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SYSTEMATIC REVIEW

Effects of shorter versus longer storage time of transfused red blood cells in adult ICU patients: a systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Purpose: Patients in the intensive care unit (ICU) are often transfused with red blood cells (RBC). During storage, the RBCs and storage medium undergo changes, which may have clinical consequences. Several trials now have assessed these consequences, and we reviewed the present evidence on the effects of shorter versus longer storage time of transfused RBCs on outcomes in ICU patients.

Methods: We conducted a systematic review with meta-analyses and trial sequential analyses (TSA) of randomised clinical trials including adult ICU patients transfused with fresher versus older or standard issue blood.

Results: We included seven trials with a total of 18,283 randomised ICU patients; two trials of 7504 patients were judged to have low risk of bias. We observed no effects of fresher versus older blood on death (relative risk 1.04, 95% confidence interval (CI) 0.97–1.11; 7349 patients; TSA-adjusted CI 0.93–1.15), adverse events (1.26, 0.76–2.09; 7332 patients; TSA-adjusted CI 0.16–9.87) or post-transfusion infections (1.07, 0.96–1.20; 7332 patients; TSA-adjusted CI 0.90–1.27). The results were unchanged by including trials with high risk of bias. TSA confirmed the results and the required information size was reached for mortality for a relative risk change of 20%.

Conclusions: We may be able to reject a clinically meaningful effect of RBC storage time on mortality in transfused adult ICU patients as our trial sequential analyses reject a 10% relative risk change in death when comparing fresher versus older blood for transfusion.

Keywords: Blood transfusion, Erythrocyte transfusion, Blood preservation, Storage, Intensive care unit and critical care

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Introduction

Patients in the intensive care unit (ICU) are often anaemic and 37–44% are transfused with red blood cells (RBCs) during their ICU admission [1, 2]; higher rates may be observed in ICU subpopulations (e.g. patients with sepsis and septic shock [3]).

Storage of red blood cell units

Donated whole blood is separated into blood products, namely cells (containing erythrocytes and a few leukocytes), plasma and platelets. The blood cells are suspended in a preservative solution and stored for a maximum of 35–42 days, depending on national regulations. The maximum storage time is defined by the in vitro amount of haemolytic cells (aim < 0.8–1%) and surviving donated RBCs after 24 h in the recipient (aim > 75%) [4]. It is common practice to use older units first, in order to avoid waste [5, 6], and the mean storage time for the overall RBC used in Europe and USA is 16 and 23 days, respectively [7, 8].

Adverse effects of RBC transfusion

When blood is stored, ex vivo rheological and biochemical changes occur. These changes are uniformly referred to as the "storage lesion" [9], which gradually develops with increasing storage time [10, 11]. The RBC becomes more fragile, and leakage and haemolysis occur more frequently, which leads to free iron, potassium, cytokines and increasing acidosis of the storage medium. The stored RBCs change in shape and become less deformable [10], and their gas transport ability changes during storage [12]. Finally, blood flow is affected by storage, because of an increased number of RBCs adhering to the endothelium [13] and inhibition of nitric oxide (NO)-mediated vasodilation [14].

Patients in the ICU may be particularly susceptible to the deleterious effects of the storage lesion, because the pro-inflammatory response of critical illness may be enhanced, and impaired microcirculatory blood flow may be further affected by transfusion of stored RBCs, resulting in tissue hypoxia and organ failure [15]. Therefore, we conducted a systematic review with meta-analysis and Trial Sequential Analysis (TSA) to investigate if transfusion with fresher blood compared with that of older blood would improve patient-centred outcome measures in adult ICU patients.

Methods

This systematic review was conducted according to the protocol which was registered in PROSPERO database (CRD42017065366) and published [16]. We followed the recommendations by the Cochrane Collaboration [17], the preferred reporting items for systematic review and meta-analysis (PRISMA) statement [18], and the grading of recommendations assessment, development, and evaluation (GRADE) guidelines [19].

Take-home message

We observed no effect of RBC storage time on mortality in transfused adult ICU patients and we may reject a 10 percent relative risk reduction of death when comparing fresher versus older blood for transfusion.

Eligibility criteria

Only randomised clinical trials (RCTs) were included in the meta-analyses, but observational studies including more than 500 transfused patients were included for possible detection of rare serious adverse events. We included studies comparing groups of adults admitted to an ICU and treated with RBC transfusions of different storage time. The ICU patients could be either the primary patient population or a predefined subgroup in the trials. Comparator group patients were required to be transfused with RBCs of longer storage time than the intervention group. We included all definitions of fresher and older (or standard-issue) RBCs.

Search strategy

We did not restrict the search by language, date, publication status or any other study characteristics. The following electronic databases were searched by one review contributor (SLK): Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Embase Ovid, MEDLINE Ovid, Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index–Science (CPCI-S), BIOSIS and CINAHL. The search strategies are published in the protocol [16].

We manually identified other potentially eligible trials by using the reference lists of the included studies, other relevant systematic reviews, and searched the trial registries. The last search date was 12 September 2017.

Selection of studies

Two review authors (SLR, ABJ) independently selected studies from the systematic search by title and abstract. All trials that fulfilled the eligibility criteria were investigated in full text.

Data extraction and management

Two review authors (SLR, ABJ) independently extracted data from the included studies [standard data extraction forms in the electronic supplementary material (ESM)].

In case of duplicate, companion publications or multiple reports of a primary study, we used the most complete dataset combined across all known publications.

Outcomes

Predefined primary outcomes were all-cause mortality and the proportion of patients with one or more severe adverse events, as defined by International Conference on Harmonisation (ICH) guidelines [20]. Secondary outcomes were health-related quality of life, proportion of patients with post-transfusion infections occurring after randomisation, proportion of patients with renal failure, proportion of patients with thromboembolic events and economic and blood stock inventory outcomes, all as defined in the included trials. Outcomes were primarily assessed at day 90, or at the time point closest to day 90.

Risk of bias assessment

Two review authors (SLR, MBM) assessed the risk of bias for each included trial separately using the Cochrane Collaboration's tool for assessment of risk of bias [17, 21] including the following domains: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of patients and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), vested financial interest, other bias risk and overall risk of bias. In addition, we assessed the domains 'Blinding of outcome assessment', 'Incomplete outcome data' and 'Selective outcome reporting' for each outcome. On the basis of this assessment, the included trials and each outcome result were defined as low risk of bias if all bias domains were judged as low risk of bias. In regards to blinding, we judged trials to be of low risk of bias if both the patients and clinical personnel were blinded, and we accepted that the blood bank personnel and clinical personnel who were not involved in the treatment of the patient were not blinded, because of necessary safety procedures related to RBC transfusions.

We judged trials to be at 'overall high risk of bias' if they were assessed as having uncertain or high risk of bias in one or more of the above domains.

Grading quality of evidence

In accordance with the GRADE approach [19], we assessed the overall quality of evidence for each outcome measure. We evaluated the quality of evidence and our confidence in the effect estimates on the basis of trial design, quality, consistency and directness. Additionally imprecision and high risk of reporting bias were contributing factors in the quality assessment. Accordingly, we rated the overall quality of evidence as "high", "moderate", "low" or "very low".

Statistical analysis

We calculated the summary estimates using Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and TSA program version 0.9 beta (www.ctu.dk/tsa) [22]. We used a P value of $0.05/[(2 + 1)/2] = 0.033$ or less as statistically significant in the analyses of the primary outcomes [23, 24], and we used a P value of $0.05/[(5 + 1)/2] = 0.017$ or less as statistically significant in the analyses of the secondary outcomes [23].

Dealing with missing data

We used the results of the analyses in the intention-to-treat populations of the trials and tried to obtain missing outcome data from the authors. If trials had non-obtainable missing outcome data, we performed sensitivity analyses using imputations of missing outcome data in best worst-case and worst best-case scenarios.

Assessment of heterogeneity

We identified statistical heterogeneity by inspecting the Forest plots and the estimates of the diversity (D^2) [25] and inconsistency (I^2) statistics. D^2 is a different heterogeneity measure than I^2 and accounts for the total relative reduction in variance, when changing the model from random-effects model to fixed-effects model [25]. In this way, D^2 can adjust for the required increase in information size due to heterogeneity. In case of substantial clinical, methodological and statistical heterogeneity, we would not report the results as pooled effect estimates in a meta-analysis. If $I^2 = 0$, we would use and report a fixed-effects model [26, 27], and if $I^2 > 0$, we would use and report both a fixed- and random-effects model [26, 28, 29]. If the intervention effects differed in the two models, we would emphasize the most conservative estimate (point estimate closest to the null effect), and if the intervention effects were approximately equal in the two models, we would emphasize the result with the widest confidence interval [23].

Subgroup analyses

We planned to report a subgroup analysis of trials with overall low risk of bias versus overall high or unclear risk of bias, and to compare estimates of the pooled intervention effect in subpopulations.

Trial Sequential Analysis

Because cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing

of accumulating data [22, 30–32], we used TSA [33] to assess this risk. The calculated required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction (RRR) and the anticipated heterogeneity variance (D^2) [34] of the meta-analysis [25]. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size [22, 31, 35].

We used a family-wise error rate (FWER) of 5% [23] leading to a statistical significance level of 3.3% for each of the two co-primary outcomes and 1.7% for the anticipated five co-secondary outcomes, a beta of 20%, and a D^2 [25] suggested by the trials in the meta-analysis [23] or a D^2 of 20% if the actual measured heterogeneity was in fact zero because in this case heterogeneity would most likely increase when further trials are added until the required information size is reached [36]. As anticipated intervention effects for the primary and secondary outcomes in the TSA we used a realistic a priori RRRs or relative risk increases (RRIs) of 20%. Furthermore, we planned to use an RRI based on the confidence limits (CL) in the traditional naïve meta-analysis. We present naïve 95% CLs and CIs adjusted for multiplicity of outcomes as well as sparse data called TSA-adjusted CIs for all estimates.

For a more detailed description of the statistical analysis plan and TSA, see the published protocol [16].

Results

Selection of studies

We identified 1705 records and assessed 25 full-text articles of these for eligibility. We included seven RCTs [37–43], six observational studies [44–49] and finally two publications of additional post hoc subgroup analyses [50, 51] and one publication of predefined secondary outcomes of one of the RCTs [52] (Fig. S1, ESM). Studies were all published in English, except for one observational study published in French [44], and all studies were published between February 2004 and October 2017. The seven RCTs included a total of 18,283 ICU patients. We excluded nine records; their details are provided in the ESM.

Characteristics of the included RCTs

Three of the included trials were multicentre trials (from 6 to 64 centres), randomising from 2510 to 10,578 ICU patients [41–43]. Four were single-centre trials randomising 20 to 100 ICU patients [37–40]. In one trial, the ICU population was a predefined subgroup of the trial population comprising 51% of the population in that trial [42]. Authors of all the trials were contacted and six responded. No missing data or additional data on outcomes of interest were available. Details regarding the included RCTs are presented in Table 1 and in the ESM.

Description of the intervention

In all trials, patients received allogenic red blood cells; and, except in one trial ($n = 20$) [40], all RBC units were leukocyte reduced. The preservative solution was saline with adenine, glucose and mannitol (SAGM) for five trials [37, 38, 41–43], and two trials did not apply information on the storage medium [39, 40]. The intervention was defined by a maximum RBC unit age in four trials [37, 39–41], ranging from 6 to 10 days. In the remaining three trials, they defined intervention as the freshest available RBC unit [38, 42, 43]. In all but two trials, the comparator was standard of care, which was equivalent to the oldest available RBC unit [38, 39, 41–43]. In the remaining two trials, the comparator was defined as an age of more than 15 and 19 days, respectively [37, 40].

The observed storage time of blood in the intervention groups in the trials varied from a median of 2 days to a mean of 12 days; in the comparator groups, the observed storage time was from a median of 21 days to a median of 28 days. The process variables from the included trials are presented in the ESM.

Risk of bias assessment

Two trials were judged as overall low risk of bias [41, 43] (Fig. 1); the remaining five trials were judged as having overall high risk of bias [37–40, 42]. Regarding blinding, four trials concealed the collection and expiration dates on the RBC unit [37, 38, 41, 43], two trials did not conceal the information on the RBC unit [39, 42] and one trial did not apply information on RBC unit concealment [40] (Table S10 in the ESM). Risk of bias assessment for each trial is provided in the ESM.

Outcomes

Mortality

Five trials reported mortality [38, 39, 41–43], and three of the trials had mortality as the primary outcome [41–43]. Three trials reported in-hospital mortality [38, 39, 42], two trials reported 90-day mortality [41, 43] and one trial followed the patients for vital status at day 180 [43].

In the two trials having overall low risk of bias, the ABLE trial and TRANSFUSE trial, randomising a total of 7504 patients, 7349 patients were included in the analysis of all-cause mortality; the relative risk of death at day 90 was 1.04 (95% CI 0.97–1.11; $P = 0.32$; $I^2 = 0\%$) for transfusion of fresher versus older RBC units [41, 43] (Fig. S3, ESM). The TSA-adjusted CI was 0.93–1.15 with the cumulative Z-curve reaching the futility area for an RRI of 10% (Fig. 2). The GRADE quality was judged to be high (Table 2).

Table 1 Characteristics of the included trials

Study	Country	Inclusion period	No. of patients/no. of trial sites	Clinical setting	Eligibility criteria	RBCs: type/suspension/leukocyte reduced	Transfusion guidelines/duration of intervention	Intervention and comparison: storage time of RBC unit
Aubron [38]	Australia	September 2010–January 2011	52/2	General ICUs	Patients aged ≥ 18 years; prescribed at least one RBC unit	Allogen/SAGM/leukocyte reduced	At discretion of the clinician/until ICU discharge	Intervention: freshest RBC unit Comparator: standard issue[a]
Cooper [43]	Australia/Finland/Ireland/New Zealand/Saudi Arabia	October 2012–December 2016	4994/59	General ICUs	Patients aged ≥ 18 years hospitalised in ICU with an anticipated stay of at least 24 h; decision to transfuse at least one RBC unit	Allogen/SAGM/leukocyte reduced	At discretion of the clinician/during the index hospital stay	Intervention: freshest RBC unit Comparator: oldest RBC unit
Damiani [40]	Italy	February 2011–February 2012	20/1	General ICU	Patients aged ≥ 18 years with sepsis, severe sepsis or septic shock as diagnosed according to standard criteria and requiring blood transfusion	Allogen/NA/not leukocyte reduced	≤ 8 g/dl or as indicated by the attending physician/NA	Intervention: < 10 days Comparator: > 15 days
Heddle [42]	Australia/Canada/Israel/USA	April 2012–October 2015	10,578 in the ICU subgroup/6	All hospitalised patients	Hospitalised patients; ≥ 18 years; requiring at least one RBC unit	Allogen/SAGM[b]/leukocyte reduced[b]	According national guidelines/throughout the initial admission and any subsequent admissions during the study period. Minimum follow-up time of 30 days	Intervention: freshest RBC unit Comparator: oldest RBC unit
Kor [39]	USA	June 2008–May 2010	100/1	General ICU	Patients aged ≥ 18 years; ET and MV; arterial catheter in situ; an order for RBC transfusion	Allogen/NA/leukocyte reduced	At discretion of the clinician but not above 9.5 g/dl/the first RBC transfusion after randomisation	Intervention: ≤ 5 days Comparator: standard issue[a]

Table 1 continued

Study	Country	Inclusion period	No. of patients/no. of trial sites	Clinical setting	Eligibility criteria	RBCs: type/suspension/leukocyte reduced	Transfusion guidelines/duration of intervention	Intervention and comparison: storage time of RBC unit
Lacroix [41]	Belgium/Canada/France/Netherlands/UK	March 2009–May 2014	2510/64	General ICUs	Patients aged ≥ 18 years; first RBC transfusion prescribed within 7 days after ICU admission; MV expected for ≥ 48 h	Allogen/SAGM/leukocyte reduced	At discretion of the clinician/until hospital discharge or 90 days after randomisation	Intervention: < 8 days Comparator: Standard issue[a]
Walsh [37]	Scotland	November 1999–December 2000	29/1	General ICU	Patients aged > 16 years; planning of transfusion of 2 RBC units with no sign of bleeding; haemoglobin level ≤ 9 g/dl; no RBC transfusion 48 h prior to inclusion	Allogen/SAGM/leukocyte reduced	NA/10.5 h (one transfusion episode of 2 RBC units)	Intervention: ≤ 5 days Comparator: ≥ 20 days

ET endotracheal tube, *ICU* intensive care unit, *IQR* interquartile range, *MV* mechanical ventilation, *NA* not available, *RBC* red blood cell, *SAGM* saline, adenine, glucose and mannitol

[a] For all studies, standard issue was the oldest compatible blood unit available

[b] According to the trial protocol, information from the Israeli site was not available

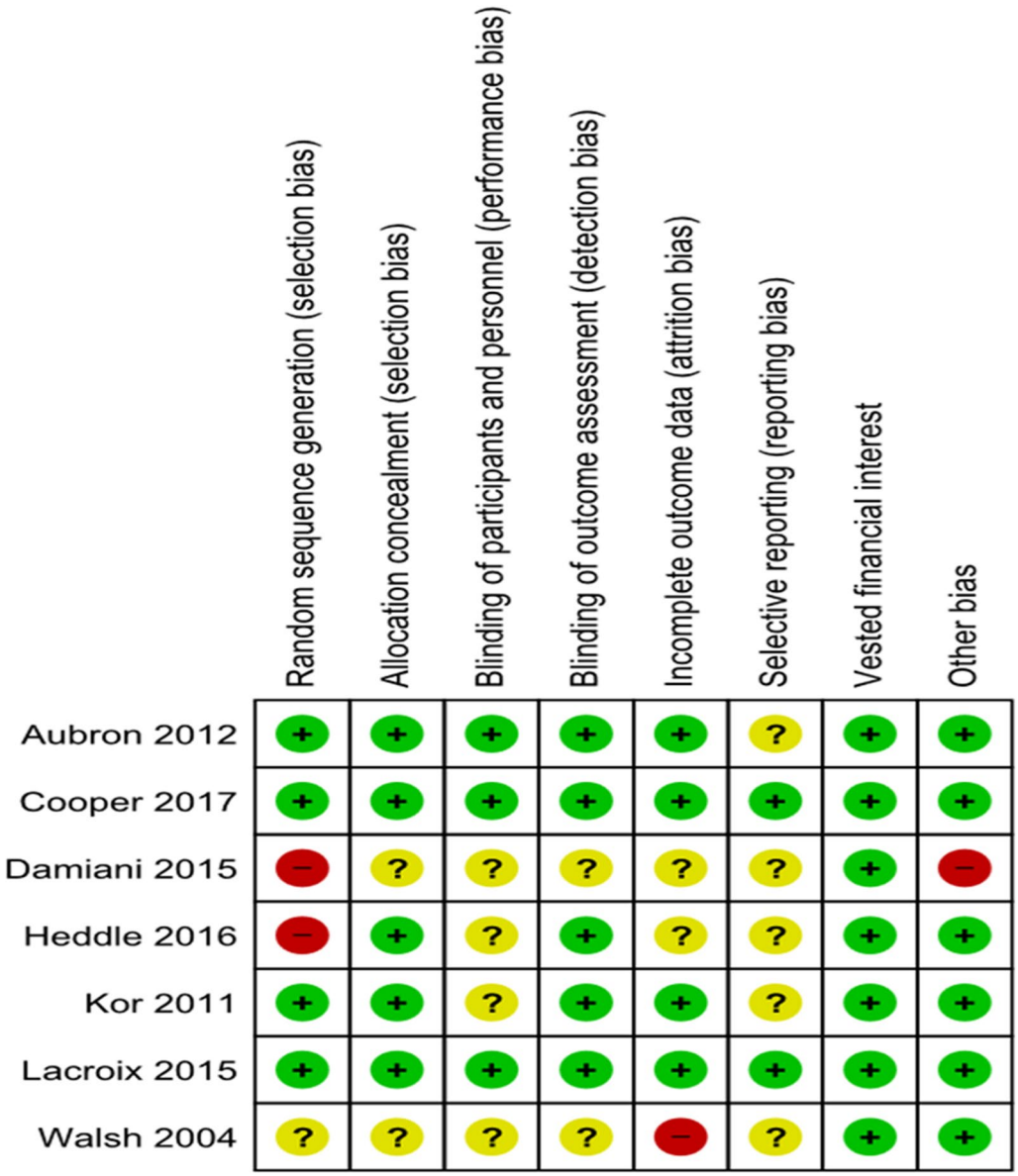

Fig. 1 Risk of bias summary for all included trials

In the five trials reporting mortality of 18,077 patients independent of overall risk of bias, fresher versus older RBC units did not affect the relative risk of death (1.04, 95% CI 0.98–1.10; $P = 0.25$; $I^2 = 0\%$) (Fig. S4, ESM) [38, 39, 41–43]. The TSA-adjusted CI was 0.96–1.11 and again with the cumulative Z-curve crossing the boundary for futility for an RRI of 10% (Fig. 3). The GRADE quality was judged to be moderate and downgraded because of bias risk (Table 2). We could not detect a bias effect in the subgroup analysis of trials with low risk of bias compared to trials with high risk of bias (Fig. 4).

The sensitivity analyses showing the range of uncertainty of the effect estimate due to losses to follow-up showed an effect estimate for the relative risk of death of 0.99 (95% CI 0.93–1.05) for the best worst-case scenario and 1.08 (95% CI 1.02–1.15) for the worst best-case scenario (Figs. S9 and S10, ESM).

Severe adverse events

Two trials reported adverse transfusion events, the ABLE and TRANSFUSE trials [41, 43]. TRANSFUSE reported febrile non-haemolytic transfusion reactions (FNHTR)

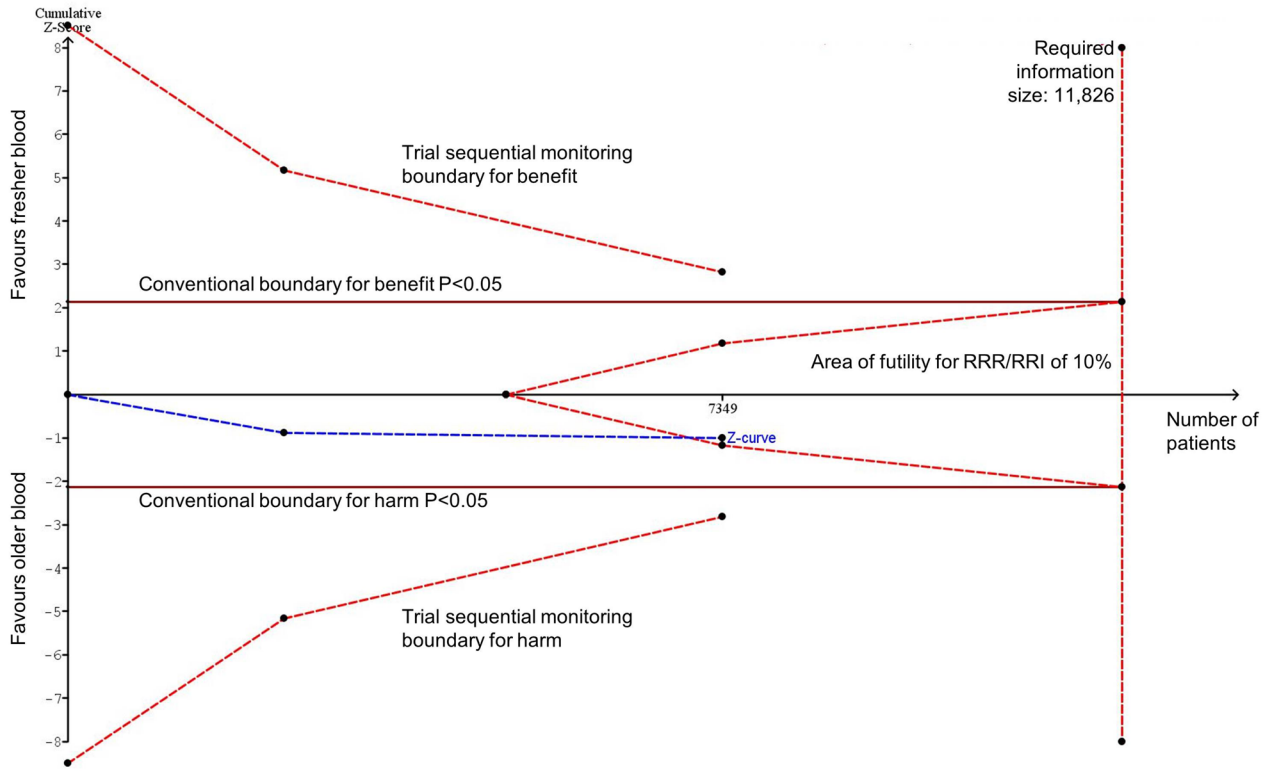

Fig. 2 Trial Sequential Analysis (TSA) of two trials with overall low risk of bias of the effect on mortality of fresher versus older blood. Control event proportion of 27.8%, diversity (D^2) of 20%, alpha of 3.3%, power of 80% and relative risk increase (RRI) of 10%. The anticipated RRI of 20% yielded a required information size (RIS) lower than the 7349 actually accrued, and we therefore used an anticipated RRI of 10%. Additionally we used a D^2 of 20%, projected in the protocol, as the actual D^2 was 0 and may be expected to increase if further trials are carried out. We used an adjusted maximal type 1 error risk (α) due to two co-primary outcomes. The relative risk (RR) was 1.04 with a naive 95% CI of 0.97–1.11 in a fixed-effect model and the TSA-adjusted CI 0.93–1.15. As the cumulative Z-curve (etched blue line) reaches the futility area we may exclude a 10% RRI. RRR relative risk reduction

[43] and ABLE reported acute transfusion reactions [41]. We did not consider FNHTR as being severe, but a mild reaction and an exclusion diagnosis, and acute transfusion reactions cover FNHTR, but also more severe reactions. Even though there was clinical heterogeneity between the outcome measures, we did pool the two outcome data for 7332 patients, and the relative risk of an adverse event was 1.26 (95% CI 0.76–2.09; $P = 0.36$; $I^2 = 21\%$) for transfusion of fresher versus older RBC units (Fig. S5, ESM). The TSA-adjusted CI was 0.16–9.87 (Fig. S6, ESM), and the GRADE quality was judged to be very low because of indirectness and imprecision (Table 2).

Post-transfusion infections

Both trials with overall low risk of bias reported infections after randomisation in 7332 patients and were included in the analysis of post-transfusion infections [41, 43]. In the ABLE trial, they reported all nosocomial infections, including nosocomial pneumonia, deep-tissue infections (peritonitis and mediastinitis) and bacteraemia; in the TRANSFUSE trial, they reported any new bloodstream infection in the ICU. The rate of infections did not differ statistically significantly between the fresher blood group and the older blood group (RR 1.08, 95% CI 0.96–1.20; $P = 0.23$; $I^2 = 0\%$) (Fig. S7, ESM) and the TSA-adjusted CI was 0.90–1.27 with the cumulative Z-curve reaching futility area for an RRI of 20% (Fig. S8, ESM). The GRADE quality was judged to be moderate because of indirectness (Table 2).

Renal failure

The TRANSFUSE trial reported the number of patients in renal replacement therapy (RRT) until day 28, and there was no statistically significant difference between the fresher and older blood group (RR 0.94 (95% CI 0.80–1.11); $P = 0.48$) [43]. In the ABLE trial, the number of days in supportive renal care (RRT) was reported

Table 2 Summary of findings including GRADE quality assessment of evidence

Outcome	Certainty assessment							No. of patients		Effect		Certainty	Importance
	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fresher blood group	Older blood group	Relative (95% CI)	Absolute (95% CI)		
Mortality (trials with low risk 6)	2	RCTs	Not serious	Not serious[a]	Not serious	Not serious[b]	None	1058/3668 (28.8%)	1024/3681 (27.8%)	RR 1.04 (0.97–1.11)	11 more per 1000 (from 8 fewer to 31 more)	⊕⊕⊕⊕ High	Critical
Mortality (all trials despite risk of bias)	5	RCTs	Serious[c]	Not serious[d]	Not serious	Not serious[e]	None	1552/7295 (21.3%)	1949/10,782 (18.1%)	RR 1.04 (0.98–1.10)	7 more per 1000 (from 4 fewer to 18 more)	⊕⊕⊕◯ Moderate	Critical
Post-transfusion infections	2	RCTs	Not serious	Not serious[f]	Serious[g]	Not serious[h]	None	446/3663 (12.2%)	417/3669 (11.4%)	RR 1.07 (0.96–1.20)	8 more per 1000(from 5 fewer to 23 more)	⊕⊕⊕◯ Moderate	Critical
Adverse events	2	RCTs	Not serious	Not serious[i]	Serious[j]	Very serious[k]	None	127/3663 (3.5%)	94/3669 (2.6%)	RR 1.26 (0.76–2.09)	7 more per 1000 (from 6 fewer to 28 more)	⊕◯◯◯ Very low	Critical

CI confidence interval, *RCT* randomised clinical trial, *RR* risk ratio, *RRI* relative risk increase, *TSA* Trial Sequential Analysis

[a] $I^2 = 0\%$, $P = 0.80$ for heterogeneity, overlap of confidence intervals

[b] TSA-adjusted CI 0.93–1.15. Z-curve reaching futility area for an RRI of 10%

[c] Three trials had overall unclear or high risk of bias in at least one bias domain

[d] $I^2 = 0\%$, $P = 0.42$ for heterogeneity, overlap of confidence intervals

[e] TSA-adjusted CI 0.96–1.11. Z-curve reaching futility area for an RRI of 10%

[f] $I^2 = 0\%$, $P = 0.63$ for heterogeneity, overlap of confidence intervals

[g] The two trials measured slightly different types of infections. One trial measured only the events of bloodstream infection, whereas the other trial measured a wider variety of infections

[h] TSA-adjusted CI 0.90–1.27. Z-curve reaching futility area for an RRI of 20%

[i] $I^2 = 21\%$, $P = 0.26$ for heterogeneity, overlap of confidence intervals

[j] The two trials assessed adverse event rates with different definitions of the adverse event

[k] Both trials had a very low event rate (0.5% and 0.04%, respectively). TSA-adjusted CI 0.16–9.87

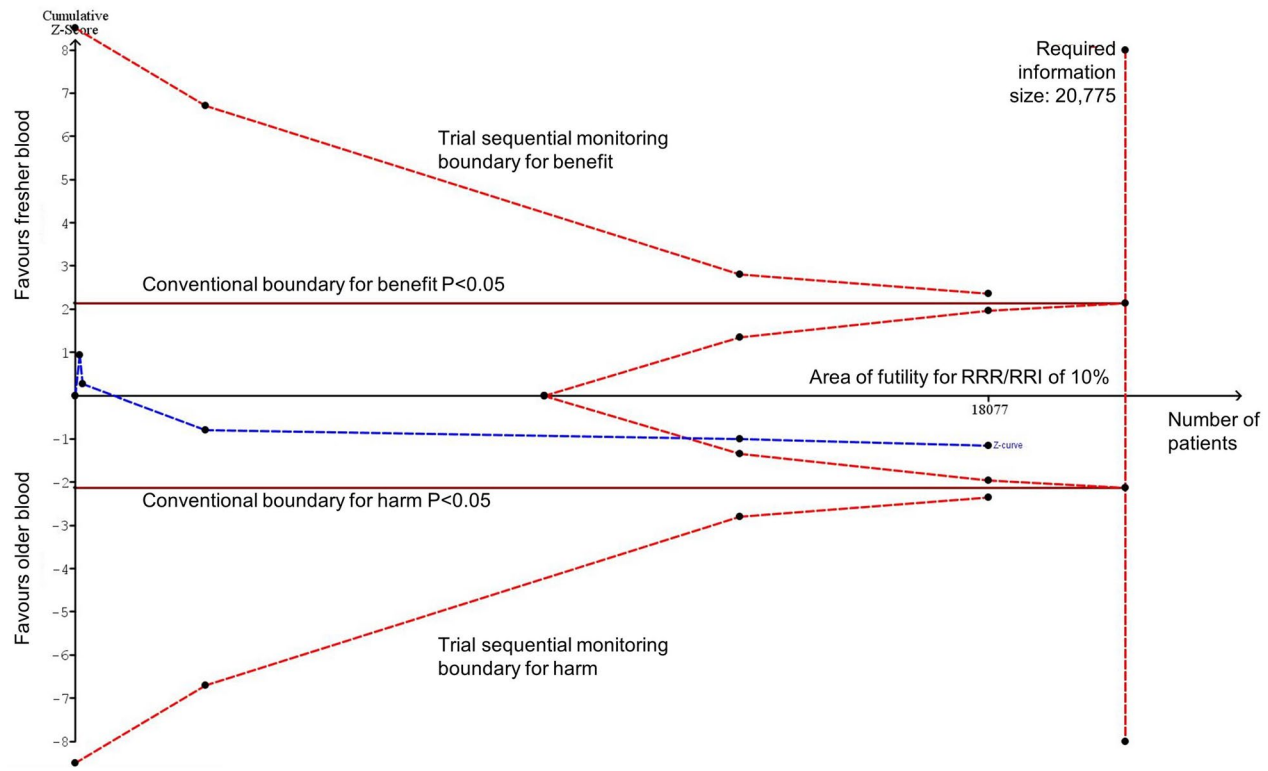

Fig. 3 Trial Sequential Analysis (TSA) of all trials of the effect on mortality of fresher versus older blood despite risk of bias. Control event proportion of 18.1%, diversity (D^2) of 20%, alpha of 3.3%, power of 80% and relative risk increase (RRI) of 10%. The anticipated RRI of 20% yielded a required information size (RIS) much lower than the 18,077 actually accrued; we therefore used an anticipated RRI of 10% similar to the upper limit of the naive 95% confidence limit, and additionally we used a D^2 of 20%, as projected in the protocol, as the actual D^2 was 0 and may be expected to increase if further trials are carried out. We used an adjusted maximal type 1 error risk (α) of 0.033 due to two co-primary outcomes. The relative risk (RR) was 1.04 with a naive 95% CI of 0.98–1.10 in a fixed-effect model and the TSA-adjusted CI 0.96–1.11. As the cumulative Z-curve (blue line) reaches the futility area we may exclude a 10% RRI. RRR relative risk reduction

as a secondary outcome, with no significant difference between the fresher and the older blood group (mean difference 0.2, 95% CI −0.6 to 0.9) [41].

Thromboembolic events

Only one trial reported thromboembolic events, and that reported no differences in the risk of cardiac ischaemia/infarction or deep-vein thrombosis/pulmonary embolism between the fresher and the older blood group (absolute risk difference of 0.8 and 0.0% points, respectively) [41].

Health-related quality of life and economic outcomes

A pre-planned cost-utility analysis of the UK cohort of the ABLE trial included an evaluation of health-related quality of life (HRQoL) using the EQ-5D-3L or EQ-5D-5L measurements and a cost-effectiveness analysis [52]. The results showed no statistically significant difference in HRQoL between the two groups at 6 and 12 months follow-up, and no statistically significant difference in healthcare costs between the fresher and the older blood group [52].

The TRANSFUSE trial planned to report HRQoL, using the EQ-5D questionnaire at day 180 follow-up, but this outcome is not reported in the primary publication, and is expected to be reported in a later publication [43].

Subgroup analyses

It was not possible to perform the predefined analyses of the intervention effect in subpopulations, as there were no outcome data for the predefined subgroups of patients. A post hoc analysis from the ABLE trial investigated the intervention effect in perioperative patients (excluding elective cardiovascular patients), comprising 13.3% of the trial patients [51]. There was no statistically significant difference in effect of fresher versus older blood for any outcomes [51]. The ABLE trial did pre-plan a subgroup analysis of the intervention effect in patients with sepsis/septic shock versus others, but this analysis awaits publication [53].

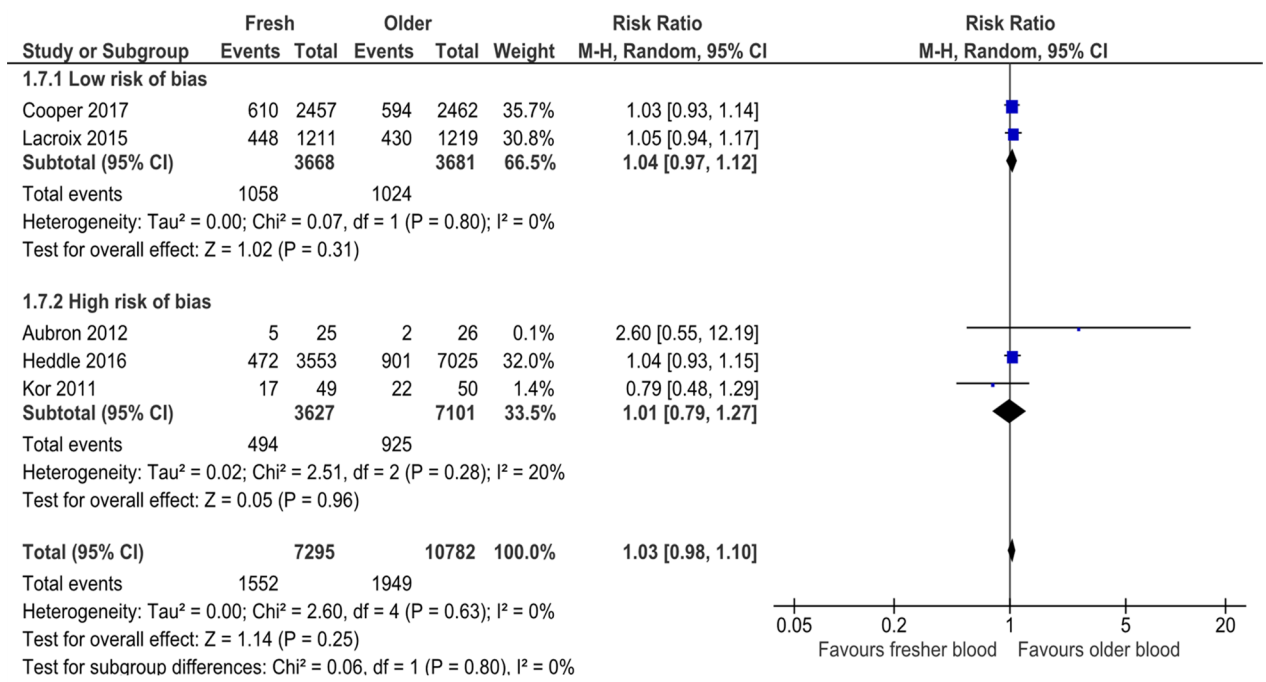

Fig. 4 Forest plot of mortality in trials with overall low risk of bias versus trials with overall high risk of bias. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals

Observational studies and adverse events

Among the six observational studies, none reported adverse events of transfusion separately, but all investigated the association of RBC storage time and mortality [44–49]. The characteristics and findings of the observational studies are presented in the ESM.

Discussion

We did not find any benefit of transfusing patients in the ICU with fresher blood versus older or standard issue blood. There were no statistically significant associations of RBC storage time with mortality or post-transfusion infections, though there may be more adverse transfusion reactions when using fresher blood as compared to standard issue, but these may be of mild character. The TSA of risk of all-cause mortality showed that the cumulative Z-curve crossed the non-inferiority boundaries after 62% of the required information size in the analysis with trials of overall low risk of bias and with 87% of the required information size in the analysis including all trials despite risk of bias. These results indicate that we now may have enough evidence to reject 10% relative risk increase/decrease or more of death when transfusing fresher versus older blood.

In the analysis of the risk of post-transfusion infections, the cumulative Z-curve reached the futility area with 67% of the required information size for an anticipated RRI of 20%. Hence, we can reject 20% relative risk increase/decrease or more of post-transfusion infections when transfusing fresher versus older blood.

The analysis of the risk of adverse events was inconclusive, as only 12% of the required information size was reached and none of the trial sequential monitoring boundaries were passed.

Other reviews and observational studies

To our knowledge, no previous systematic reviews with meta-analysis and TSA have focused on ICU patients, but other well-performed systematic reviews have focused on wider patient categories.

A Cochrane systematic review from 2015 included all types of patients with all ages, but since the data was sparse and there were clinical differences, differences in the interventions, outcome measures and methodological limitations, no meta-analysis was performed [54].

A recently published systematic review with meta-analysis included 14 trials with 26,374 hospitalised patients of all ages [55]. They found similar results to ours with a statistically insignificant higher risk of death at any time point in patients transfused with fresher blood compared to older blood (RR 1.04, 95% CI 0.98–1.12), with similar results for their secondary outcome of in-hospital mortality (reported in six trials) (RR 1.06, 95% CI 0.97–1.15).

In 2012 a systematic review with meta-analysis including both RCTs and observational studies was published [56], and this review was updated in 2016 [57]. They found similar results in the meta-analysis of five RCTs, with no statistically significant benefit or harm of fresher versus older blood (OR 1.03, 95% CI 0.72–1.47). They also performed a meta-analysis of 31 observational studies, and found a statistically significantly increased risk of death when transfusing older versus fresher blood (OR 1.13, 95% CI 1.03–1.24)—a result completely opposite to that of the meta-analysis of RCTs.

The diverging results of RCTs and observational studies are similar to the findings of our search including large observational studies in the ICU. Among the six observational studies, four studies found an association of RBC storage time and adverse clinical outcomes (complicated sepsis and hospital mortality), but no association with other outcomes (severe kidney failure and 90-day mortality). Two recently published very large observational studies among hospitalised patients and perioperative patients found results more alike the meta-analysis of this review [58, 59]. The earlier observational studies (those included in our search) did not use or did not exclusively use leukocyte reduced RBC units, which might be an explanation for the divergent results. However, the major reason for the differing results of the observational studies and the RCTs is probably the impact of confounding by indication.

Strengths and limitations of this review

The major strength in our review is the strict methodology; we followed the recommendations of the Cochrane Collaboration and PRISMA statement, including a pre-published protocol, an up-to-date literature search and independent study selection, data extraction and risk of bias assessment by at least two review authors. We also included GRADE evaluations of quality of evidence on important outcomes, and we used the TSA to evaluate the overall risk of random error to increase the reliability of the meta-analyses results and to identify the required information size.

A limitation of the results from our review is the presence of clinical differences between trials. To limit the clinical heterogeneity and to obtain clinically applicable results we only included trials with adult ICU patients; however, there still were some important differences between the study populations. Among the three largest trials, the frequency of the primary outcome differed: one trial reported hospital mortality, with a mortality rate of 13% [42], and the two others reported 90-day mortality, with a mortality rate of 36% and 24%, respectively [41, 43]. The number of RBC units transfused per patient varied between trials, but not within trial groups, and the intervention and comparator groups from the included trials did not overlap regarding the age of RBC units. Despite successful separation of RBC age in the trial groups, we still have no clear answers regarding the effect of very fresh (e.g. less than 7 days old) or very old (e.g. more than 21 days old) blood, as a result of the pragmatic design of the largest trials, but there is no evidence suggesting a different effect estimate when comparing exclusively fresh versus exclusively older blood [60].

Bias in the included trials and losses to follow-up are other limitations of this review. To account for these limitations, we performed a subgroup analysis comparing trials with overall low risk of bias with trials with overall high risk of bias, and we did not find any bias effect. Even though we are confident in the results of all trials despite risk of bias, we cannot exclude a biased effect estimate in the trials of overall high risk of bias; hence the quality of evidence for all trials estimates was downgraded. We also performed a sensitivity analysis to investigate the effect of losses to follow-up and found that the point estimate of the risk of death neither overlapped the TSA-adjusted nor the 95% CI, and the potential effect of the losses to follow-up is therefore small. Finally, limited data on the predefined secondary outcomes made it impossible to perform meta-analyses on all outcomes of interest for this review, and the subgroup analyses planned were not possible.

Conclusions

The effect of RBC storage time on outcomes of ICU patients has now been investigated in large, high quality RCTs. In the conventional meta-analyses, fresher versus older blood was not associated with the risk of death, adverse events or post-transfusion infections. The required information size was reached for both mortality and post-transfusion infections, and we may reject a more than 10% relative risk increase or reduction of death and a 20% relative risk increase or reduction of post-transfusion infections when comparing fresher versus older or standard issue blood for transfusion in adult ICU patients.

These results may positively impact the reduction of waste in blood banks, as the current practice of using the oldest available RBC unit for transfusion can be practised safely in patients in the ICU.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5069-0) contains supplementary material, which is available to authorized users.

Abbreviations

CI: confidence interval; CL: confidence limits; ESM: electronic supplementary material; FNHTR: febrile non-haemolytic transfusion reactions; FWER: family-wise error rate; GRADE: grading of recommendations, assessment, development and evaluation; HRQoL: health-related quality of life; ICU: intensive care unit; ICH: International Conference on Harmonisation; NO: nitric oxide;

PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; PROSPERO: international prospective register of systematic reviews; RBC: red blood cell; RCT: randomised clinical trial; RR: relative risk; RRI: relative risk increase; RRR: relative risk reduction; RRT: renal replacement therapy; SAE: serious adverse event; TSA: Trial Sequential Analysis.

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Author contributions
SLR, AP and JW contributed to the conception of the study protocol. The manuscript was drafted by SLR and JW and was critically revised by all other authors. All authors reviewed the manuscript and have approved the publication in this current form.

Compliance with ethical standards

Conflicts of interest
JW is a member of the task force at Copenhagen Trial Unit to develop theory and software for doing Trial Sequential Analysis which is presently freeware at www.ctu.dk/tsa. The Department of Intensive Care, Rigshospitalet receives support for research from CSL Behring, Fresenius Kabi and Ferring Pharmaceuticals. No other potential conflict of interest relevant to this manuscript was reported. SLR received funding from the Research Council at Copenhagen University Hospital Rigshospitalet. The funding parties were not involved in the conduct of this review.

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