned, the minimum effective levels to reach hemostasis are yet to be proven. That makes the experiences published by Ghosh et al. of great interest [88]. He reported on 10 patients with hemophilia and high inhibitor titre. Ghosh and colleagues managed hemostasis in their patients with minimal amounts of APCC using topical, oral, and/or intravenous EACA. Two of their patients received FEIBA 25–70–140 U per kg BW daily together with EACA. If a higher dose of FEIBA (e.g., 200 U per kg BW per day) is administered, antifibrinolytic agents should not be given because of the risk of thromboembolic complications. The authors stressed that antifibrinolytic treatment seems to be of particular value in

patients with hemophilia and inhibitors.

To sum up, although these reports deal with relatively few patients in non-randomized studies, they suggest that the use of fibrinolytic inhibitors reduces blood loss, blood transfusions, and bleeding complications in patients with hemophilia in ways similar to the effect in non-hemophilic patients. The routine at the Swedish hemophilia centres is to give 10 mg of TA per kg BW intravenously immediately before surgery, and repeat this dose thereafter every six to eight hours as long as patients have parenteral nutrition, followed by 1 to 1.5 g orally three times daily for 7 to 10 days.

TA in major surgery in patients with bleeding disorders

Major surgery: TA (10 mg per kg BW) three times daily intravenously, with the first dose immediately prior to surgery. Oral TA (15–20 mg per kg BW) three times daily is given postoperatively when the patient can take tablets; altogether antifibrinolytic treatment for 7 to 10 days.

- For total knee replacement, an additional dose of TA is given immediately before deflation of the tourniquet.
- For surgery in the lower urinary tract, 2 g of TA three times daily on the day of and the first day after the operation, provided that irrigation of the bladder is used.
- For minor surgery, only oral TA is required and is given for a maximum of one week with the first dose two hours before the operation.

Surgery in the urinary tract: Since urine contains a fibrinolysis activator (uPA) there is an obvious risk of increased bleeding when surgery is undertaken in the urinary tract. Moreover, the prostatic gland contains high fibrinolytic activity [89]. Randomized studies on prostatectomy with somewhat varying designs have shown a reduced bleeding in the groups treated with TA or EACA, compared with placebo groups [90–93]. Urological surgery, such as prostatectomy, is becoming increasingly necessary with the advancing age of patients with bleeding disorders. Approximately 20 papers regarding

prostatectomy in patients with hemophilia or VWD can be found on Medline. In some of them fibrinolytic inhibitors have been used as a supplement [94,95].

TA as supplement to recombinant FVIIa


TA is often given as a supplement in treatment with the “bypassing agent” recombinant FVIIa (rFVIIa). Fibrin glues containing aprotinin, as well as TA, were added in the first surgery using rFVIIa in a patient with congenital hemophilia and a high inhibitor titre [96]. In later treatments TA has often been used as an adjunct to rFVIIa, as described in several case reports on patients with factor inhibitors [97–103], or Glanzmann thrombasthenia [104–106].

Continuous infusion with rFVIIa and adjuvant treatment with TA has been reported as safe and efficacious in major surgery in patients with hemophilia A and inhibitors [107,108,99], factor XI deficiency, [109] and congenital factor VII deficiency [110].

Fibrinolytic inhibitors in treatment of patients with bleeding disorders

Fibrinolytic inhibitors (TA, EACA) may be used for all patients with bleeding disorders – intravenously, orally, or topically – as prophylaxis and treatment with few exceptions (renal bleeding, treatment with full dose APCC). The dose has to be reduced in patients with renal impairment.

Conclusion

To a great extent, this monograph is based on studies showing the beneficial effects of anti-fibrinolytic agents, most often TA, in patients apparently without congenital or acquired bleeding diseases. No severe side effects are documented. TA can be administered intravenously, orally, or topically. The increasing awareness of disease transmission via blood components enhanced the development of strategies for reducing allogeneic blood transfusions in surgery including the use of antifibrinolytic agents. This may also reduce the requirement for coagulation factor concentrates, thereby reducing costs. When bleeding occurs, the hemostatic process, including fibrinolysis, is activated. Therefore it seems highly reasonable to use a fibrinolytic inhibitor alone or as a supplement to other hemostatic medication in patients with bleeding disorders to counterbalance their impaired prohemostatic process. 

Abbreviations

AMCA	Tranexamic Acid – TA
APCC	Activated Prothrombin Complex Concentrate
BW	Body Weight
Da	Dalton
DDAVP	Desmopressin
EACA	Epsilon-Aminocaproic Acid
GI	Gastrointestinal
KIU	Kallikrein Inhibitor Unit
LBS	Lysine-Binding Sites
PAI	Plasminogen Activator Inhibitor
rFVIIa	Recombinant Activated Factor VII
TA	Tranexamic Acid
tPA	Tissue Plasminogen Activator
U	Unit
uPA	Urokinase
VWD	von Willebrand Disease
VWF	von Willebrand Factor

References

1. Wiman B., Wallen P. The specific interaction between plasminogen and fibrin. A physiological role of the lysine binding site in plasminogen. *Thromb Res* 1977; 10(2):213-22.
2. Thorsen S, Glas-Greenwalt P, Astrup T. Differences in the binding to fibrin of urokinase and tissue plasminogen activator. *Thromb Diath Haemorrh* 1972; 28(1):65-74.
3. Wallen P, Bergsdorf N, Ranby M. Purification and identification of two structural variants of porcine tissue plasminogen activator by affinity adsorption on fibrin. *Biochim Biophys Acta* 1982; 719(2):318-28.
4. Kruithof EK. Plasminogen activator inhibitors - A review. *Enzyme* 1988; 40(2-3):113-21.
5. Wiman B, Collen D. Molecular mechanism of physiological fibrinolysis. *Nature* 1978; 272(5653):549-50.
6. Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs* 1985; 29(3):236-61.
7. Nilsson IM. *Haemorrhagic and Thrombotic Diseases*. London: John Wiley & Sons, Ltd, 1974.
8. Andersson L, Nilsson IM, Nilehn JE, 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(3):230-47.
9. Andersson L, Nilsson IM, Colleen S, Granstrand B, Melander B. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci* 1968; 146(2):642-58.
10. Eriksson O, Kjellman H, Schannong M. 1971. The biological availability of Cyklokapron tablets compared with Cyklokapron solution administered orally. Data on file, Kabi AB, Stockholm.
11. Pilbrant A, Schannong M, Vessman J. Pharmacokinetics and bioavailability of TA. *Eur J Clin Pharmacol* 1981; 20(1):65-72.
12. Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; 49(3):241-2.
13. Ahlberg A, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. *Acta Orthop Scand* 1976; 47(5):486-8.
14. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of TA and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; 102(5):401-6.
15. Dunn CJ, Goa KL. TA: a review of its use in surgery and other indications. *Drugs* 1999; 57(6):1005-32.
16. Wellington K, Wagstaff AJ. TA: a review of its use in the management of menorrhagia. *Drugs* 2003; 63(13):1417-33.
17. Ho KM, Ismail H. Use of intravenous TA to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care* 2003; 31(5):529-37.
18. Lindoff C, Rybo G, Astedt B. Treatment with TA during pregnancy and the risk of thrombo-embolic complications. *Thromb Haemost* 1993; 70(2):238-40.
19. Rybo G. TA therapy - effective treatment in heavy menstrual bleeding. Clinical update on safety. *Therapeutic Advances* 1991; 4:1-8.
20. Hallberg L, Nilsson L. Determination of menstrual blood loss. *Scand J Clin Lab Invest* 1964; 16:244-8.
21. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; 97(8):734-9.
22. Rybo G. Clinical and experimental studies on menstrual blood loss. *Acta Obstet Gynecol Scand* 1966; 45: Suppl 7:1-23.

23. Nilsson L, Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation. *Acta Obstet Gynecol Scand* 1967; 46:572.
24. Vermynen J, Verhaegen-Declercq ML, Verstraete M, Fierens F. A double blind study of the effect of TA in essential menorrhagia. *Thromb Diath Haemorrh* 1968; 20(3):583-7.
25. Callender ST, Warner GT, Cope E. Treatment of menorrhagia with TA. A double-blind trial. *Br Med J* 1970; 4(729):214-6.
26. Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, TA, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; 164(3):879-83.
27. Gleeson NC, Buggy F, Sheppard BL, Bonnar J. The effect of TA on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding. *Acta Obstet Gynecol Scand* 1994; 73(3):274-7.
28. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and TA. *BMJ* 1996; 313(7057):579-82.
29. Winikoff R, Amesse C, James A, Lee C, Pollard D. The role of haemophilia treatment centres in providing services to women with bleeding disorders. *Haemophilia* 2004; 10(Suppl 4):196-204.
30. Kujovich JL. Von Willebrand's disease and menorrhagia: prevalence, diagnosis, and management. *Am J Hematol* 2005; 79(3):220-8.
31. Kirtava A, Drews C, Lally C, Dilley A, Evatt B. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand's disease receiving care in haemophilia treatment centres: a case-control study. *Haemophilia* 2003; 9(3):292-7.
32. Demers C, Derzko C, David M, Douglas J; Society of Obstetricians and Gynecologists of Canada. Gynaecological and obstetric management of women with inherited bleeding disorders. *J Obstet Gynaecol Can* 2005; 27(7):707-32.
33. Kouides PA. Evaluation of abnormal bleeding in women. *Curr Hematol Rep* 2002; 1(1):11-8.
34. Ong YL, Hull DR, Mayne EE. Menorrhagia in von Willebrand disease successfully treated with single daily dose TA. *Haemophilia* 1998; 4(1):63-5.
35. Onundarson PT. Treatment of menorrhagia in von Willebrand's disease. *Haemophilia* 1999; 5(1):76.
36. Mohri H. High dose of TA for treatment of severe menorrhagia in patients with von Willebrand disease. *J Thromb Thrombolysis* 2002; 14(3):255-7.
37. Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. *Br J Haematol* 2000; 111(4):1236-9.
38. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol* 1998; 105(3):314-21.
39. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139(3):379-94.
40. Kadir RA, Aledort LM. Obstetrical and gynaecological bleeding: a common presenting symptom. *Clin Lab Haematol* 2000; 22(Suppl 1):12-6; Discussion 30-2.
41. Girolami A, Scandellari R, Zanon E, Sartori R, Girolami B. Non-catheter associated venous thrombosis in hemophilia A and B. A critical review of all reported cases. *J Thromb Thrombolysis* 2006; 21(3):279-84.
42. Rybo G, Westerberg H. The effect of TA (AMCA) on postoperative bleeding after conization. *Acta Obstet Gynecol Scand* 1972; 51(4):347-50.
43. Landin L-E, Weiner E. Late bleeding after conization: the effect of TA (Cyklokapron®). *Opusc Med* 1975; 20:280-4.
44. Cox HT, Poller L, Thomson JM. Evidence for the release of gastric fibrinolytic activity into peripheral blood. *Gut* 1969; 10(5):404-7.

45. Henry DA, O'Connell DL. Effects of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. *BMJ* 1989; 298:1142-6.
46. Ramsay DM, Buist TA, Macleod DA, Heading RC. Persistent gastrointestinal bleeding due to angiodysplasia of the gut in von Willebrand's disease. *Lancet* 1976; 2(7980):275-8.
47. Fressinaud E, Meyer D. International survey of patients with von Willebrand disease and angiodysplasia. *Thromb Haemost* 1993; 70(3):546.
48. Petruson B. Epistaxis. A clinical study with special reference to fibrinolysis. *Acta Otolaryngol Suppl* 1974; 317:1-73.
49. Sandoval C, Dong S, Visintainer P, Ozkaynak MF, Jayabose S. Clinical and laboratory features of 178 children with recurrent epistaxis. *J Pediatr Hematol Oncol* 2002; 24(1):47-9.
50. Kiley V, Stuart JJ, Johnson CA. Coagulation studies in children with isolated recurrent epistaxis. *J Pediatr* 1982; 100(4):579-81.
51. Katsanis E, Luke KH, Hsu E, Li M, Lillicrap D. Prevalence and significance of mild bleeding disorders in children with recurrent epistaxis. *J Pediatr* 1988; 113(1,Pt 1):73-6.
52. Jash DK. Epistaxis - topical use of epsilon-aminocaproic acid in its management. *J Laryngol Otol* 1973; 87(9):895-8.
53. Tibbelin A, Aust R, Bende M, Holgersson M, Petruson B, Rundcrantz H, Alander U. Effect of local TA gel in the treatment of epistaxis. *ORL J Otorhinolaryngol Relat Spec* 1995; 57(4):207-9.
54. Vaiman M, Eviatar E, Segal S. The use of fibrin glue as hemostatic in endonasal operations: a prospective, randomized study. *Rhinology* 2002; 40(4):185-8.
55. Pasi KJ, Collins PW, Keeling DM, Brown SA, Cumming AM, Dolan GC, et al. Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004; 10(3):218-31.
56. Jimenez-Yuste V, Prim MP, De Diego JL, Villar A, Quintana M, Rabanal I, et al. Otolaryngologic surgery in children with von Willebrand disease. *Arch Otolaryngol Head Neck Surg* 2002; 128(12):1365-8.
57. Bjorlin G. Local fibrinolysis in the oral cavity. *Scand J Haematol Suppl* 1984; 40:411-6.
58. Bjorlin G, Nilsson IM. Tooth extractions in hemophiliacs after administration of a single dose of factor VIII or factor IX concentrate supplemented with AMCA. *Oral Surg Oral Med Oral Pathol* 1973; 36(4):482-9.
59. Vinckier F, Vermylen J. Dental extractions in hemophilia: reflections on 10 years' experience. *Oral Surg Oral Med Oral Pathol* 1985; 59(1):6-9.
60. Ramstrom G, Blomback M, Egberg N, Johnsson H, Ljungberg B, Schulman S. Oral surgery in patients with hereditary bleeding disorders. A survey of treatment in the Stockholm area (1974-1985). *Int J Oral Maxillofac Surg* 1989; 18(6):320-2.
61. Federici AB, Sacco R, Stabile F, Carpenedo M, Zingaro E, Mannucci PM. Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases. *Haemophilia* 2000; 6(2):71-7.
62. Frachon X, Pommereuil M, Berthier AM, Lejeune S, Hourdin-Eude S, Quero J, et al. Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99(3):270-5.
63. Morimoto Y, Yoshioka A, Sugimoto M, Imai Y, Kirita T. Haemostatic management of intraoral bleeding in patients with von Willebrand disease. *Oral Dis* 2005; 11(4):243-8.
64. Forbes CD, Barr RD, Reid G, Thomson C, Prentice CR, McNicol GP, et al. TA in control of haemorrhage after dental extraction in haemophilia and Christmas disease. *Br Med J* 1972; 2(809):311-3.
65. Ramstrom G, Blomback M. Tooth extractions in hemophiliacs. *Int J Oral Surg* 1975; 4(1):1-17.

66. Berry PR, Coster AB, Berry EW. Local use of epsilon-aminocaproic acid in dental therapy. *Thromb Haemost* 1977; 38:373.
67. Sindet-Pedersen S. Distribution of TA to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. *J Clin Pharmacol* 1987; 27(12):1005-8.
68. Sindet-Pedersen S, Stenbjerg S. Effect of local antifibrinolytic treatment with TA in hemophiliacs undergoing oral surgery. *J Oral Maxillofac Surg* 1986; 44(9):703-7.
69. Waly NG. Local antifibrinolytic treatment with TA in hemophilic children undergoing dental extractions. *Egypt Dent J* 1995; 41(1):961-8.
70. Zanon E, Martinelli F, Bacci C, Zerbinati P, Girolami A. Proposal of a standard approach to dental extraction in haemophilia patients. A case-control study with good results. *Haemophilia* 2000; 6(5):533-6.
71. Piot B, Sigaud-Fiks M, Huet P, Fressinaud E, Trossaert M, Mercier J. Management of dental extractions in patients with bleeding disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 93(3):247-50.
72. Rakocz M, Mazar A, Varon D, Spierer S, Blinder D, Martinowitz U. Dental extractions in patients with bleeding disorders. The use of fibrin glue. *Oral Surg Oral Med Oral Pathol* 1993; 75(3):280-2.
73. Lee AP, Boyle CA, Savidge GF, Fiske J. Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using TA mouthwash. *Br Dent J* 2005; 198(1):33-8; discussion 26.
74. Cohen AJ, Kessler CM, Ewenstein BM; Hemophilia Research Society of North America. Management of von Willebrand disease: a survey on current clinical practice from the haemophilia centres of North America. *Haemophilia* 2001; 7(3):235-41.
75. Stubbs M, Lloyd J. A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. *Aust Dent J* 2001; 46(1):37-40.
76. Schulman S. Continuous infusion. *Haemophilia* 2003; 9(4):368-75.
77. Hiiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J, et al. TA (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth* 1995; 74(5):534-7.
78. Hiiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemela HM, Mantyla SK, et al. TA radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg* 1997; 84(4):839-44.
79. Benoni G, Fredin H. Fibrinolytic inhibition with TA reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br* 1996; 78(3):434-40.
80. Cid J, Lozano M. TA reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. *Transfusion* 2005; 45(8):1302-7.
81. Benoni G, Fredin H, Knebel R, Nilsson P. Blood conservation with TA in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. *Acta Orthop Scand* 2001; 72(5):442-8.
82. Johansson T, Pettersson LG, Lisander B. TA in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. *Acta Orthop* 2005; 76(3):314-9.
83. Zufferey P, Merquiol F, Laporte S, Molliex S, Auboyer C, Decousus H, et al. Anti-fibrinolytic use in major orthopaedic surgery reduces allogeneic blood transfusion. A meta-analysis of randomised trials. *J Thromb Haemost* 2005; 3: Suppl 1:P0243.
84. Lofqvist T, Sanzen L, Petersson C, Nilsson IM. Total hip replacement in patients with hemophilia. 13 hips in 11 patients followed for 1-16 years. *Acta Orthop Scand*. 1996; 67(4):321-4.
85. Schulman S, Wallensten R, White B, Smith OP. Efficacy of a high purity, chemically treated and nanofiltered factor IX concentrate for continuous infusion in haemophilia patients undergoing surgery. *Haemophilia* 1999; 5(2):96-100.
86. Schulman S, Loogna J, Wallensten R. Minimizing factor requirements for surgery without increased risk. *Haemophilia* 2004; 10(Suppl 4):35-40.

87. Isarangkura P, Chiewsilp P, Chuansumrit A, Suwannuraks M, Keorochana S, Attanawanich S, et al. Low cost locally prepared fibrin glue for clinical applications: reported of 145 cases. Committee of Bangkok International Hemophilia Training Center. *J Med Assoc Thai* 1999 ; 82(Suppl 1):S49-56.
88. Ghosh K, Shetty S, Jijina F, Mohanty D. Role of epsilon amino caproic acid in the management of haemophilic patients with inhibitors. *Haemophilia* 2004; 10(1):58-62.
89. Andersson L. Studies on fibrinolysis in urinary tract disease and its treatment with epsilon-amino-caproic acid. *Acta Chir Scand Suppl* 1962; Suppl 301:1-29.
90. Hedlund PO. Antifibrinolytic therapy with Cyklokapron in connection with prostatectomy. A double blind study. *Scand J Urol Nephrol* 1969; 3(3):177-82.
91. Gamba G, Fornasari PM, Grignani G, Dolci D, Colloï D. Haemostasis during transvesical prostatic adenomectomy. A controlled trial on the effect of drugs with antifibrinolytic and thrombin-like activities. *Blut* 1979; 39(2):89-98.
92. Miller RA, May MW, Hendry WF, Whitfield HN, Wickham JE. The prevention of secondary haemorrhage after prostatectomy: the value of antifibrinolytic therapy. *Br J Urol* 1980; 52(1):26-8.
93. Rannikko A, Petas A, Taari K. TA in control of primary hemorrhage during transurethral prostatectomy. *Urology* 2004; 64(5):955-8.
94. Kursh ED, Ratnoff OD, Persky L. Current clotting concepts in urology. *J Urol* 1976; 116(2):214-7.
95. Goldsmith JC, Unger HA, Fried FA. Successful prostatectomy in patients with inherited abnormalities of the factor VIII molecule. *J Urol* 1980; 124(4):570-3.
96. Hedner U, Glazer S, Pingel K, Alberts KA, Blomback M, Schulman S, et al. Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988; 2(8621):1193.
97. Ingerslev J, Feldstedt M, Sindet-Pedersen S. Control of haemostasis with recombinant factor VIIa in patient with inhibitor to factor VIII. *Lancet* 1991; 338(8770):831-2.
98. Tengborn L, Kjellman B, Elfstrand PO, Bagenholm T. Recombinant factor VIIa in an infant with haemophilia A and inhibitors. *Acta Paediatr* 1992; 81(6-7):566-7.
99. Schulman S. Safety, efficacy and lessons from continuous infusion with rFVIIa. rFVIIa-CI Group. *Haemophilia* 1998; 4(4):564-7.
100. Chuansumrit A, Isarangkura P, Angchaisuksiri P, Sriudomporn N, Tanpowpong K, Hathirat P, et al. Controlling acute bleeding episodes with recombinant factor VIIa in haemophiliacs with inhibitor: continuous infusion and bolus injection. *Haemophilia* 2000; 6(2):6-5.
101. Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr. Treatment of factor XI inhibitor using recombinant activated factor VIIa. *Haemophilia* 2005; 11(1):20-5.
102. Leimkuhler K, Bach F, Kobert K, Korth M, Schmidt B, Kulbe C, Gummelt I, Mertzlufft F. [Acquired hemophilia A as a cause of postoperative bleeding] [Article in German]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2003; 38(5):359-65.
103. Friederich PW, Wever PC, Briet E, Doorenbos CJ, Levi M. Successful treatment with recombinant factor VIIa of therapy-resistant severe bleeding in a patient with acquired von Willebrand disease. *Am J Hematol* 2001; 66(4):292-4.
104. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost* 1996; 75(6):981-2.
105. Chuansumrit A, Suwannuraks M, Sri-Udomporn N, Pongtanakul B, Worapongpaiboon S. Recombinant activated factor VII combined with local measures in preventing bleeding from invasive dental procedures in patients with Glanzmann thrombasthenia. *Blood Coagul Fibrinolysis* 2003; 14(2):187-90.

106. Poon MC, D'Oiron R, Von Depka M, Khair K, Negrier C, Karafoulidou A, et al; International Data Collection on Recombinant Factor VIIa and Congenital Platelet Disorders Study Group. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost* 2004; 2(7):1096-103.
107. Tagariello G, De Biasi E, Gajo GB, Risato R, Radossi P, Davoli PG, et al. Recombinant FVIIa (NovoSeven) continuous infusion and total hip replacement in patients with haemophilia and high titre of inhibitors to FVIII: experience of two cases. *Haemophilia* 2000; 6(5):581-3.
108. Ludlam CA, Smith MP, Morfini M, Gringeri A, Santagostino E, Savidge GF. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *Br J Haematol* 2003; 120(5):808-13.
109. Schulman S, Nemeth G. An illustrative case and a review on the dosing of recombinant factor VIIa in congenital factor XI deficiency. *Haemophilia* 2006; 12(3):223-7.
110. Schulman S, Tjonnfjord GE, Wallensten R, Martinowitz U, Kenet G. Continuous infusion of recombinant factor VIIa for surgery in patients with deficiency of factor VII. *Thromb Haemost* 2005; 94(6):1177-80.

