Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: a meta-analysis

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Authors' objectives
To assess whether adjunct exchange transfusion increases survival rates in comparison with antimalarial chemotherapy alone, among patients with severe falciparum malaria.

Searching
MEDLINE, EMBASE, FEDRIP and the Cochrane Controlled Trials Register were searched from 1966 to 2001 using the search terms 'exchange transfusion', 'severe malaria' and 'complicated malaria'. In addition, the reference lists of review articles were searched manually. The search was restricted to material published in the English language.

Study selection

Study designs of evaluations included in the review
Any study that compared an intervention group with a control treated with standard therapy was eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared exchange transfusion as an adjunct to antimalarial chemotherapy with an appropriate antimalarial chemotherapy only were included in the review. The volume of exchange transfusion in the included studies ranged from 0.5 to 10 L. The primary antimalarial drug, where reported, was quinine or quinidine.

Participants included in the review
The participants included in the review were of mixed immune status (partially immune, non-immune and mixed) suffering from severe falciparum malaria. The mean age ranged from 23.6 to 53 years. The participants in the exchange transfusion group had a mean level of parasitaemia ranging from 18.5 to 31.3% and met a mean of 1.63 to 4.7 World Health Organization (WHO) criteria for severe or complicated malaria. The antimalarial therapy only groups had a mean level of parasitaemia ranging from 9 to 17% and met a mean of 0.7 to 3.7 WHO criteria.

Outcomes assessed in the review
The outcomes assessed in the review were the survival rates.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected the studies.

Assessment of study quality
Study quality was assessed using a scale developed by Downs and Black (see Other Publications of Related Interest no.1) for assessing the quality of non-randomised trials. The criteria included: statistical power; comparability of treatment groups; representativeness of treatment populations and modalities; adjustment for confounding; description of treatment group characteristics; interventions; and principal confounding variables. Two independent reviewers undertook the quality scoring process.

Data extraction
Two independent reviewers extracted the data.

Data were extracted on the year and country of publication, and the geographical region where the infections occurred. Data were also extracted on the following: the mean age of the patients in the treatment groups; their malaria immune status; the mean level of parasitaemia as a percentage; the mean number of WHO criteria for severe or complicated malaria that were met by the study patients; the antimalarial drug used; the criteria for performing exchange
transfusion; the exchange transfusion method used; and the volume of blood transfused. Data on survival were abstracted as a dichotomous variable, and the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Where available, patient-specific data were also extracted from the studies.

**Methods of synthesis**

How were the studies combined?
The studies were combined statistically in a meta-analysis. Summative ORs were calculated using the fixed-effect model of Mantel and Haenszel (see Other Publications of Related Interest no.2). Where patient-specific data were available, a secondary analysis was performed to assess the effect of exchange transfusion on the survival rate. This was carried out after adjusting between the study participant groups for level of parasitaemia, malaria immune status, and number of WHO severe malaria criteria met. For this secondary analysis, the data were analysed by logistic regression, both with and without analytic weights derived from the inverse of each study's variance (precision). Trend tests were based on the non-parametric extension of the Wilcoxon rank-sum test developed by Cuzick (see Other Publications of Related Interest no.3). Publication bias was assessed using the method described by Egger et al. (see Other Publications of Related Interest no.4).

How were differences between studies investigated?
Heterogeneity was assessed visually by a Galbraith plot and using a chi-squared test. Sensitivity analyses were also performed for quality score, year of publication, country of publication, continent of infection, and immune status for the treatment groups of each study.

**Results of the review**

Eight case-control studies (n=279) were included in the review

Adjunct exchange transfusion: the summary OR for survival after adjunct exchange transfusion, compared with antimalarial chemotherapy alone, was 1.2 (95% CI: 0.7, 2.1). This indicated no benefit to the intervention, although patients treated with exchange transfusion had higher levels of parasitaemia (means: 22% versus 12%; P=0.0005) and met a higher number of WHO severe malaria criteria (means: 3.4 versus 2.4; P=0.005).

There was no evidence of heterogeneity among the trials, either visually via Galbraith plots or statistically with the chi-squared test (P=0.4). There was no evidence of publication bias (P=0.6).

The results of the sensitivity analysis indicated that the review's results were not overly influenced by a single study. The regression analysis showed no differences when comparing the effect size of the included studies on the basis of year or country of publication, or quality score. Some of the heterogeneity was explained by the patients' malaria immunity status (P=0.007) and by the continent of infection (P=0.05). Three studies from Southeast Asia of patients with partial immunity favoured exchange transfusion.

Three of the four studies with nonimmune patients (2 from Africa and 2 where the continent was not reported) found no improvement in survival among those patients who received exchange transfusion. A subgroup analysis of studies with patients of partial immunity yielded an OR of 0.5 (95% CI: 0.2, 1.2), compared with an OR of 2.1 (95% CI: 0.9, 4.8) for nonimmune patients. This suggested that exchange transfusion might be more effective for people who have a partial immunity to malaria.

The patient-specific data analysis indicated that, with adjustment for initial level of parasitaemia, malaria immune status and number of WHO severe malaria criteria met, no significant benefit of exchange transfusion was found (OR 0.3, 95% CI: 0.1, 2.4). Patients who had elevated parasitaemia or who met a greater number of WHO severe malaria criteria were more likely to die. Patients with more than 30% peripheral parasitaemia had a four-fold increase in their odds of death (OR 4.5, 95% CI: 1.2, 16.8). Patients with more than four WHO severe malaria criteria had a five-fold increase in their odds of death (OR 5.3, 95% CI: 1.3, 21.7), with death more likely for every additional severe malaria criteria met (P<0.001) for trend.

**Authors' conclusions**
Exchange transfusion did not appear to increase the survival rate. However, until an adequately designed, randomised controlled clinical trial is conducted, adjunct exchange transfusion cannot be recommended for the treatment of severe falciparum malaria.

CRD commentary
The review question and the study selection criteria were stated clearly. The literature search seemed reasonably comprehensive, although the restriction to English language publications may mean that some studies were missed, although there is no evidence of publication bias using Egger's test. The authors provided adequate information on the review selection, validation and data extraction processes. The details of the different statistical tests undertaken were also adequate, although it is not really appropriate to present survival data as ORs. The second individual patient data (IPD) analysis was better, but was carried out on fewer patients. It would have been better to have obtained IPD for all, and to have presented survival curves or hazard ratios. The results were clearly presented and discussed. However, the authors did not specify which studies the IPD numbers were derived from, so it is not possible to know how generalisable the results are.

Otherwise, the authors' conclusions seem appropriate in the light of the data they present.

Implications of the review for practice and research
Practice: The authors offer no formal implications for practice. They state that well-equipped, well-staffed care facilities and plentiful, safe blood supplies are absolute necessities for exchange treatment and that as these provisions are not always easily available, a pragmatic approach to the consideration of adjunct exchange transfusion is necessary. They also state that adjunct exchange transfusion cannot be recommended for the treatment of severe falciparum malaria at present.

Research: The authors state that a randomised controlled, probably multicentre trial, with a sufficiently large number of patients enrolled is required to form a definitive conclusion on the role of adjunct exchange transfusion in the treatment of severe falciparum malaria.

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