CLINICAL RESEARCH STUDY

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Impact of More Restrictive Blood Transfusion Strategies on Clinical Outcomes: A Meta-analysis and Systematic Review

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ABSTRACT

BACKGROUND: There is accumulating evidence that restricting blood transfusions improves outcomes, with newer trials showing greater benefit from more restrictive strategies. We systematically evaluated the impact of various transfusion triggers on clinical outcomes.

METHODS: The MEDLINE database was searched from 1966 to April 2013 to find randomized trials evaluating a restrictive hemoglobin transfusion trigger of <7 g/dL, compared with a more liberal trigger. Two investigators independently extracted data from the trials. Outcomes evaluated included mortality, acute coronary syndrome, pulmonary edema, infections, rebleeding, number of patients transfused, and units of blood transfused per patient. Extracted data also included information on study setting, design, participant characteristics, and risk for bias of the included trials. A secondary analysis evaluated trials using less restrictive transfusion triggers, and a systematic review of observational studies evaluated more restrictive triggers.

RESULTS: In the primary analysis, pooled results from 3 trials with 2364 participants showed that a restrictive hemoglobin transfusion trigger of <7 g/dL resulted in reduced in-hospital mortality (risk ratio [RR], 0.74; confidence interval [CI], 0.60-0.92), total mortality (RR, 0.80; CI, 0.65-0.98), rebleeding (RR, 0.64; CI, 0.45-0.90), acute coronary syndrome (RR, 0.44; CI, 0.22-0.89), pulmonary edema (RR, 0.48; CI, 0.33-0.72), and bacterial infections (RR, 0.86; CI, 0.73-1.00), compared with a more liberal strategy. The number needed to treat with a restrictive strategy to prevent 1 death was 33. Pooled data from randomized trials with less restrictive transfusion strategies showed no significant effect on outcomes.

CONCLUSIONS: In patients with critical illness or bleed, restricting blood transfusions by using a hemoglobin trigger of <7 g/dL significantly reduces cardiac events, rebleeding, bacterial infections, and total mortality. A less restrictive transfusion strategy was not effective.

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Red blood cell transfusions have been the standard of care for treating anemia for more than 100 years now, with little evidence that they improve clinical outcomes.[1-3] By the early 1900s, blood transfusion was considered to be "a procedure of such simple and harmless character" that no clinical indication was needed, "the mere possibility of benefitting a condition by the addition of blood being considered sufficient warrant."[1] The practice was based on the assumption that anemia is tolerated poorly and that red blood cell transfusions improve outcomes.[1,4,5] Researchers did not begin to question the evidence behind the practice until the 1980s and 1990s, when the first randomized trials were performed.[6-12] By that time, the practice of blood transfusion was so ingrained in our medical framework that

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the approach has been to march slowly down on the transfusion trigger instead of addressing whether transfusions are beneficial at all.

The standard transfusion trigger for many years had been a hemoglobin of 10 g/dL or even higher.[6,9,12,13] This arbitrary trigger has been lowered gradually to a hemoglobin level of 6 to 8 g/dL because studies showed that blood transfusions are associated with worse outcomes in patients with anemia due to illness or bleeding, compared with simple supportive measures such as hydration.[6,9,12-20] However, a liberal transfusion practice is still common, especially for those with coronary artery disease who are thought to benefit more from blood transfusions.[21] There have been many challenges inherent in the study of our transfusion practices, such as the broad patient base included in the analyses, the multiple indications for blood transfusions, and the confounding by indication in observational studies.

CLINICAL SIGNIFICANCE

- Pooled randomized trial data show that blood transfusions increase in-hospital mortality, total mortality, rebleeding, acute coronary syndrome, pulmonary edema, and bacterial infections.
- When a restrictive hemoglobin transfusion trigger of <7 g/dL is used in patients with critical illness or bleed, the number needed to treat to prevent 1 death is 33.
- Observational data indicate that hemoglobin levels of 5 to 6 g/dL are well tolerated in normovolemic patients without affecting oxygen delivery.

We have found no randomized clinical trials comparing transfusion with no transfusion. Instead, the available trials have compared more or less restrictive transfusion strategies using different transfusion triggers. A previous meta-analysis pooled data from randomized trials that evaluated restrictive hemoglobin transfusion triggers ranging from 7 to 10 g/dL and found that restricting transfusions significantly reduced in-hospital mortality but had no effect on other clinical outcomes.[22] We have chosen a different approach to evaluate the available evidence. We now update the meta-analysis through April 2013 to include a subsequent trial[23] and restrict the primary analysis to those trials with a transfusion trigger of <7 g/dL. Trials that evaluated less restrictive strategies were evaluated in a separate analysis. We also provide a systematic review of observational studies that evaluated clinical outcomes related to other more restrictive transfusion strategies.

MATERIALS AND METHODS

Data Sources and Study Selection

We conducted a comprehensive search of the MEDLINE database from 1966 to April 2013 using the terms *blood transfusion* and *clinical trial,* and scanned selected journals and references of identified articles. Studies of any language were included in the primary analysis if they were randomized controlled trials that evaluated a restrictive blood transfusion strategy using a transfusion trigger of <7 g/dL, compared with a more liberal strategy (detailed study protocol shown in Appendix Tables 1 and 2, online). We included trials of adults or children, including neonates, involving surgical or medical conditions. Trials that used a restrictive transfusion trigger more than 7 g/dL were evaluated separately as a "less restrictive" strategy. Additional searches of related articles were done to perform a systematic review of the impact of various transfusion strategies.

Data Extraction and Quality Assessment

Two investigators (SS, JB) extracted data from the trials, reconciling differences by consensus. In addition, selected investigators were contacted for additional information. Clinical outcomes evaluated included in-hospital mortality, 30-day mortality, total mortality, acute coronary syndrome, pulmonary edema, bacterial infections, rebleeding, number of patients receiving any blood transfusion, and units of blood transfused per patient. Extracted data also included information on study setting, design, participant characteristics, and risk for bias for the included trials (detailed study protocol shown in Appendix, online).[24]

Data Synthesis and Analysis

The results were reported as a risk ratio (RR) and risk difference for dichotomous outcomes, for the restrictive strategy compared with the liberal strategy, with the confidence interval (CI) set at 95% significance. For the amount of blood transfused per patient, the results were reported as a mean difference, with 95% CIs for the restrictive compared with the liberal strategy. To test for inter-study heterogeneity, the chi-square value was calculated; statistical significance was indicated by $P < .1$. The fixed-effects method was chosen to report the results because minimal heterogeneity was seen in most of the analyses.[25] When heterogeneity was noted, the random-effects method was used.[26] In a secondary analysis, the pooled results from trials using a less restrictive strategy were evaluated and compared with the trials in the primary analysis using the test for interaction.[27] The analyses were performed using Review Manager, Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

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