Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies

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Authors' objectives
To determine whether peri-operative allogeneic blood cell transfusions are associated with adverse sequelae in patients with cancer.

Searching
The following sources were searched using a modification of the Cochrane Collaboration MEDLINE search strategy: MEDLINE from 1966 to 1997, Cancerlit from 1983 to 1997, Current Contents, CINAHL from 1982 to 1996, HealthSTAR from 1990 to 1997, BioAbstracts from 1990 to 1996, and EMBASE from 1984 to 1997. The search was restricted to studies on humans. Abstracts, letters and full manuscripts published in any language and describing human studies were sought. Handsearches of the bibliographies of all identified studies and issues of the journals Transfusion, British Journal of Surgery, Lancet and New England Journal of Medicine published between January 1995 and March 1997 (inclusive) were also performed. Members of the International Study of Perioperative Transfusion Group were contacted for additional published or unpublished relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with autologous blood transfusion or leucocyte-depleted packed cells as the control arm intervention. Prospective cohort studies with appropriate controls, which reported the outcome in patients with cancer undergoing potentially curative surgery who had received peri-operative transfusions from 24 hours to 30 days after the operation.

Specific interventions included in the review
Peri-operative allogeneic red blood cell transfusion.

Participants included in the review
Patients with localised malignancy undergoing elective potentially curative surgery were included, whilst those patients undergoing palliative or emergency surgery were excluded.

The vast majority of participants had colorectal cancer and were in their seventh decade of life. Other cancer types included were hepatoma, prostate and cervical.

Outcomes assessed in the review
All-cause mortality, cancer recurrence or post-operative infection were assessed. Cancer recurrence was defined as local recurrence or metastic disease and was accepted if the original investigators detected characteristic abnormalities on physical examination, radiography, cytology, histology or cytology. Post-operative infection was defined as occurring within the first thirty post-operative days, and was accepted if the original investigators documented evidence of bactaemia (on blood culture) or a specific focus, such as wound infection, urinary sepsis or pneumonia.

How were decisions on the relevance of primary studies made?
Two investigators independently reviewed the titles and abstracts. The full texts of all potentially relevant articles were obtained and reviewed by both investigators using prestandardised data abstraction forms.

Assessment of study quality
The quality of RCTs was determined by means of the Jadad scale (see Other Publications of Related Interest no.1), whilst the quality of the cohort studies was assessed with a modification of the McMaster checklist.
The Jadad scale was developed and validated as a means to provide quantitative estimates of the quality of clinical trials. The studies were evaluated using a 5-point scale based on methods of randomisation, double-blinding and full disclosure of withdrawals or drop-outs.

The McMaster checklist was developed by expert consensus and consisted of three sections to evaluate observational studies. The cohort studies were graded out of five using the criteria in the validity section of the checklist: presence of clearly identified comparison groups that were similar with respect to potential confounders; outcomes and exposures measured in the same way in both groups; follow-up sufficiently long and complete; correct temporal relationship; and the presence of a dose-response gradient. The papers were assessed for validity by two independent investigators. The inter-observer agreement on the quality score was determined, and any discrepancies were resolved by consensus or the judgement of a third investigator.

Data extraction
The data were extracted by two independent investigators using prestandardised data abstraction forms. The data were extracted in an intention to treat format. If the outcome data for each of the study arms were unclear, the original investigators were contacted for clarification.

Methods of synthesis
How were the studies combined?
Risk ratios (RRs) were determined for each of the eligible studies. The studies were combined using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2) and the fixed-effect model of Mantel and Haenszel (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
Cochran's Q test was carried out to assess heterogeneity in each outcome of interest. A P-value of less than 0.10 was considered to indicate statistically-significant heterogeneity.

Sensitivity analyses, defined a priori, were conducted to look at the effect of study design, study quality, year of study completion and publication status on the summary RRs.

Results of the review
Six RCTs (1,239 participants) and 2 prospective cohort studies (306 participants) were included.

The summary RR was 0.95 (95% confidence interval CI: 0.79, 1.15) for all-cause mortality, suggesting that allogeneic transfusion is not associated with an increased mortality risk in these patients. Allogeneic transfusion was not associated with an increased risk of cancer recurrence (summary RR 1.06, 95% CI: 0.88, 1.28).

There was significant heterogeneity (Q=37.97, d.f.=5, P<0.001) in the post-operative infection data. This was explained by differences in study design and patient characteristics of 2 studies. When these 2 studies were removed from the analyses, the summary RR was 1.00 (95% CI: 0.76, 1.32). This suggested that allogeneic transfusion is not associated with post-operative infection.

Sensitivity analysis confirmed the conclusion that peri-operative blood transfusion has no effect on all-cause mortality or cancer recurrence.

Given the sample sizes of these 8 studies, this meta-analysis had insufficient power to detect a relative difference of less than 20% in the frequency of death, cancer recurrence or infection between the allogenic and control confusion arms.

Authors' conclusions
There is currently no evidence that allogeneic blood transfusion increases the risk of clinically important adverse sequelae (all-cause mortality, cancer recurrence and post-operative infection) in cancer patients undergoing surgery. More studies are required before a definitive statement can be made.
**CRD commentary**
The authors presented a well-defined review question and clear inclusion criteria.

The validity of the included studies was thoroughly assessed by two investigators.

The search strategy was very thorough and included an attempt to identify unpublished studies, although none were found. Sufficient details of the individual studies included were given, with the exception of the participants’ gender and the length of follow-up.

The authors examined sources of heterogeneity when it was present. The primary studies were summarised appropriately.

The authors’ conclusions follow logically from the results.

**Implications of the review for practice and research**
The authors state that the most important conclusion to emerge from this meta-analysis is the need for more (and larger) RCTs comparing allogeneic blood products with appropriate active comparators, such as autologous or leucocyte depleted blood, in patients with cancer at time of operation.

They also suggest that given the lack of evidence for increased risk from allogeneic blood transfusions, it seems appropriate to revisit the role of autologous blood donation programmes. This is particularly important given that almost half of the autologous blood donated before operation in the United States is discarded and formal economic analyses have questioned the cost effectiveness of these programmes.

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