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Antifibrinolytic agents in current anaesthetic practice

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Editor's key points

- Antifibrinolytics are widely used to reduce the risk of blood loss and transfusion.
- The authors have reviewed the roles of aprotonin, tranexamic acid and aminocaproic acid.
- This review provides a current evidence base for rational use of these agents during cardiac and non-cardiac surgery.

Summary. Antifibrinolytic drugs have become almost ubiquitous in their use during major surgery when bleeding is expected or commonplace. Inhibition of the fibrinolytic pathway after tissue injury has been consistently shown to reduce postoperative or traumatic bleeding. There is also some evidence for a reduction of perioperative blood transfusion. However, evidence of complications associated with exaggerated thrombosis also exists, although this appears to be influenced by the choice of the individual agent and the dose administered. There is controversy over the use of the serine protease inhibitor aprotinin, whose license was recently withdrawn but may shortly become available on the market again. In the UK, tranexamic acid, a tissue plasminogen and plasmin inhibitor, is most commonly used, with evidence for benefit in cardiac, orthopaedic, urological, gynaecological, and obstetric surgery. In the USA, ε-aminocaproic acid, which also inhibits plasmin, is commonly used. We have reviewed the current literature for this increasingly popular class of drugs to support clinical judgement in daily anaesthetic practice.

Keywords: antifibrinolytic agents; cardiac surgical procedures; hepatectomy; intracranial haemorrhages; liver transplantation; orthopaedics; postoperative haemorrhage; post partum haemorrhage; wounds and injuries

Bleeding after major surgical interventions and trauma is associated with increased morbidity and mortality. Haemorrhage and subsequent transfusion of red blood cells as well as tissue trauma and surgical techniques like cardiopulmonary bypass (CPB) can lead to significant coagulopathy. Consequently, there is need not only for blood transfusion but also for the substitution of coagulation components. This often requires the use of allogeneic blood products with specific risks like haemolytic and allergic reactions, transfusion related lung injury, bacterial contamination, virus transmission, and blood group mismatch. In addition, postoperative haemorrhage can prompt further unplanned surgical interventions. Both re-exploration and transfusion are associated with an increased incidence of infection, mortality and prolonged length of intensive care and hospital stay.[1 2] Ultimately, postoperative haemorrhage not only affects patient outcomes, but also results in significant healthcare costs. This is especially relevant as a steady increase in higher risk cases and more complex surgical procedures are leading to a higher demand for blood products, which cannot always be met by supply. Therefore, a multimodal approach to blood conservation, involving surgical, anaesthetic, and pharmacological considerations, is required to reduce perioperative morbidity and to use the available resources judiciously.[3]

One target of a modern blood conservation strategy is the fibrinolytic system. Fibrinolysis is a physiological surface-bound process where activated plasminogen removes excess fibrin deposition at the site of vascular injury, which improves localization of the fibrin clot and wound healing. There are at least 50 known cleavage sites in the fibrin molecule leading to the formation of fibrin degradation products and D-dimers. Plasminogen is a single chain serine protease characterized by an active site and five Kringle domains, four of which bind to lysine residues in interacting molecules. Physiological activators of plasminogen are the two serine proteases tissue plasminogen activator (tPA) and urinary plasminogen activator. Physiological inhibition of fibrinolysis occurs as inhibition of plasminogen via plasminogen activator inhibitors (PAI-1 and PAI-2) and active centre inhibition of plasmin via polyspecific serine protease inhibitors such as α-2-antiplasmin.[4 5]

Activation of the fibrinolytic system can be quantified by laboratory-based assays (e.g. euglobulin lysis time, plasmin-α-2-antiplasmin enzyme-linked immuno sorbent assay, D-dimers) or point-of-care tests (clot lysis in viscoelastic assays, such as TEG and RoTEM). However, laboratory assays may not be used routinely, and bedside tests are not fully validated yet. Most trials have used clinical parameters or empirical treatment.

Therapeutic inhibition of fibrinolysis has been shown to reduce bleeding in various clinical situations associated with activation and dysregulation of the fibrinolytic pathway, including cardiac surgery, trauma, liver surgery, neurosurgery, and obstetric haemorrhage. The agents used in this indication are the serine protease inhibitor aprotinin and the lysine analogues tranexamic acid and ε-aminocaproic acid.

The aim of this review was to assess the role of antifibrinolytic agents as a part of a modern blood conservation strategy for patients at risk of haemorrhage after major cardiac or non-cardiac surgery, trauma, or childbirth. It summarizes the literature of the past decade with specific relevance to daily anaesthetic practice, to support clinical decision-making and to enhance further discussion of the topic. A summary of relevant publications is provided in Tables 1–5.

Aprotinin

For many years, aprotinin, a non-specific serine protease inhibitor extracted from bovine lung, was widely used as an antifibrinolytic agent, and became the most popular such drug. It is thought to act by inhibition of the serine protease plasmin that attaches to the fibrin polymer via lysine residues on the target molecules. The polypeptide aprotinin (molecular weight 6500) is an unspecific Kunitz-type protease inhibitor, targeting the active centre of serine proteases. Besides plasmin it also inhibits trypsin, kallikrein, elastase, urokinase, and thrombin. Therefore, it can interfere with contact factor activation [factor XII (FXII)], fibrinolysis, the renin-angiotensin system, and neutrophil activation. As a result, the effects of aprotinin on the coagulation system can be anti-coagulatory because of an inhibition of the intrinsic cascade (FXII and thrombin), and pro-coagulatory because of antifibrinolytic action. Preservation of the glycoprotein Ib platelet membrane receptor is also attributed to aprotinin, which may protect platelets against CPB induced activation.[6 7] An anti-inflammatory effect of aprotinin was proposed, based on reduced leucocyte activation and cytokine release (such as tumour-necrosis-factor α or interleukins) after CPB.[8–12] Animal studies suggest that this reduced inflammatory response could even improve the neurological outcome after cerebral ischaemia during CPB.[13] However, the data remain uncertain, and a meta-analysis could not confirm an anti-inflammatory effect of aprotinin in cardiac surgery.[14]

First described in the 1930s, aprotinin was introduced into clinical practice in the 1950 for the treatment of hyperfibrinolytic conditions such as pancreatitis. It became almost ubiquitous in complex cardiac surgery in the early 1990s after an impressive reduction of blood loss was demonstrated in 22 patients undergoing open heart surgery.[15] In adult cardiac surgery, aprotinin was mostly dosed according to the full 'Hammersmith' regimen with 2×10^6 kallikrein inhibitor units (KIU) as a loading dose and 2×10^6 KIU into the prime solution of the bypass circuit, followed by an infusion of 500 000 KIU h^{-1}.[15] The bovine polypeptide aprotinin carries a risk of anaphylactic reactions especially in cases of re-exposure within 6 months. A database analysis of >12 000 cardiac cases demonstrated an incidence of 0.09% (95% CI 0.05–0.16%) for primary exposure and 1.5% (95% CI 0.86–2.6%) for re-exposure. The highest rate of hypersensitivity reactions occurred between Day 4 and Day 30 after first exposure (7.4%, 95% CI 2.4–18.8%). A test dose of 10^4 KIU at least 10 min before the initial bolus dose is recommended by the manufacturer, but did not prevent severe reactions in this dataset.[16] Aprotinin is metabolized by lysosomal enzymes and excreted renally with a terminal elimination half-life of 5–10 h. For many years, aprotinin seemed to be an almost ideal drug as it reduced postoperative blood loss and transfusion without major side-effects.[17] However, its relative benefit was seriously challenged in 2006 when Mangano and colleagues compared aprotinin with other antifibrinolytic agents and placebo in an observational study of more than 4000 patients undergoing myocardial revascularization. They reported a doubling of risk for renal failure and a 55% increase in perioperative myocardial infarction and heart failure in the aprotinin group.[18] However, this study was controversial as it was retrospective, and may have been subject to multicentre bias.

The era of aprotinin seemed to come to an end with the publication of the BART trial (Blood Conservation Using Antifibrinolytics in a Randomized Trial). Marketing was temporarily suspended in November 2007 when the first data became available, and aprotinin was then permanently withdrawn from the market in May 2008. In this large multicentre study, Fergusson and colleagues randomly assigned 2331 high-risk cardiac surgical patients to receive prophylactic aprotinin, ε-aminocaproic acid, or tranexamic acid. Even though the risk of bleeding was lowest in the aprotinin group, mortality was increased in patients receiving aprotinin compared with the combined rate for the two lysine analogues [risk ratio (RR) 1.53; 95% CI, 1.06–2.22], which led to early termination of the trial.[19] A recent Cochrane review concluded that, although aprotinin appeared to be more effective in reducing blood loss and the need for blood transfusion, it was associated with higher risk of death.[20] Very recently, the data of the BART trial have been called into question. In addition, Health Canada, published a safety review of aprotinin in September 2011,[21] which concluded that the benefit of using aprotinin in non-complex cardiac surgery might outweigh the risk. After this, aprotinin was made available again in Canada for restricted use in isolated coronary bypass graft surgery.[22] The European Medicines Agency also recommended lifting the suspension of aprotinin in February 2012 after a review of the risks and benefits of antifibrionlytic drugs.[23] Those decisions are based on several further perceived shortcomings of the BART trial. First, only patients with high-risk cardiac surgical procedures (i.e. mitral valve surgery, combined coronary artery bypass graft and valve surgery, surgery on multiple valves, redo, and aortic surgery) were included and data might therefore not be applicable to all cardiac surgical patients and also not to other surgical areas. That might explain the high mortality rates reported compared with other published data.[17 24] Secondly, the trial was not targeting mortality as a primary outcome parameter and was not designed and powered for that endpoint. In addition, because the trial was terminated early, it did not reach the patient number calculated in a power analysis to detect a difference in postoperative bleeding. Finally, there are concerns about a possible underdosing of heparin, as celite activated clotting time is prolonged in the presence of aprotinin.