Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis


CRD summary
The authors concluded that aprotinin and tranexamic acid reduce transfusion requirements in patients undergoing liver transplantation; there was no evidence that antifibrinolytic drugs increase thromboembolic events. The authors’ conclusions appear to reflect the data presented, but poor reporting prevented an adequate assessment of the strength of the evidence.

Authors' objectives
To evaluate the efficacy and safety of antifibrinolytic drugs in liver transplantation.

Searching
MEDLINE, the NCBI National Library of Medicine, the Cochrane Library and ISI Science Citation Index Expanded were searched from 1966 to July 2005 using the reported search terms. In addition, reference lists of relevant studies were screened. Only studies published in English were eligible.

Study selection
Study designs of evaluations included in the review
Controlled trials, both randomised controlled trials (RCTs) and non-randomised trials, were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared antifibrinolytic drugs with placebo, control or another antifibrinolytic drug were eligible for inclusion. The included studies evaluated aprotinin, tranexamic acid (TA) and epsilon-aminocaproic acid (EACA). The controls included different doses of the same drug, other antifibrinolytic agents and placebo. Details of the drug regimens were reported.

Participants included in the review
Inclusion criteria were not specified in terms of the participants, but it was clear that studies of patients undergoing liver transplantation were included. No details of the participants were provided.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes. The review assessed the following outcomes: red blood cell (RBC) and fresh frozen plasma requirements during transplantation; hepatic artery thrombosis up to 30 days after transplantation; intra-operative and 1-month venous thromboembolic events; and intra-operative and 1-month mortality.

How were decisions on the relevance of primary studies made?
Three reviewers independently selected the studies.

Assessment of study quality
The validity of RCTs was assessed using the Jadad scale, which considers randomisation, blinding and the reporting of withdrawals. The maximum possible score was 5 points. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the number of events of interest for each treatment group were extracted. Authors were contacted to clarify definitions of adverse events and for missing data. Only explicit descriptions of the absence of any adverse
outcome event were considered as zero events.

**Methods of synthesis**

**How were the studies combined?**
The overall incidence of safety events was calculated for each drug separately using data from all relevant treatment arms. Where three or more RCTs compared the same antifibrinolytic drug with placebo, the studies were combined in a fixed-effect meta-analysis. Pooled odds ratios with 95% confidence intervals (CIs) were calculated for dichotomous data and pooled standardised mean differences (SMDs) with 95% CIs for continuous data.

**How were differences between studies investigated?**
Statistical heterogeneity was assessed by inspecting forest plots and using the Q statistic.

**Results of the review**

Twenty-three studies (n=1,407) were included in the review: 13 RCTs (n=989), 9 trials with a historical control group (n=296) and one cohort study (n=122).

The Jadad quality scores for RCTs ranged from 1 to 5.

All treatment arms.

Hepatic artery thrombosis was reported in 2.5% (7 of 275) controls, 4.6% (14 of 306) patients receiving TA, 4.8% (2 of 42) patients receiving EACA and 1.3% (5 of 372) patients receiving aprotinin.

Venous thromboembolic events were reported in 1.5% (4 of 275) controls, 0.7% (2 of 306) patients receiving TA, 0% (0 of 42) patients receiving EACA and 1.4% (5 of 349) patients receiving aprotinin.

Peri-operative mortality was reported in 7.1% (23 of 325) controls, 6.4% (19 of 296) patients receiving TA, 2.4% (1 of 42) patient receiving EACA and 4.1% (15 of 367) patients receiving aprotinin.

Aprotinin versus placebo (6 RCTs, n=396).

Aprotinin was associated with a significant reduction in intra-operative RBC (SMD 0.42, 95% CI: 0.22, 0.62, p<0.001; 6 studies) and fresh frozen plasma (SMD 0.40, 95% CI: 0.18, 0.62, p<0.001; 5 studies) requirements during transplantation compared with placebo. No statistically significant heterogeneity was found.

There was no significant difference between aprotinin and placebo in venous thromboembolic events, peri-operative mortality or peri-operative hepatic artery thrombosis (analyses based on 5 studies).

TA versus placebo (3 RCTs, n=161).

TA was associated with a significant reduction in intra-operative RBC requirement (SMD 0.43, 95% CI: 0.12, 0.74, p=0.007; 3 studies). There was no significant difference between TA, aprotinin and placebo in intra-operative fresh frozen plasma requirements. No statistically significant heterogeneity was found.

There was no significant difference between TA and placebo in hepatic artery thrombosis, venous thromboembolic events or peri-operative mortality (all analyses based on 3 studies).

**Authors’ conclusions**

Aprotinin and TA reduce transfusion requirements in patients undergoing liver transplantation. There was no evidence that antifibrinolytic drugs increase thromboembolic events.
CRD commentary
The review addressed a clear question. Inclusion criteria were only specified for the interventions and were implied for the participants and outcomes. Several relevant sources were searched, but no attempts were made to minimise publication or language bias. Methods were used to minimise reviewer error and bias in the study selection stage, but it was unclear whether similar steps were taken in the validity assessment and data extraction. Only the validity of RCTs was assessed among the included studies and only the composite score was presented; pertinent issues such as allocation concealment were not assessed, which makes it difficult to independently comment on the reliability of the evidence presented. Pooling only data from placebo-controlled RCTs was an appropriate method of combining the studies, but these represented only a quarter of those included. The authors' conclusions appear to reflect the data presented, but incomplete reporting prevented an adequate assessment of the strength of the evidence.

Implications of the review for practice and research
Practice: The authors stated that, based on the available evidence, they cannot recommend the use of prophylactic EACA in patients undergoing liver transplantation.

Research: The authors stated that more and larger studies are required to compare aprotinin with other antifibrinolytic drugs with regard to benefits and risks; to determine the lowest effective dose of drugs; and to evaluate the efficacy and safety of EACA.

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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.