Requirements for transfusion and postoperative outcomes in orthotopic liver transplantation: A meta-analysis on aprotinin

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AIM: To study the effect of aprotinin used in orthotopic liver transplantation (OLT) on the intraoperative requirement for blood products and on the incidence of laparotomy for bleeding, thrombotic events and mortality.

METHODS: A systematic review of the literature in the electronic database Medline and the Clinic Trials Registry Database was performed. Literature that did not fit our study were excluded. Patients in the reviewed studies were divided into two groups; one group used aprotinin (aprotinin group) while the other did not (control group). The data in the literature that fit our requirements were divided into two groups; one group used aprotinin (aprotinin group) while the other did not (control group). Weighted mean differences (WMD) in the requirements for blood products between the aprotinin group and the control group were tested using a fixed effect model. A Z test was performed to examine their reliability; the Fleiss method of fixed effect model was used to analyze data on postoperative events, and odds ratios (ORs) were tested and merged.

RESULTS: Seven citations were examined in our study. Among them, a requirement for blood products was reported in 4 studies including 321 patients, while postoperative events were reported in 5 studies including 477 patients. The requirement for red blood cells and fresh frozen plasma in the aprotinin group was statistically lower than that in the control group (WMD = -1.80 units, 95% CI, -3.38 to -0.22; WMD = -3.99 units, 95% CI, -6.47 to -1.50, respectively). However, no significant difference was indicated in the incidence of laparotomy for bleeding, thrombotic events and mortality between the two groups. Analysis on blood loss, anaphylactic reactions and renal function was not performed in this study due to a lack of sufficient information.

CONCLUSION: Aprotinin can reduce the intraoperative requirement for blood products in OLT, and has no significant effect on the incidence of laparotomy for bleeding, thrombotic events and mortality. © 2008 WJG. All rights reserved.

Key words: Aprotinin; Liver transplantation; Blood transfusion; Meta-analysis

INTRODUCTION

Orthotopic liver transplantation (OLT) has become the first choice approach for the treatment of patients with end-stage liver diseases[1]. However, despite great improvements in graft preservation, surgical skills, anesthetic techniques and perioperative management[2,3], OLT is still associated with severe bleeding and considerable transfusion requirements, which in turn greatly contribute to the peri-operative morbidity and mortality[4]. Severe bleeding in OLT occurs for several reasons, among which hemostatic abnormalities remain a major cause[5].

Aprotinin, a serine protease inhibitor, is more and more commonly being used in surgeries, such as cardiac surgeries and liver transplantations, to reduce bleeding and the need for transfusions. A meta-analysis of 12 trials (n = 626) of children undergoing cardiac surgery demonstrated aprotinin reduced the proportion of children receiving blood transfusions during cardiac surgery with cardiopulmonary bypass, but had no significant effect on the volume of blood transfused or on the amount of chest tube drainage[6]. Similarly, a meta analysis of 13 trials (n = 506) of patients undergoing major orthopedic surgery demonstrated the pooled blood loss and the amounts of red blood cell (RBC) units (U) transfused intraoperatively and peri-operatively were significantly lower among aprotinin-treated patients than control patients. Moreover, aprotinin was not associated with an increased incidence of anaphylactic reactions and renal function was not performed in this study due to a lack of sufficient information.
of deep vein thrombosis\cite{9,10}. However, there are still some conflicting results on whether aprotinin can reduce blood loss or the requirement for transfusion in OLT\cite{9,10,11,12}, and whether it can be beneficial to postoperative outcomes\cite{11,12}.

The objective of this systemic review was to study the effect of aprotinin used in OLT on the intraoperative requirement of blood products, and on the incidence of laparotomy for bleeding, thrombotic events and mortality.

**MATERIALS AND METHODS**

**Data source**

We searched the electronic database of Medline and the Clinic Trials Registry Database using aprotinin and liver transplantation as keywords. References cited by other retrospective articles and related articles or summaries from foreign journals were searched manually as well. After initial screening, we examined the titles and abstracts of potentially eligible trials, and selected those which met the following predefined inclusion criteria: published clinical controlled trials on the use of aprotinin in liver transplantation, English language, adult study population, with data on (1) the transfusion requirement for blood products, (2) perioperative mortality and morbidity, (3) incidence of postoperative thrombotic events and (4) incidence of laparotomy for bleeding. Citations that did not fit our study or contained insufficient information were excluded.

**Statistical analysis**

We recorded the data that fit our requirements, examined their heterogeneity, and calculated the weighted mean difference (WMD) or odds ratio (OR) between the two groups. All calculations were performed using the software Review Manager 4.2 (The Nordic Cochrane Centre, The Cochrane Collaboration 2003, Copenhagen, Denmark).

We used the difference of means \((y)\) as the effect scale of the data on requirements of blood products and examined their heterogeneity \((Q < \chi^2(0.05, k-1), P > 0.05)\), if \(P > 0.05\), fixed effect model was used to calculate WMD and 95% confidence interval (95% CI); otherwise, a random effect model was used. If the 95% CI included 0, then there was no significant difference between the two groups. However, if the 95% CI was greater than 0, then the control group was supported; otherwise, the aprotinin group was supported.

We calculated the ORs of the incidence of mortality, laparotomy for bleeding and thrombotic events, and tested their heterogeneity \((Q < \chi^2(0.05, k-1), P > 0.05)\). If \(P > 0.05\), the homogeneity was considered good, and a fixed effect model was used to calculate the total OR and 95% CI; otherwise a random effect model was chosen. If 1 was included in the 95% CI, then there was no statistically significant difference between the groups. If the 95% CI was more than 1, the control group was supported; otherwise, the aprotinin group was supported.

**RESULTS**

**Recording of data**

We identified 87 citations in a primary literature search. Titles were screened for relevance, eliminating 37 citations, and then abstracts and contents were read carefully, leading to the exclusion of a further 36 citations; 7 more were excluded because of a lack of information. Finally 7 citations\cite{9,10,13-17}, including 521 patients, were included in our study (Figure 1). Of these 7 studies, one used tranexamic acid in the control group\cite{10}; two studies contained two aprotinin groups, a high dose group and a routine dose group\cite{9,12}; one study contained two control groups\cite{17}; and two studies used the same sample\cite{10,13}, the size of which was calculated only once.

**Effect of aprotinin on RBC requirement**

Four citations, including 521 procedures, contained results on the requirement for blood products including RBCs and fresh frozen plasma (FFP)\cite{9,10,13,16,17}.

One of these studies contained two control groups\cite{17} (C1 and C2); Neither aprotinin nor any other antifibrinolytic agent was used in either group, so we just took C2 as the control group. Heterogeneity was tested: \(Q = 8.87, \gamma = 3, \chi^2(0.05, 3) = 7.81, P < 0.05\). As the homogeneity was low, a random effect model was used: WMD = -1.23 units, 95% CI, -3.17 to 0.71; no statistical significance was indicated. Considering one study used tranexamic acid in control group\cite{17}, it perhaps influenced the veracity, so we excluded that study and tested again, \(Q = 3.85, \gamma = 2, \chi^2(0.05, 2) = 5.99, P > 0.05\), calculated with fixed effect model. It was indicated the intraoperative requirement for RBCs was significantly lower in the aprotinin group than the control group (WMD = -1.80 units, 95% CI -3.38 to -0.22; Table 1A and B).

**Effect of aprotinin on FFP requirement**

The heterogeneity of the 4 citations was low (\(Q = 13.77, \gamma = 3, \chi^2(0.05, 3) = 7.81, P < 0.05\)), so a random effect model was used. No significant difference was indicated (WMD = -3.13 units, 95% CI -6.79 to 0.53). If the study using individuals treated with tranexamic acid as a control group was excluded, the heterogeneity was better (\(Q = 5.25, \chi^2(0.05, 2) = 5.99, P > 0.05\)), and a fixed effect model was chosen. It was indicated the intraoperative requirement for
Aprotinin group

| Study          | Aprotinin group | Control group | y (95% CI) |
|----------------|----------------|---------------|------------|
|                | Mean (units)   | SD (units)    | n          | Mean (units) | SD (units) | n          |
| 1 Garcia HL    | 13.0           | 8.0           | 39         | 14.4         | 9.7        | 41         | -1.14 (-5.29, 2.49) |
| 2 Marcel RJ    | 2.1            | 2.0           | 21         | 3.0          | 4.4        | 23         | -0.9 (-2.89, 1.09)   |
| 3 Dalmau A1    | 2.44           | 3.03          | 63         | 2.14         | 2.32       | 64         | 0.3 (-0.64, 1.24)    |
| 4 Llamas P     | 8.1            | 5.2           | 20         | 13           | 7.4        | 30         | -4.9 (-8.39, -1.41)  |

1Control group used tranexamic acid.

| Study          | Aprotinin group | Control group | y (95% CI) |
|----------------|----------------|---------------|------------|
|                | Mean (units)   | SD (units)    | n          | Mean (units) | SD (units) | n          |
| 1 Garcia HL    | 26.0           | 16.0          | 39         | 28.0         | 15.0       | 41         | -2.00 (-8.80, 4.80)  |
| 2 Marcel RJ    | 3.6            | 3.5           | 21         | 6.6          | 6.1        | 23         | -3.00 (-5.91, -0.09) |
| 3 Dalmau A1    | 1.09           | 2.20          | 63         | 1.20         | 2.21       | 64         | -0.11 (-0.88, 0.66)  |
| 4 Llamas P     | 16.7           | 10.4          | 20         | 28           | 14         | 30         | -11.3 (-18.07, -4.53) |

1Control group used tranexamic acid.

**DISCUSSION**

Unlike traditional reviews, a meta-analysis is a set of statistical procedures designed to accumulate experimental and correlational results across independent studies which address related sets of research questions. The aim of the meta-analysis is to determine a predefined inclusion criteria based on the systematic retrieval of literature on a given topic, and estimate the initial literatures carefully to ensure minimal bias in terms of the objectivity, validity and dependability of the results. The efficiency of the results depends on the choice of statistical method, as well as the rigidity of each study. In this meta-analysis, we performed a wide search of the literature, identified as many studies as we could, and tested their homogeneity (Q < \( \chi^2 \) \( 0.05, k-1 \), \( P > 0.05 \)). If homogeneity was good (\( P > 0.05 \)), we calculated data with a fixed effect model; otherwise we used a random effect model. Thus, we consider the statistical methods we used were correct and rigorous.

Several factors contribute to excessive bleeding during OLT, including pre-existing coagulopathy in patients, the procedure of liver transplantation itself, and the experience of the surgeon. However, hemostatic

FFP was significantly lower in the aprotinin group than in the control group (WMD = -3.99 units, 95% CI -6.47 to -1.50; Table 2A and B).

**Effect of aprotinin on postoperative outcomes**

As can be seen from Table 3A and B, no significant difference was indicated in the incidence of laparotomy for bleeding, thromboembolic events and mortality between the two groups.
The effect of aprotinin on blood loss during OLT was not the intraoperative requirement for blood products in OLT. Bleeding, thromboembolic events, and mortality between the aprotinin group than in the control group (WMD = -3.99 for fresh frozen plasma was also significantly lower in the aprotinin group. They found fibrinolytic activity (plasma D-dimer and D-dimer), as well as thromboelastography results [reaction time (R), clot formation time, and maximum amplitude] between an aprotinin group and a placebo group. They found fibrinolytic activity (plasma D-dimer and TA as control group was excluded, the OR was 0.38, the 95% CI was 0.09 to 1.64, and there was also no statistically significant deviation. It appears aprotinin has no significant influence upon the incidence of thrombosis in patients undergoing liver transplantation, possibly due to its strong antifibrinolytic and a weaker anticoagulant effect.

As a statistical method for investigation, meta analysis has been used widely, but this method can not eliminate confounding factors and biases in each study, so the result could, unavoidably, include a certain bias. In our study, the dosages of aprotinin were different, and the drugs used in the control groups were not the same, all of which could contribute to bias. In addition, there still exists the “publish bias”; that is, articles that are published often have a tendency to have positive results, which could be decreased by collecting data that is as all-encompassing as possible.

Thus, aprotinin can reduce the intraoperative requirement for blood products in OLT and has no significant effect on the incidence of laparotomy for bleeding, thromboembolic events and mortality. Of course, further clinical randomized controlled trials (RCTs) are needed to confirm this.

COMMENTS

Background
Orthotopic liver transplantation (OLT) is associated with severe bleeding and considerable transfusion requirements, while severe bleeding in OLT occurs for several reasons, among which hemostatic abnormalities remain a major cause.

Research frontiers
We performed a meta analysis to study the effect of aprotinin used in OLT on the intraoperative requirement for blood products and the postoperative outcomes.

Innovations and breakthroughs
This study clearly shows aprotinin can reduce the intraoperative requirement for blood products and has no significant effect on the incidence of laparotomy for bleeding, thromboembolic events and mortality.

Applications
Although additional clinical randomized controlled trials (RCTs) are required to clarify the role of aprotinin in OLT, this study strongly confirms the blood transfusion reducing effect of aprotinin, which has no significant effect on the incidence of laparotomy for bleeding, thromboembolic events and mortality.

Peer review
The authors investigated the effect of aprotinin used in OLT on the intraoperative
requirement of blood products and on the incidence of laparotomy for bleeding, thrombotic events and mortality, using a systematic review of the literature. They concluded aprotinin can reduce the intraoperative requirement of blood product in OLT, and has no significant effect on the incidence of laparotomy for bleeding, thrombotic events and mortality.

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S-Editor Yang RH  L-Editor McGowan D  E-Editor Ma WH

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