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Pharmacological Strategies to Decrease Transfusion Requirements in Patients Undergoing Surgery

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Abstract

Surgical procedures are inevitably associated with bleeding. The amount of blood loss may vary widely between different surgical procedures and depends on surgical as well as non-surgical factors. Whereas adequate surgical haemostasis may suffice in most patients, pro-haemostatic pharmacological agents may be of additional benefit in patients with (diffuse) surgical bleeding or in patients with

a specific underlying haemostatic defect. In general, surgical haemostasis and pharmacological therapies can be complementary in controlling blood loss.

The use of pharmacological therapies to reduce blood loss and blood transfusions in surgery has historically been restricted to a few drugs. Antifibrinolytic agents (aprotinin, tranexamic acid and aminocaproic acid) have the best evidence supporting their use, especially in cardiac surgery, liver transplantation and some orthopaedic surgical procedures. Meta-analyses of randomised, controlled trials in cardiac patients have suggested a slight benefit of aprotinin, compared with the other antifibrinolytics. Desmopressin is the treatment of choice in patients with mild haemophilia A and von Willebrand disease. It has also been shown to be effective in patients undergoing cardiac surgery who received aspirin up to the time of operation. However, overall evidence does not support a beneficial effect of desmopressin in patients without pre-existing coagulopathy undergoing elective surgical procedures. Topical agents, such as fibrin sealants have been successfully used in a variety of surgical procedures. However, only very few controlled clinical trials have been performed and scientific evidence supporting their use is still limited.

Novel drugs, like recombinant factor VIIa (eptacog alfa), are currently under clinical investigation. Recombinant factor VIIa has been introduced for the treatment of haemophilia patients with inhibitors, either in surgical or non-surgical situations. Preliminary data indicate that it may also be effective in surgical patients without pre-existing coagulation abnormalities. More clinical trials are warranted before definitive conclusions can be drawn about the safety and the exact role of this new drug in surgical patients.

Only adequately powered and properly designed randomised, clinical trials will allow us to define the most effective and the safest pharmacological therapies for reducing blood loss and transfusion requirements in surgical patients. Future trials should also consider cost-effectiveness because of considerable differences in the costs of the available pro-haemostatic pharmacological agents.

Surgical procedures are inevitably associated with bleeding. The amount of blood loss can vary widely between different surgical procedures and depends on surgical as well as non-surgical factors. In general, perioperative bleeding and the need for blood transfusions is correlated with increased morbidity, mortality and costs.[1,2] In combination with the continued concern for the risk of transmitting transfusion-mediated infections, this has stimulated the interest in strategies to reduce perioperative blood loss. Surgical factors influencing blood loss largely consist of surgical skills and experience, as well as the degree of invasiveness of the procedure. Differences in individual characters and awareness of surgeons, and the amount of time spent on careful haemostatic control can have a great impact on the amount of intraoperative and postoperative blood loss.

Non-surgical factors that may affect blood loss include the function of the haemostatic system, vascular abnormalities (e.g. connective tissue disorders), and arterial and venous blood pressure. In general, diffuse bleeding from the surgical field, which cannot be attributed to detectable bleeding vessels, is usually referred to as non-surgical bleeding. The pathogenesis of non-surgical bleeding is often multifactorial and the exact mechanisms may remain unidentified in the individual patient. The normal haemostatic system consists of a complex and delicate interaction of cellular blood components (platelets, leucocytes), endothelial and subendothelial layers, and plasmatic proteolytic enzymes and protease inhibitors. During

recent decades, extensive research in this field of medicine has greatly enhanced our understanding of the mechanisms that play a role in normal haemostasis and enabled us to identify common causes of haemostatic dysfunction. Current concepts and insights of the haemostatic system relevant for this paper are discussed.

When bleeding is the result of a specific defect in the haemostatic system, therapy should focus on correcting this abnormality. A classical example is the correction of a deficiency of factor VIII by infusion of coagulation factor concentrates in patients with haemophilia A. However, in the majority of patients experiencing non-surgical bleeding a single haemostatic defect can usually not be identified. Therefore, the transfusion of blood components, such as platelet concentrate and fresh frozen plasma, has been the mainstay of treating bleeding disorders. Ideally, pharmacological agents with a specific working mechanism should be used in those situations where a specific defect in the haemostatic mechanism has been identified and where it can be corrected by this drug. In daily practice, however, several of these specific agents (such as antifibrinolytics) have been shown to be effective in controlling bleeding even in the absence of a detectable specific haemostatic defect.

1. Rationale for Using Pharmacological Agents

It is well know that laboratory tests can be grossly abnormal in patients experiencing major intraoperative blood loss, making it difficult to formulate a goal-directed therapy. Conversely, laboratory data may be abnormal in the absence of abnormal bleeding in a given patient, whereas serious bleeding may occur in patients who have no detectable abnormalities in laboratory tests. Studies on haemostatic function during different surgical procedures are rather limited, except for a few surgical procedures, such as open-heart surgery using cardio-pulmonary bypass (CPB)[3] and liver transplantation.[4] Lack of clear insight into the pathogenesis of non-surgical peri-operative bleeding in the majority of patients has hampered the development of specific treatment strategies, including the use of pharmacological agents. On the other hand, the type and number of pharmacological agents that have been available for correction of haemostatic defects is also limited.

Until recently, pharmacological options primarily consisted of topical agents, antifibrinolytics, and agents that may enhance platelet function and improve primary haemostasis, such as desmopressin. These agents have no, or only limited, direct stimulatory effect on plasmatic coagulation at the site of tissue injury. Recently, a new compound, which does have a true procoagulant activity, has been added to this arsenal: recombinant activated factor VIIa (rFVIIa) [eptacog alfa].[5,6] Although originally introduced for patients with haemophilia and inhibitors against factor VIII or IX, it is expected that rFVIIa may become a universal haemostatic agent for treating bleeding disorders in various categories of patients, including surgical patients.

An overview of pharmacological agents that are currently available for improving haemostasis and reducing blood loss during surgery is given in table I. Although pharmacological agents can be given either as treatment or as prophylaxis for bleeding, there are very few prospective studies that have addressed actual treatment of non-surgical bleeding. Most prospective studies have focused on the

Table I. Overview of pharmacological agents used for haemostasis during surgery

Topical agents	Fibrin sealants	
	Collagen	
	Thrombin	
	Oxidised cellulose	
	Gelatin sponges	
Antifibrinolytics	Plasminogen inhibitors	Aminocaproic acid
		Tranexamic acid
	Serine protease (plasmin) inhibitors	Aprotinin
		Nafamostat
Procoagulant drugs	Desmopressin	
	Recombinant factor VIIa (eptacog alfa)	
Miscellaneous	Conjugated estrogens	
	Epoprostenol	

efficacy of the various drugs when given prophylactically. The aim of this paper is to provide a clinically oriented guide that summarises current scientific evidence and experience supporting the use of pharmacological agents to decrease transfusion requirements in surgical patients. Relevant publications were selected after a Medline® search for the time period January 1992 to August 2002, using the following search terms in various combinations: haemostatic drug, antifibrinolytic, tranexamic acid, lysine analogue, aminocaproic acid, aprotinin, serine protease inhibitor, desmopressin, estrogen, fibrin sealant or glue, recombinant factor VIIa or NovoSeven, prostacyclin, blood loss, surgery, transfusion. If available for a certain drug, randomised, controlled trials (RCT) or meta-analyses of RCT were considered as the highest level of scientific evidence. If no RCT were available for a certain drug, other publications on clinical efficacy and safety were used. References of selected papers were checked for additional and earlier publications. The use of blood products, like platelet concentrate, plasma or plasma components, is beyond the scope of this paper and is not discussed.

2. Haemostatic System

Haemostasis is a complex interaction between the vascular wall, platelets, coagulation factors and fibrinolysis. Primary haemostasis, the formation of a platelet plug, is started immediately after endothelial injury. By the disruption of the endothelial lining of the blood vessels, the subendothelium is exposed and activated platelets will adhere to the underlying surface by interaction of the glycoprotein (GP)Ib complex with von Willebrand factor. Platelet aggregation is mediated by von Willebrand factor and fibrinogen, by interaction with the GPIIb/IIIa receptor. At the same time the coagulation cascade is initiated by the exposure of tissue factor (TF), which in complex with factor VII is the most important route of thrombin generation. The factor VIIa-TF complex can activate factors IX and X. The factor Xa-Va (prothrombinase) complex converts prothrombin in thrombin. The generated thrombin also activates factor XI of the intrinsic pathway, which results in a secondary boost of thrombin formation. The conversion of fibrinogen to fibrin is the end stage of blood coagulation. After fibrin is formed it is stabilised by activated factor XIII. Fibrinolysis, the breakdown of fibrin into fibrin degradation products, is a physiologically important mechanism in controlling blood coagulation. Fibrin is degraded by plasmin, which is the active enzyme after conversion of plasminogen by plasminogen activators, such as tissue-type plasminogen activator (t-PA). A schematic presentation of the haemostatic system is given in figure 1.

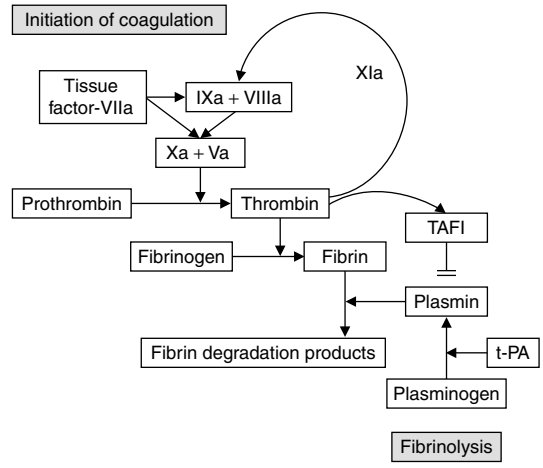

Fig. 1. Simplified scheme of the coagulation cascade. **TAFI** = thrombin-activatable fibrinolysis inhibitor; **t-PA** = tissue-type plasminogen activator.

The coagulation system is controlled at several levels by inhibitors, such as the activated protein C pathway and antithrombin. Fibrinolysis is also tightly regulated by the presence of plasminogen activator inhibitors, antiplasmin and a recently characterised thrombin activatable fibrinolysis inhibitor (TAFI). The balance between these procoagulant and anticoagulant factors is essential for haemostatic control. Disorders in this balanced system of coagulation and fibrinolysis may result in severe bleeding or, on the other hand, thrombotic complications. Bleeding disorders become most apparent during challenges of the haemo-

static system, of which surgery is one of the most extreme ones.

3. Topical Agents

Several different topical agents can be used to achieve or maintain haemostasis in surgical patients. Most of them are believed to be clinically useful, although the majority of them have not been subjected to appropriate clinical trials. Topical agents are mainly used to control local capillary bleeding, especially from injured parenchymal organs. The working mechanism of most of these agents is based on local activation of the endogenous coagulation system (e.g. thrombin, microcrystalline collagen), local vasoconstriction (epinephrine), or a combination of local clotting activation and mechanical compression (collagen, cellulose or gelatin-based sponges). In general, these compounds can be viewed as an extension of the more conventional surgical techniques for obtaining or stimulating local haemostasis, such as gauze compression, suturing and electrocautery. Because of the rather aspecific working mechanism of and paucity of randomised clinical trials with these compounds, they are not further discussed here.

There is one group of topical agents that does deserve some further discussion: the fibrin sealants. Fibrin sealants (fibrin glue or fibrin adhesive) are available as various commercial preparations in Europe and the US, but also as 'home-made' preparations from individual hospital pharmacies.[7,8] They usually consist of a combination of inactivated and purified (human or bovine) thrombin and fibrinogen in a liquid or dried form. When the two components are separately applied and mixed at the surgical wound surface, an exogenous layer of fibrin will be formed.

Although rare, allergic reactions can occur after using formulations with bovine thrombin. Antibodies against bovine thrombin can be detected in the serum of a large number of patients who have been treated with fibrin sealants with bovine plasma components.[9] More important, bovine-thrombin associated antibodies against several human clotting factors, including factor V, fibrinogen and human thrombin, have been described.[10,11] Severe bleeding complications may develop in these patients, pressing the need for a critical reassessment of the use of bovine thrombin as a therapeutic agent in modern clinical practice.[11]

Most commercially available preparations nowadays contain virally inactivated and highly purified human fibrinogen and thrombin, which virtually completely eliminates the risk of allergic reactions, cross-reactive antibodies against autologous clotting factors, and viral transmission. In some preparations, a fibrinolysis inhibitor (e.g. aprotinin) has been included to improve stability of the fibrin clot. Depending on the exact formulation some preparations contain calcium chloride and/or factor XIII, the enzyme that catalyses the cross-linking of fibrin strands, making them more resistant to dissolution. Although widely used in surgical practice, only very few RCT have been performed to demonstrate the effectiveness of these compounds. For excellent reviews on the use of fibrin sealants in surgical practice the reader is referred to recent publications in this and other journals.[7,8,12]

Probably the best studied indications for fibrin sealants are oozing from raw wound surfaces of dissected adhesions in patients undergoing cardiac re-operations,[13,14] bleeding from cut liver surfaces,[15,16] oral surgery in patients with anticoagulation or congenital coagulation disorders,[17] and bleeding from vascular anastomotic suture holes.[18,19] Preliminary studies have also suggested a beneficial effect in total knee arthroplasty[20] and in face lift operations.[21] Unfortunately, most studies were rather small and the results not always unequivocal.[12]

On the basis of their mechanical and adhesive properties, fibrin sealants are probably more effective in preventing rebleeding from a previously dry surgical wound surface than in achieving primary haemostasis at a continuously oozing surface. In the latter situation, the fibrin formed will simply be washed off, as it does not adhere to the wet surface. However, when applied to a dry liver re-

section surface, a tightly adherent fibrin layer can be formed which may prevent postoperative rebleeding from the resection surface secondary to local fibrinolysis.[22] Whether this leads to a lower incidence of postoperative complications, such as abscesses or haematomas, still needs to be proven.

In general, more clinical trials are needed to fully assess the place of fibrin sealants in reducing surgical bleeding.

4. Antifibrinolytic Drugs

Antifibrinolytic drugs should ideally be used only in those situations where hyperfibrinolysis can be detected. In these situations, the administration of antifibrinolytics may correct the haemostatic balance between coagulation and fibrinolysis, and correct the bleeding problem. Typical surgical procedures which may be associated with hyperfibrinolysis are operations requiring CPB, orthotopic liver transplantation, and some urological and orthopaedic operations. Unfortunately, there are very few laboratory tests of fibrinolysis that can be performed routinely within a certain time period, necessary for direct guidance of patient care. Thromboelastography may be the only exception, and therefore has been advocated as a point-of-care method for rapid *in vitro* detection of hyperfibrinolysis in surgical patients.[23] On the other hand, antifibrinolytics have also been widely and successfully used in patients without documented laboratory signs of hyperfibrinolysis, especially in mucosal bleeding. The reason for this is that until recently, antifibrinolytics have been the only available drugs that can be given systemically to reduce blood loss in surgical patients.

Antifibrinolytic drugs are most frequently used in cardiac surgery and the vast majority of currently available research data comes from RCT in patients undergoing various types of cardiac surgery. In a recent Canadian nation-wide survey on the use of technologies to minimise exposure to peri-operative allogeneic blood transfusion in elective surgery, it was found that pharmacological agents are used in over 70% of the cardiac surgery centres, whereas these drugs are used in less than 15% of orthopaedic, vascular and urology centres.[24] Comparable results have been observed in a similar international study in nine different countries.[25] Antifibrinolytic drugs were most frequently used in cardiac surgery. An individual discussion of the available antifibrinolytic drugs is given in the next sections.

4.1 Lysine Analogues

The activation of plasminogen into plasmin requires binding to fibrin at the lysine-binding sites. Lysine analogues reversibly bind to the lysine-binding site on plasminogen, thereby inhibiting the conversion of plasminogen into plasmin on the surface of fibrin. Aminocaproic acid (also known as epsilon aminocaproic acid or EACA) and tranexamic acid are two synthetic lysine analogues with antifibrinolytic activity in humans. Aminocaproic acid has been available for longer and is cheaper, but is also seven times less potent than tranexamic acid. There is extensive experience with the use of both drugs in clinical practice, which has resulted in numerous publications. Detailed reviews of the pharmacodynamics and pharmacokinetics of aminocaproic acid and tranexamic acid have been published before in this journal.[26,27]

4.1.1 Aminocaproic Acid

Aminocaproic acid has been used in various doses and regimens in patients undergoing surgery. The largest experience exists with patients undergoing cardiac surgery and in orthotopic liver transplantation. In general, the recommended dose of aminocaproic acid is 150 mg/kg as an intravenous bolus before surgery, followed by an infusion of 15 mg/kg/hour during the operation.

In Cardiac Surgery

Aminocaproic acid has been used in cardiac surgery since the late 1950s. More than ten RCT with prophylactic administration of this drug have been performed in patients undergoing cardiac operations using CPB (predominantly coronary artery bypass grafting or valve replacement). In the majority of these studies aminocaproic acid was compared with either tranexamic acid or aprotinin.

Only a few studies have compared aminocaproic acid directly with placebo. Several meta-analyses of all RCT have confirmed the results of individual studies that prophylactic administration of aminocaproic acid leads to a reduction in postoperative bleeding by 30 to 40%, without increasing the incidence of thromboembolic complications.[28-31] In one meta-analysis, aminocaproic acid was not found to have a statistically significant effect on the proportion of patients transfused.[29] The observed efficacy of aminocaproic acid also varies somewhat from study to study, which may be explained by differences in dosage and time of administration. When infusion of aminocaproic acid is not started at skin incision, but delayed until after heparinisation before CPB, the benefit for reducing blood loss postoperatively is only minimal.[32] Prophylactic administration of aminocaproic acid does not seem to increase the risk of peri-operative myocardial infarction.[30]

In Orthotopic Liver Transplantation

Patients undergoing orthotopic liver transplantation may have primary hyperfibrinolysis. Kang et al.[33] have described a beneficial effect of low dose aminocaproic acid (1g, single infusion) during liver transplantation after the efficacy of this agent had been confirmed *in vitro* using thromboelastography. Others could not confirm a beneficial effect of aminocaproic acid on blood loss in a small retrospective study.[34] In one large double-blind RCT, aminocaproic acid and tranexamic acid were compared with placebo. No significant differences in transfusion requirements were found in this study between the aminocaproic acid and the placebo group.[35] However, administration of the study medication was discontinued at reperfusion of the new liver and a possible therapeutic effect could, therefore, have been missed because hyperfibrinolytic bleeding is mainly seen after graft reperfusion. On the basis of empirical data, very low dose aminocaproic acid (single infusions of 300mg) is still widely used to treat severe bleeding in liver transplantation, especially in the US. Unfortunately, however, there are no RCT to confirm the efficacy of aminocaproic acid in orthotopic liver transplantation.

In Other Surgical Procedures

Systemic infusion of aminocaproic acid has been used successfully to control bleeding after transurethral prostatectomy.[36,37] However, intravesical administration had no significant effect on bleeding and may lead to clot formation in the urethra.[38] Although aminocaproic acid has also been used in patients undergoing other types of surgery, there are not enough data from prospective studies to support the wider application of this agent.

4.1.2 Tranexamic Acid

Tranexamic acid is seven times more potent and has a longer half-life than aminocaproic acid. The recommended dosage of tranexamic acid is 10 mg/kg intravenously before surgery, followed by 1 mg/kg/hour during the operation, but higher doses of up to 150 mg/kg (bolus injection) have been used as well.[39] The studied indications for tranexamic acid are very similar to those for aminocaproic acid, and include mainly cardiac surgery and liver transplantation. In addition, there has been a recent increase in reports on the use of tranexamic acid in orthopaedic surgery.

In Cardiac Surgery

Compared with aminocaproic acid, tranexamic acid seems to be equally effective in reducing blood loss after cardiac or thoracic aortic operations requiring CPB.[30,40] Prophylactic administration of tranexamic acid has been shown to reduce bleeding after CPB by 30 to 40%. When tranexamic acid is administered immediately after CPB, it is shown to be less effective.[41] In addition, patients undergoing repeat cardiac surgery as well as patients undergoing beating-heart ('off-pump') coronary surgery, seem to benefit from prophylactic treatment with tranexamic acid.[42-44] Similarly to aminocaproic acid, there is no evidence that tranexamic acid is associated with an increased risk for thromboembolic complications. No statistically significant effect of tranexamic acid on perioperative myocardial infarction has

been found in meta-analyses.[29] However, the endpoints used for detection of myocardial infarction varied among the different studies and may not always have been adequate. Tranexamic acid has not been consistently shown to reduce the need for rethoracotomy after cardiac surgery. Although one meta-analysis of the combined data for both tranexamic acid and aminocaproic acid showed that lysine analogues decrease the need for rethoracotomy,[30] no such reduction was found in a meta-analysis of tranexamic acid alone.[29] Furthermore, there is no proof of a reduction in the operative mortality risk when tranexamic acid is used in patients undergoing cardiac surgery.[30]

In Orthotopic Liver Transplantation

Tranexamic acid has also been used in patients undergoing orthotopic liver transplantation. In a small randomised, placebo-controlled study it was shown that prophylactic infusion of low-dose tranexamic acid (2 mg/kg/hour) reduced fibrinolysis, but not transfusion requirements during orthotopic liver transplantation.[45] However, in two independent RCT it has been shown that high-dose tranexamic acid (10 to 40 mg/kg/hour) significantly reduces intra-operative blood loss and perioperative donor blood exposure in patients undergoing orthotopic liver transplantation.[35,46] The effect of tranexamic acid in liver transplant recipients therefore seems to be dose related. The administration of tranexamic acid does not seem to increase the risk of hepatic artery thrombosis in liver transplantation.[47] More studies will be needed, especially to compare the efficacy of tranexamic acid with aminocaproic acid and/or aprotinin in this type of surgery.

In Orthopaedic Surgery

Patients undergoing orthopaedic surgery of the lower extremities may develop increased fibrinolytic bleeding after release of a pneumatic tourniquet that is placed around the upper extremity to provide a dry surgical field. Several double-blind RCT in patients undergoing total knee arthroplasty have shown that prophylactic administration of tranexamic acid significantly reduces total blood loss by about 35 to 50%.[27,48] Significant reductions in blood transfusion requirements have also been recorded.

In one (single-blind) RCT, tranexamic acid was compared with desmopressin.[49] This study showed a significantly lower postoperative blood accumulation in the surgical drains and less blood transfusion in the tranexamic acid group than the desmopressin group. Compared with normovolaemic haemodilution followed by postoperative autotransfusion, tranexamic acid is also associated with a superior blood-sparing effect in patients undergoing total knee arthroplasty.[50] A similar reduction in intraoperative blood loss by 35% has been found in a double-blind, placebo-controlled study in patients undergoing total hip replacement.[51,52] Although most studies included careful screening for lower limb deep venous thrombosis, no differences in the incidence of thromboembolic complications have been reported for placebo or tranexamic acid recipients undergoing orthopaedic surgical procedures. However, this finding should be interpreted with caution, since most studies did not have adequate statistical power to detect a difference in thromboembolic complications. The drug has probably little effect when used to control heavy bleeding postoperatively.[53]

In Urological Surgery

Primary hyperfibrinolysis may occur in patients undergoing prostate surgery as a result of the release of plasminogen activators from the prostatic tissue. High levels of plasminogen activators can also be found in urine, which contributes to dissolution of haemostatic clots and haematuria. The use of antifibrinolytic treatment to reduce postoperative bleeding is not very well studied, although some studies have suggested that prolonged oral administration of tranexamic acid (1g three times daily orally for 3 weeks) may reduce the incidence of secondary bleeding and the number of readmissions for haemorrhagic complications.[27]

4.2 Serine Protease Inhibitors

Plasmin, the final enzyme in the fibrinolytic cascade, is a serine protease. Inhibitors of serine proteases, therefore, possess antifibrinolytic prop-

erties. The serine protease inhibitor that has been most extensively studied as an antifibrinolytic agent is aprotinin. Aprotinin is a nonspecific serine protease inhibitor extracted from bovine lung. The pharmacology and therapeutic use of aprotinin have been subject of several review papers.[26,54,55] Nafamostat (nafamostat mesilate) is another serine protease inhibitor, which has been studied as an antifibrinolytic agent.

4.2.1 Aprotinin

Aprotinin is a naturally occurring polypeptide which inhibits various serine proteases in plasma, such as trypsin, kallikrein, plasmin and elastase, by forming reversible complexes with their active serine site. The activity of aprotinin is expressed as kallikrein inhibitor units (KIU), the amount of aprotinin that decreases the *in vitro* activity of two biological KIU by 50%. Aprotinin is metabolised in the proximal renal tubules and eliminated in a biphasic pattern: a rapid phase half-life of approximately 40 minutes and a slower phase half-life of 7 hours. Aprotinin is probably the most extensively studied pro-haemostatic drug. The drug has been used in different dose administration regimens. The most frequently used regimen is based on the original study in cardiac surgery from the Hammersmith Hospital in London, UK, and consists of a loading dose of 2 million KIU (280mg), followed by continuous infusion of 500 000 KIU/hour (70 mg/hour).[56] However, several studies have shown that smaller doses, such as a 50% reduction of this regimen, are also effective in reducing blood loss after cardiac operations. Weight-adjusted aprotinin dose administration may reduce variation of aprotinin concentration over time but does not reduce inter-individual variations in aprotinin concentration.[57]

The mechanisms by which aprotinin exerts its prohaemostatic effects are not fully understood. Apart from its antifibrinolytic activity as a result of inhibition of plasmin and kallikrein, it is also believed to have an effect on primary haemostasis by preserving platelet function via various mechanisms.[54] In addition, aprotinin has several anti-inflammatory effects.

The incidence of adverse reactions to aprotinin is low. Anaphylactic reactions occur in less then 0.5% of the patients but the risk increases after repeated use. Theoretically, aprotinin could cause venous and arterial thrombosis, and thus occlusion of coronary bypass grafts or other vascular grafts. However, individual controlled trials and meta-analyses have not shown an increased rate of mortality, acute myocardial infarction or early coronary graft occlusion, or increased risk of venous thromboembolism after hip replacement.

In Cardiac Surgery

Aprotinin was first used during CPB to inhibit plasmin-induced complement activation.[58] Unexpectedly, the initial studies showed a reduction in blood loss and transfusion requirements in the patients treated with aprotinin. Since then, multiple well-designed clinical trials have convincingly proven its safety and efficacy.[29,30,58,59] Prophylactic administration of aprotinin improves haemostasis and reduces blood transfusion requirements by 50 to 80% in patients undergoing CPB. It is the only agent approved by the US Food and Drug Administration to reduce bleeding in patients undergoing cardiac surgery. A meta-analysis of all RCT of aprotinin in cardiac surgery has confirmed the efficacy in reducing blood loss, and shown that it is also decreases mortality, the need for rethoracotomy, and the proportion of patients receiving a blood transfusion.[30] Data on the efficacy of aprotinin, when administered only postoperatively, are less consistent.[60,61] Therefore it is not advisable, at this point, to administer aprotinin (only) during the postoperative period.

Concern has been raised about possible adverse effects of aprotinin, particularly coronary vein graft thrombosis. Unfortunately, most RCT have not been large enough to adequately estimate this possible risk, while other studies have been criticised with respect to their design or the evaluation of end-points.[62] Although attempts to solve this issue by performing large randomised studies and meta-analyses have be made, arguments both in favour and against an effect on coronary graft patency can be found in the current literature.[62-64]

However, there is emerging evidence that the haemostatic activity of aprotinin is not necessarily associated with a prothrombotic activity and that the drug in fact has antithrombotic properties. It has been suggested that differences in aprotinin dose administration regimens as well as inadequate use of heparin during CPB may explain some of the observed discrepancies among different studies. In contrast to low dose aprotinin, high dose aprotinin has an anticoagulant activity and decreases thrombin generation, which does not seem to interfere with its haemostatic activity.[65] Moreover, aprotinin has a direct antithrombotic activity by blocking the proteolytically activated thrombin receptor on platelets.[66] These observations argue against a possible prothrombotic activity of aprotinin. A clinically important finding may be that recent meta-analyses have not shown a significantly increased the risk of perioperative myocardial infarction in aprotinin-treated patients compared with placebo-recipients.[30,59] Interestingly, a recent meta-analysis of the North American randomised, placebo-controlled clinical trials showed a lower incidence of stroke in patients receiving high dose aprotinin, suggesting a cerebroprotective effect of high dose aprotinin during cardiac surgery.[67]

Some studies have shown a minimal adverse effect of aprotinin on renal function, as reflected by a postoperative elevation in serum creatinine levels or decreased creatinine clearance. However, the effects are usually transient and do not appear to result in clinically relevant renal dysfunction.[54]

In Major (Non-Cardiac) Thoracic Surgery

Although most common thoracic surgical procedures (i.e. anatomical lung resections for cancer) are usually not associated with severe bleeding, blood loss can be a serious problem in surgery for inflammatory pulmonary or pleural disease, decortication procedures, and rethoracotomies for recurrent tumours. Two RCT have independently shown that aprotinin significantly reduces perioperative bleeding and blood transfusion requirements by more than 50% in patients undergoing major thoracic surgery associated with high risk for bleeding.[68,69] Activation of the haemostatic system, including hyperfibrinolysis, has also been observed during lung transplantation and this has been associated with increased blood loss.[70] Although it has been suggested that aprotinin may reduce blood loss in lung transplant recipients,[71] this has not yet been proven by properly designed RCT. Current data does not show a higher incidence of thromboembolic complications in patients undergoing major thoracic procedures, who have received prophylactic administration of aprotinin intraoperatively, but the experience is still limited.[68,69]

In Orthotopic Liver Transplantation

The use of aprotinin in orthotopic liver transplantation was first reported in 1989.[72] Routine administration of aprotinin during liver transplantation, however, has long been debated because of the lack of placebo-controlled, randomised trials confirming its safety and efficacy.[73] Recently, two placebo-controlled RCT have shown that aprotinin indeed reduces blood transfusion requirements during orthotopic liver transplantation by 30 to 40% compared with placebo.[74,75] In addition to its prohaemostatic effect, there is evidence that aprotinin may also have a stabilising effect on haemodynamics, especially after reperfusion of the new liver.[76] This has been explained by the strong antikallikrein activity of aprotinin, thereby ameliorating activation of the contact system and the subsequent release of vasodilating substances, such as bradykinin.

Although aprotinin is cleared from the circulation by the kidneys and is potentially nephrotoxic at high concentrations, there is no evidence that its use in patients undergoing liver transplantation is associated with a higher incidence of renal failure.[77] Although isolated case reports of pulmonary embolism have been described in liver transplant recipients who received aprotinin,[78] there is no evidence for a higher incidence of thromboembolic complications in patients who received aprotinin during orthotopic liver transplantation in RCT.[79] All together, there is good scientific evidence to support the use of aprotinin in patients undergoing orthotopic liver transplantation.

In Orthopaedic Surgery

Major orthopaedic surgical procedures, such as revision spine or hip surgery, pelvic surgery and surgery for infectious bone diseases, are associated with an increased risk for perioperative bleeding and subsequent need for blood transfusions. Several RCT have shown that aprotinin significantly reduces transfusion requirement in major orthopaedic procedures compared with placebo.[80-84] Although the reduction in transfusion requirements may be relatively small for procedures with a moderate expected bleeding risk (i.e. total hip replacement), clinically more relevant reductions have been obtained in high-risk revision surgery and in septic or cancer patients undergoing major orthopaedic resections.[81-84] One RCT in patients undergoing major orthopaedic surgery suggested that much higher administration of aprotinin (4 x 10^6 KIU initial dose followed by 1 x 10^6 KIU/hour) than the commonly used Hammersmith scheme may be required to obtain a significant blood sparing effect in this group of patients.[83] In this double-blind, placebo-controlled study, venous thromboembolism was systematically assessed by venography at postoperative day 3 and no significant differences were found between the patients who received aprotinin or placebo. However, the number of thromboembolic events was very small and more data from larger groups of patients have to be awaited. On the basis of currently available data, prophylactic administration of aprotinin should be considered in high risk major orthopaedic operations.

In Other Surgical Procedures

Aprotinin has been studied in RCT in several other types of surgery. It was shown to significantly reduce transfusion requirements during vascular surgery,[85] liver resections[86] and orthognathic surgery.[87] In general, aprotinin is a very effective agent for reducing blood loss and transfusion requirements in patients undergoing major operative procedures, without increasing the rate of serious adverse effects, although hypersensitivity can be rarely seen. The decision to use intraoperative, prophylactic administration of aprotinin should always be based on a careful weighing of the expected risk of bleeding on one side and the costs and potential allergic reactions on the other side.

4.2.2 Nafamostat

Nafamostat is a synthetic serine protease inhibitor with a working mechanism comparable with that of aprotinin. It inhibits thrombin, factor XIIa, kallikrein, plasmin and C1 esterase. Most experience with this drug exists in Japan, where it has been studied in a few clinical trials. Very similar to aprotinin, nafamostat has a inhibitory effect on both coagulation and fibrinolysis, but it has also been shown to preserve platelet function and attenuate systemic inflammatory response. The drug is usually administered as a continuous infusion of 2 mg/kg/hour.

Four Japanese, controlled clinical trials in patients undergoing CPB surgery, have shown a reduction of postoperative blood loss in patients who received nafamostat compared with controls.[88-91] One small, controlled study in 22 patients undergoing hepatic resection for hepatocellular carcinoma showed a significant reduction of fibrinolytic activity and a reduced blood transfusion rate in patients who were treated with nafamostat.[92] Larger placebo-controlled RCT are needed to define the exact role of nafamostat in reducing blood loss and transfusion requirements during surgery.

5. Procoagulant Drugs

5.1 Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin or DDAVP) is a synthetic analogue of vasopressin. After intravenous or intranasal administration it increases the plasma levels of factor VIII and von Willebrand factor.[93] These factors are most likely released from intracellular storage pools in the endothelial cells, which explains the immediate effect after intravenous administration of desmopressin. Platelet membrane expression of GPIb and GPIIb/IIIa is also enhanced, which is believed to explain its haemostatic effect in patients with quantitative or qualitative platelet dis-

orders. The increase of coagulation factors, which mimics replacement therapy with blood products, contributes to the prohaemostatic effect of desmopressin in patients with mild haemophilia A and von Willebrand disease.

Many studies have shown the efficacy of desmopressin in decreasing bleeding times and blood loss during surgical procedures in patients with pre-existing haemostatic disorders.[93] Adverse effects of desmopressin include mild facial flushing, headache, palpitations and hypotension. Other adverse effects are the result of the potent antidiuretic effect of this agent, and include water retention and hyponatraemia.[94] Several case-reports on acute myocardial infarction after desmopressin infusion have been published.[95] Desmopressin should therefore be used with caution in patients with coronary heart disease. It is considered to be contra-indicated in patients with unstable coronary artery disease.

5.1.1 In Congenital Bleeding Disorders

The use of desmopressin in surgical patients was first described by Mannucci et al.[96] for patients with haemophilia A and von Willebrand's disease. The optimal dose in patients with congenital bleeding disorders is an intravenous bolus of 0.3 μg/kg. Doses can be repeated at intervals of 12 to 24 hours, although tachyphylaxis can develop after repeated doses. Although RCT have never been performed to demonstrate the efficacy of desmopressin in patients with haemophilia A or von Willebrand disease, the empirical evidence is so strong that such trials are found to be unnecessary and unethical.

5.1.2 In Acquired Bleeding Disorders

Desmopressin reduces the bleeding time in patients with uraemia, cirrhosis or aspirin-induced platelet dysfunction. It is assumed that this reduction in bleeding time correlates with a reduction in surgical blood loss. However, controlled studies have not been performed to substantiate this assumption, except for the use during cardiac surgery in patients with aspirin-induced thrombopathy. Several randomised, placebo-controlled trials have shown decreased blood loss and transfusion requirements during cardiac surgery in patients with aspirin-induced platelet dysfunction treated with desmopressin compared with placebo-recipients.[97-99]

5.1.3 In Patients Without Pre-existing Bleeding Disorders

Desmopressin has been used in patients undergoing cardiac operations to reduce postoperative blood loss and transfusion requirements. Although the initial studies seemed to favour a beneficial effect of desmopressin in reducing blood loss after CPB,[100] these promising results were not confirmed in subsequent, large RCT.[101-104] In a recent meta-analysis of all RCT, the use of desmopressin resulted in a small decrease in peri-operative blood loss but was not associated with a beneficial effect on other clinical outcomes.[30] In fact, desmopressin was associated with a 2.4-fold increased risk of peri-operative myocardial infarction compared with placebo (odds ratio 2.39; 95% confidence interval 1.02–5.60). Therefore, the routine use of desmopressin in uncomplicated cardiac operations is not recommended.

However, its use may be beneficial in subgroups of patients with an increased risk of bleeding complications, such as re-operations or combined valve replacement-coronary artery bypass grafting. This is supported by one randomised, double-blind, placebo-controlled trial, which demonstrated that a subgroup of patients, who can be identified to have a high risk of excessive bleeding after cardiac surgery by using a new point-of-care test (hemoSTATUS), can benefit from the administration of desmopressin.[105] As discussed in the previous section (5.1.2), some studies have shown that desmopressin reduces blood loss and transfusion requirements in patients who received aspirin up to the time of operation. In one randomised trial in patients undergoing surgery for complex congenital cardiac defects, no differences in blood loss and transfusion requirements were found between desmopressin and placebo groups.[106]

Other surgical procedures in which the use of desmopressin has been studied are orthopaedic operations, such as scoliosis surgery[107] and elective total hip arthroplasty,[108,109] and vascular proce-

dures, such as elective aortic surgery.[110,111] There were no significant differences in blood loss or transfusion requirements when desmopressin was used in any of these types of surgery. Although one initial trial in patients undergoing Harrington rod spinal fusion surgery reported a 32% reduction in blood loss and 26% reduction in transfusion requirements in patients who received desmopressin compared with placebo, this could not be duplicated by others.[112] Therefore, overall evidence does not support a beneficial effect of desmopressin in haemostatically normal patients undergoing elective surgical procedures.

5.2 Recombinant Factor VIIa (Eptacog Alfa)

rFVIIa acts by enhancing the natural coagulation pathway by activating formation of the prothrombinase complex, and has a local action only at sites where tissue factor and phospholipids are exposed. Another possible mechanism of action of rFVIIa may be tissue factor-independent. Several studies have shown that rFVIIa can bind activated platelets. Bound to the platelet surface, rFVIIa activates factor X. Therefore, high levels of rFVIIa enhance the amount of thrombin generated at the platelet surface.[113] This last mechanism may explain the effectiveness of rFVIIa in treatment of bleeding episodes in patients with platelet function disorders.[114]

5.2.1 In Haemophilia Patients with Inhibitors

rFVIIa has a short half-life of only 2.7 hours. It was originally developed for patients with haemophilia with inhibitors.[5] Patients with haemophilia can develop neutralising antibodies against the missing coagulation factor (factor VIII or IX). This may result in life-threatening bleeding, because these bleedings are difficult to manage by usual measures, such as the infusion of large amounts of coagulation factor concentrates. Surgical interventions in these patients are a real challenge and were contra-indicated in the past because of the risk of uncontrollable bleeding.

Several studies have shown that surgery in these patients with high-titre inhibitors against factor VIII or IX can be performed safely using rFVIIa. The first study by Shapiro et al.,[115] showed that a dosage of 90 μg/kg immediately before and during surgery, every 2 hours post-operatively for 48 hours, and every 2 to 6 hours for the next 3 days was effective in achieving haemostasis in almost all patients. Since then these findings have been confirmed in other studies and rFVIIa is considered to safely treat haemophilia patients with inhibitors.

The mode of administration of rFVIIa is still a matter of debate. Some studies have shown that continuous infusion, which is easier to handle than bolus injections every 2 hours, results in a satisfactory haemostatic response,[116,117] however, others have reported continuous infusion to be ineffective.[118] Mauser et al.[119] recently reported that continuous infusion was not effective in most patients with mucosal bleedings after surgery in the oral cavity but very effective in other types of surgery. They suggested that this might be because of the inability of continuous infusion of rFVIIa to inhibit fibrinolysis. Despite these conflicting results, rFVIIa can be administered by continuous infusion as long as levels of factor VII:C of 30 to 40 IU/ml are achieved in the immediate postoperative period and levels are maintained above 10 U/ml thereafter.[120]

A major concern when using activated coagulation factors such as rFVIIa is the possible induction of disseminated intravascular coagulation (DIC) or thromboembolism. However, in the many studies on the use of rFVIIa performed so far, laboratory investigations have not revealed systemic activation of the coagulation cascade.[6] In the same analysis of nearly 2000 patients treated with rFVIIa no venous nor arterial thromboembolic events occurred.[6] More recently, a case of acute myocardial infarction following administration of rFVIIa has been reported.[121] However, the patient received additional treatment with rFVIIa after coronary intervention without further complications.

5.2.2 In Other Hereditary or Acquired Disorders of Haemostasis

In the past decade it has become apparent that rFVIIa is a pan-haemostatic agent, and that its use

can be extended to covering surgical procedures and treating bleeding episodes in other disorders of haemostasis, such as factor VII deficiency, thrombocytopenia and –pathia, acquired von Willebrand disease, uraemia and liver disease. This is illustrated by a series of case reports and small studies.[114,122-126]

Recently, the use of rFVIIa has been studied in patients with liver disease, undergoing orthotopic liver transplantation[127] or laparoscopic liver biopsy.[128] Patients with liver disease frequently have a bleeding diathesis due to multiple coagulation defects. Not only a decrease of coagulation factors (especially factor VII) due to a decreased synthesis by the diseased liver, but also thrombocytopenia and –pathia, and excessive fibrinolysis may result in excessive bleeding during surgery. A preliminary study on prothrombin time (PT) in patients with cirrhosis showed a correction of the PT in all patients treated with rFVIIa in a dosage of 90 μg/kg.[129] Similar observations have been made in a RCT comparing four different doses of rFVIIa (5, 20, 80 and 120 μg/kg bodyweight) in patients with liver disease undergoing laparoscopic liver biopsy.[128] The PT was corrected to normal values in the majority of patients and duration of this effect was dependent on the dose of drug. However, the authors could not demonstrate a correlation between the dose of rFVIIa and the time to haemostasis at the biopsy site. A recently reported pilot-study in six patients undergoing orthotopic liver transplantation showed a significant reduction of blood loss and red cell transfusions in patients treated with a single dose of rFVIIa.[127] A limitation of this study was the comparison with a historical control group. A recently performed randomised, placebo-controlled trial on single-dose rFVIIa (20, 40 or 80 μg/kg) in liver transplantation, however, could not confirm the previous findings.[130] There was no significant reduction of red cell transfusion or blood loss. Importantly, there were no more adverse effects in patients treated with rFVIIa, especially not an increased risk of hepatic artery thrombosis. Future studies will focus on higher and more frequent dose administration of rFVIIa during liver transplantation.

5.2.3 In Surgery in Patients with Normal Haemostasis

The use of rFVIIa is not restricted to patients with a pre-existing disorder of haemostasis. Friederich et al.[131] recently reported the use of rFVIIa in patients without coagulation defects undergoing radical prostatectomy. Before surgery a single dose of rFVIIa 20 or 40 μg/kg was given and compared to placebo. A significant reduction of blood loss of 45% was seen in the patients treated with rFVIIa and no adverse effects were noted. This study is of major importance because it indicates that red cell transfusion can be reduced in individuals with normal haemostatic function during surgery by a single dose of rFVIIa.

In several case reports of patients without pre-existent coagulation disorders, who bled profusely during various surgical procedures, the use of rFVIIa was reported to stop bleeding very efficiently.[132-134] Therefore, one might consider the use of rFVIIa in severe bleeding during surgical procedures, if other treatment modalities have failed. However, results of currently ongoing large RCT are awaited before wider application of rFVIIa is considered.

6. Miscellaneous

6.1 Conjugated Estrogens

Conjugated estrogens have a variety of effects on the haemostatic system. Although the exact mechanisms whereby conjugated estrogens exert their effects are unknown, there is evidence that they increase levels of factors XII and VII, and von Willebrand factor. They may also increase levels of physiological inhibitors of coagulation, such as antithrombin. Clinically, the use of estrogens results in shortening of prolonged bleeding times, especially in patients with uraemia. The recommended dosage in uraemic patients is a single daily infusion of 0.6 mg/kg for 4 to 5 days, which will result in a shortening of the bleeding time by approximately 50%.

Very few randomised, placebo-controlled trials have been conducted to determine the efficacy of estrogens in reducing blood loss during surgery. In one randomised, placebo-controlled trial in patients undergoing orthotopic liver transplantation conjugated estrogens were shown to significantly reduce blood transfusion requirements.[135] In a non-randomised study, the use of conjugated estrogens has also been shown to significantly reduce postoperative bleeding after paediatric scoliosis surgery by 37% compared with controls. In general, conjugated estrogens are very well tolerated, and have no or negligible adverse effects.

6.2 Epoprostenol

Epoprostenol (prostacyclin or prostaglandin I_2) is a naturally occurring inhibitor of platelet activation and aggregation. It stimulates platelet adenylate cyclase and increases platelet cyclic adenosine monophosphate. Epoprostenol has a very short half-life of approximately 3 minutes. On the basis of its inhibitory effect on platelets it was hoped that epoprostenol could restore or preserve platelet function and number during CPB. The use of epoprostenol before or during CPB has been studied in a few RCT.[136-138] There were no significant differences in intraoperative or total blood losses, but major problems with hypotension were encountered as a result of its powerful vasodilator effects. Because of these serious adverse effects and the lack of a proven effect on blood loss, the use of this drug cannot be recommended in surgical patients.

7. Conclusions

In general, surgical haemostasis and pharmacological therapies can be complementary in controlling blood loss in surgical patients. Whereas adequate surgical haemostasis may suffice in many patients, even when there is a mild coagulation defect present, pro-haemostatic pharmacological agents may be of additional benefit in patients with (diffuse) surgical bleeding or in patients with a specific underlying haemostatic defect. The use of pharmacological therapies to reduce blood transfusions in surgery has historically been restricted to a few drugs. Novel and potentially very potent drugs, like rFVIIa, are currently under investigation. Topical agents, such as fibrin sealants have been successfully used in a wide variety of surgical procedures. However, only very few RCT have been performed and scientific evidence supporting their use is still limited. Desmopressin is the treatment of choice in patients with mild haemophilia A and von Willebrand disease.

Until recently, most research in patients without congenital coagulation disorders has focused on patients undergoing cardiac surgery using CPB. Other types of surgery, such as major orthopaedic procedures, liver surgery and major vascular procedures have been studied more recently. Of the therapies that have been used to reduce blood loss and transfusion requirements in cardiac surgery, the antifibrinolytic agents have the best evidence supporting their use. The lysine analogues aminocaproic acid and tranexamic acid are probably equally effective as, and have similar safety to, the serine protease inhibitor aprotinin in reducing blood loss during cardiac surgery. However, aprotinin has the additional advantage of inhibiting the systemic inflammatory response during CPB as compared with the lysine analogues. Moreover, there is evidence for a cerebroprotective effect of high-dose aprotinin. Desmopressin has not been consistently shown to decrease blood transfusion requirements in uncomplicated cardiac surgery and its routine application is therefore not supported. However, more recent studies have indicated that it may be beneficial with improved monitoring and in subgroups of patients with platelet dysfunction.

Outside the field of cardiac surgery, there is very limited or contradictory evidence of efficacy of most haemostatic drugs in surgical patients without congenital haemostatic abnormalities. The only exceptions are patients undergoing (major) orthopaedic surgery and patients undergoing orthotopic liver transplantation, who have been shown to benefit from antifibrinolytic therapy, especially aprotinin, in a number of RCT.

rFVIIa is a novel and potent procoagulant drug that has been used for the prevention or treatment of bleeding in patients with haemophilia and inhibitors, either in surgical or non-surgical situations. Preliminary data indicate that it may also be effective in surgical patients without pre-existing coagulation abnormalities. It has been successfully used as salvage therapy in difficult surgical cases where bleeding had been refractory to various other treatment modalities. More clinical trials are warranted before definitive conclusions can be made about the safety and the exact role of this new drug in surgical patients.

Only adequately powered and properly designed RCT will allow us to define the most effective and the safest pharmacological therapies for reducing blood loss and transfusion requirements in surgical patients.

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