Age of Red Cells for Transfusion and Outcomes in Critically Ill Patients: A Meta-Analysis

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Keywords

Transfusion · Safety · Red blood cell · Mortality · Critically ill patients

Abstract

Objective: Whether the age of red blood cells (RBCs) affects mortality after transfusion in critically ill patients is controversial. **Methods:** We searched MEDLINE, EMBASE, PubMed, Web of Science, and the Cochrane Library Central Register of Controlled Trials databases from inception to January 10, 2018 to identify systematic reviews or meta-analyses and published randomized controlled trials of the effects of fresh versus older blood transfusion on mortality of adults in the intensive care unit (ICU). There were no date restrictions, but the language was restricted to English. The primary outcome was mortality. Risk ratios (RR) and 95% confidence intervals (CI) were calculated. **Results:** We included six trials that enrolled 8,467 critically ill patients and compared fresh RBC transfusion with current standard practice. There were no significant differences in 90-day mortality (RR 1.04, 95% CI 0.97, 1.12), 28/30-day mortality (RR 1.04, 95% CI 0.96, 1.13), in-hospital mortality (RR 1.06, 95% CI 0.94, 1.19), and in-ICU mortality (RR 1.11, 95% CI 0.97, 1.27) with fresh RBC transfusion compared with older blood transfusion. **Conclusions:** The study concluded that age of red cells for transfusion did not affect the outcomes in critically ill patients.

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Introduction

Critically ill patients frequently have anemia. Moreover, anemia is present throughout the duration of the patients' intensive care unit (ICU) and hospital stay. Almost 70% of patients have a baseline hemoglobin level of ≤ 12 g/dL, and half of these have a hemoglobin level of ≤ 10 g/dL by 48 h after ICU admission [1]. The pathogeny of this anemia is multifactorial, involving blood loss from diagnostic phlebotomy, intraoperative hemorrhage, and gastrointestinal bleeding, decreased iron availability, a blunted erythropoietin response, and nutritional factors [2, 3]. Rodriguez et al. [4] found that even at an early point of critical illness (ICU day 2 or 3), most patients in the ICU had low serum ferritin (Fe) levels, total iron-binding capacity, and iron (ferrum) saturation of serum transferrin (ferritin/total iron-binding capacity). Transfusions serve as a lifesaving therapy and are also the only medical practice for treating clinical symptoms related to bleeding and anemia. Transfusions are a common therapeutic intervention among patients in the ICU, especially in older patients and those with a longer ICU stay [5–7].

Based on the “first in, first out” policy, blood banks deliver the oldest available red cell units when transfusion is requested to reduce wastage [8, 9]. Therefore, critically ill patients may receive red blood cells (RBCs) older than 2 weeks [10]. However, during storage, a series of functional, metabolic, and biochemical changes in RBCs, including decreased pH, increased titers of lactate and free hemoglobin, reduced concentrations of adenosine 5-triphosphate and 2,3-diphosphoglycerate, accumulation of

extracellular potassium, membrane loss, and changes in RBC deformability over time, are collectively called storage lesion [11–13]. Accumulation of toxic substances of older RBCs may affect mortality of patients. Koch et al. [14] performed a meta-analysis of 21 studies that included 409,966 patients and showed that older blood transfusion was associated with a significantly increased risk of death [15]. In rats with anemia and myocardial infarction, transfusion of fresh (storage time <4 h) but not stored blood (storage time <7 days) significantly improved survival and cardiac function compared with non-transfused anemic rats [16]. This finding indirectly showed that fresh blood was superior to stored blood. Patients in the ICU are vulnerable and the severity of illness may increase their susceptibility to adverse effects of RBC storage [10]. Similarly, with transfusion of RBCs at a mean age of 16.2 days in patients in the ICU, ICU mortality and 28-day overall mortality rates were significantly higher in transfused versus non-transfused patients in an observational study [6]. Two large observational studies also showed that exposure to the maximum age of RBCs was independently associated with an increased risk of hospital death in critically ill adults [17, 18]. However, several published, randomized controlled trials (RCTs) showed that there were no significant differences in in-hospital mortality and 90-day mortality with transfusion of fresh versus standard RBCs in critically ill patients [19–21]. A recent meta-analysis that included these RCTs indicated that patients did not benefit from fresh transfusion compared with older RBCs [22]. Dessertaine et al. [23] concluded that ICU outcomes were related to the number of leukodepleted red cells transfused, but not with their storage time. Observational trials are easily influenced by cofounders. The number and sample size of relevant RCTs were too small and important clinical differences could not be detected.

Whether the age of RBCs affects mortality after transfusion in critically ill adults remains unclear. Therefore, we performed a study to determine if fresh RBCs reduce mortality compared with standard blood in critically ill adults.

Methods

A meta-analysis of RCTs was conducted to compare fresh or short-term versus older, long-term, or standard RBC transfusion in outcomes of critically ill adults. All of the data in the study were collected from published RCTs. Therefore, informed consent of the included patients was not required for publication. Additionally, review and consent of the ethics committee were not necessary for our research. In the study, we stated that the data were available due to the fact that all of them came from the published RCTs.

Search Methods

We extracted relevant studies from MEDLINE, PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials databases. The MeSH terms “blood”, “erythrocyte*”, “red cell*”, “red blood cell*”, “RBC”, “whole blood”, “erythrocyte

transfusion”, “transfusion”, “age”, “aged”, “aging”, “fresh*”, “old”, “older”, “new”, “newer”, “young”, “store*”, “storage”, “storing”, and “preserve*” were used. There were no date restrictions, but the language was restricted to English. The search was restricted to systematic reviews, reviews, or meta-analyses, including RCTs. Another search was performed to identify published RCTs at any time using the same keywords as above. The population only involved critically ill adults. These searches were updated in January 10, 2018, and additional unpublished data or studies were excluded.

Selection Criteria

All RCTs that compared fresh or short-term with older, long-term, or standard RBC transfusion and reported death as an outcome in critically ill adults were included. Inclusion criteria were as follows: (1) anemia present after ICU admission with a requirement for transfusion, (2) comparison of fresh or short-term with older, long-term, or standard RBC transfusion, and (3) reported outcomes of in-ICU mortality, in-hospital mortality, 28/30-day mortality, or 90-day mortality. Exclusion criteria were as follows: (1) the study included duplicate data, (2) the trial did not show death as an outcome, (3) the trial did not contain adequate data for inclusion, (4) the study did not meet the inclusion criteria, and (5) neonates and children in the ICU.

An appropriate methodology of RCT design was defined as the whole methodological design of RCTs, including the following: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias.

Collection and Analysis of Data

In this meta-analysis, in-ICU mortality was the primary outcome in critically ill patients with fresh RBC or standard transfusion. From the eligible trials, we abstracted and collected data, including the first author, published year, country, sample size, participants' baseline characteristics, Acute Physiology and Chronic Health Evaluation (APACHE) score, methods, interventions, and outcomes.

Endpoints

The primary outcome of this study was in-ICU mortality at any time point. The secondary outcomes were in-hospital mortality, 28/30-day mortality, and 90-day mortality.

Statistical Analyses

We calculated risk ratios (RRs) for dichotomous variables, with 95% confidence intervals (CIs). All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. We estimated heterogeneity using the χ^2 and I^2 tests among studies. All statistical analyses were performed using RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Sample Characteristics

Using Medical Subject Headings (MeSH) terms, 1,141 potentially eligible records from a search of reviews, systematic reviews, and meta-analyses were identified (Fig. 1). After deletion of duplicate records, 1,020 records

Fig. 1. Literature search and screening process.

Table 1. Characteristics of included randomized clinical trials

Study name	Country conducted	Sample size		Age, years		Male, n (%)		APACHE score ^{†‡}	
		fresh/ short-term	older/ long-term/ standard	fresh/ short-term	older/ long-term/ standard	fresh/ short-term	older/ long-term/ standard	fresh/ short-term	older/ long-term/ standard
Aubron, 2011	Australia	25	26	62±19	66±19	20 (80)	12 (46)	67.1±30.1 [‡]	55.3±18.3 [‡]
Cooper, 2017	Australia, New Zealand, Ireland, Finland, Saudi Arabia	2,457	2,462	62.5±16.8	61.4±17.3	1,311 (53.4)	1,258 (51.1)	72.6±29.2 [‡]	73.2±29.6 [‡]
Hebert, 2005	Canada	26	31	68.3±8.5	63.3 ±15.3	15 (58)	15 (48)	/	/
Heddle, 2012	Canada	309	601	72 (60–78)	70 (59–78)	171 (55.3)	327 (54.4)	/	/
Kor, 2012	USA	50	50	65 (47–73)	65 (52–72)	28 (56)	29 (58)	82 (64–108) [‡]	82 (71–112) [‡]
Lacroix, 2015	Canada and Europe	1,211	1,219	61.3±16.7	61±16.7	682 (56.6)	643 (53.3)	21.9±7.7 [†]	21.6±7.6 [†]
Methods		Interventions (fresh/short-term vs. older/long-term/standard stored blood)							
Aubron, 2011	Multicenter, feasibility pilot, ICU admitted, critically ill patients	Randomized to fresher blood (freshest available) vs. older stored blood (oldest available), units were leukocyte-reduced							
Cooper, 2017	Multicenter, critically ill, ICU patients in 59 hospitals	Randomized to either the freshest available or the oldest available, leukocyte-reduced							
Hebert, 2005	Multicenter, pilot study of patients admitted to ICU at 1 of 4 Canadian hospitals	Randomized to either RBCs stored for <8 days or standard issue RBCs based on standard blood bank procedure, leukocyte-reduced							
Heddle, 2012	Single-center pilot trial, consecutive patients admitted to an academic acute care hospital	Randomized to either the freshest available or standard issue, leukocyte-reduced							
Kor, 2012	Single-center, medical or surgical patients admitted to an ICU at Mayo clinic	Randomized to either fresh arm (blood ≤5 days of storage) or standard issue, leukocyte-reduced							
Lacroix, 2015	Multicenter, critically ill, ICU patients in 64 hospitals	Randomized to RBC units stored for ≤8 days or to RBC units that were standard issue, units were leukocyte-reduced							

[†] Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating a higher risk of death. [‡] APACHE III scores range from 0 to 299, with higher scores indicating a higher probability of death.

remained. Among them, titles and abstracts were screened for inclusion. A total of 72 records were read and nine systematic reviews or meta-analyses met the inclusion criteria. A total of 63 records were excluded for including a traditional (not systematic) review, guideline, or recommendation, an unrelated topic, cohort studies, and a consensus, statement, or study protocol of a systematic review. Finally, four studies that compared fresh or short-term versus older, long-term, or standard RBC transfusion in ICU patients were included in the study. Additional searches of published RCTs identified 5,449 records. Fifty-four records that were considered appeared to meet the inclusion criteria and the full text was reviewed. However, 51 RCTs were excluded because of a meeting abstract, study protocol or design, pilot study, secondary study, systematic review or meta-analysis, subjects not being critically ill adults, or the study aim being inconsistent with our study. Finally, three RCTs were included in the study. A total of six trials of seven studies were included in the final analysis [19–21, 24–26], and one study was duplicate.

Table 1 shows the baseline characteristics of these trials. The six studies involved 8,467 critically ill adults. Among them, 4,078 patients were assigned to receive fresh or short-term RBCs and 4,389 patients were transfused with older, long-term, or standard RBCs. Three studies were pilot trials of RCTs [24–26]. The mean age of patients in the six trials was more than 60 years. Among the available data of the APACHE score in four studies, three studies showed an APACHE III score [19, 20, 25] and one showed an APACHE II score [21]. All of these studies showed higher scores and a higher risk of death in these patients. Treatment and control group interven-

tions are also shown in Table 1. The definition of fresh and standard RBCs varied among the studies. The six trials included in this study all compared fresh and standard blood transfusions. We considered that standard, older, and long-term blood were the same because the blood bank delivers the oldest blood, namely standard RBCs, according to the “oldest unit, first out” policy without special requirements [9].

Mortality

Mortality was the only variable in our study (Fig. 2). In-ICU mortality occurred in 328 of 1,240 (26.5%) patients who received fresh transfusion and in 297 of 1,248 (23.8%) patients who received standard RBCs (RR 1.11, 95% CI 0.97, 1.27, $p = 0.14$, $I^2 = 0\%$). A total of 413 of 1,263 (32.7%) patients with transfusion of fresh blood and 391 of 1,268 (30.8%) patients with transfusion of older blood died in hospital (RR 1.06, 95% CI 0.94, 1.19, $p = 0.34$, $I^2 = 10\%$). Twenty-eight/30-day mortality occurred in 869 of 3,747 (26.5%) patients in the fresh arm and in 841 of 3,768 (23.8%) in the standard arm (RR 1.04, 95% CI 0.96, 1.13, $p = 0.36$, $I^2 = 0\%$). Ninety-day mortality was 28.8% in the fresh arm (1,063/3,694) and 27.7% in the standard arm (1,028/3,712) (RR 1.04, 95% CI 0.97, 1.12, $p = 0.30$, $I^2 = 0\%$). These findings showed that there were no significant differences in in-ICU, in-hospital, 28/30-day, and 90-day mortality among the types of transfusion.

Risk of Bias

Figure 3 shows an evaluation of the risk of bias. All of the trials were randomized and double-blind. The six included studies described an explicit generation process of a random sequence and the methods that were

Fig 2-1 Fresh/Shortterm Blood vs Older/Longterm/Standard Blood for ICU-mortality

Fig 2-2 Fresh/Shortterm Blood vs Older/Longterm/Standard Blood for in-hospital mortality

Fig 2-3 Fresh/Shortterm Blood vs Older/Longterm/Standard Blood for 28/30-day mortality

Fig 2-4 Fresh/Shortterm Blood vs Older/Longterm/Standard Blood for 90-day mortality

Fig. 2. Fresh/short-term blood versus older/long-term/standard blood for ICU mortality, in-hospital mortality, 28/30-day mortality, and 90-day mortality.

Fig 3-1. Risk of bias graph.

According to the review authors' judgements about each risk of bias item presented as percentages across all included studies

Fig 3-2. Risk of bias summary

According to the review authors' judgements about each risk of bias item for each included study

Fig. 3. Risk of bias graph and summary.

applied to allocation concealment. We did not report publication bias because the number of trials was less than 10. All of the trials were estimated to have a low risk of bias.

Discussion

This meta-analysis produced point estimates that were negative in the six trials on mortality of patients with transfusion of fresh or short-term and older, long-term, or standard RBCs in critically ill patients. This con-

clusion is consistent with previous reports. Fergusson and colleagues [27] showed that fresh blood transfusion did not improve the mortality rate compared with standard blood transfusion in critically ill premature infants. Karam and colleagues [28] investigated critically ill children who received old RBCs compared with those who received fresh RBCs. They found no significant difference in the mortality rate (6.3% vs. 4.3%, $p = 0.6$). The CIs around the estimate of mortality were too wide in the six studies to provide valid power to detect a statistical difference. Our study only focused on critically ill adults, regardless of the categories of diseases, and mortality is

the unique measurement. Our study suggests that fresh or short-term RBC transfusion does not reduce mortality compared with older, long-term, or standard RBCs transfusion in critically ill adults. Accordingly, we support the current blood transfusion strategy in critically ill patients.

Strengths of Our Meta-Analysis

Our meta-analysis has three main strengths. First, all of the eligible studies were RCTs and only a single variable (mortality) was selected and used in the meta-analysis. To a certain extent, our analysis precluded confounding factors from other variables. Second, our target population mainly focused on critically ill adults. Therefore, our results had a certain reference value for blood transfusion in the ICU. Finally, the variable of mortality is easy to measure during follow-up in patients after fresh or standard blood transfusion. This decreases the risk of dropout from an RCT.

Limitations of Our Meta-Analysis

This meta-analysis had four main limitations. First, the sample size of mortality in RCTs that compared fresh or short-term RBC transfusion with older, long-term, or standard RBCs transfusion was relatively small. Therefore, the statistical power of the results was limited. Second, the definition of fresh and standard RBCs was not uniform in the six studies. Investigators adopted various cutoff points to define fresh and standard blood that would have affected the conclusions reached. Third, the quality of the RCTs (including random sequence generation, allocation concealment, blinding of participants/personnel/outcome assessment) was suboptimal. Fourth, the target population in our meta-analysis was critically ill adults, and we excluded infants in the ICU and hospitalized patients.

Generalizability of Our Results

Although our meta-analysis has the limitations mentioned above, our results indicate that the age of RBCs does not affect mortality after transfusion in critically ill adults.

Conclusions

The study concluded that age of red cells for transfusion did not affect the outcomes in critically ill patients.

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Statement of Ethics

Review and consent of the ethics committee were not required for the research due to the fact that the participants came from the published studies. Informed consent of included patients was not needed for publication due to the fact that this research is a meta-analysis of RCTs. In the study, the data were available due to the fact that all of them came from the published RCTs.

Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

Wei Zhang had full access to all of the data in the present study and accepts responsibility for data management and the accuracy of data analyses. Study concept and design: Wei Zhang and Kun Yu. Acquisition, analyses, and interpretation of data: Wei Zhang, Kun Yu, and Ni Chen. Drafting of the manuscript: Wei Zhang and Kun Yu. Critical revision of the manuscript for important intellectual content: Wei Zhang and Miao Chen. Administrative, technical, or material support: Wei Zhang and Ni Chen. Study supervision: Wei Zhang and Miao Chen. All authors agreed to submission of the final version of the manuscript. Wei Zhang is the study guarantor.

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