A systematic review of randomized controlled trials for plasma exchange in the treatment of thrombotic thrombocytopenic purpura
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CRD summary
This review concluded that plasma exchange is more effective than plasma infusion in the treatment of thrombotic thrombocytopenic purpura, but it is unclear which replacement fluid for plasma exchange is best. There are limitations with the included studies, but the authors take these into account in their synthesis and the conclusions are likely to be reliable.

Authors' objectives
To assess the safety and efficacy of different replacement fluids for plasma exchange (PE) in the treatment of thrombotic thrombocytopenic purpura (TTP).

Searching
MEDLINE (1996 to 2005), EMBASE (1980 to 2005), the Cochrane Library (2005), Current Controlled Trials Register, the UK National Research Register, National Health and Medical Research Council of Australia, and Trials Central were searched and updated to July 2006. In addition, conference abstracts and reference lists of identified studies and relevant review articles were handsearched, and experts in the field were contacted. Publications were not restricted by language or status.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing two different types of PE, or a PE with plasma infusion (PI), were eligible for inclusion. The included studies used PE with the following types of replacement fluids: standard fresh frozen plasma (FFP), solvent-/detergent-treated plasma (SDP), cryosupernatant plasma, or cryoprecipitate-poor plasma as the intervention, and PI (FFP) or PE (FFP) as the comparator. Adjunctive treatment included dipyridamole, aspirin and methylprednisolone. Studies reporting treatment doses used different measures, and treatment durations also varied.

Participants included in the review
Patients of any age with a diagnosis of TTP were eligible for inclusion. Where reported, the included studies identified patients with the following types of TTP: intermittent or initial onset, acute, or idiopathic adult.

Outcomes assessed in the review
Studies reporting on related clinical and/or laboratory outcomes were eligible for inclusion. The review included mortality, response to treatment, time to resolution of the presenting signs of TTP, adverse events and quality-of-life outcomes.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened for relevant studies and any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the quality of the included studies using modified criteria from a published study, including randomisation, treatment allocation concealment, follow-up and blinded outcome assessment. Any disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted the data and any disagreements were resolved through discussion.
extracted on study and patient characteristics, type and cause of TTP, intervention details, comparator and associated treatment details, outcomes and study quality. The outcome data were presented as summary risk ratios (RRs) for studies comparing PE with PI.

**Methods of synthesis**

**How were the studies combined?**

Summary RRs were pooled using a fixed-effect model with 95% confidence interval (CI) where appropriate. Where not appropriate, the studies were grouped by replacement fluid type and described narratively.

**How were differences between studies investigated?**

Due to clinical and methodological heterogeneity the majority of findings were presented narratively, grouped by treatment type.

**Results of the review**

Seven RCTs (n=281 (actually n=301); n=157 receiving intervention and n=144 receiving comparator) were included in the review; two compared PE with PI and five compared different replacement fluids for PE. The sample sizes ranged from 18 to 102 participants. The longest follow-up reported was 12 months, with one study reporting only interim data.

**PE versus PI (2 studies).**

All patients received aspirin and dipyridamole as an adjunctive treatment. A significant difference was identified for mortality rates after 7 treatment sessions; both studies favoured PE (RR 0.31, 95% CI: 0.12, 0.79). No significant differences in mortality rates were reported at follow-up. Cause of death was reported in 9 patients, 5 of which were treatment related.

A significant difference in response rates was reported after 7 treatment sessions, with almost twice as many patients responding in the PE group (RR 1.85, 95% CI: 1.06, 3.21) and fewer failures to respond (RR 0.71, 95% CI: 0.52, 0.96). No significant differences were identified for adverse events.

**PE with SDP versus PE with FFP (2 studies).**

Due to methodological heterogeneity the studies could not be pooled. Mortality rates were reported to be greater with SDP than with FFP in both studies. One study reported 33.3% and 0% mortality rates for SDP and FFP, respectively; however, the second study identified similar mortality rates. One study reported greater remission rates in the FFP group compared with the SDP group: 100% and 58%, respectively. No significant differences were reported for mean number of relapses in both studies, and no differences were found in one study for adverse events. Other outcomes were reported in the review.

**PE with cryosupernatant plasma or cryoprecipitate-poor plasma versus PE with FFP (3 studies).**

Due to methodological heterogeneity the studies could not be pooled. No significant differences are reported for mortality rates and studies presenting rates for partial remission, response and relapse reported no significant differences. No adverse events were reported and other outcomes were discussed in the review.

**Authors’ conclusions**

Treatment with PE is associated with reduced mortality in comparison with PI. However, the most effective method of clinical management, including optimal schedule and type of replacement fluid for PE, remains uncertain.

**CRD commentary**

The review question was clear and supported by appropriate inclusion criteria relating to the patients, interventions, outcomes and study designs. Relevant literature searches, without restrictions on language or publication status, were undertaken using electronic databases and other appropriate sources, and measures were taken to minimise errors and bias. Validity was assessed according to published criteria; however, the assessment of methodological quality for
included studies was limited by low levels of reporting. Appropriate methods were used to pool or describe the results and heterogeneity was investigated, but sample sizes were small and follow-up durations were short; this means that the reliability of the included studies and their subsequent synthesis is unclear. However, the authors appear to have taken these limitations into account and their conclusions are therefore likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the use of PE therapy in clinical management remains uncertain, and clinical outcome may be affected by adjunctive treatment and duration of PE treatment. The authors highlighted that SDP was not used in U.S. clinical practice at the time, owing to a number of patient deaths following administration.

Research: The authors stated that future studies should identify the optimal schedule (e.g. dose and type of replacement fluid) and volume for PE, and assess the cost-effectiveness of different replacement fluids. Future research should also provide more accurate methodological and outcome reporting, including reporting of definitions, full reporting of events and details, and measurement of quality of life. Data should also be reported for co-morbid conditions and underlying causes of TTP to enable more accurate comparison and analysis.

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