

Anti-fibrinolytic therapy: A forgotten option for minimising blood loss and transfusion requirements?

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ABSTRACT

Donor blood transfusion was once considered a cheap, effective and safe treatment for haemodynamically compromised patients. In the last decade, the rising incidence of AIDS, hepatitis and Creutzfeldt-Jakob disease has led to a change of attitude. Research has focused on finding ways to reduce blood loss and high transfusion requirements in specialties where both are common. While techniques such as preoperative autologous transfusion and intraoperative cell salvage help to reduce transfusion requirements, they do not address the primary cause of blood loss which is, in some cases, excessive fibrinolysis. The advent of anti-fibrinolytic drugs has enabled physicians and surgeons to address this problem at source. Aprotinin is a serine protease inhibitor that is effective at reducing both blood loss and transfusion requirements in many different clinical situations although it is underused due to the perceived risk of anaphylactic and thrombotic complications. The lysine analogues (tranexamic acid and epsilon aminocaproic acid) are cheaper and do not carry the same risks. There is a great deal of supportive clinical evidence now available for all of the anti-fibrinolytics, however take up has been surprisingly slow worldwide. This article reviews the evidence for their effectiveness and discusses the various risks and their importance.

Introduction

Allogenic blood transfusion was once considered a safe, simple and potentially life-saving procedure but the AIDS pandemic of the 1980s and more recent concerns about Creutzfeldt-Jakob disease have led to a change of attitude in the medical profession. In the last decade, where allogenic blood transfusion was once considered a low-risk routine treatment, it is now more often viewed as a procedure to be avoided. With this change in attitude, many methods have been developed to reduce both the need for allogenic blood transfusion and the risk that it entails. In addition, haemoglobin (Hb) and haematocrit blood transfusion thresholds of 100 g·l⁻¹ and 30% respectively, which were common in the 1970s and 80s, are now considered unnecessarily high. In fact, provided intravascular volume is maintained, patients can survive with much lower levels. Today, transfusion thresholds of less than 80 g·l⁻¹ Hb or a haematocrit of 24% are used routinely (1, 2).

Autologous transfusion virtually eliminates the risk of viral transmission and allergic reaction when compared with allogenic blood transfusion and there are several ways of utilising this technique. In preoperative autologous donation, the patient can donate blood several weeks in advance of their procedure which is then stored and given back to the patient postoperatively if required. Acute normovolaemic haemodilution is a method used immediately pre-procedure where blood is collected and the haemoglobin concentration is reduced, while tissue oxygen saturation is monitored and intravascular volume maintained. As soon as surgical bleeding

has been stopped, this blood is reinfused, thus raising the haemoglobin concentration. A third method, intraoperative cell salvage, is used particularly in procedures where high blood loss is predicted (e.g. cardiac, liver and orthopaedic surgery). Lost blood is removed from the site of the wound by suction, filtered and washed in saline solution and then returned to the patient intravenously. This method allows large volumes of blood to be salvaged and reinfused without the need for allogenic blood transfusion. Autologous blood transfusion is used routinely in over 80% of hospitals in the USA (1-4).

While these approaches undoubtedly dramatically reduce the risk of infection from blood transfusion, they may not address the fundamental cause of the blood loss, which is often a defect in haemostasis. Specifically, surgical trauma, the use of tourniquets and cardiopulmonary bypass have all been implicated as causes of hyperfibrinolysis, a pathological hyperactivity of the fibrinolytic enzymes, resulting in reduced clotting and increased bleeding. The development of pharmacological agents to manipulate fibrinolysis has enabled clinicians to address this problem at the source thereby reducing bleeding by limiting the hyperfibrinolysis that caused it. These agents and their use will be outlined in this review.

Method

A literature search of MEDLINE was carried out for the period 1996 to April 2003. MESH headings were used as search terms as well as relevant keywords. The bibliographies of retrieved publications were reviewed for additional references.

Background

Coagulation and fibrinolysis (5-11)

The coagulation cascade is a series of enzyme-catalysed reactions that ultimately convert soluble fibrinogen to produce an insoluble fibrin clot. It is initiated *in vivo* by the binding of factor VII, which is present in the plasma, to tissue factor, which is released from endothelial cells in response to injury. This complex catalyses the activation of factor IX which, in conjunction with factor VIII, catalyses the activation of factor X. Kallikrein amplifies the rate of activation of factor XII, which activates XI and then also activates factor IX. Factor X catalyses the activation of prothrombin (factor II) to thrombin. Thrombin has two roles: it breaks the arginine-glycine bonds in fibrinogen (factor I) making fragments that polymerise to form fibrin, and it activates factor XIII which strengthens the fibrin to form stabilised fibrin; it is this that forms the rigid structure of the clot (Figure 1).

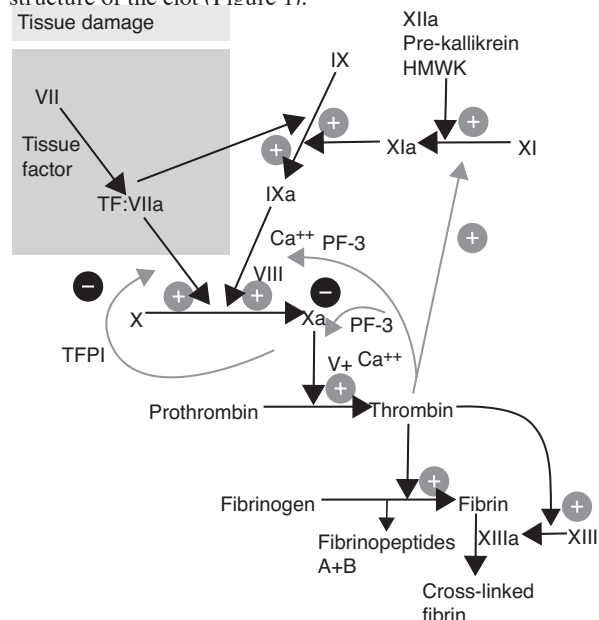


Fig. 1. The coagulation cascade (HMWK, high molecular weight kininogen; TFPI, tissue factor pathway inhibitor) (85).

Fibrinolysis is the process for breakdown of a fibrin clot and is catalysed by the serine protease plasmin, which is found in the blood as the inactive proenzyme plasminogen. Plasminogen is activated by the presence of a plasminogen activator. As the plasminogen activator also has a fibrin binding site, it will only activate plasminogen in the presence of fibrin. The major plasminogen activator *in vivo* is tissue plasminogen activator (tPA), which is released from vascular endothelial cells in response to various stimuli, in particular thrombin and urokinase. The plasmin-activator complex binds to plasmin via lysine binding sites and proteolytically breaks down fibrin to fibrin degradation products (FDPs) (Figure 2).

The thrombelastograph

Although the thrombelastograph (TEG) was developed during the Second World War, the technology was not exploited clinically until 1985 when Kang et al. used it for patients

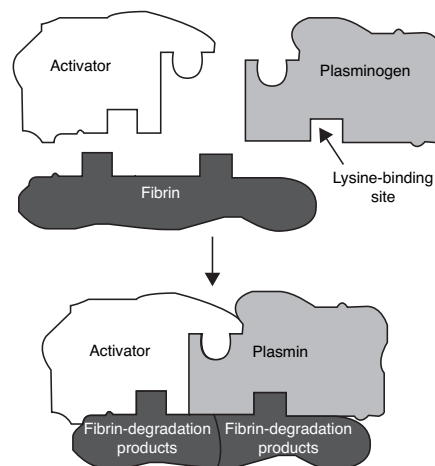


Fig. 2. The activation of fibrinolysis (6).

undergoing liver transplantation and it was found to be a reliable and rapid way of monitoring haemostasis (12, 13).

The TEG is a measure of elasticity during clot formation and the results are depicted as an easily interpretable graph illustrating the efficiency of coagulation and fibrinolysis. Initial results are available in less than 30 minutes and the test is usually completed within an hour, providing results more quickly than almost any other laboratory investigation. TEG has been used to direct blood product administration in orthotopic liver transplantation, cardiac surgery and orthopaedic surgery, all of which carry a high risk of bleeding that is due in part to disorders of fibrinolysis and coagulation (14).

The test itself is carried out by taking a small sample of whole blood and placing it in a heated cup. A pin is suspended in this cup and is connected to a transducer that graphically records movement. When the test is started, the cup oscillates from side to side, and as there is no clot initially the pin remains stable, thus recording a straight line trace. As the clot forms, the pin moves with the clot, recording a slope on the graph (Figure 3) (14). TEG equipment is now available that is easy to operate, requires very little specialist knowledge and can be used with any modern computer for analysis of results (Figure 4).

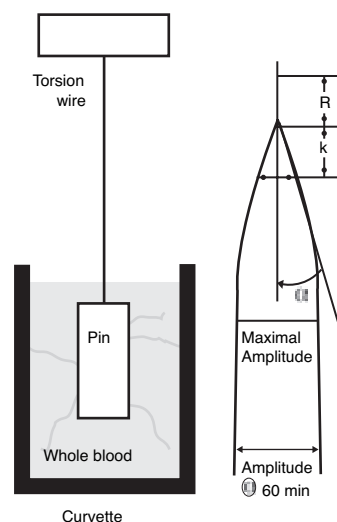


Fig. 3. Thrombelastograph equipment (86)



Fig. 4. Thrombelastograph® 5000 coagulation analyser (Medicell Ltd) (14)

Several parameters are usually recorded: the reaction time (r time), which is the time between placing the blood in the cup and the initiation of clot formation; the K time is the time it takes for the clot trace to reach 20 mm (an arbitrary point), and the angle is the slope recorded between the end of the r time and end of the K time, signifying the rate of clot formation. MA is the maximum amplitude recorded and indicates the strength of the clot. LY30 is taken 30 minutes after the MA is reached and A60 after 60 minutes. These record the amplitude of the trace as a percentage of the MA and indicate the rate of reduction of clot strength, therefore showing the rate of fibrinolysis (Figure 5). The simple, graphical nature of the TEG enables rapid and accurate analysis with minimal training (Figure 6).

For patients undergoing cardiac surgery, the TEG can be used to ascertain whether any excessive bleeding is due to heparinisation rather than a coagulopathy. A modified version of the blood specimen cup has been developed which contains heparinase and if there is a significant difference between normal and heparinase results, protamine administration would be indicated (8). Figure 7 shows a TEG taken from a heparinised patient which illustrates the difference between the standard and heparinase recordings. Figure 8 and Figure 9 show that the TEG is useful not only for diagnosis but also for assessing the effectiveness of treatment.

Orthotopic liver transplantation is a procedure with a major risk of bleeding, not only for surgical reasons, but also because the liver is the major site of production of the coagulation factors and therefore disruption of haemostasis and excessive fibrinolysis are common. Hyper-fibrinolysis is especially common during the anhepatic phase of the procedure, and can lead to sudden and massive blood loss. The TEG enables the medical team to monitor the haemodynamic status of the patient and administer anti-fibrinolytics or blood products as required (Figure 10).

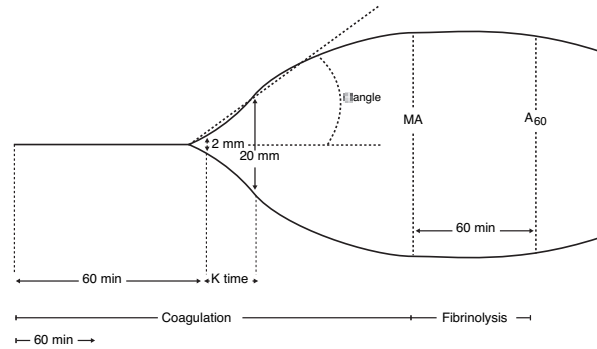


Fig. 5. Commonly measured TEG parameters (14).

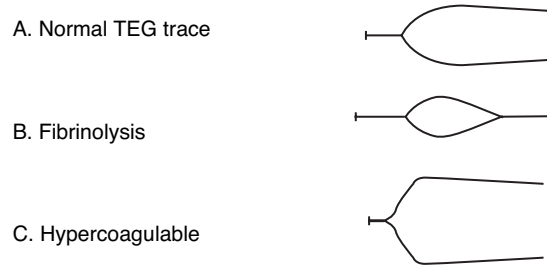


Fig. 6. Different haemostatic disorders simply illustrated by TEG recording (14)

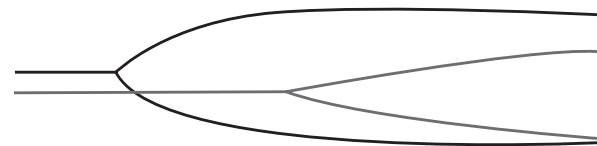
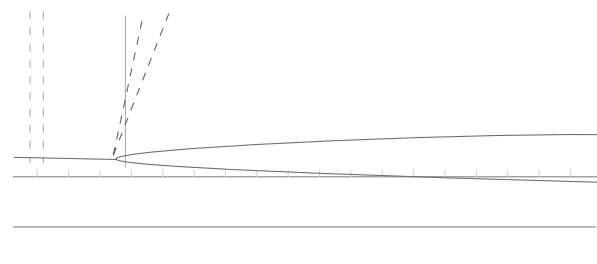
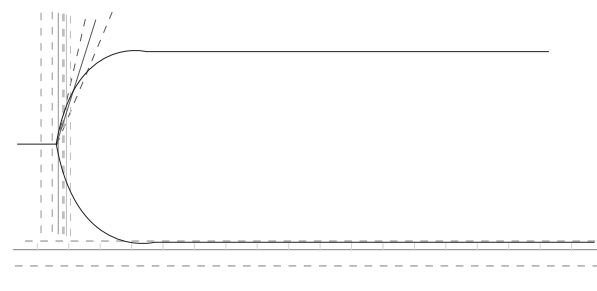


Fig. 7. Simultaneous TEG recording of a standard cup (grey) and a heparinase cup (black). (14)



R	K	Ang	MA
20.9 (4-6)	29.1 (1-2)	7.5 (66-77)	4.5 (60-75)

Fig. 8. TEG recording from a patient immediately following cardiac surgery showing increased R and K times, decreased angle and decreased maximum amplitude. (numbers in parentheses are normal values)



R	K	Ang	MA
5.8 (4-6)	1.3 (1-2)	73.5 (66-77)	70.5 (60-75)

Fig. 9. TEG recording taken from the same patient four hours later after administration of 2 units of platelets and 2 units of FFP.

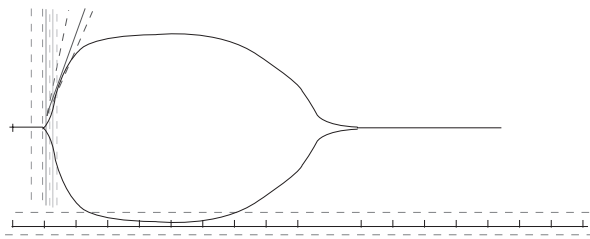


Fig. 10. TEG trace indicating hyper-fibrinolysis during the anhepatic phase of liver transplantation surgery.

The quantitative nature of the TEG enables institutions to devise evidence-based algorithms for the treatment of particular groups of patients, thus minimising operator error. Centres that have already done this have seen significant decreases in allogenic blood use (15). Tab. 1 shows the guidelines used for post-operative cardiac surgery patients at Southampton University Hospital, UK.

Aprotinin

Aprotinin is a naturally occurring serine protease inhibitor that is extracted from bovine lung tissue. It forms a reversible enzyme inhibitor complex with several serine proteases, namely trypsin, chymotrypsin, plasmin and kallikrein. The inhibition of plasmin prevents the breakdown of fibrin into FDPs and the inhibition of kallikrein prevents the activation of factor XII in the coagulation cascade; thus, both coagulation and fibrinolysis are inhibited (Figure 11) (6, 16, 17). Aprotinin prolongs TEG r time, confirming its mild anticoagulant effect (18). Aprotinin has an inhibitory effect on inflammation by reducing cytokine and leukotriene release as this process is mediated in part by serine proteases (17, 19). The drug may also have a role in preserving platelet function (17).

Tab. 1. TEG results and possible causes (87)

TEG Result	Indicates	Action
Normal	No coagulopathy or hyper fibrinolysis	Investigate surgical cause of bleeding
Low MA	Weak clot formation	Administer platelets
LY30 > 7.5% or A60 > 15 %	Hyperfibrinolysis	Consider anti-fibrinolytic therapy
Increased r time, increased K time or decreased α angle	Clotting factor deficiency or heparin effect (compare with heparinase TEG)	Administer FFP (if heparin effect, administer protamine)

Aprotinin is orally inactive and has a half-life of approximately 1 hour. The drug is usually administered as an initial loading dose along with a continuous infusion in order to maintain a stable plasma concentration. In some situations, such as in tissue adhesives, it is administered locally (20). The concentration and activity of aprotinin is usually measured in kallikrein inactivation units (KIU). For adequate plasmin inhibition, a plasma aprotinin concentration of 50-125 x 103 KIU·l⁻¹ is

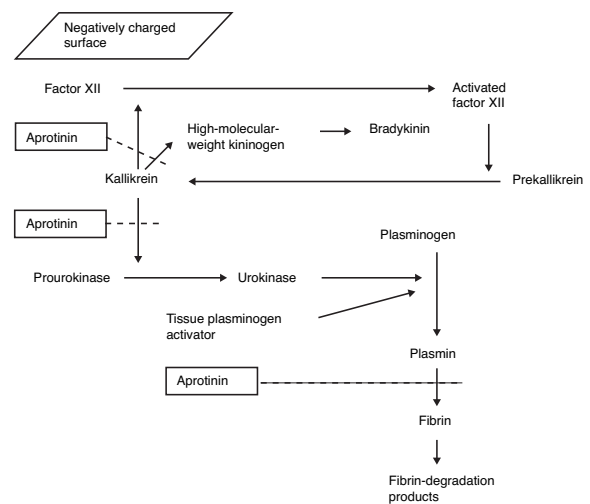


Fig. 11. Sites of action of aprotinin (6).

necessary, and for kallikrein inhibition, a concentration of 200-250 x 103 KIU·l⁻¹ (17). Aprotinin has a high affinity for renal tissue, in particular the proximal convoluted tubule, and there has been some concern about the effect of aprotinin on renal function (16). Several studies have found that aprotinin has no deleterious effect on renal tissue function in the majority of patients and that, if it does occur, it is usually mild and transient (16, 21, 22).

As aprotinin is derived from animal lung, it has antigenic properties and anaphylactic reactions have been described in patients receiving the drug both intravenously and locally (20, 23). An anaphylactic response is reported to occur in between 2.5% and 2.8% of patients that are re-exposed to aprotinin and as such it would be desirable to try to identify predictors for adverse reactions so that 'at-risk' patients could be offered alternative treatments (24, 25). A recent study found that having detectable IgG or IgE anti-aprotinin antibodies was not clinically relevant, but that the expression of high concentrations of IgE anti-aprotinin antibodies may identify patients at risk of an anaphylactic response. The authors of this study concluded that aprotinin should be used with caution where the second exposure was within six months of the first (24). There is clearly a compromise to be made between allergic risk and potential benefit, and for patients who are not expected to bleed excessively, this risk may not be justified (26).

Another obvious concern about the use of aprotinin would be that it may have prothrombotic properties. There have been several case reports of patients undergoing liver transplantation who have had thrombotic complications following aprotinin administration, but as this procedure could be viewed as having a high thrombotic risk anyway, it has been difficult to establish a causal relationship (27-29). Most studies using aprotinin use thrombotic complications as end-points; there is a growing body of evidence that aprotinin does not have a prothrombotic effect and may even have an anti-thrombotic effect (18).

Recent publicity about transmission of Bovine Spongiform Encephalopathy (BSE) to humans as variant Creutzfeldt-Jakob

disease (vCJD) has resulted in investigation into the potential for aprotinin, given its bovine derivation, to be a possible vector for transmission. The manufacturing process has been designed to minimise this risk as far as possible. Animals are selected from countries where no cases of BSE have ever been recorded and if a single case is reported, the use of source animals from the country is permanently stopped. The drug cannot therefore be produced using animals from the United Kingdom and many other European countries. Aprotinin is currently manufactured from Argentinean herds that have been certified BSE free. Additionally, various techniques are used to ensure that the infective BSE agent is inactivated or removed during the purification process, in the unlikely event that it is present. Two studies have been carried out by the manufacturer (Bayer), both concluding that aprotinin ‘... is safe with regard to BSE and viruses’ (30, 31).

The lysine analogues

Plasminogen, the proenzyme precursor to plasmin, which breaks down fibrin during the process of fibrinolysis, contains structures called lysine binding sites, and these bind to the lysine residues that are found in stabilised fibrin. Tranexamic acid (4 aminomethyl cyclohexanecarboxylic acid) and epsilon-aminocaproic acid (6-aminohexanoic acid) are two synthetic lysine derivatives that have anti-fibrinolytic activity in humans (6, 16). They act by saturating the lysine binding sites and preventing the binding of plasminogen to fibrin, thus retarding fibrinolysis (Figure 12). They are particularly effective at reducing excessive bleeding from mucosal sites such as the GI tract and urethra.

Epsilon aminocaproic acid (EACA) was the first lysine analogue to be synthesised. It is active both orally and intravenously, has a short half-life of between one and two hours and is rapidly excreted in urine, with 80% being excreted within 12 hours. This rapid excretion in conjunction with a relatively short half-life means that relatively large doses are required to provide clinically effective plasma concentrations, and a continuous infusion is required to maintain these levels. EACA has been used prophylactically for prevention of blood loss in patients undergoing dental, cardiac, orthopaedic, prostate and liver surgery, although evidence for its efficacy is limited.

Tranexamic acid (TXA) is ten times more potent than EACA, with a similar toxicity and side effect profile (16). Like EACA, the drug has a short half-life and is excreted rapidly and is therefore usually administered as an initial bolus followed by a continuous infusion for as long as anti-fibrinolytic activity is required. TXA was originally licensed for the prophylactic treatment of haemophiliacs undergoing dental surgery. Since then, it has been used to reduce blood loss and transfusion requirement in patients undergoing a number of different types of surgery and has also been used to reduce menstrual blood loss and bleeding in pregnancy. The most commonly reported side effects are nausea and diarrhoea.

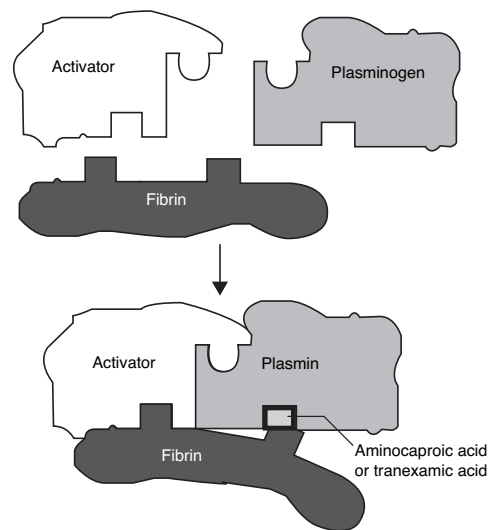


Fig. 12. Site of action of the lysine analogues (6).

Therapeutic uses

Cardiac surgery

The use of cardiopulmonary bypass, hypothermic circulatory arrest, heparin and a large surgical wound all predispose patients undergoing cardiac surgery to a high risk of serious blood loss: some of this can be attributed to hyper-fibrinolysis. In 1987, this risk prompted Royston et al. to examine the effectiveness of aprotinin at reducing blood loss in a cohort of patients undergoing repeat cardiac surgery. Their results were encouraging: aprotinin use reduced mean blood loss by 80% and transfusion requirement by 60% ($p < 0.001$) (32). Since then, a number of studies have been carried out to determine the optimum aprotinin dosage regimen. Initially, most studies administered a high-dose aprotinin regimen: 2 x 106 KIU (280 mg) intravenously post induction of anaesthesia, 0.5 x 106 KIU·h⁻¹ (70 mg·h⁻¹) during surgery and 2 x 106 KIU (280 mg) added to the pump. More recently, investigators have used a low-dose aprotinin regimen which was half the high-dose aprotinin regimen (17). More sophisticated dosing schedules have also been devised, including adjusting aprotinin dosage to weight. This method does appear to produce more stable plasma aprotinin concentrations but, so far, there are no data available as to whether this is more effective. It is not known whether there is any correlation between plasma aprotinin concentration, safety and efficacy (33).

Meta-analysis of 4937 patients undergoing routine cardiac surgery found that use of aprotinin (both low-dose and high-dose) reduced mean blood loss by 446.5 ml and transfusion requirement by almost one unit. High-dose aprotinin was more effective at reducing blood loss and transfusion requirement when compared with lower doses.

Aprotinin was found to reduce mortality by almost half (analysis of 3212 patients) and decrease the rethoracotomy rate from 5% to 1.8% (3644 patients), although the incidence of perioperative myocardial infarction was unchanged (1995 patients) (34). Two further studies showed a reduction in the incidence of thromboembolic neurological complications in

aprotinin treated patients (35, 36). Aprotinin is also effective at treating high risk patients such as those undergoing heart transplantation and concurrent aspirin administration does not diminish its effectiveness (2, 37).

The anti-inflammatory mechanism of aprotinin is especially useful for patients undergoing cardiac surgery because cardiopulmonary bypass is known to cause a systemic inflammatory response (38). In particular, aprotinin has been shown to significantly reduce neutrophil activation, which is thought to be the main mechanism for this enhanced inflammatory response (39).

Concerns have been raised about the effect of aprotinin on graft patency for patients undergoing coronary artery bypass grafting which have been exacerbated by conflicting data. Four trials measuring graft patency angiographically in the month following surgery found that aprotinin had no effect (40-43), but a further trial which studied patients one year postoperatively found that 44.1% of patients in the aprotinin group had occluded grafts versus 26.3% in the placebo group (p 0.029) (44). The wide variability of results prompted the manufacturer to commission a multi-centre randomised controlled trial (796 patients randomised), concluding that the probability of graft occlusion was slightly increased by aprotinin (15.4% vs. 10.9%, p 0.03), but this risk was multiplied by various risk factors such as female gender, lack of prior aspirin therapy and poor distal vessels (45). For patients with none of these risk factors, aprotinin caused no significant increase in risk of occlusion.

The lysine analogues could potentially be a better therapeutic option than aprotinin for cardiac surgery because they are cheaper, they do not appear to induce anaphylaxis and do not have an association with graft occlusion. Various doses of TXA have been evaluated, but the most effective is 10 mg·kg⁻¹ pre-operatively and a 1 mg·kg⁻¹·h⁻¹ infusion during the procedure (46). Administering TXA post-operatively is not beneficial and should be limited to patients with excessive bleeding specifically caused by fibrinolysis (47). A meta-analysis shows that TXA significantly decreases both blood loss and transfusion requirement in patients undergoing cardiac surgery (2). The optimum dose of EACA is 150 mg·kg⁻¹ preoperatively and 15 mg·kg⁻¹·h⁻¹ during the procedure. This reduces blood loss by 35% and transfusion requirement by 61% when compared with placebo (48, 49). The lysine analogues do not reduce the need for rethoracotomy or significantly alter the frequency of myocardial infarction (34, 49).

All of the anti-fibrinolytics discussed in this review reduce both postoperative bleeding and blood transfusion requirement, so the next step is to evaluate the suitability of each drug. Aprotinin is by far the most expensive drug, with TXA substantially cheaper and aminocaproic acid cheaper still (Tab. 2). High-dose aprotinin is the most effective at reducing blood loss; low-dose aprotinin and aminocaproic acid are equally

efficacious (49). There does not seem to be a difference in efficacy between aprotinin and TXA, although the trend is towards aprotinin being more effective (2). This information seems to indicate that aprotinin would be the preferred option, but given the re-exposure risk, along with the expense, perhaps aprotinin should be reserved for patients with a high risk of bleeding and one of the lysine analogues would be more suitable for routine cases. Additionally, patients undergoing CABG with risk factors such as female gender, lack of prior aspirin therapy and poor distal vessels probably should not be treated with aprotinin due to increased risk of graft occlusion. Unfortunately, data that compares the clinical effectiveness of TXA with aminocaproic acid is limited.

Orthopaedic surgery

In contrast with cardiac surgery, the routine use of anti-fibrinolytics for orthopaedic procedures is much less well established. Early trials with high-dose aprotinin produced favourable results, although uncertainty about the thrombogenic nature of the drug caused one study to be halted (21, 50). Since then, most trials have used deep vein thrombosis (DVT) as one of the endpoints to ascertain the safety of antifibrinolytic drugs in this type of surgery. It appears that these early worries were unfounded as recent trials have reported no increased incidence of thrombotic events in patients treated with anti-fibrinolytic drugs (26, 51-56).

Tab. 2. Cost comparison of anti-fibrinolytic drugs (average wholesale prices from 2000 Drug Topics Red Book) (88).

Medication	Dosage form	Cost (US\$)	Cost based on dosing regimen (US\$)
Aminocaproic acid	250 mg·ml ⁻¹ (20 ml)	2.69	4.30 (8 g)
Aprotinin (100 ml)	10,000 units·ml ⁻¹	206.68	Low-dose (3 million KIU): 620.04 High-dose (6 million KIU): 1240.08
TXA	100 mg·ml ⁻¹ 10 ml	27.90	29.30 (15 mg·kg based on 70 kg weight)

The difficulties associated with re-exposure to aprotinin and anaphylaxis are well documented, and for this reason it has been suggested that anti-fibrinolytics should not be used for orthopaedic procedures carrying a low bleeding risk because the 2-3 units usually required can easily be supplied by autologous blood transfusion programmes (6, 57). Despite this, aprotinin does seem to reduce blood loss in routine surgery. In one study, for patients undergoing total hip replacement surgery, high-dose aprotinin reduced total blood loss from 1,943 (± 700 ml) to 1,446 (± 514 ml p < 0.05), and the amount of blood transfused from 3.4 (± 1.3) units to 1.8 (± 1.2) units (21). Similar results have been reported elsewhere (58). However, a retrospective study (372 patients) found that low-dose aprotinin was not effective at reducing either blood loss or transfusion requirement (59).

For major orthopaedic surgery, there is a growing body of evidence that aprotinin can dramatically decrease both blood loss and transfusion requirement. This is particularly relevant as it is not unknown for perioperative bleeding to exceed the patient's own blood volume. Two randomised controlled trials (published in 1998 and 2002), which studied a total of 81 patients who underwent major orthopaedic surgery (such as trauma surgery, cancer surgery, surgery for sepsis), found that aprotinin was safe and effective at reducing both blood loss and transfusion requirement (26, 51). The 1998 trial found that in the aprotinin group, the total number of red cell transfusions was less than half that of the controls ($p < 0.01$) (51). The later study demonstrated that both low-dose and high-dose aprotinin significantly reduced postoperative drainage and high-dose aprotinin reduced both the total calculated bleeding (from 3577 ml to 2203 ml, $p < 0.05$) and the volume of red cell transfusion (from 2 to 0 units, $p < 0.05$) (26).

Ekbäck et al. administered TXA to 40 patients undergoing total hip replacement in a double-blind randomised controlled trial (55). Twenty patients received a bolus of TXA at skin incision and another three hours later; they were also given a continuous infusion during the procedure. The remaining patients formed a control group. In addition, preoperative autologous blood donation and intraoperative cell salvage were used. The results showed a statistically significant decrease in intraoperative, postoperative and total bleeding (total bleeding 1770 vs. 1130 ml for control vs. TXA groups, $p < 0.001$). There was no significant difference in incidence of complications. To determine whether TXA could have a useful role postoperatively, Benoni et al. administered TXA at the end of the procedure and three hours later. This regimen was found to reduce transfusion requirement but not postoperative blood loss (60).

Data on the efficacy of TXA for major orthopaedic surgery, with a high risk of blood loss, are limited. Forty paediatric patients undergoing scoliosis surgery were randomised to either TXA or placebo and although intraoperative blood loss was not reduced in the TXA group, transfusion requirement was significantly decreased (56).

A study carried out in 2002 found that aminocaproic acid can reduce blood loss and thus reduce the likelihood of requiring a blood transfusion in hip replacement surgery (61). Results are less positive for major surgery: two studies found that aminocaproic acid did not reduce blood loss or transfusion requirement (52, 62). For children undergoing spinal surgery for scoliosis, a study of 28 patients found that total blood loss was reduced (53).

Some joint replacement procedures are carried out using a pneumatic tourniquet to produce a dry surgical field. This is associated with enhanced local fibrinolytic activity, and therefore increased blood loss after the tourniquet is removed (63). Consequently, administration of anti-fibrinolytic drugs

perioperatively may be indicated. Benoni et al. studied 179 patients undergoing knee arthroplasty and found the average postoperative blood loss was 340 ml less in patients who had received TXA (64). Two similar studies (a total of 117 patients) reported decreases in both blood loss and transfusion requirement (54, 65). A more recent study compared the effects of aprotinin and TXA, with a particular emphasis on analysing the effects on fibrinolytic activity. The investigators found that both aprotinin and TXA caused no significant modulation of fibrinolysis and no decrease in postoperative bleeding and transfusion requirements (66). They hypothesised that this was probably due to improved surgical technique, such as the use of bone cement and surgical haemostasis techniques and concluded that it would be preferable to employ these techniques rather than administer anti-fibrinolytics because the risk of adverse drug effects is avoided.

Liver transplantation

Orthotopic liver transplantation is associated with a high risk of blood loss and while improvements in surgical and anaesthetic techniques have reduced this risk, excessive bleeding is still a common problem (67). In a 2001 study, transplant patients required approximately 2.5 L of donor red blood cells and 3.4 L of fresh frozen plasma (68). While there is no doubt that the surgery itself can cause serious blood loss, hyperfibrinolysis is a major contributing factor and occurs particularly during the anhepatic and post-reperfusion stages of surgery (67-69).

The use of aprotinin for patients undergoing liver transplantation was first reported in 1989, reducing blood loss by 35% and blood transfusion by 50% (70). A more recent multi-centre randomised control trial compared the effects of both low-dose and high-dose aprotinin with placebo. Intraoperative blood loss was 60% lower than placebo in high-dose aprotinin study patients and 44% lower in low-dose patients. Total RBC transfusion requirement (both autologous and donor RBCs) was 37% and 20% lower in the high and low-dose groups respectively. There was no significant difference in risk of thromboembolic complications in any of the treatment groups (68). There is anecdotal evidence that aprotinin may have prothrombotic properties, but a large randomised controlled study has found no increase in the incidence of perioperative thrombotic complications in patients given aprotinin (18).

The first major randomised controlled trial evaluating the efficacy of TXA was carried out in 1996; administration of high-dose TXA ($40 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ infusion perioperatively) reduced intraoperative blood loss by approximately half and patients in this group required significantly fewer transfusions (71). Low-dose TXA ($2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ infusion perioperatively) reduces fibrinolysis but not transfusion requirement (72).

Several studies have compared the efficacy of TXA with EACA and found that TXA is more effective than EACA at reducing red blood cell transfusion requirements when compared with placebo (73, 74). Aprotinin also appears to be more effective

than EACA but further trials are required to compare the effectiveness of TXA versus aprotinin (75).

Other uses

Anti-fibrinolytic drugs are also used for various other conditions which, although less acute than the conditions already discussed, place the patient at an increased risk of blood loss. For reasons of cost and hypersensitivity, aprotinin should not be used unless the patient has a significant chance of increased blood loss, and cannot be used for the treatment of chronic conditions as re-exposure must be avoided; however, the lysine analogues can be very effective in such cases.

The GI tract is known to have high local concentrations of the fibrinolytic enzymes and in patients who have gastrointestinal lesions such as ulcers, oesophagitis and angioma, they can reduce bleeding significantly. A meta-analysis of 1267 patients admitted to hospital with upper GI bleeding and treated with daily TXA, which showed a 20-30% reduction in bleeding rate and a 30-40% reduction in mortality (76).

The urinary tract is rich in plasminogen activators, such as tPA, which facilitate clot lysis, haemorrhage and anaemia. In addition, urine itself can dissolve clots, so patients who have undergone urinary tract surgery such as prostatectomy are at risk from increased bleeding. Both TXA and EACA have been used to irrigate the bladder and urethra postoperatively and while they reduce this lysis and decrease blood loss by approximately 50%, they increase the risk of formation of intravesicular thrombi which may then require surgical removal. They do not reduce transfusion requirement, length of hospital stay or mortality, so they cannot be recommended for routine use (77-79).

Like the urinary tract, the oral mucosa and saliva have high local concentrations of plasminogen activators and for patients at risk of bleeding following dental extractions, the lysine analogues can be effective at reducing oral bleeding. Patients who have undergone cardiac surgery often need to take lifetime anticoagulants and, as such, are at increased risk of prolonged bleeding following dental surgery. A TXA mouthwash, taken four times per day for seven days postoperatively reduces bleeding events by 90%, without placing the patients at further risk by stopping the anticoagulant therapy (80). Similar treatment is equally successful for haemophiliacs (81). Clotting factor replacement therapy is often required for haemophilia patients after oral surgery and both TXA and EACA reduce this requirement as well as reducing blood loss (82, 83).

Menorrhagia is a potentially serious condition that affects approximately 20% of women and is defined as blood loss exceeding 80ml at menstruation. This blood loss is obviously distressing, but can also cause iron deficiency anaemia. Treatment options include surgery (hysterectomy) or medication, and as the surgical option has a significant risk of morbidity, treating the condition pharmacologically may be preferable. The uterus is thought to contain high concentrations

of plasminogen activator, promoting fibrinolysis. If hormonal treatment has failed and organic disorders have been ruled out, TXA can be used to reduce bleeding. In one trial, patients were randomised to receive 1g TXA six hourly for five days from day one of menstruation. Compared with control, TXA reduced blood loss by 54% (84).

Conclusion

Surgical trauma and cardiopulmonary bypass can cause pathologically excessive fibrinolysis which is a major cause of bleeding in the surgical patient. Anti-fibrinolytic drugs allow the clinician to address this problem at source by inhibiting fibrinolysis while, according to the vast majority of evidence currently available, not increasing the risk of thromboembolic complications. The TEG is a valuable tool available for the correct diagnosis of a variety of coagulopathies, and its rapidity and ease of use make it particularly suitable for use in the surgical and intensive care environments. Analysis of results can guide clinicians in their management of patients and help to determine the most suitable treatment. Major surgery can result in patients developing life threatening haemorrhage very rapidly, the ability to quickly diagnose the cause of such blood loss ensures that the patient can be offered the most appropriate treatment.

Aprotinin is effective at reducing both blood loss and transfusion requirement in cardiac surgery and also significantly reduces mortality and risk of rethoracotomy. Its anti-inflammatory and platelet preserving properties make it ideally suited for this type of surgery as cardiopulmonary bypass is known to induce inflammation and platelet dysfunction. Although there is some evidence that aprotinin increases the risk of graft occlusion, most trials assessing this have been small. The only major randomised controlled trial showed wide variation of results between different centres and it is difficult to draw definitive conclusions from their data (45). If aprotinin does have prothrombotic properties, they are minor in comparison with the range of benefits that the drug provides. The drug is also effective in reducing blood loss and transfusion requirement in other types of major surgery, such as liver transplantation and orthopaedic surgery, and should be used routinely where excessive blood loss is predicted, or where religious beliefs forbid transfusion. The drug is likely to be used more in the future and as such it will be especially important to be aware of the risk of anaphylaxis following re-exposure.

The lysine analogues, TXA and EACA, provide a cheap and effective means of inhibiting fibrinolysis. Both drugs benefit from having a short half life and few troublesome side effects. TXA has a similar side effect profile to EACA but is more effective and can be given at lower doses. TXA and EACA are particularly suited to treating chronic conditions requiring repeat administration where aprotinin would clearly be unsuitable. Data comparing the efficacy of aprotinin with TXA and EACA are rather sparse, and more research needs to be carried out in this area as the lysine analogues may be only slightly less efficacious at greatly reduced cost.

Thrombelastography, autologous blood transfusion and antifibrinolytic drugs provide the clinician with a wide range of techniques to minimise blood loss and transfusion requirement. The clinical evidence currently available suggests that these are effective in many surgical situations although take up has been surprisingly slow, particularly of anti-fibrinolytic drugs (Tab. 3) (3). Recombinant coagulation factors have recently been developed to address another common cause of blood loss - factor deficiency. Their use is currently at an experimental stage but initial results are encouraging and their use may help to reduce perioperative blood loss further still.

Tab. 3. Percentage of US hospitals using pharmacological techniques to reduce allogenic blood transfusion (3).

Use	APR	TXA	EACA
Routine	2	0	15
Sometimes	17	1	15
Almost never	42	8	18
Never	39	90	50

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