Review Article

Antifibrinolytics and Cardiac Surgery: The Past, The Present, and The Future

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Abstract

Cardiac surgery is usually associated with significant blood loss, which often necessitates blood transfusion. In order to decrease the risks associated with the latter, pharmacological as well as nonpharmacological strategies have been used to reduce blood loss. Among the pharmacological approaches, antifibrinolytic drugs are the mainstay. Aprotinin, which was the first ubiquitously used drug, fell into disrepute only to re-emerge after much debate. The decline of aprotinin paved the way for the lysine analogs. However, we must be aware with the side effects of these drugs as well as the dose modification required in special situations. Nonsaccharide glycosaminoglycans have been under investigation to overcome the drawbacks of the lysine analogs. It remains to be seen whether these drugs can replace the traditional antifibrinolytics.

Keywords: *Aprotinin, cardiac surgery, glycosaminoglycans, lysine analogs*

Introduction

The issue of excessive blood loss, sometimes necessitating re-exploration, often plagues cardiac surgery. Surgical blood loss has been found to be an independent predictor of in-hospital mortality.[1] Re-exploration for bleeding has been linked to numerous adverse events, such as renal failure, infections, arrhythmias, and prolonged hospital stay.[2] Besides these, delay in re-exploration tends to use up the blood bank resources, thereby exposing the patients to the hazards of blood transfusion. Approximately 50% of cardiac surgical patients receive blood transfusion,[3] which can pose substantial risk.[4,5] Numerous strategies have been used to decrease the same.

Pharmacological strategies have been used from time-to-time to minimize perioperative bleeding and thereby transfusion. Of these, the antifibrinolytic drugs have been the most promising. This has led to their extensive use in cardiac surgery and has been recommended by the European Association of Cardio-Thoracic Surgery and Anaesthesiology[6] and the American Heart Association.[7] Before its withdrawal, aprotinin was believed to be the most powerful and popular antifibrinolytic.[8] Tranexamic acid (TA) and epsilon-aminocaproic acid (EACA) are synthetic derivatives of lysine unlike aprotinin, which is a serine protease inhibitor derived from bovine lung.

The resurgence of aprotinin and the side effects of other antifibrinolytics, as demonstrated by some trials, have left us pondering as to which drug seems to be the most efficacious drug in controlling perioperative blood loss. In this editorial, the role of various antifibrinolytics in managing the perioperative blood loss will be discussed. We searched PubMed and Google Scholar database with the keywords as cardiac surgery and antifibrinolytic drugs for literature search.

Hemostatic Derangements During Cardiac Surgery

What exactly happens during surgery that promotes bleeding? Cardiac surgery, similar to any other surgical procedure, promotes tissue damage, inflammation, and thereby bleeding. Added to this is the insult from cardiopulmonary bypass (CPB), which promotes the activation of the coagulation system due to the contact of blood with foreign surfaces. Systemic heparinization and inadequate protamine reversal too take a toll on the patient, not to forget surgical hemostasis. It has been observed that the fibrinogen levels decrease by about

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40% at the end of cardiac surgery.[9,10] The composition of the priming solution used in CPB has been shown to have an effect on the production of fibrinogen,[11] thereby impeding coagulation during on-pump surgery. The fibrinolytic activity at the surgical site has been seen to increase by eight-fold following extensive surgery.[12] The reduced generation of thrombin that occurs post cardiac surgery presents an additional insult to the bleeding patient.[13] Soluble fibrin is nonhemostatic fibrin formed due to dysregulation of hemostasis. Normally, only approximately 1% of the fibrin formed circulates as soluble fibrin with the rest residing in the wound.[14] When CPB commences, total fibrin formation is reduced because of heparinization whereas soluble fibrin formation is increased. The quality of fibrin-based clot has more impact than the reduced thrombin generation and platelet dysfunction on the magnitude of bleeding.[15]

The contact activation pathway is activated when blood comes in contact with the CPB circuit.[16] Biocompatible materials added to the CPB circuit have been shown to have an equivocal effect on bleeding and transfusion requirements.[17] However, the activation of the tissue factor (TF) pathway may be a primary reason of thrombin generation during CPB. This pathway gets activated when blood comes in contact with the pericardium and damaged tissues.[18] Washing and concentrating blood that has been aspirated from the pericardium[19] and tissue factor pathway inhibitor (TFPI) release by heparin administration[20] probably have an important role in the suppression of the TF pathway during CPB. CPB promotes the formation of bradykinin[21] that appears to be the primary stimulus for tissue plasminogen activator (tPA) secretion as documented by studies that have successfully employed bradykinin receptor blockers.[22] This tPA promotes fibrinolysis that has been shown to have a positive correlation with the magnitude of postoperative blood loss.[23,24]

Does off-pump cardiac surgery fare better? It should, since CPB is eliminated from the scene, but that solves only one issue. The tissue trauma, which activates the TF, is inevitable.[25] There is activation of coagulation and subsequently fibrinolysis albeit to a lesser extent during off-pump surgery.[26,27] However, in off-pump as well as in on-pump surgeries, fibrinolytic activity is similar by the end of 24 h.[28] Therefore, cardiac surgery can be considered a hostile milieu for the patient wherein derangements of the coagulation system are encountered.

Role of Antifibrinolytics

The technique of using pharmacological measures to reduce blood loss dates back to the 1980s when desmopressin and prostacyclins were introduced in cardiac surgery. However, they were found to be ineffective, except in selected cases.[29,30] Antifibrinolytics, by inhibiting fibrinolysis, and thereby fibrin degradation product formation have been shown to reduce transfusion requirements by up to 50%. The commonly used antifibrinolytics in today's era include the protease inhibitors and lysine analogs. When aprotinin was banned in 2007, two additional pharmacological agents were clinically evaluated, namely, ecallantide and MDCO-2010. Recently, synthetic allosteric plasmin inhibitors are undergoing research as a tool to reduce perioperative bleeding.

Aprotinin

α_2-plasmin inhibitor is a natural plasmin inhibitor in our body that rapidly inactivates free plasmin with little effect on the bound form. Free plasmin is associated with pathological fibrinolysis. Hence, hemostasis is maintained and physiological clot lysis is not inhibited.[31] Aprotinin, a serine protease inhibitor, inhibits free plasmin but with little effect on bound plasmin, similar to α_2-plasmin inhibitor. The initial plasma half-life is 150 min and the terminal half-life is 10 h. The kidneys eliminate aprotinin, with almost complete elimination in 4–5 h. Aprotinin clearance is reduced, and half-lives are prolonged in patients with renal insufficiency undergoing CPB.[32] A full-dose regimen consists of 2 million kallikrein international units (KIU) as a bolus, followed by the same bolus on CPB prime and a continuous infusion of 50,000 KIU. A half-dosing regimen is also available. In addition, aprotinin possesses antiinflammatory properties,[33,34] thereby decreasing the systemic inflammatory response to cardiac surgery. There was a controversy regarding the optimal dose of aprotinin to be administered to produce the desired clinical effect. The 2 million KIU dose was found to be necessary to produce the plasma concentration of 200 KIU/ml associated with kallikrein inhibition.[35] Royston *et al*. demonstrated that in coronary artery bypass grafting (CABG), a full-dose regimen was associated with a lower risk of adverse cerebrovascular outcomes and a reduced need for use of vasoactive drugs.[36] Hayashida *et al*. opined that minimal-dose aprotinin inhibited enhanced fibrinolytic activity and reduced transfusion requirements after bypass equivalently to low-dose aprotinin.[37] Lemmer *et al*. concluded that low-dose and pump-prime-only aprotinin regimens provide reductions in transfusion requirements similar to those of high-dose regimens.[38] A retrospective analysis by Strouch *et al*. showed that half-dosing regimen was associated with a significant increase in blood products administration and re-exploration rates as compared to the full dose.[39] However, recently it has been demonstrated that a half-dosing regimen should suffice in low-risk cardiac patients.[40]

The Aprotinin saga: Introduction, decline, and resurgence

Aprotinin was isolated from bovine lung in 1936, and was first used by Royston *et al*.,[41] in redo cardiac surgery. Bidstrup *et al*.[42] used high-dose aprotinin in cardiac surgery in 1989. The Food and Drug Administration (FDA) in 1993 gave the nod for its use in high-risk CABG, which

ultimately expanded to all CABG patients. Post approval it was noticed that aprotinin was associated with decreased perioperative transfusion requirements not only in cardiac surgeries but also in noncardiac surgeries. Perhaps this led to misuse of the drug, thus landing it into controversy.

In 2006, FDA issued a public health advisory regarding the use of aprotinin, based on a series of observational studies. Mangano *et al*.[43] reported that aprotinin use might be associated with increased risk of cardiovascular, neurological, and renal events. They further stated that aprotinin was independently predictive of 5-year mortality.[44] Karkouti *et al*.,[45] as well as Shaw *et al*.,[46] showed that patients who received aprotinin had a higher mortality rate and larger increases in serum creatinine levels than those who received EACA or no antifibrinolytic agent. By the end of 2006, FDA revised its guidelines and placed a ceiling on aprotinin's use in surgeries. In 2007, the Blood Conservation using Antifibrinolytics in a Randomized Trial (BART) study was published, which saw the demise of aprotinin.[47] Instantaneously, the manufacturer of aprotinin (Bayer Inc.) temporarily suspended production and by mid-2008, aprotinin was removed from the markets.

The withdrawal of aprotinin was not met with a favorable response from many quarters. Though a few studies had demonstrated a poor outcome with aprotinin, others did not. Schneeweiss *et al*.[48] concluded that in-hospital mortality was higher with aprotinin, post cardiac surgery. Fan *et al*.[49] found that aprotinin did no good apart from decreasing postoperative bleeding in pediatric cardiac surgical patients. In fact, they concluded that its use was detrimental. On the contrary, Wang *et al*.[50] and Sniecinski *et al*.[51] concluded that aprotinin use was associated with less blood loss when compared to TA or no aprotinin at all. DeSantis *et al*.[52] in their retrospective analysis concluded that in the post aprotinin era with the exclusive use of lysine analogs, the relative risk of early postoperative outcomes such as mortality and renal dysfunction did not improve, but the risk for the intraoperative use of blood products had increased. Scott *et al*.[53] analyzed a retrospective data and concluded that bleeding in infant cardiac surgery increased following the change from aprotinin to EACA, thereby necessitating the use of factor VIIa. Many questions were raised regarding the validity of the studies that had disfavored aprotinin, especially the study by Mangano *et al*.[43,44] and the BART trial.[47] There were several issues with the data from Mangano *et al*.[43,44] First, the study was nonrandomized and used unmatched groups. Next, multivariate logistic regression analyses were used for between-group differences at baseline. This analysis did not indicate as to which type of patients received aprotinin. Finally, the details of the surgery itself were not reported. Thus, the choice of antifibrinolytic drug and the outcome were biased. This led to a meeting by the regulatory authority of Canada in December 2008. It was seen that the primary outcome in BART was not mortality but massive bleeding and that the trial was underpowered. Similarly, the exclusion of 137 patients from the study after randomization of primary endpoints was questioned. The panel concluded that the reclassification of endpoints from the original reported data were in opposite directions for aprotinin and EACA, thereby favoring EACA. These changes were magnified with the duration of the study. The anticoagulant used in the BART trial was heparin, whose effect was not monitored appropriately, as activated clotting time could be influenced by aprotinin. Thus in 2011, Health Canada lifted the ban on aprotinin and licensed its use for isolated CABG in Canada, only after balancing the risk versus benefit.[54] Following this, the European regulatory authority gave a nod for the use of aprotinin for isolated CABG in Europe.[55] Interestingly, the authors of the BART study have refuted the criticism drawn from their work.[56] The use of aprotinin, post re-introduction, in isolated CABG has been debated. Meybohm *et al*. found that the use of aprotinin is associated with an increased risk of mortality in low and intermediate risk cardiac surgery.[57] Likewise, the arterial revascularization trial (ART) showed a significant increased risk of early and late mortality with aprotinin.[58] However, Deloge *et al*. have demonstrated the superiority of aprotinin over TA in isolated CABG.[59] Currently, the European guidelines recommend the use of aprotinin only in adult patients undergoing isolated CABG, who are at a high risk of major blood loss.[60]

Although aprotinin use is associated with nephrotoxicity, Bosman *et al*.[61] opined that there is no evidence for an increased risk of developing new renal failure requiring dialysis/renal replacement therapy. Maslow *et al*. echoed similar findings in their assessment of perioperative renal outcome in cardiac surgical patients with preoperative renal dysfunction when comparing EACA with aprotinin.[62] Aprotinin-induced anaphylaxis is yet another major concern, especially after a second exposure.[63,64] A 6 months gap between the first and the subsequent exposure might alleviate this problem.

Ecallantide and MDCO-2010

Ecallantide is a recombinant human peptide derived from the first Kunitz domain of the TF pathway inhibitor-1 that inhibits the TF pathway.[65] FDA approved it for the treatment of hereditary angioedema. It was demonstrated to decrease perioperative transfusion in cardiac surgery. Bokesch *et al*.[66] found out that ecallantide was less effective at reducing perioperative blood loss than TA and the study had to be prematurely terminated due to mortality in the study group.

MDCO-2010 is a synthetic molecule inhibiting plasmin, kallikrein, Xa, Xia, and protein C. It exerts more potent inhibitory activity than TA and aprotinin toward plasma kallikrein, plasmin, and FXa.[67,68] However, further studies are needed to demonstrate its safety and efficacy.[69]

Tranexamic acid and epsilon amino caproic acid

TA and EACA are the most widely used antifibrinolytics in this era, especially following the withdrawal of aprotinin. Both are synthetic derivatives of lysine. They prevent excessive plasmin formation by binding to the lysine-binding site on plasminogen, thereby preventing fibrin from binding to plasminogen. They primarily inhibit tPA-induced physiological fibrinolysis.[70] Both are eliminated through the kidneys necessitating dose reduction in renal failure and have a half-life of 3 and 2 h, respectively. Age has been shown to be a better covariate than body weight, affecting both the distribution and the elimination of TA.[71] TA can be given as a high dose of 30 mg/kg bolus, 2 mg/kg on CPB, and 16 mg/kg/h later or as a low dose of 10 mg/kg bolus, 1–2 mg/kg on CPB, and 1 mg/kg/h. It has been approved for use in USA, Canada, and Europe. EACA is given in a dose of 100 mg/kg bolus, 5 mg/kg on CPB, and 30 mg/kg/h. TA is at least 7–10 times as potent as EACA. Both TA and EACA have been shown to reduce the need for transfusion as compared with controls.[72]

The optimal plasma concentration of TA to inhibit 80-85% fibrinolysis has been set at 10–20 mcg/ml. 100 mcg/ml of TA completely inhibits fibrinolysis.[73] Sharma *et al*. analyzed plasma TA concentrations of eight patients undergoing elective cardiac surgery with CPB and high-dose TA. The authors found that actual plasma levels of TA were significantly higher than expected, and that 100% inhibition could be achieved at lower TA doses.[74] There is also a considerable debate on its dosing. Hodgson *et al*. concluded that patients with a high risk of bleeding should receive high-dose TA, while those at low risk of bleeding should receive low-dose TA.[75] Sigaut *et al*.[73] found that although a high dose of TA does not reduce the incidence of blood product transfusion up to day 7, it is more effective than a low dose of TA in decreasing transfusion, blood loss, and repeat surgery. This study was criticized for its design and analysis, but the need for high dose was partially accepted. However, Du *et al*.[76] showed that lower-dose TA regimen was as effective as the higher-dose regimen in reducing postoperative bleeding and transfusion needs in patients undergoing cardiac valve surgery. Faraoni *et al*.[77] evaluated the effect of two doses of TA on fibrinolysis during cardiac surgery and concluded that dose does not make a difference in clinical outcome.

EACA causes inhibition of fibrinolysis at 130 mcg/ml.[78] There is no consensus on the dosage on EACA too. Different dosage regimens have been experimented by Chauhan *et al*.[79] and Hardy *et al*.[80] Sarupria *et al*.[81] compared two different protocols of EACA in pediatric cardiac surgery, namely continuous and discontinuous regimen. One group received 100 mg/kg of EACA after induction, upon initiation of CPB, and after protamine. Group 2 received 75 mg/kg of EACA after induction, followed by a maintenance infusion of 75 mg/kg/h until chest closure, and an additional 75 mg/kg upon initiation of CPB. Group 3 did not receive any antifibrinolytic agent or placebo. They noted that both the regimens were equally effective in reducing blood loss.

Seizures have been reported with the use of lysine analogs,[82] especially TA that could be due to γ-amino butyric acid receptor antagonism or due to cerebral vasospasm/thrombosis. However, the clinical impact of TA-induced seizures is difficult to determine. A large retrospective study reported an incidence of 0.9%, with a 2.5–3 times mortality in patients treated with TA. In this study, TA administration was shown to be an independent predictor of seizures. The occurrence of seizures has been linked to the dose, with larger doses being implicated in the development of seizures.[75,83] Sharma *et al*.[84] found that independent predictors of postoperative seizures included age, female sex, redo surgery, hypothermic circulatory arrest, increased duration of aortic cross-clamp, and TA. When tested in a multivariate regression analysis, TA was a strong independent predictor of seizures. A follow-up of three patients who presented with seizures after TA administration might support the hypothesis of cerebral hypoperfusion as a cause of seizures.[85] Montes *et al*. linked preoperative renal dysfunction to the development of seizures and opined that the drug dose should either be reduced or completely avoided in such patients.[86] Further well-designed prospective studies are required to come to a firm conclusion on this aspect. In order to reduce these undesirable side effects, topical application of TA and EACA has been described. This has shown promising effects with some authors reporting an increased efficacy when topical and systemic methods are combined as compared to individual technique.[87,88]

Recent Developments

The lysine analogs can provoke convulsive seizures from their effects on the central GABA receptor. In particular, the variable efficacy of TA sometimes necessitating high doses causes postoperative seizures and renal dysfunction. Thus, discovering more potent and safer plasmin inhibitors became important. Research into glycosaminoglycans (GAGs), which are known to allosterically inhibit plasmin, has led to the synthesis of small, synthetic, homogenous, nonsaccharide GAG mimetics (NSGMs). Among the 55 NSGMs investigated, the flavonoid quinazoline heterodimers and bisflavanoid homodimers afford allosteric inhibition of plasmin. Advantages of these NSGMs include: (i) adequate aqueous solubility which is expected to help antifibrinolytic use during surgeries, (ii) limited cellular and central nervous system toxicity, (iii) reasonable chemical stability, and (iv) ease of chemical synthesis.[89] Further efforts are necessary to develop these sulfated NSGMs into clinically relevant molecules.[90]

Conclusion

Prophylaxis for blood loss in cardiac surgery is desirable, of which antifibrinolytic drugs have been the most sought after. Literature recommends their use, albeit with other methods to prevent and treat bleeding. Their use should be driven by cost, clinician's familiarity with the drug, drug profile, and institution protocol. The development and increased use of point-of-care-based, whole-blood assays of the coagulation system may have a role in the detection of intraoperative hyperfibrinolysis and be able to guide the more rational use of antifibrinolytic agents. No particular drug is recommended, although TA is more potent than EACA. Though the regulatory agencies have licensed aprotinin only in isolated CABG, its use in other cardiac surgeries needs to be reassessed. In the absence of lucid Indian guidelines on aprotinin, we recommend that either we do not use it or use it in accordance with the European guidelines. Thus, we have to rely only on lysine analogs with low-dose TA being the most appropriate. The allosteric plasmin inhibitors seem a viable option, but warrant further research.

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Conflicts of interest

There are no conflicts of interest.

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