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Re-Evaluation of the Role of Antifibrinolytic Therapy with Lysine Analogs in Liver Transplantation in The Post-Aprotinin Era

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Abstract

Purpose of review: Hemorrhage, blood and blood product transfusions and the need for surgical re-exploration for bleeding can have a detrimental effect on patient outcome during liver surgery. Following the suspension of aprotinin from the market only the antifibrinolytics tranexamic acid (TA) and epsilon-aminocaproic acid (EACA) are left as pharmacological options to reduce hemostatic activation and associated bleeding complications. Considering the apparent usefulnes of aprotinin in liver surgery and transplantation, its loss has left a void within the armamentarium of drugs available to reduce blood loss. The need for large independent safety studies has become evident. The current review focuses on the drugs that are available, the safety and efficacy data that supports their use and the indications warranting further trails.

Recent findings: Both TA and EACA are effective in reducing blood loss and transfusion requirements in liver surgery. Analysis of data is complicated as the dosing regimens, especially for tranexamic acid, varies enormously and the agents are highly overdosed in most relevant trials. New data indicates that in a dose-dependent fashion, TA is associated with an increase in adverse events with transient renal failure highlighted as a particular problem. It appears that all the anti-fibrinolytics have side effects that may impact on morbidity and mortality and it may be that aprotinin is no worse. The use of these agents needs to be balanced against benefit especially in the management of high risk cases.

Abbreviations: OLT: Orthotopic Liver Transplantation; TA: Tranexamic Acid; EACA: Epsilon-Aminocaproic Acid; RBC: Red Blood Cells; FFP: Fresh Frozen Plasma

Introduction

Orthotopic Liver Transplantation (OLT) is a major surgical procedure which can be complicated by excessive blood loss and associated increased morbidy and mortality [1]. The cause of excessive blood loss during OLT is multifactorial [2], but hyperfibrinolysis is an important mechanism leading to non surgical bleeding in these patients [3,4].

During the last few decades, blood loss and transfusion requirements during OLT have diminished. The reasons for this are complex and multifactorial however increasing overall clinical experience, improvements in surgical and anaesthetic techniques and training, the introduction of sensitive near patient coagulation monitoring and the judicious use of antifibrinolytic drugs have all contributed to this reduction [5].

Enhanced fibrinolysis during OLT is caused by an alteration in the balance between activators and inhibitors in the fibrinolytic system. Increased activity of these activators, mainly tissue-type plasminogen activator and urokinase-type plasminogen activator and the decreased activity of inhibitors, plasminogen activator inhibitors and a reduction of alpha-2 antiplasmin have all been demonstrated during OLT. The result of this imbalance is enhanced degradation of the polymerized fibrin with resultant clot lysis leading to oozing and eventually overt bleeding in the surgical field [6].

There are a number of laboratory tests currently available that can assist the clinician with monitoring, diagnosis and treatment. These include the shortened whole blood clot lysis time (WBCLT), the euglobin clot lysis time (ELT), reduced clot lysis index (CLI) on the Thromboelastogram (TEG), Maximum Lysis (ML)>15% by Rotational Elastometry (ROTEM), elevation of fibrin degradation products (FDPs) and D-dimers, and decreased levels of fibrinogen detected on ROTEM with Maximum Clot firmness (MCF) <8mm and MCFext (extrinsic) <45 mm [7-10]. As hyperfibrinolysis occurs frequently, mainly in the anhepatic phase of OLT and during the reperfusion of the liver graft [7,8,11], antifibrinolytics have been used in the attempt to reduce blood loss since the early era of OLT, to reduce transfusion requirement and their associated risks. Despite being commonly used in the clinical setting, there has never been a general consensus on how, when or which drug should be administered and at what dose. Despite this many liver transplant centres still use antifibrinolytics prophylactically or in cases of documented fibrinolysis on TEG or ROTEM [7-9].

The aim of this review is to describe the pharmacology, efficacy, side effects, indications and contraindications of the 3 main antifibrinolytics that have been documented and used in OLT (Aprotinin, TA and EACA) as well as to examine the controversies surrounding their use and a possible link with intraoperative thrombotic events, increased morbidity and mortality.

Search Strategy and Data Analysis

A literature search was conducted using online Pubmed and the

Cochrane Library from 1966 to date. The search strategy used the following single text words and combination: aprotinin, Epsilon-aminocaproic acid (EACA), tranexamic acid (TA), anti-fibrinolytics and liver transplantation. Reference lists of relevant articles were cross-checked for other relevant articles. The following data was considered: Red blood cell (RBC) and fresh frozen plasma (FFP) transfusion requirements during transplantation, perioperative hepatic thrombosis and venous thrombolic events and evidence of transient and established renal failure.

The article also compared the various drugs used (aprotinin, TA and EACA) and the different dosage regimens that have been documented.

Haemostatic Changes during Liver Transplantation

Haemostasis is a complex process that is a balance of platelet activation, coagulation cascade and fibrinolysis. Although described simplistically this is a complex process and the "cascade" is much more involved as described in Hoffman's cell based theory. The liver plays a central role in this haemostatic system as it synthesizes the majority of coagulation factors and proteins involved in platelet generation, coagulation and fibrinolysis. Included amongst these is thrombopoietin, also known as megakaryocyte growth and development factor (MGDF), which is responsible for platelet production in bone marrow. Unlike other factors this is also made outside of the liver in renal tissue and striated muscle and as such the impact of liver dysfunction is not as great.

In liver disease, both acute and chronic, there is a severe impact on the haemostatic balance [11]. Synthetic function may be markedly impaired with a resultant decrease in all liver derived coagulation protein leading to a state of hypo-coagulability. In addition, thrombocytopenia secondary to reduced thrombopoetin production and/or increased platelet turnover due to intravascular activation and splenic sequestration contributes to this haemostatic derangement [12,13]. Portal hypertension also contributes to this altered haemostatic process as it both increases platelet loss due to splenomegaly as well as enhancing endothelial activation and release of haemostatic proteins [14,15].

Routine laboratory tests of haemostasis such as platelet count, prothrombin time (PT) and the activated partial thromboplastin time (APTT) are frequently abnormal in patients with liver disease. The combination of thrombocytopenia with a prolonged PT and APTT is suggestive of a potential bleeding diathesis and it is traditionally assumed that patients with liver failure are at risk of bleeding as a result of these Continuous low-grade activation of endothelial cells results in release of several hemostatic proteins such as von Willebrand factor (VWF) and levels are frequently elevated in patients with liver disease hemostatic changes. The changes that occur in liver disease that tend to promote increased fibrinolytic activity and clot instability (such as increased tissue plasminogen activator (tPA), low levels of alpha 2 antiplasmin, factor XIII and reduced thrombin activated fibrinolysis inhibitor (TAFI) are balanced out by increased levels of the acute phase reactant plasminogen activator inhibitor (PAI-1) [16]. Levels of PAI-1 are particularly high in acute liver failure and in cholestatic liver disease and significant fibrinolysis are rare in this group. Bleeding during OLT is therefore related to two different mechanisms of haemostasis [4]. There is no doubt that the extensive surgical trauma plays a role in the origin of serious bleeding. However, the bleeding can be enhanced by defects in the hemostatic system. Hemostasis defects can be divided into those present before the operation and secondary to the underlying liver disease and those originating during

the operation. Intraoperative defects can be classified according to the three main systems of hemostasis: coagulation, fibrinolysis and platelet function. Serious problems with coagulation are also clearly related to the quality of the liver graft and appear to be less frequent now since better graft preservation techniques have been introduced [4]. They are also rarely seen during living related liver transplantation where preservation fluids are rarely used and the time to transplantation is short. Adequate intraoperative monitoring of coagulation is crucial to prevent massive bleeding [7]. However, problems resulting from hyperfibrinolysis seem to be of clinical importance, especially during the anhepatic stage and after graft reperfusion and can be associated with explosive primary hyperfibrinolysis [7,65] with some patients developing diffuse uncontrolled bleeding. Usually hyperfibrinolysis subsides within an hour but it may persist in the presence of a poorly functional or marginal graft [17]. While lack of hepatic clearance seems to be an important cause of t-PA increase during the anhepatic stage, enhanced release may be important for the rise seen after graft reperfusion [18]. There is also evidence that decreased platelet numbers and function plays a significant role especially after graft reperfusion [15,65]. In addition, dilutional coagulopathy, hypothermia, inadequate surgical expertise and a marginal graft, can worsen the bleeding [65].

As can be seen haemostasis is a complex process even when functioning normally. Liver disease seriously impairs the precarious balance between coagulation and fibrinolysis and this is further complicated by surgery and poor graft function following transplantation.

Antifibrinolytic Agents

Two groups of drugs have been demonstrated to modulate and inhibit fibrinolysis and include the lysine analogues epsilon aminocaproic acid (EACA) and tranexamic acid (TA) and the serine protease inhibitor aprotinin.

Aprotinin

The use of Aprotinin, a naturally occurring serine protease inhibitor derived from bovine lung, as antifibrinolytic in OLT was first described by Neuhaus et al. and Mallett et al. more than 20 years ago [19,20]. The drug is active against most serine proteases but especially trypsin, chymotrypsin plasmin and kallikrein. Its action on kallikrein leads to the inhibition of formation of factor XIIa thus inhibiting both the intrinsic pathway of coagulation and fibrinolysis. They found that 2 milion kallikrein inhibitory units (KIU) of aprotinin significantly decreased blood loss, transfusion of red blood cells, FFP use, and duration of surgery when compared to a patient group not given aprotinin. Their findings were supported by a subsequent report involving a small number of patients [22-28]. In 2000, Porte et al. [29] reported the first multi centre, prospective, double-blinded, controlled trial of aprotinin in OLT A total of 141 patients were enrolled in the study. Patients were randomly assigned into 1 of 3 groups: group 1, high dose aprotinin (2 million KIU bolus followed by 1 million KIU/hour infusion, and an additional 1 million KIU before graft reperfusion); group 2, regular dose aprotinin (2 million KIU bolus followed by 500.000 KIU/hour infusion); and group 3, placebo. Transfusion criteria were standardized for all six liver transplant centers. Total blood loss in this study was lower in the aprotinin treated groups (60% reduction in the high dose group and 44% reduction in the low dose group) than in the placebo group. The transfusion of red blood cells was 37% lower in the high dose group and 20% lower in the regular dose group than in the placebo group. Milroy et al. [26] first reported more stable hemodynamics in patients who received aprotinin during OLT. In this study 52 patients

were randomized to receive either aprotinin or placebo. Significant differences between the two groups were noticed in cardiac index, systemic vascular resistance index, O_2 delivery, and O_2 extraction ratio 5 minutes after reperfusion. Molenaar et al. [30] demonstrated that patients treated with either high or regular dose aprotinin required less epinephrine for intervention compared to patients in the placebo group. Two possible mechanisms of hemodynamic stability by aprotinin were postulated: decrease in blood loss resulting in fewer hypotensive events and inhibition of the kallikrein-kinin system by high dose aprotinin, resulting in more stable hemodynamic state. Some benefits, such as anti-inflammatory and antioxidant effects, which have been shown in cardiac surgery, were also suggested in patients undergoing OLT [31,32]. These findings have stimulated an increasing use of aprotinin during liver transplants procedures in many centers. The mechanism of all these postulated actions of aprotinin is complex and not clearly defined. However as stated the main effect is the inhibition of the serine proteases plasmin, trypsin, kallikrein, chymotrypsin, activated protein C and thrombin [32,33].

Following a intravenous bolus, aprotinin is redistributed into the extracellular compartments with an initial half-life of about 1 hour. The terminal half-life ($T_{1/2}$ 7-10 hours) depends on the release of aprotinin from tissues like the kidneys [31-33]. Antifibrinolytics drugs such as aprotinin have been associated with two important safety concerns: the risk of inducing thromboembolic complications and the risk of renal dysfunction [34-38]. Aprotinin has an high affinity for renal tissue and it can cause a reversible overload of the tubular reabsorptive mechanisms, resulting in transient renal dysfunction [29,30]. Aprotinin may also have a direct toxic effect on the proximal tubular cells and reduce intrarenal blood flow through inhibition of renin and kallikrein activity [30]. Warnaar et al. [38] compared postoperative renal function in 1043 adults undergoing OLT. Postoperative renal function was compared in patients who received aprotinin (n=653) or did not (n=390). In this study Aprotinin was identified as a risk factor for severe renal dysfunction within the first week. No differences in renal function at 30 and 365 days postoperatively were recorded. Moreover, no significant differences were found between the two groups in the requirement for renal replacement therapy or in one year patient survival rate. In this study aprotinin was shown to be associated with a higher risk or transient renal dysfunction in the first week after OLT, but not with an increased risk of mortality [38]. Several case reports highlighted the risk of developing extensive hyperacute venous and systemic thrombosis and tromboemboli during aprotinin infusion after the reperfusion of the graft [39,40]. Although in a recent systematic review and meta-analysis of a total of 1407 patients, Molenaar et al. [37] did not provide evidence for an increased risk of thromboembolic events associated with antifibrinolytic drugs in OLT.

Published evidence of hypersensitivity and/or anaphylactic reactions to aprotinin is relatively common [41]. However, hypersensitivity reactions are rarely reported in patients without prior exposure to the drug. The incidence in patients who have been previously exposed to aprotinin was reported to be 2.5% and fell significantly with time after initial exposure [42,43]. Rapid injection of aprotinin can also cause profound hypotension probably due to histamine release [42].

Tranexamic acid (TA)

Tranexamic Acid (TA) is a synthetic derivative of the aminoacid lysine that exerts its antifibrinolytic effect by blocking the binding site of plasminogen to fibrin with a resultant increased clotting potential of blood and subsequent reduced blood loss [44]. At high concentrations,

TA may also act as a noncompetitive inhibitor of plasmin. TA has been suggested to have a higher antifibrinolytic activity than EACA in peripheral compartments, such as renal, intestinal and prostatic tissues [45]. TA is 6 to 10 times more potent than EACA and has a longer half-life. The kidney is the primary organ for drug excretion with more than 95% of the drug removed unchanged in the urine [45,46].

Since the European Medicines Agency suspended the marketing authorization for aprotinin and also because aminocaproic acid is not licensed for such in UK, TA has become the agent of choice to reduce blood loss and transfusion associated with cardiac surgery in UK [47,48]. It has no specific licence for use in OLT.

TA has been shown to reduce blood loss in surgical patients and risk of death in patients with traumatic bleeding and there has been no apparent increase in vascular occlusive events documented with its use. [50,51]. Although the first reported use of TA was in the 1980s it was not until 1996 that its use was reported in a prospective trial [52].

A comparison between TA and placebo in terms of efficacy and safety, has been performed in three randomized controlled trials [52-54] in the period between 1996 and 2000. Boylan JF et al. [52] found and published in 1996, that TA reduces blood loss, transfusion requirements and clotting factors use in patients undergoing OLT. Kasper et al. [53] in 1997 found that a continuous small dose of TA achieves a reduction of fibrinolysis, but doesn't reduce transfusion requirements during OLT. In 2000, Dalmau et al. [54] achieved better results with TA in comparison to Epsilon-Aminocaproic acid and placebo in terms of transfusion requirements. Recently, the same group compared the efficacy of TA and aprotinin in a double-blinded, prospective and randomized study [55]. A total of 161 patients were included in the recent meta-analysis on TA performed by Molenaar et al. [37] 83 receiving TA and 78 receiving placebo.

In terms of efficacy, the results showed a remarkable difference between the two groups with lower transfusion requirements in the patients who received TA (standardized mean difference 0.43, 95% CI 0.12-0.74, p=0.007) [20].

No significant difference was found when comparing the intraoperative use of FFP in the TA-and placebo-treated patients.

A safety analysis was performed by Molenaar et al. [37] data on the occurrence of hepatic artery thrombosis (HAT) and venous thromboembolism (VTE) was obtained from three trials conducted between 1996-2000.

Combined analysis demonstrates an incidence of HAT of 6% in TA treated patients, compared with 2.6% in the patients who received placebo. The overall incidence of thromboembolic events was 1.3% (1/78) in the placebo group and there were no venous thromboembolic events observed in the TA treated patients. Mortality rates in the TA and placebo treated patients were 4.8% (4/83) and 9% (7/78) respectively [20]. Comparison of different studies using TA in OLT is difficult because all trials used different dosage regimens ranging from low dosage (2mg/kg/hour) to high dosage (40 mg/kg/hour). Nonetheless, it appears that TA suppresses fibrinolysis and may decrease blood loss and blood components requirement [37]. However, the optimal dose of TA for OLT has not yet been elucidated [56].

Epsilon aminocaproic acid (EACA)

Epsilon-aminocaproic-acid (EACA), like TA, is a synthetic lysine analogue. It binds reversibly to the Kringle domain of the enzyme plasminogen, and competitively inhibits the binding of plasminogen

to lysine residue on the surface of fibrin and prevents conversion of plasminogen to plasmin. The Kringle domain is an autonomous protein domain folded into large loops stabilised by disulphide bridges and is important in many protein-protein interactions with many of the coagulation and fibrinolytic proteins. Some studies report that EACA also inhibits pro-urokinase-induced plasminogen activation by this same action, thus preserving platelets function [44]. Primarily metabolized and eliminated by kidney, EACA has like TA, been implicated with possible renal complications inducing acute renal failure secondary to acute tubular necrosis, renal infarction, myopathy, pigment-induced renal complications, glomerular capillary thrombosis and elevated excrection of beta-2-microglobulin [44].

The first reported use of EACA in liver transplantation was in 1966 [38]. Von Kaulla et al. [57] reported giving EACA 1g/h to three patients during OLT and for several days postoperatively. EACA appeared to stop fibrinolysis in all three patients, but one died intraoperatively with uncontrollable bleeding. Deep venous thrombosis developed in one patient and pulmonary emboli in the other. After observing a high incidence of hypercoagulable state and pulmonary emboli in their patients with and without EACA therapy Von Kaulla et al. [57] postulated that the fibrinolysis during OLT is a self-limiting process caused by organ systems and that pharmacologic manipulation of the coagulation system during OLT is not necessary and may be harmful [57].

The optimal clinical dose of EACA has not been identified. McNicol et al. [39] recommended oral or intravenous administration of 1 g EACA every hour after a priming dose of 4-5 g to achieve an EACA plasma level of 13mg%. They showed that a larger dose of EACA (130 mg%) was needed to inhibit plasminogen activity in vitro while reported that a dose four times smaller than the in vitro dose was sufficient to arrest fibrinolysis during open heart surgery [59].

Similarly Kang et al. [60] found that the dose of EACA used for in vitro evaluation of fibrinolysis was five fold larger than the clinical dose. They studied 79 adult patients receiving a liver transplant. The use of EACA being reserved for only when certain criteria were met: severe fibrinolysis seen on TEG, improvement of fibrinolysis in vitro by adding EACA, and generalized oozing from a previously dry surgical field. It is well known that EACA may lead to thrombotic complications. However, in Kang's study [60], haemorrhagic or thrombotic complications developed intra or postoperatively in four patients but none of these received EACA. Subsequently, several studies have showed no benefits of EACA in OLT, but the value of these studies was limited since they were retrospective and involved small numbers of patients. In a prospective double-blind, randomized, controlled trial, in which 16 mg/kg/hour of EACA was compared to TA and placebo, EACA was reported to reduce red blood cell transfusion requirements though this reduction was not statistically significant compared to the placebo group. In patients undergoing OLT, Kang et al. recommended the judicious use of a small dose of EACA when its efficacy had been confirmed in vitro and they reported that it effectively treats severe fibrinolysis without clinical thrombotic complications [60,61].

Discussion

The systematic review and meta-analysis on efficacy and safety of antifibrinolytics in OLT, Molenaar et al. [37], clearly showed that both Aprotinin and TA significantly reduces RBC transfusion requirements during OLT, but only Aprotinin reduced the intraoperative use of FFP. In addition, they showed that the safety analysis of all published trials does not provide evidence for an increased risk of Hepatic artery Thrombosis, venous thromboembolic events or mortality in patients who received an antifibrinolytic drug during OLT [37].

Since the clinical introduction of antifibrinolytics to prevent or reduce blood loss during major surgery, it has been extensively debated whether these drugs may be prothrombotic and increase the risk of developing ischemic end-organ damage. Several case reports of patients who experienced an intraoperative pulmonary embolism have fed this debate in the past few decades [39,40,60,62-64].

OLT has constantly received much attention for the risk of excessive peri-operative bleeding but less attention has been paid to the risk of thromboembolic complications [60]. Venous pulmonary embolism has been described in patients undergoing OLT and in whom antifibrinolytics have not been used [65] but it has become increasingly clear that the prophylactic use of anti fibrinolytics is not exempt from such complications although the incidence is far from clear.

There may be multiple causative factors for excessive bleeding during OLT such as thrombocytopenia, dilutional coagulopathy, hypothermia, technical surgical difficulties and inadequate surgical expertise [60,66]. Antifibrinolytics will only reduce bleeding in cases where the cause is one of enhanced fibrinolysis. Their use may be harmful in patients with prothrombotic states like Budd-Chiari syndrome, multiorgan transplantation, retransplantation, fulminant liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, renal failure, malignant disease, preexisting thrombotic disease (i.e. portal vein thrombosis), disseminated intravascular coagulation and in pediatric patients [49]. In a retrospective review of over 600 OLT cases, Gorlinger found hyperfibrinolysis developed in 60% of OLT cases, but only 40% required treatment with antifibrinolytic therapy [67]. In this series, prophylactic antifibrinolytic therapy was only administered to patients with a significantly reduced MCF(< 30 mm) at baseline.

The actions of Aprotinin and TA have been widely studied whereas only one randomised controlled trial of the use of EACA is available [54,55], and this reportedly showed no therapeutic benefit in comparison with placebo. In the absence of aprotinin and the presence of data supporting the use of TA the role of EACA in OLT needs to be addressed.

TA has been shown equally effective as aprotinin in reducing blood loss [55]. TA in comparison to Aprotinin is cost-effective and the side effects appear less frequent.

In our institution we have totally moved away from the prophylactic use of antifibrinolytic agents and our transfusion practice is protocol driven. TA is only administered in cases of documented fibrinolysis on TEG/ROTEM with or without oozing in a previously dry surgical field. It is probably no longer acceptable to use antifibrinolytics in the empirical management of bleeding or control of coagulation disorders.

Many centers still use antifibrinolytics prophylactically but it is important pre-operatively to identify those patients who are potential candidates and will benefit most from the administration of an antifibrinolytic drug. This avoids potential side effects and additional costs in those patients who do not need the drug. There is no uniform definition of high risk cases, but patients with chronic hepatitis, cirrhosis and portal hypertension may have a higher incidence of hyper fibrinolysis with massive peri-operative blood loss and the use of anti fibrinolytic therapy should be considered. Antifibrinolytics should generally be avoided in patients with pre-existing thrombosis, Budd-Chiari Syndrome, hepatic artery thrombosis or portal venous thrombosis.

The evidence for avoiding the use of anti-fibrinolytics during a

Reference	Total number of patients	Prospective study	Dose	Results
Aprotinin				
Neuhaus et al.1989(20)	20	No	2 million KIU	Reduction in RBC,FFP and surgical time
Mallett et al. 1990(19)	24	No	2 million KIU followed by 500.000 KIU/hour during surgery: 70.000 KIU each RBC	
Cottam et al.1991(21)	8	No	2 million KIU and followed by 500.000 KIU/hour, 50.000 KIU given to each unit of RBC	Reduce t-PA production and increase alpha-2 antiplasmin
Grosse et al.1991(22)	50	No	2 million KIU followed by 500.000 during surgery	Reduce fibrinolysis(measured by TEG),RBC,FFP, and platelets
Himmelreich et al.1992(23)	23	No	500.000 KIU bolus before, during and after reperfusion	Smaller increase in t-PA in comparison to other studies
Soilleux et al., 1995(24)	189	Yes	2 million KIU load plus 500.000 KIU/hour infusion or 500.000 KIU load plus 150.000	No differences in RBC in the high and low dose aprotinin group
Scudamore et al., 1995(25)	66	No	1 million KIU bolus plus 500.000 KIU/hour infusion	Reduction in Cryo,FFP, RBC in the aprotinin but not in the EACA group
Milroy et al.,1995(26)	52	Yes	Load 280 mg pus 70 mg/hour infusion,additional 140 mg to bypass	Greater SVRI,O2 extraction ratio and less CI,DO2 5 minutes after reperfusion
Marcel et al.,1996(27)	44	Yes	200.000 KIU/hour infusion	Reduce FFP,Cryo but not RBC or platelets,less EACA rescue
Garcia-(28)Huete,1997	80	Yes	2 million KIU plus 500.000/hour	No difference in EBL, blood products
Porte et al.,2000(29)	137	Yes	High: 2 million KIU load plus 1 million/hour plus 1 million 30 min before reperfusion,low: 2 million plus 500.000/hour	60% and 44%EBL,37% and 20% RBC reduction in high and regular dose groups, compared to placebo
Findlay et al.,2001(70)	63	Yes	1 million KIU load plus 250.000 KIU/hour	Reduce RBC requirements but not FFP, platelets or cryo
Molenaar et al., 2001	93	Yes	High: 2 million load plus 1 million/hour plus 1 million before reperfusion,low:2 million + 500.000 KIU/hour	No renal toxicity
Molenaar et al.,2001	137	Yes	High: 2 million load plus 1 million/hour plus 1 million 30 min before reperfusion,low:2 million + 500.000KIU/hour	Better 1- month graft survival
Molenaar et al.,2001	67	Yes	High and low regimen comparison	Less epinephrine use in high or low dose group
Rentoul et al.,2003(71)	24	No	15.000 KIU/kg load plus 5000/hour infusion	Reduce RBC and FFP requirements
Findlay and (72)Kufner,2003	63	Yes	1 million KIU load plus 250.000KIU/hour	Less vasoactive infusion in the aprotinin group
Warnaar et al.,2007	1043	No	2 million KIU load plus 500.000 KIU/hour	2 time higher risk of severe renal dysfunction within the first week
Tranexamic acid(TA)				
Carlier et al.,1987(49)	33	No	15 mg/kg for 8 hours	41%of patients with normal ECLT
Boylan et al.,1996(52)	45	Yes	40 mg/kg/hour uo to 40 g	Reduced EBL,plasma,platelet and cryo; no RBC
Kasper et al.,1997(53)	32	Yes	2mg/kg/hour	TA decreased fibrinolysis and need for EACA rescue but not transfusion requirements
Epsilon aminocaproic acid (EACA)				
Kaulla1966(57)	3	No	Not reported	Patients died of severe hemorrhage or thrombolic complication
Kang et al.1987(60)	20	No	1 gm	fibrinolysis's improvement
Scudamore et al. 1995 (13)	No	No	Non reported	No effects on transfusion

Table 1: Antifibrinolytics in Orthotopic liver transplantation.

procedure that has a heightened degree of alteration of coagulation with marked blood loss is not compelling. There are well documented incidences of thrombotic complications with and without antifibrinolytic use. Recent reports of absence of complications of aprotinin use in major cardiac surgery sheds doubts on Mangano recommandations [69].

Another longstanding concern is the optimal dosing of the drug. Several regimen dose have been described in different studies, but no consensus is available regarding the optimal dose of any of these three antifibrinolytic drugs.

Conclusion

It is well established that Aprotinin and TA can reduce perioperative bleeding and transfusion requirements in patients undergoing OLT. The evidence for the use of EACA in OLT is not so clear. Significant

complications have been documented with all of their use however this is in the presence of major surgery commonly associated with its own similar inherent complications rates. The withdrawal of Aprotinin from the market place has potentially removed a valuable drug from the limited armamentarium of powerful antifibrinolytics that are available. The evidence to do so needs re-evaluating in the presence of conflicting evidence regarding safety. In conclusion however there does remain an important place for the use of anti fibrinolytics in OLT but patient selection should be on an individual basis to avoid complications. Further large scale studies are required to establish the lowest effective dosages required to minimise the risk of thromboembolic complications with their use.

References

1. Kang Y (1997) Transfusion based on clinical coagulation monitoring does reduce hemorrhage during liver transplantation. Liver Transpl Surg 3: 655-659.

2. Bechstein WO, Neuhaus P (1997) A surgeon's perspective on the management of coagulation disorders before liver transplantation. Liver Transpl Surg 3: 653-655.

3. Porte RJ, Bontempo FA, Knot EA, Lewis JH, Kang YG, et al. (1989) Systemic effects of tissue plasminogen activator- associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. Transplantation 47: 978-984.

4. Porte RJ (1993) Coagulation and fibrinolysis in orthotopic liver transplantation: Current views and insights. Semin Thromb Hemost 19: 191-196.

5. De Boer MT, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ (2005) Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. Dig Surg 22: 265-275.

6. Mannucci PM (1998) Hemostatic drugs. N Engl J Med 339: 245-253.

7. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, et al. (1985) Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 64: 888-896.

8. Kang YG (1995) Thromboelastography in liver transplantation. Semin Thromb Hemost 21: 34-44.

9. Gorlinger K, Dirkmann D, Weber CF, Rahe-Meyer N, Hanke AA (2011) Algorithms for transfusion and coagulation management in massive haemorrhage. Anasthesiologie & Intensivmedizin 52: 145.

10. Afshari A, Wikkelso A, Brok J, Moller AM, Wetterslev J (2011) Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database of Sys Rev 3.

11. Lisman T, Leebeek FW, de Groot PG (2002) Haemostatic abnormalities in patients with liver disease. J Hepatol 37: 280-287.

12. Witters P, Freson K, Verslype C, Peerlinck K, Hoylaerts M, et al. (2008) REview article: blood platelet number and function in chronic liver disease and cirrhosis. Aliment Pharmacol Ther 27: 1017-1029.

13. Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, et al. (2006) Elevated levels of von Willebrand factors in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology 44: 53-61.

14. Cahill PA, Redmond EM, Sitzmann JV (2001) Endothelial dysfunction in cirrhosis and portal hypertension. Pharmacol Ther 89: 273-293.

15. Aster RH (1966) Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombcytopenia. J Clin Invest 45: 645-657.

16. Segal H, Cottam S, Potter D, Hunt BJ (1997) Coagulation and fibrinolysis in primary biliary cirrhosis compared with other liver disease and during orthotopic liver transplantation. Hepatology 25: 683-688.

17. Homatas J, Wasantapruek S, Von Kaulla E, Von Kaulla KN, Eiseman B (1971) Clotting abnormalities following orthotopic and heterotopic liver transplantation of marginally preserved pig livers. Acta hepato-splenol 18: 14-26.

18. Ferro D, Celestini A, Violi F (2009) Hyperfibrinolysis in liver disease. Clin Liver Dis 13: 21-31.

19. Mallett SV, Cox D, Burroughs AK, Rolles K (1990) Aprotinin and reduction of blood loss and transfusion requirements in orthotopic liver transplantation. Lancet 336: 886-887.

20. Neuhaus P, Bechstein WO, Lefebre B, Blumhardt G, Slama K (1989) Effect of aprotinin on intraoperative bleeding and fibrinolysis in liver transplantation. Lancet 2: 924-925.

21. Cottam S, Hunt B, Segal H, Ginsburg R, Potter D (1991) Aprotinin inhibits tissue plasminogen activator-mediated fibrinolysis during orthotopic liver transplantation. Transplant Proc 23: 1933.

22. Grosse H, Lobbes W, Framback M, von Broen O, Ringe B, et al. (1991) The use of high dose of aprotinin in liver transplantation: the influence of fibrinolysis and blood loss. Thromb Res 63: 287-297.

23. Himmelreich G, Kierzek B, Neuhaus P, Slamer KJ, Riess H (1991) Fibrinolytic changes and the influence of early perfusion in orthotopic liver transplantation with intraoperative aprotinin treatment. Transplant Proc 23: 1936-1937.

24. Soilleux H, Gillon M, Mirand A, Daibes M, Leballe F, et al. (1995) Comparative effects of small and large aprotinin doses on bleeding during orthotopic liver transplantation. Anesth Analg 80: 349-352.

25. Scudamore CH, Randall TE, Jewesson PJ, Schackleton CR, Salvian AJ, et al. (1995) Aprotinin reduces the need for blood products during liver transplantation. Am J Surg 169: 546-549.

26. Milroy SJ, Cottam S, Tan KC, Hilmi I, Oyesola B (1995) Improved haemodynamic stability with administration of aprotinin during orthotopic liver transplantation. Br J Anaesth 75: 747-751.

27. Marcel RJ, Stegall WC, Suit CT, Arnold JC, Vera RL, et al. (1996) Continuous small dose aprotinin controls fibrinolysis during othotopic transplantation. Anesth Analg 82: 1122-1125.

28. Garcia Huete L, Domenech P, Sabate A, Matinez-Brotons F, Jaurrieta E, et al. (1997) The prophylactic effect of aprotinin on intraoperative bleeding in liver transplantation: a randomized clinical study. Hepatology 26: 1143-1148.

29. Porte RJ, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, et al. (2000) Aprotinin and transfusion requirements in orthotopic liver transplantation: A multicenter randomized double-blind study. EMSALT Study Group. Lancet 355: 1303-1309.

30. Molenaar IQ, Begliomini B, Martinelli G, Putter H, Terpstra O, et al. (2001) Reduced need for vasopressors in patients receiving aprotinin during orthotopic liver transplantation. Anesthesiology 94: 433-438.

31. Robert S, Wagner BK, Boulanger M, Richer M (1996) Aprotinin. Ann Pharmacother 30: 372–380.

32. Landis RC, Asimakopoulos G, Poullis M, Haskard DO, Taylor KM (2001) The antithrombolic and anti-inflammatory mechanisms of action of aprotinin. Ann Thorac Surg 72: 2169-2175.

33. Peters DC, Noble S (1999) Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. Drugs 57: 233–260.

34. Lemmer JH, Stanford W, Bonney SL, Chomka EV, Karp RB, et al. (1995) Aprotinin for coronary artery bypass grafting: effect on postoperative renal function. Ann Thorac Surg 59: 132-136.

35. Mangano DT, Tudor JC, Dietzel C (2006) The risk associated with aprotinin in cardiac surgery. N Engl J Med 354: 353-365.

36. Ramsay MA, Randall HB, Burton EC (2004) Intravascular thrombosis and thromboembolism during liver transplantation: Antifibrinolytic therapy implicated? Liver Transpl 10: 310-314.

37. Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, et al. (2007) Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. Am J Transplant 7: 185-194.

38. Warnaar N, Mallett SV, de Boer MT, Rolando N, Burroughs AK, et al. (2007) The impact of Aprotinin on renal function after liver transplantation: an analysis of 1043 patients. Am J Transplant 7: 2378-2387.

39. Baubillier E, Cherqui D, Dominique C, Khalil M, Bonnet F, et al. (1994) A fatal thrombotic complication during liver transplantation after aprotinin administration. Transplantation 57: 1664-1666.

40. Sopher M, Braunfeld M, Shackleton C, Busuttil RW, Sangwan S, et al. (1997) Fatal pulmonary embolism during liver transplantation. Anesthesiology 87: 429-432.

41. Xia VW, Steadman RH (2005) Antifibrinolytics in orthotopic liver transplantation: Current status and controversies. Liver Transpl 11: 10-18.

42. Royston D (1998) Aprotinin versus lysine analogues: the debate continues. Ann Thorac Surg 65: 9-19.

43. Himmelreich G, Muser M, Neuhaus P, Bechstein WO, Slama KJ, et al. (1992) Different aprotinin applications influencing changes in orthotopic liver transplantation. Transplantation 53: 132-136.

44. Wells PJ (2002) Safety and efficacy of methods for reducing perioperative allogenic transfusion: a critical review of the literature. Am J Ther 9: 377-388.

45. Hardy J, Desroches J (1992) Natural and synthetic antifibrinolytics in cardiac surgery. Can J Anaesth 39: 353-365.

46. Rang HP, Dale MM, Ritter JM (2003) Haemostasis and Thrombosis. Rang and Dale's Pharmacology New York Elsevier LTD, Churcill Livingstone: 344-345.

47. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, et al. (2008) A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Enql J Med. 358: 2319-2331.

48. McMullan V, Alston RP (2010) The effects of the suspension of the licence for aprotinin on the care of patients undergoing cardiac surgery: A survey of cardiac anesthesiologists' and surgeons' opinion in the United Kingdom. J Cardiothoracic Vasc Anesth 24: 418-421.

49. Carlier M, Veyckemans F, Scholtes JL, Gouverneur JM, Gribomont BF, et al.

(1987) Anesthesia for pediatric hepatic transplantation: Experience of 33 cases. Transplant Proc 19: 3333-3337.

50. CRASH-2 collaborators (intracranial bleeding study) (2011) Effect of tranexamic acid in traumatic brain injury: a nested randomized, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). 343: 3795.

51. CRASH 2 trial collaborators (2010) Effects of Tranexamic Acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrage (CRASH-2): a randomized, placebo-controlled trial. Lancet 376: 23-32.

52. Boylan JF, Klinck JR, Sandler AN, Arellano R, Greig PD, et al. (1996) Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. Anesthesiology 85: 1043-1048.

53. Kaspar M, Ramsay MA, Nguyen AT, Cogswell M, Hurst G, et al. (1997) Continuous small dose Tranexamic Acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. Anesth Analg 85: 281-285.

54. Dalmau A, Sabaté A, Acosta F, Garcia-Huete L, Koo M, et al. (2000) Tranexamic Acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. Anesth Analg 91: 29-34.

55. Dalmau A, Sabaté A, Koo M, Bartolomé C, Rafecas A, et al. The prophylactic use of tranexamic acid and aprotinin in othotopic liver transplantation: a comparative study. Liver Transpl 10: 279-284.

56. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, et al. (2007) Antifibrinolytic use for minimizing perioperative allogenic blood transfusion. Cochrane Database Syst Rev 17: CD0018.

57. Von Kaulla KN, Kaye H, von Kaulla E, Marchioro TL, Starzl TE (1966) Changes in blood coagulation. Arch Surg 92: 71-79.

58. McNicol GP, Fletcher AP, Alkjaersig N, Sherry S (1962) The absorption, distribution and excretion of Epsilon-aminocaproic-acid following oral or intravenous administration to man. J Lab Clin Med 59: 15-24.

59. Lerner RG, Reed GE, Nelson JC, Pooley R, Moggio R, et al. (1982) Rapid monitoring and treatment of fibrinolysis associated with heart surgery. Circulation 66: 2-319.

60. Kang Y, Lewis JH, Navalgund A, Russell MW, Bontempo FA, et al. (1987) Epsilon- aminocaproic acid for treatment of fibrinolysis during liver transplantation. Anesthesiology 66: 766-773.

61. Ramsay MA, Randall HB, Burton EC (2004) Intravascular thrombosis and thromboembolism during liver transplantation. Antifibrinolytic therapy implicated? Liver Transplant 10: 310-314.

62. Fitzimous MG, Peterfreund RA, Raines DE (2001) Aprotinin administration and pulmonary thromboembolism during orthotopic liver transplantation: report of two cases. Anesth Analg 92: 1418-1421.

63. Manji M, Isaac JL, Bion J (1998) Survival from massive intraoperative pulmonary thromboembolism during orthotopic liver transplantation. Br J Anaesth 80: 685-687.

64. Bergqvist P (2004) Low molecular weight Heparin for the prevention of venous thromboembolism after abdominal surgery. Br J Surg 91: 965-974.

65. Lerner AB, Sundar E, Mahmood F, Sarge T, Hanto DW, et al. (2005) Four cases of cardiopulmonary thromboembolism during liver transplantation without the use of antifibrinolytic drugs. Anesth Analg 101: 1608-1612.

66. Kang Y, Gaisor TA (1999) Hematologic considerations in the transplant patient. In: Sharpe MD, Gelb AW, eds. Anesthesia and transplantation Boston: Butterworth Heinemann: 363-387.

67. Gorlinger K (2006) Coagulation management during liver transplantation. Hamostaseologie 26: S64-76.

68. Makwana J, Paranyape S, Goswami J (2010) Antifibrinolytics in liver surgery. Indian J Anaesth 54: 489-495.

69. Pagano D, Howell NJ, Freemantle N, Cunningham D, Bonser RS, et al. (2008) Bleeding in cardiac surgery: the use of aprotinin does not affect survival. J Thorac Cardiovasc Surg 135: 495-502.

70. Findlay JY, Rettke SR, Ereth MH, Plevak DJ, Krom RA, et al. (2001) Aprotinin reduces red blood cell transfusion in orthotopic liver transplantation: a prospective, randomized, double-blind study. Liver Transpl 9: 802-807.

71. Rentoul TM, Harrison VL, Shun A (2003) The effect of aprotinin on transfusion requirements in pediatric orthotopic liver transplantation. Pediatr Transplant 7: 142-148.

72. Findlay JY, Kufner RP (2003) Aprotinin reduces vasoactive medication use during adult liver transplantation. J Clin Anesth 15: 19-23.