

Management of Bleeding Disorders by Prohemostatic Therapy

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Abstract

Pro-hemostatic therapy aims at an improvement of hemostasis, which may be achieved by amelioration of primary hemostasis, stimulation of fibrin formation or inhibition of fibrinolysis. These treatment strategies may be applied to specifically correct a defect in one of the pathways of coagulation, but have in some situations also been shown to be effective in reducing bleeding in patients without a primary defect in coagulation. Besides the transfusion of platelets in case of thrombocytopenia or severe platelet disorders, a pharmacological improvement of primary hemostasis may be achieved by the administration of desmopressin. The administration of DDAVP results in a marked increase in the plasma concentration of Von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable potentiation of primary hemostasis as a consequence. DDAVP is used for the prevention and treatment of bleeding in patients with von Willebrand disease or mild hemophilia A, and further in patients with an impaired function of primary hemostasis, such as in patients with uremia, liver cirrhosis or in patients with aspirin-associated bleeding. Based on the current insight that activation of coagulation in vivo predominantly proceeds by the tissue factor/ factor VII(a) pathway, recombinant factor VIIa has been developed as a prohemostatic agent and has recently become available for clinical use. Indeed, in uncontrolled clinical studies this compound has been shown to exert a potent procoagulant activity and appeared to be highly effective in the prevention and treatment of bleeding, although most experience so far has been obtained in patients with severe and complicated coagulation defects. At present, a more general use of this agent for bleeding patients without an apparent coagulation defect is the subject of a number of ongoing clinical trials. Agents that exert anti-fibrinolytic activity are aprotinin and the group of lysine analogues. The pro-hemostatic effect of these agents proceeds not only by the inhibition of fibrinolysis (thereby shifting the procoagulant/anticoagulant balance towards a more procoagulant state), but also due to a protective effect on platelets, as has been demonstrated at least for aprotinin. The mechanism of this platelet-protective effect has, besides a potential prevention of plasmin-mediated loss of platelet receptors not been elucidated. Whether the pro-hemostatic effect of the anti-fibrinolytic agents will eventually result in a higher incidence of thromboembolic complications is still a matter of debate (see further), however, this has so far not been shown in straightforward clinical trials.

1. Introduction

Pharmacological agents may interfere in the balance between activation of coagulation and physiological anticoagulation. Anticoagulant strategies are frequently used in clinical practice and have proven to be effective in the prevention and treatment of thrombotic disease. Similarly, other agents are capable of promoting hemo-

stasis or fibrin formation, or can block fibrinolytic activity. These so-called 'pro-hemostatic agents' may be useful in the prevention and treatment of bleeding in patients with coagulation defects, but also in patients with an a priori normal coagulation system, who experience severe (post-operative) bleeding or are to undergo procedures known to be associated with major blood loss [1,2]. In this review we will discuss the aims and

potential risks of prohemostatic therapy, the various agents with a prohemostatic potential and the efficacy of prohemostatic drugs to reduce perioperative blood loss or treat excessive (postoperative) bleeding.

2. General Considerations Regarding Efficacy and Safety of Pro-hemostatic Treatment

Most experience with pro-hemostatic therapy has been accumulated in the prevention and treatment of bleeding in patients with congenital and acquired coagulation defects. Indeed, specific correction of a hemostatic defect is highly effective in this situation, as for example has been shown in the management of hemophilia with coagulation factor concentrates. There is, however, increasing evidence that also in patients with less specific abnormalities or even a normal coagulation status and who encounter severe bleeding or are at high risk for bleeding, promoting hemostatic function may be of benefit [3,4]. Interestingly, there seems in general not to be a strong need to specifically target a factor or pathway in the coagulation or fibrinolytic system that is causally related to the hemostatic defect, since interference in one part of the system may be able to compensate for a defect in another part.

The safety of pro-hemostatic therapy also deserves some consideration. Interfering in the balance between coagulant and anticoagulant mechanisms can indeed result in undesirable adverse effects. The best illustration may be the higher risk of bleeding in patients receiving anticoagulant therapy. Conversely, pro-hemostatic agents may, at least theoretically, predispose for thrombotic complications. The occurrence of such complications, which are fortunately relatively rare, seems to be very much dependent on considerate clinical use of this therapy. In fact, the expected benefit of the application of pro-hemostatic agents in distinct clinical situations should be balanced with the risk of thrombosis in that particular patient population. Ideally, the benefit/risk ratio should be evaluated in properly controlled clinical trials.

3. Platelets, Plasma and Coagulation Factor Concentrates

Platelet transfusion may be considered in patients with severe thrombocytopenia and bleeding or at risk for bleeding [5]. Platelet concentrates usually contain a mixture of the platelet preparation of a blood donation from 5-6 donors (equals 5-6 units). After platelet transfusion, the platelet count should rise with at least $5 \times 10^9/l$ per unit of platelets transfused. A lesser response may be present in patients with fever, a consumptive coagulopathy, or splenomegaly, or may indicate alloimmunization of the patient after repeated transfusion. Platelet transfusion is particularly effective in patients with a thrombocytopenia due to impaired platelet production or increased consumption, whereas in disorders of enhanced platelet destruction (for example immune thrombocytopenia) alternative therapies, such as

Table 1.

Suggested transfusion guidelines for platelet concentrates

- platelet count $< 10 \times 10^9/l$
- platelet count $< 50 \times 10^9/l$ with demonstrated bleeding or a planned surgical/invasive procedure
- documented platelet dysfunction (e.g. prolonged bleeding time) with (microvascular) bleeding or undergoing a surgical/invasive procedure and (assumed) insufficient efficacy of other interventions (e.g. desmopressin)
- bleeding patients or patients undergoing a surgical procedure who require more than 10 U of packed red cells

Suggested transfusion guidelines for fresh frozen plasma

- correction of multiple or specific coagulation factor deficiencies in bleeding patients or if a surgical/invasive procedure is planned
 - congenital deficiencies of a specific factor (provided specific factor concentrates are not available, e.g. factor XI)
 - acquired deficiencies, e.g. related to liver disease, massive transfusion or disseminated intravascular coagulation
- volume replacement in case of severe bleeding to avoid massive transfusion of gelatin or crystalloid solutions
- thrombocytopenic thrombotic purpura

steroids or human immunoglobulin, may provide better results. Basic guidelines for platelet transfusion are given in Table 1.

Fresh or frozen plasma contains all coagulation factors and may be used to replenish congenital or acquired deficiencies in these factors. For more specific therapy or if the transfusion of large volumes of plasma is not desirable, fractionated plasma of purified coagulation factor concentrate is available. Suggested guidelines for the use of fresh frozen plasma are given in Table 1.

Prothrombin complex concentrates (PCC's) contain the vitamin K-dependent coagulation factors II, VII, IX and X. Hence, these concentrates may be used if immediate reversal of coumarin therapy is required. Also, PCC's may be used if a global replenishment of coagulation factors is necessary and large volumes of plasma are not tolerated. One should realize, however, that in such cases only a selected number of coagulation factors is administered and important deficiencies of for example factor V or fibrinogen are not treated.

Cryoprecipitate is fractionated plasma, which mainly contains von Willebrand factor, factor VIII and fibrinogen. However, due to the problems in the production of cryoprecipitate, particularly with regard to the standards to prevent the transmission of infectious agents, in most parts of the Western world cryoprecipitate is not available anymore.

For a selected number of clotting factors purified concentrates, containing only that specific factor, are available. These concentrates are in particular useful in case of an isolated (usually congenital) deficiency of a

single clotting factor, such as factor VIII concentrate for the treatment of hemophilia A. These concentrates may consist of clotting factors that are purified by affinity chromatography of plasma, however, recombinant coagulation factors are increasingly used [6].

4. Desmopressin

De-amino D-arginine vasopressin (DDAVP, desmopressin) is a vasopressin analogue that despite minor molecular differences has retained its antidiuretic properties but has much less vaso-active effects [7]. DDAVP induces release of the contents of the endothelial cell associated Weibel Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable potentiation of primary hemostasis as a consequence. DDAVP can be administered parenterally by different routes (intravenously, subcutaneously, and intranasally) but is mostly administered by intravenous administration, which results in an immediate pro-hemostatic effect. DDAVP is used for the prevention and treatment of bleeding in patients with von Willebrand disease or mild hemophilia A, and further in patients with an impaired function of primary hemostasis, such as in patients with uremia, liver cirrhosis or in patients with aspirin-associated bleeding [8].

A rare but important adverse effect of DDAVP is the occurrence of acute myocardial infarction, particularly in patients with unstable coronary artery disease, probably due to the remaining vaso-active effect of the drug. Hence, in these patients the use of DDAVP is contraindicated. The antidiuretic effect of DDAVP is clinically not very significant and may be dealt with by fluid restriction for some time. An exception to this rule are children, who may experience a severe dilution hyponatremia after the administration of DDAVP, which should be monitored clinically for 24 hours after its administration.

5. Recombinant Factor VIIa

Based on the current insight that activation of coagulation *in vivo* predominantly proceeds by the tissue factor/factor VII(a) pathway, recombinant factor VIIa (NovoSeven[®]) has been developed as a prohemostatic agent and is now available for clinical use [9]. Indeed, recombinant factor VIIa appears to exert potent pro-hemostatic effects. Most experience with recombinant factor VIIa has been accumulated in patients with severe coagulation defects that are difficult to treat, such as patients with antibodies to coagulation factors and excessive bleeding. In addition, in patients with severe thrombocytopenia or disorders of primary hemostasis that fail to respond to conventional treatment, recombinant factor VIIa has been applied. In most of these situations administration of recombinant factor VIIa was shown to be effective in controlling bleeding, although most of

the reports are uncontrolled series. Recombinant factor VIIa acts primarily by a tissue factor-dependent mechanism, which limits its action to the site of bleeding, although some tissue factor-independent effects (potentially on the platelet surface) may play a role as well [10]. At present, a more general use of this agent for bleeding patients without an apparent coagulation defect is the subject of a number of ongoing clinical trials. One of these trials in patients who underwent abdominal prostatectomy demonstrated that the administration of recombinant factor VIIa was associated with a 50% reduction in perioperative blood loss, thereby completely eliminating the need for blood transfusion [11]. Preliminary results of other trials in liver surgery and trauma patients show promising results as well. Although so far only a very limited number of thrombotic complications of recombinant factor VIIa treatment have been reported in these trials, the safety of this strategy in a general, elderly population with potential co-morbidity remains to be established. Lastly, but importantly, the very high costs of recombinant factor VIIa, might limit its widespread use in clinical practice.

6. Antifibrinolytic Agents

Agents that exert anti-fibrinolytic activity are aprotinin and the group of lysine analogues [1,2]. The pro-hemostatic effect of these agents proceeds not only by the inhibition of fibrinolysis (thereby shifting the procoagulant/anticoagulant balance towards a more procoagulant state), but also due to a protective effect on platelets, as has been demonstrated at least for aprotinin. The mechanism of this platelet-protective effect has, besides a potential prevention of plasmin-mediated loss of platelet receptors not been elucidated. Whether the pro-hemostatic effect of the anti-fibrinolytic agents will eventually result in a higher incidence of thromboembolic complications is still a matter of debate (see further), however, this has so far not been shown in straightforward clinical trials.

Aprotinin is a 58 amino acid polypeptide, mainly derived from bovine lung, parotid gland or pancreas. Aprotinin directly inhibits the activity of various serine proteases, including plasmin, coagulation factors or inhibitors, and constituents of the kallikrein-kinin and angiotensin system. This rather aspecific mode of action of aprotinin is frequently considered as a disadvantage for its use, however, the interactions of aprotinin with proteases other than plasmin have never been demonstrated to cause clinically important adverse effects. The clinically most important side effect of aprotinin is a rarely occurring but sometimes serious allergic or anaphylactic reaction. The use of aprotinin is contra-indicated in case of ongoing systemic intravascular activation of coagulation, as in disseminated intravascular coagulation (DIC), and in patients with renal failure.

Lysine analogues, i.e. ϵ -aminocaproic acid and tranexamic acid are potent inhibitors of fibrinolysis [1,2]. The antifibrinolytic action of lysine analogues is based on the competitive binding of these agents to the lysine-

binding sites of a fibrin clot, thereby competing with the binding of plasminogen. Impaired plasminogen binding to fibrin delays the conversion of plasminogen to plasmin and subsequent plasmin-mediated fibrinolysis, which then proceeds at an inefficient and slow rate. Subtle molecular variations between different lysine analogues may have important consequences for their fibrinolysis-inhibiting capacity. Indeed, tranexamic acid (Cyklokapron[®]) is at least ten times more potent than ϵ -aminocaproic acid (Amicar[®]). The use of lysine analogues is contra-indicated in situations with ongoing systemic activation of coagulation (such as in DIC) and furthermore in case of macroscopic hematuria, since the inhibition of urinary fibrinolysis due to the high concentrations of the antifibrinolytic agent in the urine may result in deposition of urinary tract-obstructing clots.

7. Other Prohemostatic Agents

Conjugated estrogens preparations may cause an improvement of primary hemostasis. However, except for a limited number of mostly uncontrolled studies in patients with an uremic thrombocytopathy and preliminary observations in patients who undergo liver transplantation, there is no sound evidence for the use of these agents to prevent or treat peri-operative bleeding.

Fibrin sealant, usually consisting of a combination of human fibrinogen and bovine thrombin may be used as a topical hemostatic agent. Although a number of controlled studies have shown the efficacy of this treatment in various surgical situations, there is no evidence that application of fibrin sealant results in a reduction of intraoperative or postoperative blood loss or other clinically significant outcome measures. Besides, fibrinogen is usually derived from human donor plasma, which may carry the risk of transmission of blood borne diseases. Moreover, the bovine origin of the thrombin may result in the formation of anti-coagulation factor antibodies that may cross-react with human coagulation factors, resulting in a potentially severe bleeding tendency.

8. Reduction of Peri-operative Blood Loss

Peri-operative blood loss may be due to surgical causes or to a defective hemostasis and in some complicated situations a combination of these causes may be present³. For example, cardiac surgery, in particular coronary artery bypass surgery and heart valve replacement, is frequently associated with major blood loss. A large number of studies have focussed on the potential beneficial effect of aprotinin on the prevention of (excessive) bleeding in patients undergoing cardiac surgery. Randomized, controlled trials invariably showed that administration of aprotinin resulted in a reduction of perioperative blood loss, postoperative chest tube drainage, the number of transfused units and the number of patients receiving any transfusion. Most studies showed at least a 40% reduction in perioperative blood loss in patient with various a priori risks for the de-

velopment of excessive perioperative bleeding (low risk patients, re-operations, patients undergoing prosthetic valve implantation in combination with coronary artery by-pass grafting etc.) and a 50% reduction in transfusion requirements. However, these figures need to be interpreted with caution because of the substantial inter-center variations in blood-saving techniques and transfusion practice, for example due to different "transfusion triggers". Furthermore, a number of clinical studies revealed that aprotinin reduced the incidence of re-thoracotomy due to excessive bleeding, however, the number of patients in the trials was not sufficiently high to reach statistical significance. Recently, several meta-analyses have been performed summarizing the placebo-controlled clinical trials with aprotinin [12,13]. These meta-analyses show a mean reduction in blood loss of 400 ml and a 3-fold lower need to give any transfusion in cardiac surgery patients that had received aprotinin. Moreover, the two most recent meta-analyses show that the use of aprotinin results in a 3-fold reduction in the incidence of re-exploration and the results of one of these studies indicate a 2-fold reduction in mortality as compared with placebo.

The potential blood loss-reducing effect of another anti-fibrinolytic therapy, i.e. with lysine-analogues, has also been investigated in a number of clinical trials. Generally, ϵ -aminocaproic acid showed insufficient efficacy as compared to tranexamic acid and most studies have focussed on the latter agent. Tranexamic acid reduced bleeding after cardiac surgery, resulting in reduced transfusion requirements and a smaller number of patients that needed any transfusion. The effects of high dose tranexamic acid (up to 10 gram peri-operatively) resulted in a 40% reduction in blood loss and a 50% reduction in the number of transfused units in most controlled clinical trials. The above mentioned meta-analyses of all studies with lysine-analogues showed a 40% reduction in the number of patients that received any blood product and an about 2.5-fold reduction in the incidence of re-exploration [12]. A number of recent studies have been initiated directly comparing aprotinin and tranexamic acid. A meta-analysis of these trials appear to indicate a higher efficacy of aprotinin as compared with lysine analogues, although the differences in the most important clinical endpoints, i.e. mortality and re-thoracotomy, did not reach statistical significance. Also, it should be noted that the use of aprotinin may result in a severe anaphylactic reaction, whereas lysine analogues are devoid of such serious adverse events. Lastly, aprotinin is much more expensive as compared with lysine analogues.

Placebo-controlled trials have provided evidence that the administration of desmopressin reduces peri-operative blood loss (15-40%) and decreases transfusion requirements (30%) in patients undergoing coronary artery bypass surgery [14]. However, these favorable findings were not confirmed in other trials that did show no beneficial effect of desmopressin in the prevention of (excessive) peri-operative blood loss.

Another example is major liver surgery and in par-

ticular orthotopic liver transplantation, which may be associated with excessive blood loss. Factors which, in addition to surgical causes, contribute to this complication are impaired synthesis of coagulation proteins by the diseased liver, a pre-existing thrombocytopenia and thrombocytopeny, and impaired clearance of activated coagulation and fibrinolytic factors during the brief anhepatic phase. A few number of relatively small randomized controlled trials show that the administration of either aprotinin or tranexamic acid results in the reduction of blood loss and transfusion requirements¹⁵. However, studies on the appropriate dose of these agents have yielded conflicting results and the definitive place of these pro-hemostatic agents in extensive liver surgery needs to be established. Initial experience with recombinant factor VIIa (see before) seems to show a beneficial effect of this agent in patients undergoing liver transplantation.

9. Management of Excessive (Postoperative) Bleeding

Systemic coagulation defects in severely bleeding patients with a previously normal coagulation system may in general be caused by two different mechanisms: (1) loss of platelets and coagulation factors due to bleeding and dilution of these elements upon massive transfusion of red cells and plasma substitutes, and (2) consumption of platelets and coagulation factors in the framework of disseminated intravascular coagulation [3].

Patients with severe blood loss may require massive fluid replacement therapy with blood substitutes such as crystalloid, colloid, dextran and starch solutions. The use of these synthetic plasma volume expanders in excess of 1 liter/hour is, however in some cases associated with an impairment of primary hemostasis (most probably due to interference with von Willebrand factor function) and the plasma coagulation system (due to dilution). This has in particular been established for dextrans and gelatin-based plasma volume expanders [16]. Hence, the disproportionate use of these products may result in a deterioration of the hemostatic capability of a patient and potentially aggravate the bleeding. Therefore, if there is need for massive expansion of circulating volume in bleeding patients or patients at risk for bleeding, these preparations should be used in combination with fresh frozen plasma.

Transfusion with large amounts of packed red cells without concomitant replacement of platelets and coagulation factors may cause a generalized dilution coagulopathy¹⁷. This might be easily monitored by a decrease in platelet count to usually $50-100 \times 10^9/l$ and a prolongation of global clotting times (aPTT and PT). Although there is no evidence from clinical studies to support this practice, it is generally recommended that in bleeding patients who need massive transfusion of red cells, for every 2-3 units of red cells, 1 unit of plasma is administered. In the absence of other factors that may cause a coagulation defect, this will result in a (near) normalization of coagulation times. Regarding the

low platelet count a more conservative strategy appears to be justified. A prospective trial showed no benefit of prophylactic transfusion of platelets in patients that received more than 12 units of red cells in a short period of time. However, retrospective analyses show that in bleeding patients with a platelet count lower than $50 \times 10^9/l$, transfusion of platelets is effective. Hence, the threshold for platelet transfusion in patients with bleeding can be held at $50 \times 10^9/l$, unless a defective platelet function is suspected. In that case a platelet transfusion at higher platelet counts could be considered.

Pharmacotherapeutic interventions to improve hemostasis may in some exceptional cases be contemplated, although there is not a lot of evidence from clinical trials to support this strategy. These interventions may consist of antifibrinolytic treatment, such as the administration of -aminocaproic acid, tranexamic acid, or aprotinin. It is from a theoretical viewpoint not useful to combine these antifibrinolytic therapies. Lysine analogues have been shown to be helpful in the management of patients with upper gastro-intestinal bleeding, although this may be less relevant with the current possibilities of local hemostatic therapy in these patients. The administration of recombinant factor VIIa has shown impressive effects in patients with excessive bleeding in a small series of case-reports, but the safety and efficacy of this approach will definitely need further study.

10. Conclusions

Pro-hemostatic therapy may achieve an improvement of hemostasis, by amelioration of primary hemostasis, stimulation of fibrin formation or inhibition of fibrinolysis. Pro-hemostatic interventions appear to be effective in reducing peri-operative blood loss and reducing transfusion requirements in specific situations and may be helpful adjuncts in the management of severe spontaneous and post-operative bleeding. The risk of a higher incidence of thrombotic complications associated with the use of pro-hemostatic therapy is unknown but seems not to be very high in clinical practice. There is a need for more systematic and adequately controlled clinical observations to better establish the efficacy and safety of pro-hemostatic interventions.

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