Antifibrinolysis and Blood-Saving Techniques

Antifibrinolytic Therapy in Cardiac Surgery

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Bleeding remains an important complication after repeat and complicated cardiac surgery. Although aprotinin has recently been approved by the Food and Drug Administration for use as an antifibrinolytic agent, many surgeons continue to have concerns about its added cost and potential side effects. We review here the current state of antifibrinolytic therapy for excessive bleeding in cardiothoracic surgery and suggest the use of a single intravenous dose of 10 g of ε-aminocaproic acid immediately before cardiopulmonary bypass as a safe, inexpensive, and effective alternative to aprotinin. Further clinical and laboratory studies are needed to confirm or modify this protocol. ***(Tex Heart Inst J 1995;22:211-5)***

Bleeding continues to be a significant complication after cardiac surgery, even in the current, state-of-the-art, surgical practice. Public apprehension of transfusion-related communicable diseases, particularly acquired immunodeficiency syndrome, has refocused the attention of cardiac surgeons on the importance of hemostasis to minimize the need for, and therefore the risks of, blood transfusion.[1-3] Recent approval by the Food and Drug Administration of aprotinin as an agent for reducing blood loss during surgery has generated enthusiasm among cardiac surgeons. However, the use of aprotinin in routine practice has not been widely accepted because of the added cost, the risk of anaphylactic reaction, and the potential for increased incidence of postoperative myocardial infarction and graft thrombosis.[4-7]

Because both laboratory and clinical data support fibrinolysis as the mechanism of postoperative bleeding in open-heart surgery,[8-12] the use of an antifibrinolytic agent seems appropriate. Three such agents are currently available: aprotinin, tranexamic acid (AMCA), and ε-aminocaproic acid (EACA). Of these, we suggest that EACA, the oldest and least expensive, may also be the best, if it is administered appropriately.

Mechanism and Treatment of Postoperative Bleeding in Cardiac Surgery

Heparin makes open-heart surgery possible because it maintains blood fluidity by markedly enhancing the function of antithrombin III.[13] The appropriate dosage of heparin and its reversal with protamine are essential to achieving hemostasis.[14] However, the large, negatively charged, blood-contacting surface encountered in the perfusion circuits during cardiopulmonary bypass (CPB) incites complement activation, contact activation of the intrinsic pathway of the coagulation cascade, fibrinolysis, and platelet dysfunction.[15,16] The inevitable fibrinolysis in CPB is chiefly caused by the increased production of tissue-type plasminogen activator (t-PA) from endothelium.[17-19] This event creates a locally excessive presence of plasmin, which causes a variety of enzymatic reactions and also results in the dysfunction of platelet receptors, including the Von Willebrand factor receptor (glycoprotein [GP]Ib)[20-23] and the fibrinogen receptor (GP IIb/IIIa).[24-26] This evidence has led Blauhut and colleagues[20] to postulate that hyperfibrinolysis causes secondary platelet dysfunction. Their hypothesis remains controversial, however, in light of other, contradictory data.[27]

In the 1960s and 1970s, treatment of fibrinolysis with EACA in patients with hemorrhagic diathesis was mostly successful.[14,28-32] However, antifibrinolytic therapy was soon dismissed because of the emerging theory that platelet dysfunction was the cause of excessive bleeding; this theory dominated from the late 1970s to the early 1980s.[33,34] Platelet transfusion became the principal treatment for post-

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operative bleeding, especially after protamine neutralization when the bleeding time exceeded 20 minutes. Prophylactic platelet transfusion, however, failed to prevent excessive bleeding.[35,36]

The serendipitous discovery that aprotinin dramatically reduced blood loss and the ensuing active European studies[14,37-39] established the effectiveness of prophylactic therapy with high-dose aprotinin in minimizing the need for blood transfusion in cardiac surgery. Although aprotinin also diminishes contact activation in the coagulation cascade and bradykinin formation, some authors credit the antifibrinolytic function of aprotinin for its reduction in excessive blood loss.[11,20,40] Interest in prophylactic therapy with EACA and AMCA has also been renewed; with 1 exception (in a study of AMCA[28]), all such recent studies have reported a significant reduction in blood loss.[4,14,41-46]

Fibrinolysis and Hemostasis

Like the conversion of prothrombin to thrombin in the coagulation cascade, the conversion of plasminogen to plasmin takes place mainly on the negatively charged surface of platelets and other phospholipids.[13,47] In the presence of fibrin, t-PA markedly enhances the activation of plasminogen.[48,49] Plasmin is a general, nonspecific protease against fibrinogen, fibrin, factor V, factor VIII, protein C, and the platelet glycoprotein receptors.[47,50,51] There are also many plasmin inhibitors, including the α_2-antiplasmin and the reserve inhibitors of α_2-macroglobulin, antithrombin III, C1 esterase inhibitor, α_1-antitrypsin and inter-α-trypsin inhibitor. Surface binding of plasminogen and its activator t-PA, in the tertiary complex with fibrinogen or fibrin, minimizes their degradation by inhibitors and maximizes their enzymatic reactions. In this way, the body appropriately directs the fibrinolytic reaction to the site of injury and repair and simultaneously prevents free plasmin from reacting in the systemic circulation.[47-51]

Coagulopathy in Cardiac Surgery

Despite adequate heparin dosage, the limited but inevitable activation of the intrinsic pathway of the coagulation cascade increases the production of thrombin and plasmin. This phenomenon can be seen during CPB in the significantly elevated levels of fibrin(ogen) degradation product, thrombin–antithrombin complex, and plasmin–α_2-antiplasmin complex.[17,18,20,40] All these activities create a dynamic yet delicate balance between coagulation and fibrinolysis.

Moderate hypothermia has been used routinely to protect the myocardium and the brain in the event of a malfunction in the CPB pump line. Deep hypothermia is also frequently applied for complex congenital repairs or resection of an aortic aneurysm. At 37 °C, a high concentration of plasmin activates platelet aggregation, and a low concentration inhibits platelet aggregation. At 22 °C, however, even very small concentrations of plasmin result in marked platelet activation and culminate in platelet destruction and depletion,[52,53] in addition to the aforementioned dysfunction of platelet receptors and decreased formation of thromboxane.[20,54] This may be the mechanism of postoperative hemorrhagic diathesis in deep hypothermic arrest. Viewed from another perspective, under conditions of low or no flow, the body requires this plasmin effect to ensure a safety margin to maintain the patency of the microvascular circulation and minimize end-organ injuries.

Patients who take aspirin or other nonsteroidal analgesics and undergo cardiac surgery sustain significant postoperative bleeding[55] due to dysfunction of the cyclooxygenase of the nonnucleated platelets in their 7- to 10-day life cycle. Ideally, such patients should delay surgery for 5 to 7 days after stopping the analgesic.[56] Fortunately, this type of thromboxane inhibition is not complete[57] and can be rectified by antifibrinolytic therapy.[7,58,59] Thrombolytic therapy and failed percutaneous angioplasty are other challenging factors in elective or emergent surgery due to the ongoing hyperfibrinolytic process, urgency, and hemodynamic instability.[60]

Because of extensive areas of dissection, multiple anastomoses, and the increasing number of repeat and complex operations in cardiac surgery, surgeons should be careful to stop all surgically correctable bleeding rather than to routinely attribute the bleeding to hypothermia and coagulopathy.

The Timing of Antifibrinolytic Therapy

Antifibrinolytic therapy functions primarily through the lysine binding site of plasminogen or plasmin by interfering with plasminogen activation or the effector mechanism of plasmin.[14,50] The effect of t-PA is enhanced more than 400-fold in the presence of fibrin;[48] therefore, to prevent locally excessive activity of t-PA and plasmin, antifibrinolytic drugs should optimally be present as the coagulation cascade, with its fibrin formation during CPB, is initiated.[48-51] Otherwise, α_2-antiplasmin will instantly begin degrading plasmin, and the decreased concentration of α_2-antiplasmin may contribute to excessive bleeding.[61-63]

Research in which antifibrinolytic therapy was begun before the start of CPB revealed significant reductions in blood loss, whereas studies in which therapy was begun at the conclusion of bypass showed mixed efficacy.[14] The theory behind the use of antifibrinolytic therapy after CPB originated in the finding that fibrinolytic activity increased dramatically after protamine neutralization;[28,64] however, no

data about fibrinolytic activity at the end of CPB were used for comparison. More recent reports[18,20,40] using more sophisticated tests have demonstrated that both coagulation and fibrinolysis peak during or at the end of CPB. Once weaned from CPB, the patient will not be subject to further insult from its effects. Moreover, since the plasma has high concentrations of plasminogen activator inhibitor-type 1 (PAI-1) and C1 esterase inhibitor, as well as a host of plasmin inhibitors,[50,51,65] antifibrinolytic therapy at the end of CPB may not be as crucial as was thought initially and may carry the hazards of hypercoagulability in the period immediately after CPB.

Many questions remain with regard to the delicate and intricate balance between coagulation and fibrinolysis. To further complicate the issue, important fibrinolytic mechanisms exist independent of plasminogen, including other enzyme functions of leukocytes, macrophages, and platelets.[50] Surgeons, therefore, should follow the advice of Hippocrates: first, do no harm. The controversial but significant concerns about an increased tendency toward myocardial infarction, saphenous vein graft thrombosis, and renal dysfunction after aprotinin therapy[6,7] have been echoed in a recent review.[5] Other concerns about aprotinin include the possibility of anaphylaxis, increased antigenicity with repeated use, or increased complement activation.[5,20] Taken together, these uncertainties regarding aprotinin administration indicate that high doses should be used with caution. A report[45] of saphenous vein graft thrombosis after a large dose of AMCA at the conclusion of CPB also raises the possibility of inappropriate timing and dosage of antifibrinolytic therapy. Thus far, there has been no report of thrombotic complication with use of EACA in the presence of adequate heparinization.[66,67]

Currently, many prophylactic protocols for minimizing surgical bleeding require that antifibrinolytic therapy be administered immediately after induction of anesthesia.[4,7,20,38-40] Originally, this policy was based on reports of increased fibrinolytic activity with skin incision[68] and especially with sternotomy.[29] These reports, however, were old or the data were limited. More recent reports of levels of thrombin-antithrombin complex, cross-linked D-dimer, and α_2-antiplasmin have failed to show any meaningful changes in fibrinolysis until after the initiation of CPB.[18,20,40] From these reports, it seems reasonable to conclude that instituting antifibrinolytic therapy well before CPB may not be as essential as emphasized previously.

EACA versus AMCA as an Antifibrinolytic Agent

Compared with EACA, AMCA is 6 to 10 times more potent, has fewer minor side effects, and maintains its concentration in tissue longer.[14,69,70] However, this longer tissue concentration may result in prolonged, unnecessary presence of AMCA in blood and multiple organs. Alternatively, the biological half-life of EACA is around 77 to 80 minutes,[14,69-71] which should be long enough to offset the excessive fibrinolysis that occurs during CPB. Furthermore, the minor side effects of EACA occur only after a prolonged period of administration[69] and have not been reported after CPB.

Treating an established, systemic fibrinolysis requires a serum level of EACA of at least 130 μg/mL; this level can be achieved with an intravenous dose of 5 g of EACA followed by a dose of 1 to 2 g/h.[69-71] However, in an in vitro study designed to simulate prophylactic antifibrinolytic therapy, inhibition of fibrinolysis in samples preincubated with plasmin required a concentration of AMCA less than 10% of that required in samples not preincubated.[72] Studies of EACA have also shown that a serum level of 13 μg/mL is sufficient to inhibit activation of plasminogen.[49,73] Intravenous administration of 10 g of EACA will maintain a serum concentration above 13 μg/mL for more than 6 hours. The 10-g dose of EACA is sufficient to inhibit even an established fibrinolysis for 1 hour and, in clinical practice, to inhibit activation of plasminogen even during a long period of CPB, thereby preventing excessive fibrin degradation.

Three studies in the literature support the protocol of a single intravenous dose of EACA just before CPB. In 1971, Midell and associates[32] reported a 58% reduction in blood loss using 125 mg of EACA per kg of body weight. Jordan and coworkers[46] recently reported a 66% reduction in the transfusion requirement using a 10-g dose of EACA. Arom and Emery[43] have also shown a significant reduction in postoperative drainage using a 5-g dose of EACA.[43] On the basis of these results and of the theoretic advantage discussed earlier, a protocol requiring a single, intravenous, 10-g dose of EACA just before CPB appears to be appropriate.

Conclusion

Prophylactic antifibrinolytic therapy with aprotinin has been established as an effective means of reducing excessive blood loss during cardiac surgery. However, the added cost, the potential life-threatening side effect of anaphylaxis, and the potential increase in incidence of myocardial infarction and saphenous vein graft thrombosis have prevented aprotinin from being used universally in the United States. On the basis of the current literature, we suggest that the intravenous administration of 10 g of ε-aminocaproic acid before cardiopulmonary bypass appears to be a simple, inexpensive, effective, and

safe means to reduce excessive bleeding. This protocol deserves more attention and additional clinical research (particularly in repeat and complex cardiac surgery), including studies of aspirin-pretreated patients and studies of pharmacokinetic and fibrinolytic mechanisms.

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