

FIBRINOLYTIC INHIBITORS IN THE MANAGEMENT OF BLEEDING DISORDERS

Revised edition

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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 decreased fibrinolytic activity in plasma, mucosa, and certain tissues; and on controlled randomized studies showing a positive effect of fibrinolytic inhibitors in reducing bleeding and minimizing exposure to blood products. 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 today only synthetic products are on the market, namely epsilon-aminocaproic acid (EACA), and the more potent tranexamic acid (TA or AMCA). Moreover, a similar product, p-aminomethyl benzoic acid (PAMBA), is available in some countries but rarely included in studies; it will not be further discussed in this monograph. The naturally occurring inhibitor aprotinin was withdrawn from the market in 2008 (see page 4).

The fibrinolytic system

Activation of the fibrinolytic system

The key reaction is the activation of the proenzyme plasminogen to the serine protease plasmin, which is responsible for the degradation of many proteins, notably fibrin clots. 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-type plasminogen activator (uPA) is another plasminogen activator, present in high concentrations of urine, for example.

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.

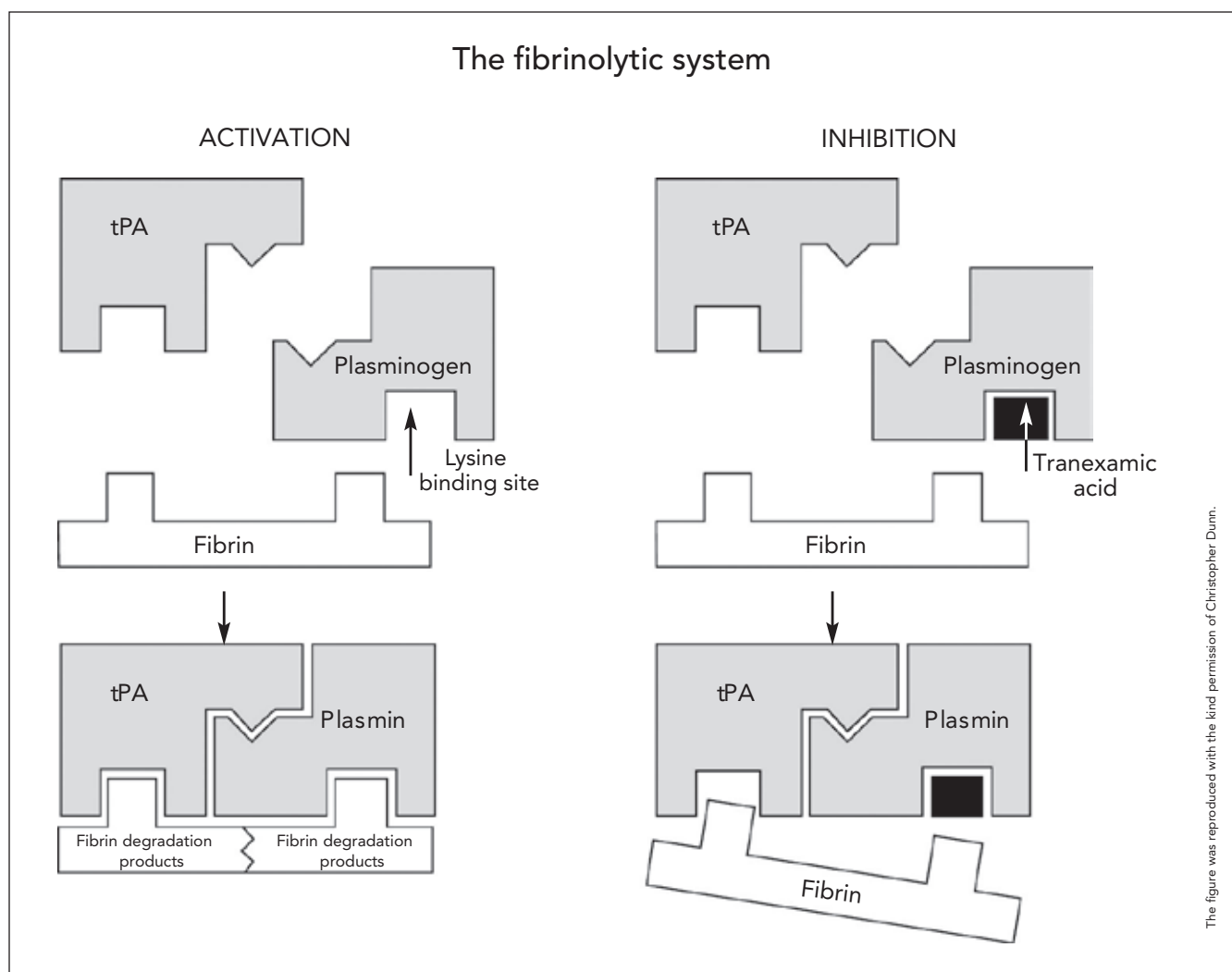


FIGURE 1. On the left, binding of plasminogen to fibrin occurs at a lysine-binding site. Plasminogen is converted to plasmin in the presence of tissue plasminogen activator. On the right, TA forms a reversible complex with plasminogen. Even though plasminogen is still converted to plasmin by tPA, the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

Pharmacological inhibitors of fibrinolysis

Mechanism of action

The lysine derivatives EACA and TA are bound to the LBS (Figure 1) in a reversible and competitive manner, thereby reducing plasminogen's affinity for binding to fibrin. This reduces the activation of plasminogen to plasmin. Thus, EACA and TA are indirect plasmin inhibitors. Aprotinin, on the other hand, derived from bovine lung tissue, is a direct inhibitor of plasmin as well as several other serine proteases, among them kallikrein. Accordingly, both aprotinin and lysine analogues reduce fibrinolysis but via different mechanisms.

With the use of fibrinolytic inhibitors the plasmin activity will be diminished, which is valuable in conditions with abnormally high fibrinolytic activity, local or systemic. Moreover, in patients with most types of bleeding disorders, the clot formation is altered with an abnormal fibrin network due to a diminished and delayed thrombin generation [6]. The crosslinking process induced by thrombin is compromised, resulting in a more soluble clot than normal, as demonstrated by Brummel et al using whole blood samples from people with hemophilia [7]. A study by Hvas et al [8] using thromboelastography showed that simultaneous treatment with TA and recombinant FVIII significantly improved clot stability in patients with severe

hemophilia A, compared to factor concentrate alone. This indicates that treatment with fibrinolytic inhibitors is efficient to improve hemostasis.

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 (TA), was found to be about 10 times more effective than EACA and has proven to be more tolerable [9].

EACA is a small 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 has a molecular weight of 157 Da. Pharmacokinetic studies in healthy individuals have shown that after intravenous administration of 10 mg per kg of body weight (BW), the highest plasma concentration was reached within one hour after injection [10,11]. After the first hour, 30% of the given dosage was excreted in the urine and after 24 hours, 90% was excreted. The elimination half-life has been reported to be 80 minutes [12]. After oral doses of 10 to 15 mg per kg BW, the maximum plasma concentration was reached within 3 hours [13]. Food has no influence on gastrointestinal absorption [14]. TA accumulates in tissues [11] and rapidly diffuses to joint fluid and synovial membrane [15]. It passes through the placenta to the fetus [16] and it is present in breast milk—but in concentrations 100 times lower than in serum [11]. No teratogenic effects were revealed in toxicological studies [9].

Administration and dosage

The following doses of EACA are recommended for adults: EACA infusion of 4–5 g in 250 ml of diluent 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 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.

TA may be administered intravenously, orally, or topically. The intravenous dosage is generally 10 mg per kg BW, 3

to 4 times daily. Orally the dosage is 15 to 20 mg per kg BW, 3 to 4 times daily. For surgery, the first intravenous dose is given immediately before starting. However, if the first dose is administered orally, it should be given two hours before the procedure. The same dose can be used for adults and children. If TA is topically administered as a mouthwash, 10 ml of a 5% aqueous solution is to be used, which is equal to 0.5 g if swallowed. TA may be used as 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.

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 better tolerated than EACA. The most commonly reported adverse events are GI effects. 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 4 times daily for four days [17]. 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, coronary graft occlusion, venous thrombosis) have been reported during treatment with TA, as have cases of acute renal failure [18]. However, it is uncertain that TA was the causative agent. No thrombogenic 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 [19]. TA is widely used in Sweden and in a review of women treated for menorrhagia containing 238,000 patient-years of treatment, there has been no reported increase in the incidence of thromboembolic events [20]. A recent Cochrane review [21] concluded that TA at the time of surgery, in addition to reducing bleedings, was safe and no serious events occurred. Ker et al [22] published a review and meta-analysis on surgical bleeding and found that the effect of TA on thromboembolic (TE) events and mortality was uncertain. In the controlled CRASH-2 trial 13,273 trauma patients were randomized to TA or placebo within 3 hours of the trauma. The total

mortality including TE was lower in the TA-treated patients than the placebo-treated [23]. A review and meta-analysis of observational and randomized studies showed that TE events were infrequent on TA or EACA after spontaneous bleedings, apart from subarachnoid hemorrhage [24].

Novel formulations of oral TA

TA has been used for decades but recently clinical studies have started to investigate the dosing, efficacy, and safety of two novel formulations of oral TA: one with modified-intermediate-release and one with delayed-release [25-27].

Contraindications

Ongoing acute venous or arterial thrombosis is a contraindication as well as macroscopic hematuria with its origin in the upper urinary tract. Subarachnoid hemorrhage is another contraindication with the exception of “ultra-early” TA-treatment prior to neurosurgical intervention of the aneurysm [28]. During treatment with estrogens caution should be taken in the presence of other thrombotic risk factors, however evidence is lacking. If prothrombin complex concentrates (PCCs) are given in high and repeated doses TA should be avoided because of the risk of thromboembolism. In the rare cases treated with Feiba™ TA/EACA is principally contraindicated.

Aprotinin

Aprotinin is a naturally occurring serine protease inhibitor extracted from bovine lung tissue. It has been widely used for decades especially in extensive cardiac surgery and liver transplantation. However, the product was taken off the market in 2008 after resolution from the Food and Drug Administration (FDA) in the U.S.A. as well as its counterpart in Europe. The reason was that severe side effects were noted with increased 30-day mortality in the BART study [29]. Therefore, aprotinin as systemic treatment will not be discussed further in this monograph. However, it should be mentioned that some human analogues to aprotinin are engineered where animal models have demonstrated a prevention of bleedings without renal toxicity [30-32].

Local hemostatics

Many types of fibrin glue or fibrin sealant contain aprotinin in a low concentration, most of which have now been withdrawn from the market. Local hemostatics containing human virus-inactivated coagulation products with or without TA are available such as Omrix™ and TachoSil™.

Clinical uses

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 [33]. In later studies, this method has been replaced by the simpler pictorial bleeding assessment chart (PBAC) [34].

The rationale for treating idiopathic menorrhagia with fibrinolytic inhibitors is that these women have higher plasminogen activator content/tPA in their endometrium on the first days of their periods than women who have normal blood loss [35,36]. Several controlled clinical trials have shown that TA taken during menstruation reduced blood loss by 34–59% compared with placebo or controls [37-42]. In 2009 a new formulation of TA sold under the brand name Lysteda™ was approved by the FDA. Lysteda™ was studied in a double-blind, placebo-controlled, randomized multicentre trial in women with heavy menstrual bleeding at a dosage of 1.3 g thrice daily for 5 days per menstrual cycle, through 6 cycles. Compared to placebo, it reduced the menstrual blood loss significantly and improved quality of life. The GI side-effects were comparable with placebo [43].

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 [44]. The reported prevalence of VWD in women with menorrhagia is currently estimated to be from 5-20% [45]. Menorrhagia is one of the most common bleeding manifestations of VWD, reported by 60-95% of women with this disorder [45]. 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 [46].

Demers et al developed a consensus document based on a Medline search on the management of inherited bleeding disorders, notably VWD, for the Society of Obstetricians and Gynecologists of Canada [47]. 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.”

A comprehensive review of the management of menorrhagia in women with bleeding disorders is presented in the WFH publication, *Reproductive health in women with bleeding disorders* [48]. Among women with abnormal menstrual bleeding, 20-30% have impaired platelet function and fibrinolysis disorders that may be an additional cause of menorrhagia, as suggested in a review by Kouides [49]. In all these cases TA seems to be an appropriate approach for reducing blood loss based on the above-mentioned findings.

For some time desmopressin has been advocated to patients with mild bleeding disorders with a positive response to the drug at examination. A randomized double-blind, cross-over study on patients with mild platelet dysfunctions by Edlund et al [50] showed that the combination of 1.5 g orally of TA (Cyklokapron™) 3 times daily and intranasal desmopressin during the 2 days with highest bleeding caused a statistically significant decrease in menstrual blood loss, while the reduction with desmopressin alone did not reach statistical significance. Kouides et al [51] presented a large study consisting of 116 patients with menorrhagia and negative gynecological examination. Seventy per cent had mild platelet dysfunctions and a few had VWD or mild coagulation factor deficiencies. The degree of menorrhagia was estimated with PBAC. The study was designed for two menstrual cycles cross-over with two cycles' washout. Intranasal desmopressin 300 microgram was administered on days 2 and 3 of menstrual bleeding. TA was administered in tablet form at a dosage of 1 g 4 times each day for the first 5 days of menstrual bleeding, according to a schedule previously published by Bonnar & Sheppard [42]. Both drugs diminished the menstrual flow compared to pretreatment but the reduction of the bleeding was significantly greater with TA than desmopressin. Quality of life was improved by both drugs.

The recommended oral dose of TA is approximately 15 mg per kg BW every 6 to 8 hours. If the effect seems to be insufficient, the intervals may be shortened since TA has a relatively short half-life. The dosage may also be increased but then there is a risk for GI disturbances. In a few patients with VWD the total daily dose of 3 or 4 g was taken as a single dose. Such a regimen has been

well tolerated, is convenient and efficient in controlling menorrhagia [52-54]. It is recommended to start with TA when the bleeding starts and to continue until it has stopped. There are no reported serious side effects of TA, only occasionally mild GI -indisposition.

Pregnancy

Congenital bleeding disorders only rarely cause bleeding problems during pregnancies. Even in women with a severe bleeding disorder such as type 3 VWD, pregnancies are generally uneventful [55]. 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 [56]. There is no evidence of teratogenicity or other side effects, either on the fetus or in the mother [19] and therefore, there is no contraindication for TA during pregnancy if bleeding occurs.

Parturition

Appropriate delivery of care to women who suffer from hemostatic disorders should take place in collaboration with hemophilia treatment centres. Treatment during vaginal or caesarean delivery should be tailored to the individual patient and include fibrinolytic inhibitors. Abnormal bleeding peri- or postpartum may be due to a variety of causes. From the hemostatic point of view several alterations have taken place during a normal pregnancy. Firstly, fibrinolysis is decreased because of placental production of the plasminogen inhibitor PAI-2. When the placenta is separated from the uterus, PAI-2 will promptly disappear and the fibrinolytic activity will increase. Moreover, the uterine tissue is extremely rich in plasminogen activators. Secondly, von Willebrand factor and coagulation factors VII and VIII gradually increase during pregnancy and will diminish within a few weeks postpartum to their basal levels. Peitsidis and Kadir [57] reviewed the available evidence regarding the efficacy and safety of TA in the management of hemorrhage during pregnancy and for prevention and treatment of postpartum hemorrhage. Thirty-four articles published between 1976 and 2010 were scrutinized. Most were observational studies or case reports that showed that TA successfully prevented and treated bleeds. Pulmonary embolism was reported in two cases; however, the possible involvement of TA could neither be confirmed nor excluded. Meta-analysis of five randomized, controlled

studies also showed that TA reduced blood loss compared to placebo. In severe bleeding disorders e.g. type 3 VWD, factor concentrate has to be administered but if TA is also given the amount and duration of concentrate can be reduced [55]. In these women, adjuvant therapy with TA may therefore be of value. Moreover, high-dose TA may be an efficient alternative as shown in a randomized, controlled study in women with postpartum hemorrhage exceeding 800 ml following vaginal delivery [58]. A loading dose of 4 g followed by infusion 1 g per hour for 6 hours was used.

The ongoing WOMAN (World Maternal Antifibrinolytic) trial should also be mentioned in this context [59]. It is estimated that each year, approximately 530,000 women worldwide die from causes related to pregnancy and childbirth. Of the deaths, 99% are in low and middle-income countries. Obstetric hemorrhage is the leading cause of maternal mortality; the number of women with primary bleeding disorders unknown. The trial is randomized, double-blind, placebo-controlled and will include 15,000 women with the clinical diagnosis of postpartum hemorrhage. The results may have a great impact, especially in countries with limited health care.

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 [60,61]. 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.

Gastrointestinal (GI) bleeding

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 [62]. A recent systematic review studied upper GI bleeding in 7 randomized trials. Mortality was reduced in the TA-treated patients but no benefit was seen regarding bleeding, surgery, or transfusion requirements [63]. No patient with a primary bleeding disorder seems to have been included.

Angiodysplasia in the gut can be another source of bleeding. Up to 6% of patients with VWD are reported to have this disorder [64,65], which may indicate that

VWD unmasks the vessel abnormality. In treatment of these conditions—with or without VWD—TA may be a supportive agent.

Bleedings in the nose and mouth

The cause of nosebleeds is most often multifactorial. The fibrinolytic activity was extensively studied by Petruson in patients with recurrent long-standing epistaxis, as well as in controls [66]. 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 3 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.

Nosebleeding is 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 [67]. Studies suggest that 5 to 10% of children with recurrent nosebleeds may have mild, previously undiagnosed VWD [68,69]. There are two studies on antifibrinolytic agents applied topically for nosebleeds: one on EACA [65] and one on TA [66]. TA appeared to have no better effect than placebo. However, the trials seem to be too small for drawing any firm conclusions.

A simple way of treating a non-severe nosebleed is to take a big piece of cotton wool, dip the tip in oil or Vaseline and a crushed tablet of TA, blow the nose, and put the tip in the nostril.

Oral or topical TA is recommended in patients with VWD, either alone or together with desmopressin 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 [72]. TA is also indicated in patients with other bleeding disorders. Bleedings 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 desmopressin or VWF concentrate for patients with VWD undergoing otolaryngologic surgery [73].

Dental surgery

As early as the 1960s, Björlin started studying fibrinolysis in the oral cavity [74]. 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 desmopressin [75-80]. In some of the trials, a limited number of patients were randomized. Forbes et al showed that in patients with hemophilia, treatment for 5 days with 1 g of TA 3 times daily starting 2 hours before surgery was associated with significantly less post-operative bleeding than in a placebo group [81]. 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 [82].

The beneficial effect of local application of EACA as mouthwash was first demonstrated by Berry et al [83]. 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 [84]. 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 2 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 1% who received TA systemically and locally (10 ml of 5% solution for 2 minutes 4 times daily) at dental surgery developed no bleeding complications, even though they did not receive replacement therapy [85].

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 [86]. In their retrospective analysis of 63 patients with VWD who had dental extraction or periodontal surgery, Federici et al reported that TA, administered systemically and combined with mouthwash, irrigation at surgery, and fibrin glue in more extensive surgeries, could considerably reduce the need for VWF concentrate. [78]. Based on their positive experiences with patients with hemophilia, Zanon et al proposed a protocol for dental extraction with 20 mg of TA per kg of 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 [87]. Twenty milligrams of TA per kg BW was administered orally 8 and 16 hours later, then 3 times daily for the next 7 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 (Figure 2), 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 administered systemically (20 mg per kg BW orally every 8 hours for 10 days) and locally as mouth rinse. The local hemostatic measures consisted of collagen fleece in the dental sockets, suturing, and fibrin glue [88].

FIGURE 2. Flowchart for choice of treatment in dental extractions [88].

Severe bleeding disorder	Non-severe bleeding disorder	
General or local anesthesia*	General anesthesia or nerve trunk infiltration	Local anesthesia
Replacement therapy <ul style="list-style-type: none"> • Severe or moderate hemophilia A • Severe or moderate hemophilia B • Type 3 VWD 	Replacement therapy <ul style="list-style-type: none"> • Mild hemophilia B • Non-responders hemophilia A and type 1 VWD 	No treatment <ul style="list-style-type: none"> • Mild hemophilia B
Desmopressin or replacement therapy <ul style="list-style-type: none"> • Type 2 VWD 	Desmopressin or replacement therapy <ul style="list-style-type: none"> • Mild hemophilia A • Type 1 VWD • Platelet disorders 	No treatment or desmopressin <ul style="list-style-type: none"> • Mild hemophilia A • Type 1 VWD • Platelet disorders

* including nerve trunk infiltration

Thus, a variety of regimens are reported in patients with hemophilia and VWD undergoing dental surgery and tooth extractions but it is clear that TA is always strongly indicated [89]. Traditionally, international guidelines have advocated the use of clotting factor replacement for all surgical procedures and inferior alveolar nerve block [72,90]. However, in areas where factor products are unavailable or unaffordable, patients with inherited bleeding disorders may be prevented from receiving oral health care. Therefore, other treatment models have been used. Rakocz et al found that fibrin glue plus “swish and swallow” rinses of TA without preventive replacement therapy was safe and cost-effective in dental extractions in patients with bleeding disorders [91]. Their fibrin glue contained aprotinin, but on the market nowadays such products containing TA as well as virus-inactivated human coagulation components are available, thereby avoiding the possibility of adverse reactions.

An approach based on guidelines for patients on oral anticoagulants within the therapeutic prothrombin time range has been suggested by Hewson et al [92]. The authors describe a protocol where, by employing rigorous local measures, minimal factor replacement is required to obtain hemostasis. The extractions should be performed by an experienced oral surgeon in as non-traumatic a manner as possible with slow and careful removal. The sockets were carefully filled with 5% TA, collagen hemostatic fleece like Surgicel™ and finally the sockets were tightly closed with absorbable sutures. If inferior alveolar nerve anesthesia was required, a 27-gauge needle and auto-aspiration syringe were used. Postoperatively gentle mouthwash was prescribed with 5% TA 3 times a day for 7 days or patients were instructed to use gauze to apply pressure to the socket in the case of moderate bleeding. This protocol was applied in 50 consecutive patients with varying severity of hemophilia and VWD for a total of 113 tooth extractions. No replacement therapy was given pre-, peri- or post-operatively. Patients who were on regular prophylactic factor cover continued with the same cover, though the timing of self-administration before the procedure was not constant. Three of the 9 patients with severe hemophilia A were on a regular prophylaxis dose of 13-19 IU per kg of BW 3 times a week. Four of the 50 patients, 2 with severe hemophilia A, 1 with moderate A (3%) and one moderate B (2%), developed severe bleeds on days 1-5 and were treated with factor concentrate, and in one case a redressing of the socket

was also necessary. Altogether they spent eight days in the hospital for their bleeds. On day 8, 41 patients had no bleeds, 6 had mild bleeds (some blood in the saliva), 3 had moderate bleeds (pressure to the socket was efficient), and none had severe bleeds. After this study their previous protocol including preoperative replacement therapy was shifted at the authors' hospital, resulting in a significant reduction in the amount of factor concentrate used in oral surgery.

As pointed out by Schulman, it is not known what minimum factor level provides sufficient hemostatic effect in various types of interventions [93]. With its standardized procedures, oral surgery is a field where prospective studies are warranted.

It should be added that 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 [94].

Minor surgery

An example of minor surgery where TA is useful is circumcision. This is one of the oldest and most commonly performed operations in the world [95]. Circumcision is a very important procedure in order to become a member of society and it is a social obligation for Muslim and Jewish men. In hemophilia patients this minor surgery is life-threatening but can be carried out successfully even in severe hemophilia under the cover of clotting factor concentrates. The Izmir protocol, which includes five doses of factor concentrate for 48 hours, fibrin glue, and TA for 7 days, proved to be a safe and cheap option [95]. The use of a “diathermic knife” may be an option to reduce the risk of bleeding complications [96]. For more information on this procedure, see the WFH monograph *Circumcision in Hemophilia: An Overview*.

Major surgery

Orthopedic surgery

Pharmacokinetic studies in patients undergoing total hip replacement (THR) showed that a dose of TA (10 mg per kg BW) prior to surgery, and a similar dose 3 hours later kept the plasma concentration of TA at therapeutic levels for approximately 8 hours [97]. Prospective randomized controlled studies in THR showed the total blood loss was reduced by about 25% in the TA groups who

received this regimen compared to the placebo groups, without increased risk of thromboembolism [98,99]. A meta-analysis of total knee arthroplasty showed that a dose of TA (10-15 mg per kg BW) prior to tourniquet deflation with or without an additional dose on the day of surgery reduced the total blood loss by approximately 50% and significantly reduced the need for blood transfusions [100].

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 study of 11 patients with hemophilia (8 severe, 1 moderate, 2 mild) undergoing hip replacement [101] (one patient was excluded because he had bilateral arthroplasty in the same operation). In addition to factor replacement, the patients were also given TA orally (15-20 mg per kg BW) at 6- to 8-hour intervals for 7 days with the first dose of 10 mg per kg BW administered intravenously before surgery. The total bleeding was calculated to be 740 ± 400 ml, which is almost exactly the same as in 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 [98].

Continuous infusion of factor concentrates is often given to patients with bleeding disorders during major surgery. There is evidence, albeit scientifically weak, that with continuous infusion less factor concentrate is required compared with intermittent bolus injections [93]. 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 [93,102]. In a study of 27 patients undergoing total knee replacement and/or total hip replacement, Schulman et al [103] stressed the possibility of reducing the amount of factor concentrate if continuous infusions were used in combination with local hemostatic and antifibrinolytic agents, which could be done without any serious bleeding complications.

Surgery in the urinary tract

Since urine contains the fibrinolysis activator uPA, the prostatic gland contains high fibrinolytic activity [104],

and the prostate has a rich blood supply, prostatectomy is associated with a risk of significant blood loss even in patients with normal hemostasis. There are only few randomized controlled studies on TA and prostatectomy, one of them by Rannikko et al [105]. Oral TA 2 g thrice daily on the day of the operation and first postoperative day was used in the treatment group in patients undergoing endoscopic prostate surgery for benign disease. TA significantly reduced the intraoperative bleeding but did not reduce postoperative rates of blood transfusions compared to the placebo group. In a double blind, placebo-controlled trial, two hundred patients undergoing radical retropubic prostatectomy were randomized to low-dose TA, 0.5 g preoperatively followed by 0.25 g per hour in continuous infusion during surgery. The intraoperative blood loss and the transfusion rate were significantly lower in the TA group compared to the placebo group. At six months follow-up, five thromboembolic events had occurred in the control group and two in the TA group [106].

Urological surgery such as prostatectomy is becoming increasingly necessary with the advancing age of patients with bleeding disorders. There are only few publications in this subject [107-109], but the above-mentioned studies in patients with normal hemostasis suggest that TA is a valuable concomitant medication in the management of surgery in the lower urinary tract in patients with various bleeding disorders.

Patients with inhibitors

Surgery and bleeds in patients with bleeding disorders complicated by inhibitors against a coagulation factor constitute a challenge for treatment. The bypassing agents activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa (rFVIIa) may be associated with thromboembolic events, although rarely—especially when administered for the approved indications, which include congenital hemophilia with inhibitors and acquired hemophilia [110]. Concomitant treatment with TA/EACA and Feiba™ is generally contraindicated but may be used in very special conditions [111]. In contrast, TA is often used as an adjuvant to rFVIIa. However, cerebrovascular thrombosis and myocardial infarction are reported mostly in patients with acquired hemophilia [110,112]. Therefore, caution should be entertained regarding supplementation of TA to rFVIIa in elderly patients with cardiovascular disease.

Conclusion

Treatment with synthetic fibrinolytic inhibitors such as TA is effective and safe as demonstrated in a large number of controlled clinical trials in patients without primary bleeding disorders. Controlled studies with TA in patients with primary bleeding disorders are few because of the rarity and heterogeneity of such diseases, but there is firm evidence that the easily dissolved porous clots seen in these patients are significantly stabilized by TA. Therefore, there is evidence that the administration of TA will reduce bleeding, improve hemostasis, and diminish the requirement of blood transfusion and plasma-derived factor concentrates. TA may be used as an adjuvant to other

hemostatic therapy or alone, systemically or topically, in mild bleeding disorders for minor bleedings, trauma, or surgery. TA and EACA may be used in any type of bleeds, some examples of which are given in this monograph. Note fibrinolytic inhibitors are contraindicated in connection with ongoing thrombosis. Moreover, they should not be used in bleedings with origin in the upper urinary tract because of the risk of clot formation and ureter obstruction. In renal insufficiency the dose has to be reduced. The half-life of TA is short but slow-release formulations are on the way. 🌐

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