Meta-analysis of HLA matching and the outcome of unrelated umbilical cord blood transplantation (CBT)
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CRD summary
The review assessed the effects of human lymphocyte antigen mismatching on the success of cord blood transplantation. Mismatching was found to increase graft failure rates, severe graft versus host disease and mortality and decrease disease-free survival. The low number of included studies of unknown quality mostly with small sample sizes, suggested that the conclusion should be treated cautiously.

Authors’ objectives
To compare human lymphocyte antigen (HLA) typing with outcomes for unrelated umbilical cord blood transplantation.

Searching
MEDLINE via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Center for International Blood and Marrow Transplant Research (CIBMTR) were searched from January 1989 to December 2008. Search terms were reported. Bibliographies of retrieved articles were searched for additional material. Articles in any language were eligible for inclusion.

Study selection
Any study on cord blood transplantation or HLA typing were eligible for inclusion. Patients who required umbilical cord blood transplantation for treatment of malignant disorders were eligible for inclusion. Articles had to contain data for outcome measures. Exclusion criteria were: lack of a comparator group; articles that reiterated previous data; and case trials of poor quality and little data.

Primary outcome was survival. Secondary outcomes included were neutrophil and platelet engraftment (counts above 500 neutrophils/mL for three consecutive days or 20,000 platelets/mL without transfusions for at least seven days); graft versus host disease (graded according to Seattle consensus criteria); and transplantation related mortality.

The age of included patients ranged from 0 to 56 years. All patients were being treated for malignant disease and had a follow-up of 0.3 to six years.

Two reviewers independently selected studies. Disagreements were resolved by consensus.

Assessment of study quality
The quality of the studies was assessed with allocation concealment, randomisation method, treatment blinding and inclusion/exclusion criteria.

Two reviewers independently performed the validity assessment. Disagreements were resolved by consensus.

Data extraction
Outcome data was extracted to calculate odds ratios (ORs) and 95% confidence intervals (CI).

Patients and their outcome data were divided into three groups: HLA matched; 1-antigen (1-Ag) mismatched; 2-Ag mismatched. Data was extracted into a predesigned data abstraction form. Two reviewers independently extracted data, disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios and 95% CI were calculated using a fixed-effects model. Heterogeneity was assessed using the $I^2$ statistic. A random-effects model was used to pool odds ratios and 95% CI in the presence of significant study heterogeneity ($I^2 > 50\%$). Publication bias was assessed with a funnel plot.

**Results of the review**

Ten RCTs were included in the review (n=1,589 total participants, range 11 to 550).

**Neutrophil engraftment:** There was no significant difference in the rate of neutrophil engraftment between matched and 1-Ag mismatched cord blood treatment groups (seven studies, n=493 participants). 2-Ag mismatched treatments showed a significant reduction in engraftment in comparison to matched (OR 2.28, 95% CI 1.22 to 4.23; seven studies, n=413 participants). There was no significant heterogeneity in either analysis.

**Platelet engraftment:** The rate of platelet engraftment was significantly lower in 1-Ag mismatched (OR 1.72, 95% CI 1.02 to 2.89; six studies, n=419 participants) or 2-Ag mismatched (OR 2.31, 95% CI 1.36 to 3.94; six studies, n=352 participants) treatments compared to the matched group. There was no significant heterogeneity in the analyses.

**Graft versus host disease:** For grade 0 to 1 there was no significant difference between the three treatment groups. The occurrence of grade >II disease was significantly increased in the 2-Ag mismatched group (OR 2.00, 95% CI 1.04 to 3.85; five studies, n=323 participants), but not by the 1-Ag mismatched group (five studies, n=307 participants) compared to matched groups. There was no significant heterogeneity in the analyses.

**Early transplant related mortality:** Mortality rates were significantly higher with 2-Ag mismatched treatments (OR 3.08, 95% CI 1.15 to 8.23; four studies, n=395 participants), but not 1-Ag mismatched treatments (four studies, n=424 participants) compared to matched groups. Heterogeneity was significant in both analyses (2-Ag mismatch, $I^2=54\%$; 1-Ag mismatch, $I^2= 56\%$).

**Disease free survival:** There was no significant difference in survival rates between matched and 1-Ag mismatched treatments (nine studies, n=845 participants). There was a significantly lower rate of survival in the 2-Ag mismatched treatments (OR 1.70, 95% CI 1.17 to 2.48; nine studies, n=565 participants), in comparison to the matched treatment. There was no significant heterogeneity in the analyses.

The studies were symmetrically distributed on the funnel plot, which indicated that publication bias was low.

**Authors’ conclusions**

HLA mismatched cord blood transplants increased the rate of graft failure, severe graft versus host disease, transplant-related mortality and decreased disease free survival.

**CRD commentary**

The review addressed a clear research question with clear inclusion criteria. Several sources were searched to locate the included studies. There were no specific attempts to locate unpublished studies, which could have introduced publication bias. The authors assessed the risk of publication bias and found it to be low. Study selection, data extraction and quality assessment were conducted in duplicate, which reduced the potential for error and bias. Methods were described to examine the study quality, but results of this analysis were not presented. The chosen methods for synthesis appeared appropriate. The authors’ conclusions reflected the evidence presented. Given that the results were based on a small number of studies of unknown quality mostly with small sample sizes, the conclusions should be viewed with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that large-sample, well-designed trials were required to exclude the possibility of bias.

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