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REVIEW

Risks of antifibrinolytics in allogeneic blood saving techniques

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Abstract. Despite the increased safety of allogeneic blood products, adverse effects such as transfusion reactions, increased infections, and possible immunosuppressive effects have contributed to the demand for alternative techniques, the so-called "blood saving techniques", which also may have adverse reactions. Retrospective studies with aprotinin underscore the importance of controlled randomized trials or cohort studies large enough to detect the incidence of these adverse effects or differences in side effects with allogeneic blood transfusions. The safety of aprotinin is currently under debate and the drug has been withdrawn from the market. Tranexamic acid, on the other hand, is a safe and potent drug, and is approximately as effective as aprotinin. No data are available thus far to contraindicate its use in liver surgery, in contrast to macroscopic haematuria. Thus, tranexamic acid appears to currently be the safest antifibrinolytic product.

Keywords: aprotinin, tranexamic acid, adverse effects, side effects

Introduction

As a result of new insights, the safety of allogeneic blood products has been enhanced by strict rules for donor selection including sensitive assays for infectious agents, leukocyte reduction of blood products, introduction of plasma disinfectant techniques, and introduction of quarantined plasma and culture of thrombocyte products. Adverse effects such as transfusion reactions, human error, graft versus host disease, alloimmunization, nosocomial infections and comorbidity after allogeneic blood transfusions, as well as possible immunosuppressive effects, have contributed to the demand for alternative blood products or techniques to decrease the transfusion of allogeneic blood products, the so-called "allogeneic blood saving techniques". These techniques can be used independently, but more often a combination of several methods is used in an approach known as "blood management".

Both pharmacological and non-pharmacological methods are available for blood management. Antifibrinolytic agents are one of the pharmacological methods used. This article will critically review the literature regarding the incidence of adverse effects of antifibrinolytic agents available in the Netherlands.

Literature search strategy and results

A Medline search (MeSH) was performed for articles on aprotinin, tranexamic acid and antifibrinolytics which were published between 1966 and 1 July 2008. These terms were combined with 'adverse effects or side effects' and 'surgical procedures or surgery'. Limitations of the search were adults, randomized controlled trials, non-randomized controlled trials (clinical studies) (RCT; non RCT), reviews, meta-analyses, case reports and English or German language. The title and abstracts were investigated for the words 'safety' or 'adverse effects and elective surgery'. References were searched for other potentially useful articles.

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The search for aprotinin yielded eight systematic reviews and one Cochrane Database [1-9]. A broad and sensitive literature search produced 35 additional articles [10-45,50].

The search for tranexamic acid yielded six systematic reviews, one Cochrane Database, and three additional articles [1-3,6-9,23,27,46].

Results

Aprotinin

Aprotinin is a naturally occurring polypeptide and a serine protease inhibitor [47] found in mast cells of mammals and lower animals, and is mostly isolated from bovine (95%) or porcine (5%) lungs for use in humans. Originally used for treatment of pancreatitis (1959), aprotinin was later found to reduce bleeding [40]. The FDA approved aprotinin for the reduction of blood loss and blood transfusions in re-operations or coronary artery bypass graft surgery (CABG) at high risk for excessive bleeding (1998). Over subsequent years its use has broadened to other CABG operations, off-pump CABG, and thoracic, orthopaedic, neurosurgery, liver and transplant surgery. Aprotinin treatment causes the inhibition of several proteases with a serine in the active site, although its exact mechanism of action is unknown. Depending on the dose, aprotinin preferentially forms reversible complexes with (chymo)trypsin, plasmin, plasma and tissue kallikrein, and, to a lower degree, with urokinase, activated protein C and thrombin. Aprotinin stimulates a balance between clot formation and lysis, thereby preserving clotting factors and platelet function and blunting the inflammatory response. Aprotinin has been suggested to have a cardioprotective effect, to reduce myocardial ischaemia during reperfusion and to reduce NO production, resulting in an enhanced vascular tone.

The use of fibrinolytic agents is also based on the increase of plasminogen activator levels after sternotomy and during cardiopulmonary bypass (CPB), which lasts for 1 to 2 hours postoperatively followed by a hypofibrinolytic state with high plasminogen inhibitor levels (24-48 hours postoperatively).

Aprotinin is excreted by the kidney ($T_{1/2}$ = 1-2 hours); less than 10% is excreted unchanged. After 4 hours, 80-90% of the aprotinin

Table 1. Reduction of blood transfusions and adverse effects by aprotinin in meta-analyses1,2

First author and year of publication	Search	Reduction of blood transfusion3	Adverse effect3
Laupacis [1] (1997) Faught [2] (1998)	CABG; 1966-1997 45 RCT; n = 5808	OR 0.31 -1.43 U EC	Allergy: 2nd dose within 200 days: 4.5 – 5% RD: ↑ Creatine level, no RF4 DVT: OR: 0.14 Mortality: not ↑ 5
Levi [3] (1999)	CABG; 1966-1998; 43 RCT vs placebo; n = 4821	OR 0.37 - 0.98 U EC	Rethoracotomy ↓: OR 0.37 Mortality ↓: OR 0.55
Sedrakyan [4] (2004)	CABG; 1988-2001; 35 RCT vs. placebo; n = 3879	RR 0.61	n.s.
Shiga [5] (2005)	Orthopaedic; 1980-2004 13 RCT vs. placebo; n = 506	- 1.1 U EC	n.s.
Brown [6] (2007)	CABG; 1985-2006 138 trials; 78 HD vs 32 LD	HD: RR 0.60 LD: RR 0.76	RD ↑ HD group: RR 1.47 Rethoracotomy: HD RR 0.47
Henry Cochrane [7] (2007)	CABG; 1966-1999; 55 RCT n = 6569: 6313: + BT protocol; 714: - BT protocol	+ BT-prot.: RR 0.68 - BT=prot.: RR 0.77	n.s.
Henry Cochrane [7] (2007)	Ortho + liver surgery 7 RCT; n = 458	RR 0.63; n.s.	n.s.
Molenaar [8] (2007)	LT; 1966-2005; 23 RCT vs. placebo or TXA; n = 1407	EC: - 0.42 (SMD) FFP: - 0.40 (SMD)	n.s.
Umscheid [9] (2007)	CABG; 1966-2007 Efficacy, safety and costs	All doses: RR 0.69	Stroke ↓: RR 0.57 CD ↓: RR 0.62 CD after 6 weeks ↓: RR 0.42 Rethoracotomy ↓: RR 0.40

1: ACT = Activated Clotting Time; BT = Blood Transfusions; CABG = Coronary Artery Bypass Graft; EC = Erythrocyte Concentrate; FFP = Fresh Frozen Plasma; HD = High Dose; LD = Low Dose; LT = Liver Transplantation; n.s. = not significant; OR = Odds Ratio; RCT = Randomized Controlled Trial; RD = Renal Dysfunction; RR = Relative Risk; SMD = Standardized Mean Difference; TXA = Tranexamic Acid; U = Unit.
2: All figures are significant unless specifically mentioned.
3: Aprotinin versus control. Only significant results are given
4: Except D'Ambra and Sundt: RF increased (ACT not adjusted)
5: Except Sundt 35 vs 5% ($p < 0.05$)

is actively resorbed in tubulus and binds to the tubulus membrane or accumulates in the cytoplasm. In the cell, aprotinin inhibits the secretion of several proteases. Degradation is slow [48], and total metabolism is 12-24 hours or longer.

Aprotinin activity is given intravenously in kallikrein inactivating units (KIU) (1 mg is 7143 KIU). There are several dose regimens (high dose regimen is ≥ 5-6 x 10^6 KIU per patient).The target concentration is 200 KIU / ml (some say 50-125 KIU / ml). A 10 000 KIU test dose must be administered before starting full dose regimen.

Efficacy

Several dose finding and dose efficacy studies have been performed (Table 1). Aprotinin efficiently reduces the proportion of patients requiring a blood transfusion and the mean number of transfused units (1 U less). A high dose regimen seems to have a higher efficacy [6].

Side effects and interactions of aprotinin

The most common side effects reported are hypersensitivity reactions, renal dysfunction, and arterial thrombosis (Tables 1 and 2).

Hypersensitivity

The incidence of several types of hypersensitivity from the first injection is < 1% in prospective studies [2].Analysis of prospectively collected files of 12 403 CABG patients revealed an incidence of 4.1% if aprotinin therapy was administered within 6 months after the first dose, which decreased to 0.4% when the second dose was given more than 12 months after the first dose [14, 15].

Beierlein (2005) identified 124 cases in the literature published between 1963 and 2003 that reported aprotinin-induced anaphylaxis (several after ear nose and throat surgery) [11]. More than 50% were life threatening, and eleven patients died (9%). The profile of patients at risk was re-exposure within 3-6 months and detection of aprotinin specific IgE or IgG antibodies. Absence of IgG aprotinin-specific antibodies indicates a low risk for hypersensitivity reaction. Skin tests are not predictive, but have their value retrospectively.

A test dose should be administered after the cannulation sites are exposed; the loading dose after the test dose confirmed safety for use. Aprotinin should not be used in patients scheduled for re-operation within the following months or, in congenital surgery requiring staged palliation. The outcome of anaphylaxis is more favourable when combined with prophylaxis (H1-, H2 antagonists, corticosteroids) [11]. A prophylactic regimen is not 100 % effective. In nine cases, acute sensitivity reactions occurred despite prophylactic therapy.

Interaction with Activated Clotting Time test

In the early nineties, aprotinin was found to interact with the activated clotting time (ACT) test used for control of heparinization, causing a prolongation of the ACT [27, 47]. This interaction, causing unreliable ACT results, could be the basis for the reported negative results.

Jones (2004) assessed the influence of aprotinin on heparinized and unheparinized blood in 12 different commercial ACT tests using Kaolin, glass or Celite as an activator [27]. Each test responded uniquely to aprotinin, giving test results of 12-51% above nonaprotinized values. The author advised the assessment of the institutionally chosen test before development of guidelines.

Table 2. Adverse effects of aprotinin reported in original articles (aprotinin versus placebo/control) 1, 2

First author (year)	Search2	Adverse effects
Mangano [35] (Mora; 2001)	CPB (aorta) + DHCBA; Retrospective; n = 183	RD > 25% ↓: related to: ffl 5 EC (OR 2.1) ffi 800 ml urine output intraoper.(OR 1.9) or ffi 2100 ml first 24 hours (OR 2.0) no dopamine (OR 1.6) Ht ffi 21 mg% (OR 1.5)
Grady [22] (2002)	Complex cerebrovasc. + DHCBA; Retrospective n = 13	n.s.
Findlay [18] (2001)	LT; RCT; n = 63	n.s.
Frumento [20] (2003)	CABG; Retrospective 1999-2001; n = 1524	Stroke: FD 0% vs 16% NA
Harmon [25] (2004)	CABG; RCT; blinded; n = 36	CD ↓ 4 days p.o.: 58 vs 94% CD ↓ 6 weeks p.o.: 23 vs 55%
Olivencia-Yurvati [37] 2004)	CABG; RCT; n = 90 AT; + or – leukocyte filtration;	Pulmonary shunt 40% ↓
Kincaid [30] (2005)	CABG; retrospective; n = 1209; AT + or – ACEI	RD if AT + ACEI: (OR 2.9) Other risk factors Age (OR 1.2) Valve (OR 2.7) Ht (OR 2.2) BT EC (OR 1.04) BT platelets (OR 1.7)
Augustides [10] (2006))	CPB + DHCBA retrospective AT vs. ACA; n = 144	RD ↑: 43.2 vs 28.6%; related to: sepsis (OR 9.7) AT (OR 5.9) HT (OR 4.5) age (OR 1.06) BT (OR 1.03) AF: 31.6 vs 38.8 Stroke: 10.5 vs 4.1% Mortality: 11.6 vs 10.2%
Karkouti [28] (2006)	CABG n=449 AT matched to 449 TXA	RD ↑: 24 vs. 17% ; Subgroup pre-RF: 31 vs 18%
Mangano [33,34] (2006; 2007)	CABG; Observational and propensity; n=4347: 1295 AT; 822 TXA; 833 ACA; 1374 C	RF: Primary surgery: OR 2.34 Complex surgery: OR 2.59 CV complications: 22 vs 16% Stroke: prim surg: OR 2.15 Mortality: Prim. Surg: 2.8 vs 1.3% 5 years: OR 1.48

Renal dysfunction

Several concerns suggest that aprotinin may cause renal dysfunction by blocking the tubular resorption process by a direct toxic effect on tubuli or changes in renal perfusion due to inhibition of kallikrein or renin. , With the exception of the study of D'Ambra and Sundt [2], older studies have shown a mild increase of plasma creatinin without clinical implications [2]. Other studies showed a lack of association with the incidence of postoperative renal dysfunction in patients with pre-existent renal dysfunction [47]. Deep hypothermia and circulatory arrest caused a significant increase in renal dysfunction [10].

A recent prospective observational study of 4374 patients by Mangano showed a doubled incidence of renal dysfunction [33]. Patients received aprotinin (1295), aminocaproic acid (883) or tranexamic acid (822) and were compared with 1374 patients not receiving antifibrinolytics. Aprotinin therapy in patients undergoing CABG surgery for the first time was related to a higher incidence of renal dysfunction, and 5.5% of patients required dialysis compared with1.8% of controls. A similar trend was observed in patients undergoing complex surgery. The risk was dose-dependent, with 7% observed in the low dose group compared to 18% in the high dose group.

Graft thrombosis and myocardial infarction

Like other haemostatic drugs, aprotinin may cause thrombosis. Older randomized trials showed a significant increase of Q-waves, venous graft thrombosis or myocardial infarction, though other studies failed to confirm these data [2]. In several of these studies, the ACT was not optimal. The International Multicenter Graft Patency Experience trial (IMAGE) demonstrated that the incidence of early graft occlusion in 870 patients was higher in the aprotinin group (15.4 vs.10.9%) [2], and found a relationship with risk factors such as female sex, no preoperative salicylate medication, poor graft quality and perfusion of the graft with fluid containing aprotinin. Patients without risk factors had the same incidence of graft thrombosis as the placebo group.

Four meta-analyses showed that the risk was not elevated.

In contrast, however, Mangano found an increase of cardiovascular complications (20.4 vs.13.2%; p=0.0001), myocardial infarctions (48%) and heart failure (109%) in patients undergoing cardiac surgery for the first time, but not in patients undergoing complex surgery [33]. This was not supported by the data of Karkouti [28]. Interestingly, Mangano found that the subgroup of patients with massive blood loss had a higher incidence of complications compared with patients without high blood loss (34 vs.19%; p = 0.04).

Table 2 continuing

First author (year)	Search2	Adverse effects
Dietrich [15] (2007)	Prospective cardiac surgery n = 13.315: 12.403 AT	Allergy: 1st dose: 0.09%; none severe 2nd dose: 1.5%; 5 severe < 3 days: none < 6 months 4.1 % 6-12 months 1.9% > 12 months 0.4%
Furnary [21] (2007)	Prospective data of 12 centres: 2000-Feb 2006 CABG n = 15.174, of which 11.198 BT; of which 2757 AT	RD: 1.6 vs 1.3%: AT + BT: OR 1.23/unit EC
Kertai [29] (2007)	Cardiac Surgery Retrospective n = 674; 550 AT	n.s.
Orthopaedic cohort [36] (2007)	Matched cohort; 40 HD vs 41 NA	RF: n = 4 (1 chronic) vs n = 1
Ott [38] (2007)	CABG prosp observ international;n = 5065; 3180 selected of 4 countries (GB; Can; US; Germ) ; Complications analysed by blinded investigators.	Significant differences in mortality/outcome related: - Aprotinin; FFP and PC; Postoperative use of heparin; Late start aspirin postop.
Van der Linden [44] (2007)	Strict blood management policy Low risk BT: NA n = 854;High risk BT: AT n = 1210	RF related to: HF, RD, Redo, Femal Cardiac complication: related to complex surgery
Warnaar [45] (2007)	Retrospective propensity score stratification;1043 LT; 653 AT	RD: First week p.o.: OR 1.97 > 1 week p.o.: n.s.; 1 year survival: n.s.
Fergusson [51] (2008)	High risk cardiac surgery, 781 AT 770 TXA 780 EACA	Massive bleeding: AT: 9.5%; TXA: 12,1%; EACA: 12.1% RR AT vs other 2 therapies: 0.79 Mortality 30 days: AT: 6%; TXA: 3.9%; EACA: 4 % RR AT vs other 2 therapies: 1.53

1. ACA: AminoCaproic Acid; AF = Atrium Fibrillation; AT = Aprotinin Therapy; ACEI = Angiotensin-Converting Enzyme Inhibitors; BT = Blood Transfusions; C = Control group; CABG = Coronary Artery Bypass Graft; Can. = Canada; CD = Cognitive Dysfunction; CPB = Cardio Pulmonary Bypass; DHCBA = Deep Hypothermic Cardiopulmonary Bypass ArrestEACA = Epsilon Amino Caproic Acid; EC = Erythrocyte Concentrate; GB = Great Britain; Germ. = Germany; HD = High Dose; HF = Heart Failure; FD = Full Dose; Ht = haematocrit; HT = Hypertension; FFP = Fresh Frozen Plasma; LT = Liver Transplantation; NA = No Aprotinin; n.s. = not significant; OR = Odds Ratio; PC = Platelet Concentrate; RCT = Randomized Controlled Trial; RC = Renal Clearance; RD = Renal Dysfunction; RF = Renal Failure RR = Relative Risk;; SMD = Standardized Mean Difference; TXA = Tranexamic Acid; U = Unit; US = United States.
2. Figures are significant unless specifically mentioned.
3. Aprotinin versus control. Only significant results are mentioned.

Deep venous thrombosis

Only a few studies have investigated the incidence of deep venous thrombosis (DVT) with aprotinin therapy during orthopaedic surgery using ultrasound or venography, and no significant increase was detected. Cooper identified nine cases of fatal pulmonary embolism in patients undergoing end-stage heart failure operations after heparin reversal [12], eight of which received aprotinin. Other rare cases have been described [42]. In orthotopic liver transplant surgery, lung embolism has been reported ranging from 1.2 - 6.25% [17,19,31, 32,39]. A recent report of 27 cases found that 69% of the cases used antifibrinolytic agents (in two cases more than one drug) with a slight predominance in the reperfusion phase [31,32].This was not confirmed in randomized trials [8].

Hypercoagulability was found in 28% of patients with biliary cirrhosis and 43% of patients with primary sclerosing cholangitis. Findlay found that 60% of the patients with these diseases did not exhibit thromboembolic complications [18].

Cerebral complications

Harmon found less cognitive dysfunction in patients receiving aprotinin therapy: 58 and 23% (p=0.005) of the aprotinin group at 4 days and 6 weeks, respectively, compared with 94 and 55% in the placebo group (p=0.05) [25], probably because of less infusion of unwashed drain blood (fewer micro-emboli) due to less blood loss.

These results were confirmed by Frumento (2003), who reviewed medical records of 1524 patients undergoing CABG [20]. The predicted stroke index in these patients was 20%, but patients receiving full-dose aprotinin had a 0% actual stroke rate, compared with 22% of those receiving a half-dose aprotinin and 16% of those not receiving aprotinin [20,43]. This finding was confirmed by Umscheid [9], and the mechanism underlying this observation was the subject of a recent review [13].

Mangano reported increased cerebral complications (4.5 vs. 1.6%; p<0.001, respectively) and a 181% increase of stroke or encephalopathy in patients undergoing cardiac surgery for the first time [33], and referred to Sundt who found post mortem thrombi in the cerebral vessels of patients who received aprotinin [2]. Eaton described a hemispheric infarction in a case report [16].

Mortality

Mangano found that patients undergoing cardiac surgery for the first time and receiving aprotinin had increased short-term mortality (2.8 vs. 1.3%; p = 0.02) [33]. Levi found a 50% reduction of mortality [3]. Mangano's recent prospective study of the 5-year survival in the same database [34] revealed an increase in mortality in the aprotinin group (223 deaths among 1072 patients; 20.8%) compared with controls (128 deaths among 1009 patients; 12.7%) or those receiving tranexamic acid (65 deaths among 442 patients; 14.7%). Recent

Table 3. Reduction of blood transfusions and adverse effects by tranexamic acid in meta-analyses and RCT1,2

First author and year of publication	Search	Reduction of blood transfusion3	Adverse effects
Laupacis [3] (1997) Faught [4] (1998)	CABG; 1966-1997 12 RCT; n = 882	OR 0.50 - 0.78 U EC	In cardiac surgery: CV complications ↓: OR 0.48
Levi [5] (1999)	CABG; 1966-1998;14 RTC;n = 801	OR 0.46	Rethoracotomy ↓ : OR 0.44;
Brown [8] (2007)	22 RCT; 1966-2006; n = 2429	RR 0.75	n.s.
Henry Cochrane [9] (2007)	CABG: 1966-1999; 15 RCT; n = 1151	RR 71 - 1.03 U EC	n.s.
Henry Cochrane [9] (2007)	Non-cardiac; 3 RCT; n=191	RR 0.52	n.s.
Molenaar [10] (2007)	LT: 1966-2005; 23 RCT; n= 306	EC: SMD 0.42 E FFP: SMD 0.30	n.s.
Umscheid [11] (2007)	Cardiac surgery 1966-2007 TXA vs placebo; n = 1905;AT vs TXA n = 1825	RR 0.65 Vs AT RR 0.98	n.s.
Jimenez [48] (2007)	CPB inflammatory response. Case control n = 165;RCT n = 50		Inflammatory response ↓; 17 vs 42% (p = 0.047) Significant reduction shock, vasopressors, artificial ventilation, RD, D-dimer.

AT= Aprotinin Therapy; CABG = Coronary Artery Bypass Graft; EC = Erythrocyte Concentrate; FFP = Fresh Frozen Plasma; LT = Liver Transplantation; n.s. = not significant; OR = Odds Ratio; RCT = Randomized Controlled Trial; RD = Renal Dysfunction; RR = Relative Risk; SMD = Standardized Mean Difference; U = Unit.
All figures are significant unless specifically mentioned.
TXA versus control/placebo.

meta-analyses were unable to confirm these results, although the preliminary results of 30 000 files investigated by the FDA and the results of the BART trial support these findings [50]. The BART study concluded that despite a modest reduction in massive bleeding, the negative mortality results precludes its use in high-risk cardiac surgery.

Tranexamic acid

Tranexamic acid (TXA) is a synthetic lysine analogue that reversibly inhibits plasmin(ogen) by blocking the lysine binding sites and preventing binding of plasmin(ogen) to fibrin. TXA also preserves platelet function by preventing degradation of the platelet glycoprotein 1b receptor. According to some authors, TXA may have some anti-inflammatory effects [46]. TXA can be administered both orally and intravenously.

Efficacy

TXA has been used to limit blood loss and reduce the amount of allogeneic blood transfusions in cardiac, orthopaedic, liver transplantation and prostate surgery; its use in prostrate surgery has been based on the fact that bleeding during surgery has been attributed to primary fibrinolysis due to plasminogen release.

TXA is highly efficient drug, as shown in a meta-analysis of 12 RCTs, reducing the proportion of transfused patients undergoing cardiac surgery by approximately 50%. In liver transplant surgery, low dose therapy (2 mg/kg/hour) suppresses fibrinolysis without an effect on transfusion requirements, in contrast to a high dose regimen [23, Table 3]. Several authors consider TXA less effective than aprotinin [6].

TXA is excreted 95% by the kidney. The usual dose of TXA is a 10 mg/kg bolus administered intravenously, followed by a 10-12 hour infusion of 1 mg/kg/hour. Orally, TXA is administered at a dose of 1-2 grams, 3-6 times per day.

Adverse effects of TXA

Side effects are gastrointestinal symptoms, myonecrosis, and thrombosis [2, 47, Table 3].

Gastrointestinal side effects

Gastrointestinal side effects have only been described with oral therapy and include nausea, diarrhoea, and abdominal cramps.

Myonecrosis and myoglobinuria

Although similar in structure to epsilon amonicaproic acid, another synthetic lysine inhibitor, myonecrosis and myoglobinuria have not been reported(2).

Visual problems

Disturbances in colour vision have been reported, and patients presenting this symptom should be withdrawn from the therapy [53].

Thrombosis, myocardial infarction and stroke

No studies have been performed focusing on adverse effects. In the 12 cardiac RCTs described in the meta-analysis, the incidence of myocardial infarction in the TXA group was 0.4% compared with 1.8% in the control group (p = 0.3).

In 17 RCTs not specially focused on reduction of blood transfusion, 10 mentioned statistically insignificant adverse effects, such as thrombosis and myocardial infarction.

No increase in deep venous thrombosis has been found during orthopaedic surgery (only 3 RCTs) [7,47]; similar findings were made in patients receiving TXA during liver transplantation. In older literature, however, no consensus is reached regarding TXA safety due to the risk of DVT during the hypofibrinolytic state. No controlled study has shown an increase in DVT [4], although blood clot formation in the bladder, and one case of fatal pulmonary embolism has been described [4].

Mortality

TXA therapy is not associated with an increase in short or long term mortality.

Discussion

Antifibrinolytic agents are important drugs for allogeneic blood transfusion saving therapies, saving approximately 1 unit of blood

per patient (see Tables 1 and 3). These agents are incorporated into a complete treatment plan, referred to as a blood management plan. In the Netherlands, only two antifibrinolytic drugs are available i.e. aprotinin and tranexamic acid, and of these two drugs, aprotinin exhibits other modes of action, specifically related to anti-inflammatory effects. These effects render this drug particularly interesting for CPB surgery due to the systemic inflammatory response caused by the heart-lung machine. Randomized studies did not indicate the side effects to be a major concern, thus they were disregarded. Current meta-analyses of these studies confirm this view. The retrospective studies of Mangano and Karkouti, however, challenged this perspective and caused an explosion of investigations, including two new meta-analyses, review articles, hospital results, and debates on the advantages and disadvantages of this treatment (see Tables 1 and 2). In particular, the fact that the use of aprotinin was not a part of a protocol in the Mangano and Karkouti study, causing a bias towards the use in high-risk patients, is a point often noted [6,26,40]. The decision to administer aprotinin was made by the surgeon or anaesthesiologist, but the reason was not motivated. RCTs, on the other hand, may include low risk patients in a highly controlled study. In the Mangano study, there appeared to be a prevalence of risk factors such as diabetes, hypertension, heart failure, carotid stenosis or complex surgery in the aprotinin group, but most were not statistically significant. Mangano showed that in cases of hypothermia, high kallikrein plasma levels, or in patients with haemorrhage, the metabolic effects of aprotinin were more pronounced and may be complicated by the dose-dependent vasoconstrictive effects of the afferent vessels of the kidney. Together with loss of autoregulation and decreased NO release, this could result in vascular thrombus formation and consequently tubulus necrosis.

Other important factors, such as the use of angiotensin-converting enzyme inhibitors (ACEI) and perioperative ACT values, were not mentioned in the article, while Kincaid reported an increase in renal dysfunction when aprotinin and ACEI were combined [30]. Brown showed that the intention to treat was violated on many aspects and patients were excluded. He reconciled these patients to their original arms and found no renal failure [6].

Based on the results from the Mangano study showing a doubled incidence of renal dysfunction associated with aprotinin [33], the FDA published a reminder in February 2006 that these studies were not randomized [26] and advised intense monitoring of renal function and use of this drug only in situations where the clinical advantage outweighs the potential risks.

In September 2006, the FDA could not report any increased risk of fatal or nonfatal events, though the FDA lacked full access to the Mangano data. Despite this information, the committee supported an acceptable safety profile, as evidence was insufficient to require additional warning on the label for aprotinin. Days after this meeting, the FDA was given access to 67 000 observational data not presented by Bayer to the committee [26].

In November 2006, the company Bayer published a revision of the prescription information, warning against treatment of patients with pre-existing renal dysfunction and those who perioperatively receive drugs that may worsen renal function [50]. Bayer also warned of anaphylactic reactions and provided a new contraindication for use in patients with known or suspected exposure during the preceding 12 months.

In September 2007, Bayer reported preliminary results of the investigation of the 67 000 records of high-risk patients receiving various treatments selected by the physician. The report suggested that aprotinin treatment (30 000 patients) was related to an increased risk for kidney failure, congestive heart failure and death.

More data on safety were expected to be provided from an ongoing study, the largest blinded RCT of antifibrinolytics in high-risk cardiac surgery in Canada (the BART study). Patients were randomized to receive aprotinin, TXA or EACA, and the primary outcome included bleeding and secondary outcome included organ failure. The target enrollment was 2970 patients. On 19 October 2007, the FDA was notified of the Data Safety Monitoring Board's recommendation to stop the BART study. Aprotinin increased the risk for 30-day mortality compared with tranexamic acid, although aprotinin was associated with less serious bleeding. Its use is contraindicated in high-risk cardiac surgery [50].

At this time the drug has been withdrawn from the market.

In the studies and publications thus far, no adverse effects were shown for TXA, supporting TXA as the current drug of choice for cardiac and orthopaedic surgery patients. TXA may be used for more indications than aprotinin, and currently, no data contraindicate its use in liver surgery, in gynaecological or gastroenterological bleeding, or in patients with other types of massive blood loss. Its safety in TURP, however, should be thoroughly investigated in studies with patients receiving adequate DVT prophylaxis. Its use in patients with macroscopic haematuria is contraindicated.

Conclusion

Aprotinin effectively reduces the use of allogeneic blood products during cardiac, liver, cerebral and orthopaedic surgery by means of a broad field of action. Recently reported serious complications challenged its indication. It resulted in withdrawal from the market.

Tranexamic acid is a safe, potent and effective drug in cardiac and orthopaedic surgery, as well as in liver surgery, and in gynaecological or gastroenterological or other types of massive blood loss. Its safety in TURP must be more investigated. It may be slightly less effective and is a pure antifibrinolytic agent that may have some anti-inflammatory effects. It is contraindicated in the case of macroscopic haematuria. Together these results suggest that tranexamic acid is currently the safest antifibrinolytic product.

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