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**Methods to decrease blood loss and transfusion requirements for liver transplantation (Review)** Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

# [Intervention Review]

# Methods to decrease blood loss and transfusion requirements for liver transplantation

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# ABSTRACT

# Background

Excessive blood loss and increased blood transfusion requirements may have significant impact on the short-term and long-term outcomes after liver transplantation.

## Objectives

To compare the potential benefits and harms of different methods of decreasing blood loss and blood transfusion requirements during liver transplantation.

## Search methods

We searched The Cochrane Central Register of Controlled Trials in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded, and metaRegister of Controlled Trials until September 2011.

## **Selection criteria**

We included all randomised clinical trials that were performed to compare various methods of decreasing blood loss and blood transfusion requirements during liver transplantation.

## Data collection and analysis

Two authors independently identified the trials and extracted the data. We analysed the data with both the fixed-effect and the randomeffects model using RevMan Analysis. For each outcome we calculated the risk ratio (RR), mean difference (MD), or standardised mean difference (SMD) with 95% confidence intervals (CI) based on available data analysis. We also conducted network meta-analysis.

## **Main results**

We included 33 trials involving 1913 patients. The sample size in the trials varied from 8 to 209 participants. The interventions included pharmacological interventions (aprotinin, tranexamic acid, epsilon amino caproic acid, antithrombin 3, recombinant factor (rFvIIa), oestrogen, prostaglandin, epinephrine), blood substitutes (blood components rather than whole blood, hydroxy-ethyl starch, thromboelastography), and cardiovascular interventions (low central venous pressure). All the trials were of high risk of bias. Primary outcomes were reported in at least two trials for the following comparisons: aprotinin versus control, tranexamic acid versus control, recombinant factor VIIa (rFVIIa) versus control, and tranexamic acid versus aprotinin. There were no significant differences in the 60-day



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mortality (3 trials; 6/161 (3.7%) in the aprotinin group versus 8/119 (6.7%) in the control group; RR 0.52; 95% CI 0.18 to 1.45), primary graft non-function (2 trials; 0/128 (0.0%) in the aprotinin group versus 4/89 (4.5%) in the control group; RR 0.15; 95% CI 0.02 to 1.25), retransplantation (3 trials; 2/256 (0.8%) in the aprotinin group versus 12/178 (6.7%) in the control group; RR 0.21; 95% CI 0.02 to 1.79), or thromboembolic episodes (3 trials; 4/161 (2.5%) in the aprotinin group versus 5/119 (4.2%) in the control group; RR 0.59; 95% CI 0.19 to 1.84) between the aprotinin and control groups. There were no significant differences in the 60-day mortality (3 trials; 4/83 (4.8%) in the tranexamic acid group versus 5/56 (8.9%) in the control group; RR 0.55; 95% CI 0.17 to 1.76), retransplantation (2 trials; 3/41 (7.3%) in the tranexamic acid group versus 3/36 (8.3%) in the control group; RR 0.79; 95% CI 0.18 to 3.48), or thromboembolic episodes (5 trials; 5/103 (4.9%) in the tranexamic acid group versus 1/76 (1.3%) in the control group; RR 2.20; 95% CI 0.38 to 12.64) between the tranexamic acid and control groups. There were no significant differences in the 60-day mortality (3 trials; 8/195 (4.1%) in the recombinant factor VIIa (rFVIIa) group versus 2/91 (2.2%) in the control group; RR 1.51; 95% CI 0.33 to 6.95), thromboembolic episodes (2 trials; 24/185 (13.0%) in the rFVIIa group versus 8/81 (9.9%) in the control group; RR 1.38; 95% CI 0.65 to 2.91), or serious adverse events (2 trials; 90/185 (48.6%) in the rFVIIa group versus 30/81 (37.0%) in the control group; RR 1.30; 95% CI 0.94 to 1.78) between the rFVIIa and control groups. There were no significant differences in the 60-day mortality (2 trials; 6/91 (6.6%) in the tranexamic acid group versus 1/87 (1.1%) in the aprotinin group; RR 4.12; 95% CI 0.71 to 23.76) or thromboembolic episodes (2 trials; 4/91 (4.4%) in the tranexamic acid group versus 2/87 (2.3%) in the aprotinin group; RR 1.97; 95% CI 0.37 to 10.37) between the tranexamic acid and aprotinin groups. The remaining outcomes in the above comparisons and the remaining comparisons included only only trial under the primary outcome or the outcome was not reported at all in the trials. There were no significant differences in the mortality, primary graft non-function, graft failure, retransplantation, thromboembolic episodes, or serious adverse events in any of these comparisons. However, the confidence intervals were wide, and it is not possible to reach any conclusion on the safety of the interventions. None of the trials reported the quality of life in patients.

Secondary outcomes were reported in at least two trials for the following comparisons - aprotinin versus control, tranexamic acid versus control, rFVIIa versus control, thromboelastography versus control, and tranexamic acid versus aprotinin. There was significantly lower allogeneic blood transfusion requirements in the aprotinin group than the control group (8 trials; 185 patients in aprotinin group and 190 patients in control group; SMD -0.61; 95% CI -0.82 to -0.40). There were no significant differences in the allogeneic blood transfusion requirements between the tranexamic acid and control groups (4 trials; 93 patients in tranexamic acid group and 66 patients in control group; SMD -0.27; 95% CI -0.59 to 0.06); rFVIIa and control groups (2 trials; 141 patients in rFVIIa group and 80 patients in control group; SMD -0.05; 95% CI -0.32 to 0.23); thromboelastography and control groups (2 trials; 31 patients in thromboelastography group and 31 patients in control group; SMD -0.73; 95% CI -1.69 to 0.24); or between the tranexamic acid and aprotinin groups (3 trials; 101 patients in tranexamic acid group and 97 patients in aprotinin group; SMD -0.09; 95% CI -0.36 to 0.19). The remaining outcomes in the above comparisons and the remaining comparisons included only only trial under the primary outcome or the outcome was not reported at all in the trials. There were no significant differences in the blood loss, transfusion requirements, hospital stay, or intensive care unit stay in most of the comparisons.

#### Authors' conclusions

Aprotinin, recombinant factor VIIa, and thromboelastography groups may potentially reduce blood loss and transfusion requirements. However, risks of systematic errors (bias) and risks of random errors (play of chance) hamper the confidence in this conclusion. We need further well-designed randomised trials with low risk of systematic error and low risk of random errors before these interventions can be supported or refuted.

# PLAIN LANGUAGE SUMMARY

# Methods to decrease blood loss and transfusion requirements for liver transplantation

The liver is the powerhouse of the body. It acts as a store of energy and a centre of metabolic activity. Liver transplantation is the main treatment for severe liver disease resulting in destruction of the liver (which can happen suddenly or over a period of time) due to various causes including alcoholism, viral infections, and autoimmune diseases. Liver transplantation is a major surgical procedure and is associated with significant loss of blood. Various methods have been used to decrease blood loss and transfusion requirements in patients undergoing liver transplantation, with a view to improve the results of liver transplantation. We performed a detailed review of the medical literature (available until September 2011) to determine the benefits and harms of different methods of decreasing blood loss and transfusion requirements in patients undergoing liver transplantation. We sought evidence from randomised clinical trials only, as when conducted properly such studies provide the best evidence. Two authors independently identified the trials and obtained the information from the trials.

We included 33 trials involving 1913 patients. The number of patients included in the trials varied from 8 to 209. The comparisons included various drugs that affect the blood clotting (congealing) such as aprotinin, tranexamic acid; blood substitutes (blood components rather than whole blood); use of thromboelastography (a bedside measure of blood clot formation); and lowering the pressure in the veins with an aim to decrease the blood loss from veins. We found no significant difference in the risk of death or graft loss, or in the major complication rates between the compared groups in any of the comparisons. Quality of life was not reported in any of the trials. There does not appear to be any consistency in the results between blood loss and blood transfusion requirements. Aprotinin, tranexamic acid, recombinant factor VIIa, low central venous pressure, and thromboelastography may lower blood loss and transfusion requirements. However, these findings are based on few trials with a high risk of bias (systematic overestimation of benefits) and high risk of play of chance (random error due to small number of patients). There were no differences in the hospital stay or intensive care unit stay in any of the comparisons. Nor was there any significant difference in the intensive therapy unit stay, or hospital stay between the compared groups. Again, most of the trials



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were of high risk of systematic errors (a potential to arrive at wrong conclusions because of the way the trial was conducted) and random errors (a potential to arrive at wrong conclusions because of play of chance).

Aprotinin is a drug which has been withdrawn from market since there was a suspicion that it increased death after major heart operations. The results from this review do not reveal any increased mortality with aprotinin in the liver transplantation setting although one has to interpret this information with caution because of the few patients included in the trial. We are unable to advocate or refute any method of decreasing blood loss and transfusion requirements in patients undergoing liver transplantation. Further well designed trials with low risk of systematic error and low risk of random errors are necessary.