Aprotinin and Nafamostat Mesilate in Liver Surgery: Effect on Blood Loss

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Key Words

Aprotinin • Nafamostat mesilate • Liver transplantation • Hepatic resection

Abstract

The origin of blood loss during liver surgery is multifactorial. Surgical skill, technique, anesthesiological care, but also hyperfibrinolysis have been shown to play a role in the origin of bleeding during partial hepatectomy and liver transplantation. The latter has provided the scientific basis for the prophylactic use of antifibrinolytic drugs, such as aprotinin and nafamostat mesilate in liver surgery. Recently however, concern has been voiced about potential risks associated with aprotinin, including renal failure and thromboembolic events. In this review we discuss the efficacy and safety issues of aprotinin and nafamostat mesilate in liver surgery. We identified a total of 19 studies on the use of either aprotinin or nafamostat mesilate in liver surgery reported in the time period between 1966 and July 2006. The use of aprotinin or nafamostat mesilate in partial hepatectomies was studied in three studies. In 16 studies the use of aprotinin in liver transplantation was investigated. With respect to partial hepatectomy, improvements in surgical technique and anesthesiological care seem to be more important in reducing blood loss than the use of the antifibrinolytic drugs. Aprotinin may be indicated in a selected group of patients with cirrhosis undergoing liver resection, but further studies

in this specific group of patients will be needed. In liver transplantation, the use of aprotinin is associated with a significant reduction in blood loss and transfusion requirements of around 30–40%. Results of prospective studies do not provide support for safety concerns as no increased risk for thromboembolic events or renal dysfunction has been observed in liver transplant patients treated with aprotinin. In conclusion, there is currently no scientific support for the routine use of aprotinin or nafamostat mesilate in patients undergoing partial hepatectomy, whereas the efficacy of aprotinin in liver transplantation is well established. More studies will be needed to address the safety aspects of aprotinin in patients undergoing liver surgery in more detail.

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Introduction

Surgeons have long recognized blood loss as the major impediment to the successful completion of an operation. It has been clearly shown during the last decades that reducing blood loss during major surgery improves outcome and reduces postoperative morbidity and mortality. In the past, surgery of the liver was a long and risky operation with large amounts of blood loss [1–3]. During the last decade, improvements in surgical techniques, surgical skills and anesthetic care have significantly reduced blood loss in liver surgery [4]. Despite these

improvements, liver surgery still carries the risk of significant bleeding. Besides the obvious relation between perioperative blood loss and surgical skills, specific intraoperative hemostatic disorders, especially hyperfibrinolysis, have been shown to play a role [5–7].

Extensive research, especially in the field of liver transplantation, has improved the knowledge about specific intraoperative changes in coagulation that may occur during liver surgery. It has been shown that hyperfibrinolysis occurs due to increased levels of tissue-type plasminogen activator (t-PA), mainly during the anhepatic period of the operation [5–8]. t-PA leads to the conversion of plasminogen into plasmin hereby causing premature degradation of fibrin clots, resulting in increased bleeding. Investigations by Tsuzuki et al. [9] have shown that hyperfibrinolysis may also occur during partial hepatectomies, especially in cirrhotic patients. These observations have provided the scientific basis for the prophylactic use of antifibrinolytic drugs, such as serine protease inhibitors, in liver transplantation and during partial hepatectomies.

Aprotinin is a serine protease inhibitor, derived from bovine tissue. It has the ability to inhibit several proteases with serine at their active side, such as plasmin, kallikrein, trypsin and elastase. By blocking plasmin, serine protease inhibitors reduce hyperfibrinolysis and thus blood loss [5–7]. Apart from inhibiting plasmin, aprotinin may reversibly inhibit other proteases involved in the coagulation and inflammatory cascades. This may explain the ability of aprotinin to improve hemodynamic stability and to ameliorate the inflammatory response during major surgery [10, 11].

Another synthetic serine protease inhibitor with a similar mode of action is nafamostat mesilate (6-amino-2-naphthyl *p*-guanidinobenzoate dimethane-sulfonate). This drug is mostly used in Japan for the treatment of disseminated intravascular coagulation and acute pancreatitis, as well as an anticoagulant during hemodialysis in patients with a bleeding tendency [12–15]. Nafamostat mesilate inhibits various serine proteases generated during the coagulation cascade, as well as during inflammatory processes [16–18]. Nafamostat mesilate also inhibits coagulation factors such as factor VIIa [16] and thrombin [17], and has been found effective in treating patients with severe coagulopathy [14]. In addition, it may reduce fibrinolysis by blocking plasmin.

Aprotinin is widely used in liver transplantation [19]. The use of aprotinin and nafamostat mesilate during partial hepatectomies, however, is less extensively studied. Recently, two large observational studies in patients un-

dergoing cardiac surgery have questioned the safety aspects of aprotinin, especially with respect to the risk of inducing renal dysfunction [20, 21]. In addition, several case reports have suggested that aprotinin is associated with the risk of thromboembolic complications during liver transplantation [19]. In this review we will discuss the available literature and evaluate the efficacy and safety issues of both aprotinin and nafamostat mesilate in patients undergoing liver surgery.

Methods

Search Strategy and Selection of Trials

A systemic literature search was conducted. Literature was searched for the time period between 1966 and July 2006 using PubMed and Cochrane Library. The strategy was set up using the following single text words and combinations: aprotinin, liver transplantation, liver resection, hepatic resection, hepatectomy and nafamostat mesilate. Reference lists of relevant articles were cross-checked for other potentially relevant articles.

Inclusion Criteria

In the current review all reports of descriptive, randomized and non-randomized controlled studies on aprotinin or nafamostat mesilate in patients undergoing either partial hepatectomy or liver transplantation were included. The only exclusion criterion was non-English language publications.

Results

The trial selection process yielded a total of 156 abstracts from the combined searches. Thirty-five appeared to be duplicates yielding a total of 121 studies which were retrieved for more detailed information. After critical appraisal of these publications, 19 studies were identified that met the inclusion criteria of our review. Those 19 studies were divided in two groups. The first group consisted of studies investigating the use of aprotinin or nafamostat mesilate in partial hepatectomy [22–24]. In two studies the use of nafamostat mesilate [22, 23] and in only one study the use of aprotinin in patients undergoing partial hepatectomy was evaluated [24]. The second group consisted of studies investigating the use of aprotinin in liver transplantation. In 13 studies, aprotinin and placebo or control groups were compared in patients undergoing liver transplantation [8, 25–38]. In three studies a direct comparison of different dosages of aprotinin was made [28, 29, 39].

Aprotinin and Nafamostat Mesilate in Partial Hepatectomies

Although the use of aprotinin in liver transplantation has been studied extensively, only one randomized controlled trial on the use of aprotinin in partial hepatectomies has been conducted [24]. In this study the effect of aprotinin on blood loss and transfusion requirements was investigated in 97 patients undergoing partial hepatectomy in the period between 1992 and 1995. Patients were stratified according to diagnosis; cirrhotic versus normal livers and benign versus malignant tumors. Aprotinin was administered according to a large-dose scheme, which consisted of a loading dose of 2×10^6 kIU of aprotinin over a 20-min period after induction of anesthesia, followed by a continuous infusion of 0.5×10^6 kIU/h administered by an infusion pump until skin closure. An additional bolus of 0.5×10^6 kIU of aprotinin was infused after every 3 units of red blood cell (RBC) transfusion. Standardized anesthesiological and surgical techniques (Kelly fracture, pedicle occlusion) were used. 48 patients received aprotinin and 49 patients received placebo. Intraoperative blood loss, percentage of transfused patients, and total transfusion requirement per group were significantly lower in aprotinin-treated patients, compared with patients who received placebo ($1,217 \pm 966$ vs. $1,653 \pm 1,221$ ml, $p = 0.048$; 17 vs. 39%, $p = 0.02$, and 30 vs. 77 units of RBC, $p = 0.015$, respectively). This study suggests that aprotinin reduces blood loss during partial liver resection; however, this study conducted in the mid-1990s has never been confirmed by another study.

The efficacy of nafamostat mesilate to reduce blood loss and transfusion requirements in patients undergoing a hepatic resection has been studied mostly in Japan [22, 23]. In one controlled trial the effect of nafamostat mesilate on coagulation and fibrinolysis was investigated in 22 patients with hepatocellular carcinoma, who underwent a partial hepatectomy [22]. Patients were divided into two groups: the first group (group 1) was a control group ($n = 11$), the second group (group 2) received intra- and postoperative infusion of nafamostat mesilate ($n = 11$). Nafamostat mesilate was continuously administered from the start of the operation until the end of the first postoperative day (0.4 mg/kg/h). After postoperative day 1 the dose was reduced to 0.2 mg/kg/h until postoperative day 3. In this study, nafamostat mesilate was shown to suppress coagulation activity, as reflected by a reduction in plasma levels of thrombin-antithrombin III complex and fibrinopeptide, and both during and immediately after the operation. Moreover, nafamostat mesilate signifi-

cantly reduced fibrinolysis as reflected by a decreased euglobulin lysis activity both during and after the operation. However, no significant differences in blood loss during liver resection were seen between the two groups (blood loss in group 1: $1,393 \pm 601$ ml, vs. $1,509 \pm 590$ ml in group 2). The number of patients who required RBC transfusions was not significantly different for the two groups (5/11 in group 1 vs. 2/11 in group 2) [22].

In a second study, also performed in Japan, nafamostat mesilate was studied in 20 patients undergoing extensive liver resections [23]. Patients were randomly allocated into two groups of 10 patients each. In one group, patients received nafamostat mesilate (2 mg/kg/day) during and after the operation for 7 days. The control group received standard postoperative intensive care, but no nafamostat mesilate. In this study, the use of nafamostat mesilate was also associated with reduced activation of the coagulation system during surgery. Fibrinolytic activity was increased after the operation in both groups and no differences in fibrinolysis were seen between the two groups.

The two controlled studies on the efficacy of nafamostat mesilate in reducing blood loss in patients undergoing partial hepatectomies both indicate that this drug has no major impact on bleeding during this type of surgery.

Aprotinin in Liver Transplantation

The use of aprotinin in patients undergoing liver transplantation was first reported by Neuhaus et al. [25] in 1989. These investigators described significant reductions in blood loss and transfusion requirements of 35 and 50%, respectively, in a small group of patients, compared to historical controls. Similar observations have subsequently been reported by other groups, however, again in comparison to historical control groups [40–42]. A reduction in blood loss due to time-dependent factors such as improved surgical and anesthetic care could, therefore, not be excluded.

The European Multicenter Study on the use of Aprotinin in Liver Transplantation (EMSALT) was the first large randomized, controlled trial that provided definite proof for the blood loss reducing effect of aprotinin in liver transplantation [8]. In the EMSALT study, 137 patients were randomized into three groups: high-dose aprotinin ($n = 46$), regular-dose aprotinin ($n = 43$), or placebo ($n = 48$). Patients in the high-dose group received a loading dose of aprotinin of 2×10^6 kIU followed by a continuous infusion of 1×10^6 kIU/h and an additional bolus of $1 \times$

10^6 kIU before graft reperfusion. In the regular-dose group, patients received the same loading dose, followed by 0.5×10^6 kIU/h without an extra bolus. Administration of aprotinin or placebo was discontinued at 2 h after graft reperfusion. The total amount of intraoperative blood product transfusion was 40% lower in the high-dose group and 31% lower in the regular-dose group than the median value in the placebo group [8]. Very similar results have been found in another prospective, randomized, double-blind study performed at the Mayo Clinic [38]. In this study, 63 patients were randomized to receive either placebo or a low dose of aprotinin. 33 patients were administered an aprotinin according to the following scheme: loading dose of 1×10^6 kIU, followed by a continuous infusion of 0.25×10^6 kIU/h. In the control group, 30 patients were administered equivalent volumes of saline. The total amount of intraoperative RBC transfusion was 28% lower in the low-dose aprotinin group, compared to placebo-treated patients. Although both the EMSALT study and the study performed at the Mayo Clinic did not show any significant differences in thromboembolic complications, both studies were not large enough to make any definitive conclusions about safety aspects.

To study the safety aspects of aprotinin in liver transplant recipients, we recently performed a systemic review and meta-analysis of all studies on antifibrinolytic drugs in liver transplantation, including a total of 1,407 patients [19]. The meta-analysis included the results of six randomized controlled trials in some of which also other antifibrinolytic drugs than aprotinin were studied. This analysis confirmed previous individual trials indicating that aprotinin significantly reduces RBC and fresh-frozen plasma (FFP) transfusion requirements during liver transplantation [8, 32, 34–36, 38]. The overall incidence of side effects, such as venous thromboembolic events, was 1.9% (4/208) in aprotinin-treated patients versus 1.8% (3/168) in patients who received a placebo (odds ratio 0.92, 95% CI 0.28–3.00, $p = 0.89$). Furthermore, analysis of perioperative hepatic artery thrombosis also showed no significant difference between aprotinin-treated patients and patients receiving placebo (incidence of 1.4% (3/208) and of 3.0% (5/168) respectively, odds ratio 0.68, 95% CI 0.17–2.75, $p = 0.59$) [19].

Discussion

In this review we evaluated the available literature on the efficacy and safety of the serine protease inhibitors aprotinin and nafamostat mesilate in reducing blood loss

during partial hepatectomies and liver transplantation. During liver surgery, coagulopathy may occur especially in patients with cirrhosis, and this can lead to increased blood loss, disseminated intravascular coagulation or postoperative hepatic failure [9]. It is noted that primary hyperfibrinolysis may occur during hepatic resections and therefore the use of antifibrinolytic agents has been proposed as a method to reduce blood loss during partial hepatectomies and liver transplantation [22].

In 1997, Lentschener et al. [24] were the first to suggest that aprotinin may reduce blood loss and transfusion requirements in patients undergoing partial hepatectomy. Unfortunately, this has remained the only clinical study in which the efficacy and safety of aprotinin has been studied in patients undergoing liver resections. Therefore, this study has not been confirmed by another independent study. In addition, the amount of intraoperative blood loss observed in this trial was higher than what would be expected nowadays. Currently, most high-volume centers report partial hepatectomies without any blood cell transfusion requirements in up to 45% of the elective cases [43]. Improvements in surgical techniques, surgical skills and anesthetic care have contributed to a marked decrease of the number of patients needing blood products from over 80% to less than 40% [43]. Therefore, it is questionable whether the results obtained by Lentschener et al. can still be extrapolated to current practice. In general, it can be concluded that improvements in surgical techniques and anesthetic care have been more important to reduce blood loss during partial hepatectomies in patients with normal livers than the use of aprotinin or nafamostat mesilate. One aspect that has not been studied in great detail is the use of antifibrinolytic drugs in patients with cirrhosis undergoing partial hepatectomy. Cirrhotic patients are more prone to develop primary hyperfibrinolysis especially under stressful circumstances such as surgery. The use of antifibrinolytic drugs may be beneficial in these patients when undergoing a partial liver resection. This subject will need further research. Based on the current literature, the routine prophylactic use of antifibrinolytic drugs such as aprotinin and nafamostat mesilate cannot be recommended in patients undergoing partial hepatectomy.

Much more evidence exists with respect to the use of antifibrinolytic drugs in liver transplantation. The efficacy and safety of antifibrinolytics in liver transplantation has recently been evaluated in a systematic review and meta-analysis [19]. Results of this systematic review and meta-analysis clearly show that aprotinin significantly reduces RBC and FFP transfusion requirements

during liver transplantation. The blood reducing effect could also be observed in the patients receiving another antifibrinolytic drug, tranexamic acid [19]. Since the amount of blood loss and thus transfusion requirements is decreasing due to improvements in surgical and anesthesiological care, careful examination of the risk-benefit ratio it is becoming more relevant. During the last decade, several possible side effects have been associated with the use of aprotinin. With respect to the use of aprotinin in liver transplantation, these concerns have mainly focused on the occurrence of thromboembolic complications. Intraoperative pulmonary embolism and intracardiac thrombus formation have been described in several case reports of patients receiving aprotinin during liver transplantation [44, 45]. However, there are also several reports of these types of thromboembolic complications in patients undergoing liver transplantation who did not receive aprotinin or another antifibrinolytic drug [46–50]. The exact incidence of thromboembolic complications in patients undergoing liver transplantation is unknown. It has been suggested that the risk of venous thromboembolic complications is underestimated and that pulmonary embolisms may occur in up to 1% of the patients undergoing liver transplantation [46]. In the prospective studies reported so far, no difference in incidence of thrombotic complication has been reported between patients who received aprotinin or placebo. In our meta-analysis, venous thromboembolic events were also not significantly more observed in the aprotinin-treated patients [19]. Another potential side effect of aprotinin that was recently highlighted in two studies in patients undergoing cardiac surgery is the risk of renal failure [20, 21]. Based on a large observational multicenter study involving 4,374 patients, Mangano et al. [20] have recently suggested that the use of aprotinin in patients undergoing primary or complex coronary-artery surgery is associated with a doubling of the risk of renal failure requiring

dialysis. In another single-center study, Karkouti et al. [21] also reported a higher incidence of renal insufficiency in patients receiving aprotinin during cardiac surgery, compared to tranexamic acid, another type of antifibrinolytic drug. Unfortunately, in both studies, patients were not randomized and baseline characteristics and condition of patients receiving aprotinin or other antifibrinolytic drugs were not comparable. Although the authors of both papers have tried to overcome this source of bias by performing multivariate analyses using propensity score adjustment, this statistical method also has its limitations and does not correct for unknown confounding variables. In liver transplantation, renal function in relation to the use of aprotinin has been evaluated in only one study in a subgroup of patients enrolled in the European multicenter trial EMSALT [51]. This study did not reveal significant differences in postoperative renal function in patients receiving aprotinin, compared to patients receiving placebo. However, this study consisted of a total of 93 patients, which may have been too small to detect small, but clinically relevant differences in the incidence of renal failure.

In conclusion, based on this review of the literature on the efficacy and safety of aprotinin and nafamostat mesilate in liver surgery, we currently cannot recommend the prophylactic use of these two drugs in patients undergoing partial hepatectomy. There might be a role for aprotinin in a selected group of patients with cirrhosis and undergoing hepatic resection, but further studies in this subgroup of patients are needed. In liver transplantation, there is adequate scientific support for the prophylactic use of aprotinin. More studies, however, are needed to establish the impact of aprotinin on renal function in these patients. In addition, more and larger studies will be needed to settle the potential benefits and risks of aprotinin in comparison to other antifibrinolytic agents in liver transplantation.

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