Restrictive versus Liberal Blood Transfusion Strategy in Patients With Acute Myocardial Infarction: A Meta-Analysis of Randomized Clinical Trials

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Restrictive versus Liberal Blood Transfusion Strategy in Patients With Acute Myocardial Infarction: A Meta-Analysis of Randomized Clinical Trials

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Abstract

**Background:** A meta-analysis of observational studies comparing differences in outcomes between restrictive blood transfusion (RBT) and liberal blood transfusion (LBT) in patients with acute myocardial infarction (AMI) reported that LBT is associated with higher all-cause mortality. Few randomized clinical trials (RCTs) have compared RBT to LBT in patients with AMI and anemia, but no meta-analysis of RCTs was performed to date.

**Aim:** To assess the clinical effect of RBT compared to LBT in patients with AMI and anemia regarding was all-cause mortality, recurrent MI, revascularization, and heart failure exacerbation.

**Methods:** The electronic databases Ovid MEDLINE, EMBASE, Cochrane Central, Scopus, and Google Scholar, were systematically searched to identify eligible studies published before June 19th, 2021. RCTs that assessed the effect of RBT compared to LBT were included. The primary endpoint was all-cause mortality. Secondary endpoints included recurrent MI, revascularization, and heart failure exacerbation.

**Results:** Three RCTs with 821 patients were included (421 received RBT, and 400 received LBT). The mean age was 75.9 ± 6.1 years, and 56% were male. Our meta-analysis showed that RBT was not associated with reduced all-cause mortality (RR = 1.61; 95% CI = 0.38–6.96, p = 0.52), recurrent MI (RR = 0.98; 95% CI = 0.48–1.96, p = 0.94), revascularization (RR = 1.18; 95% CI = 0.26–5.44, p = 0.83) and heart failure exacerbation (RR = 0.86; 95% CI = 0.23–3.22, p = 0.82) when compared to LBT.

**Conclusion:** RBT was not associated with reduced all-cause mortality, recurrence of MI, need for revascularization, or heart failure exacerbation in patients with AMI and anemia compared to LBT. A larger RCT is required to confirm the above findings.

**Keywords:** Blood transfusion, Liberal, Restrictive, Myocardial infarction, Acute coronary syndrome, Anemia, Systematic review, meta-Analysis

1. Introduction

Blood transfusion is indicated in patients with severe anemia to improve tissue oxygenation, symptoms, and possibly clinical outcomes. Anemia in patients with acute myocardial infarction (AMI) is a strong predictor of cardiovascular morbidity, mortality, and ischemic events. Current guideline suggests that restrictive blood transfusion (RBT) (transfusion at hemoglobin [Hb] level of <7 g/dL) is as effective as liberal blood transfusion (LBT) (transfusion at Hb of <10 g/dL) with the exception of patient with MI. There are no clear guidelines in this patient population to date. The result of a recent randomized clinical trial (RCT) favored RBT over LBT in this population. Data from a meta-analysis of observational studies also favored RBT and reported that LBT is associated with higher all-cause mortality. Our meta-analysis aims to analyze the most recent data from randomized clinical trials to update the...
current evidence on whether RBT has clinical benefits regarding all-cause mortality, recurrent myocardial infarction (MI), revascularization, and heart failure exacerbation in patients with AMI and anemia when compared to LBT.

2. Methods

2.1. Data sources and search strategy

This systematic review was conducted according to The Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) as recommended by Cochrane Collaboration. A systematic literature review using MEDLINE, EMBASE, Cochrane Central, Scopus, and Google Scholar was performed using the terms (“Transfusion” OR “Blood transfusion” OR “Liberal” OR “Restrictive”) AND (“Myocardial infarction” OR “Coronary” OR “Angina”) for literature published up until June 19th, 2021. In addition, we included additional articles found in the review of bibliographies or suggested by co-authors based on their relevance to the selected search terms.

2.2. Study selection and eligibility criteria

Search results were saved in EndNote and transferred to Covidence. Two reviewers (BM and EK) independently performed the title and abstract screening. Conflicts were resolved through a third author (BA). The selected articles were further screened using the following inclusion criteria: RCT; study population involving patients with MI; outcomes including all-cause mortality, recurrent MI,
| Study          | Country/Length of Study | Study Design                          | Total Participants (LBT/RBT) | Intervention                                                                 | Reported outcomes                                      |
|---------------|-------------------------|---------------------------------------|------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------|
| Cooper et al. 2011 [11] | USA  
May 2003 to October 2009 | Prospective, multicenter parallel group randomized pilot trial | 45 (21/24) | Liberal Transfusion group: transfuse if Hct <30%, goal to maintain between 30 and 33%.  
Restrictive transfusion group transfused when Hct <24%, the goal between 24 and 27%. If Hct was >5% below targets, 2 U of PRBCs were given prior to reassessment  
liberal transfusion strategy received 1 U of blood to target Hb ≥ 10 g/dL.  
Restrictive transfusion strategy received blood for symptoms from anemia or for hemoglobin <8 g/dL if symptomatic, no lower threshold for infusion in the restrictive group.  
Blood was only given to raise Hb above 8 g/dL or alleviate symptoms and signs. | In-hospital death, recurrent ischemia/MI, new or worsening heart failure, CCU and hospital LOS |
| Carson et al. 2013 [10] | USA  
March 2010 to May 2012 | Multicenter, randomized pilot trial | 110 (55/55) | Recurrent MI/Ischemia, Death, unscheduled re-admission, adverse events (stroke, PE, DVT, CHF) |
| Ducrocq et al. 2021 [4] | France and Spain/March 2016 to September 2019 | Open label, noninferiority, randomized trial | 668 (324/342) | Major adverse cardiovascular events, death, recurrent ischemia/MI, adverse events (AKI, stroke, CHF, infection) |

LBT: Liberal blood transfusion; RBT: Restrictive blood transfusion; Hct: Hematocrit; U: Units; PRBCs: Packed red blood cells.
revascularization; English written text; Full text. We excluded the observational studies, studies that included non-cardiac patients, and non-full text articles. Conflicts were resolved through the third author (BA).

2.3. Data extraction

Data from included studies were extracted independently by two reviewers (BM, EK). The consensus was reached in case of any inconsistency by the third author (BA). The data extracted for qualitative synthesis included location, year of study, study design, sample size, population age (in years), all-cause mortality, recurrent MI, revascularization, heart failure exacerbation. The data were entered in Microsoft Excel by (BM, EK) and reviewed by a third author (BA). Any discrepancy was resolved by discussion between authors.

2.4. Risk of bias assessment

We used The Cochrane Collaboration tool to perform quality assessment and assess the risk of bias in the included clinical trials for random sequence generation, allocation concealment, blinding of participants and health care personnel, blinding of outcome assessment, incomplete outcome data, evidence of selective reporting, and other biases.8 The risk of bias assessment of the studies was categorized into low risk, high risk, or unclear risk of bias.

2.5. Outcomes of interest

The primary outcome was all-cause mortality. Secondary outcomes included recurrent MI, revascularization, and heart failure exacerbation.

2.6. Statistical analysis

We calculated the pooled Relative Risk (RRs), 95% confidence intervals (CIs) for dichotomous data. We used a random-effects model for the analysis. We assessed heterogeneity using $I^2$ statistics. $I^2$ more than 50% indicated a high level of heterogeneity. All analyses were performed using RevMan manager v5.4 software.9

3. Results

3.1. Study identification and selection

We identified 496 relevant citations through the literature search. After removing the duplicates, 277 citations were selected as potentially relevant. The titles and the abstracts were screened, and 37 full-text articles were selected for further review. Thirty-four articles were excluded; 21 did not include the targeted population, 9 were not randomized controlled trials (RCTs), two failed to report the intervention of interest, one failed to report the defined endpoints, and one is an ongoing trial. Finally, three articles were included in our systematic review and meta-analysis (Fig. 1).

Table 1 outlines the summaries of each study included. Two RCTs used hemoglobin (Hb) levels of 10 g/dL for LBT and 8 g/dL for RBT.10 The third RCTs used a hematocrit value of 30% for LBT and 24% for RBT.11 Three randomized clinical trials included 821 patients (421 received RBT, and 400 received LBT). The mean age of participants was 75.9 ± 6.1, and 56% were males. Co-morbidities in patients at enrollment included hypertension, hyperlipidemia, and diabetes mellitus in 79%, 60%, and 52%, respectively. The patients’ demographics and baseline characteristics are presented in Table 2.

3.3. Assessments of bias, study quality, and heterogeneity

Most of the studies included in this systematic review were RCTs that provided high-quality evidence. All RCTs had a low risk for selection, and attrition biases. All RCTs had a high risk of performance bias as blinding of participants and personal was not applicable. Detection bias was unclear in two RCTs and low risk of bias in the third one. The detailed assessment of the risk of bias is summarized in Fig. 2.

3.3.1. Primary endpoints

No significant difference was found between RBT and LBT groups regarding all-cause mortality: (RR = 1.61; 95% CI = 0.38–6.96, p = 0.52) (Fig. 3).

3.3.2. Secondary endpoints

There were no significant difference with regards to recurrent (MI) (RR = 0.98; 95% CI = 0.48–1.96, p = 0.94), revascularization (RR = 1.18; 95% CI = 0.26–5.44, p = 0.83), and heart failure exacerbation (RR = 0.86; 95% CI = 0.23–3.22, p = 0.82) (Fig. 3).

4. Discussion

In this updated meta-analysis of RCTs, which included 821 participants comparing RBT to LBT in
Table 2. The patient demographics and baseline characteristics.

| Study          | Subgroup     | Age (years), Mean ± SD | BMI (kg/m2), Mean ± SD | Male % | Female % | White % | Smoker % |
|----------------|--------------|------------------------|------------------------|--------|----------|---------|----------|
| Cooper et al.  | Liberal (n = 21) | 76.4 ± 13.5            | N/A                    | 48     | 52       | 76      | 10       |
| 2011           | Restrictive (n = 24) | 70.3 ± 14.3            | N/A                    | 54     | 46       | 61      | 33       |
| Carson et al.  | Liberal (n = 55)  | 67.3 ± 13.6            | 29.1 ± 7.2             | 50.9   | 49.1     | 70.9    | 12.7     |
| 2013           | Restrictive (n = 55) | 74.3 ± 11.1            | 28.3 ± 6.1             | 49.1   | 50.9     | 74.6    | 14.6     |
| Ducrocq et al. | Liberal (n = 324) | 78                     | 26.9 ± 5.3             | 56.8   | 43.2     | 82.6    | 37.9 former/14.0 current |
| 2021           | Restrictive (n = 342) | 76                     | 26.4 ± 5.0             | 58.8   | 41.2     | 88.7    | 36.7 former/16.1 current |

BMI: Body mass index; HTN: Hypertension; HLP: Hyperlipidemia; DM: diabetes mellitus; ESRD: end stage renal disease; CHF: congestive heart failure; H/O: History of; CABG: Coronary artery bypass graft; PCI: percutaneous intervention.

Fig. 2. Risk of bias assessment. A: Risk of bias summary: review authors’ judgments about each risk of bias item for each included study. The items are scored (+) low risk; (-) high risk; (?) unclear risk of bias. B Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.
patients with AMI and anemia, there was no difference between RBT and LBT with regards to all-cause mortality, recurrent MI, revascularization, and heart failure exacerbation. These results are considered reassuring for providers in a time of significant nationwide blood product shortages.

A previous meta-analysis by Chatterjee et al. assessed the benefits of blood transfusion in patients with AMI and reported that LBT was associated with higher all-cause mortality (RR = 2.91; 95% CI = 2.46–3.44; P < 0.001).5 They included nine observational studies and only one RCT with diverse study designs and patients’ characteristics, leading to heterogeneity in the outcome and limiting their applicability. Our meta-analysis only included RCTs and demonstrated no difference between RBT and LBT regarding all-cause mortality, recurrent MI, revascularization, and heart failure exacerbation.

Holst et al. conducted a similar meta-analysis reviewing the benefits and harms of RBT and LBT.12 They reported that there was no difference in all-

| Study or Subgroup | Restrictive transfusion | Liberal transfusion | Total | Weight | M-H, Random, 95% CI | Risk Ratio | M-H, Random, 95% CI |
|-------------------|-------------------------|---------------------|-------|--------|---------------------|-----------|---------------------|
| Carson et al. 2013 | 7                       | 54                  | 1     | 55     | 26.2%               | 7.13 [0.91, 56.02] | 1.13 [0.48, 2.62] |
| Cooper et al. 2011 | 2                       | 24                  | 1     | 25     | 22.9%               | 1.75 [0.17, 17.95] | 1.75 [0.17, 17.95] |
| Ducrocq et al. 2021 | 19                      | 342                 | 25    | 324    | 50.9%               | 0.72 [0.40, 1.32]  | 0.72 [0.40, 1.32]  |
| Subtotal (95% CI) | 420                     | 400                 | 100   | 400    | 100.0%              | 1.61 [0.38, 6.90]  | 1.61 [0.38, 6.90]  |
| Total events      | 28                      | 27                  |       |        |                     |            |                     |
| Heterogeneity:    | Tau² = 1.00; Chi² = 4.92, df = 2 (P = 0.09); I² = 59% | Test for overall effect: Z = 0.84 (P = 0.52) |

Fig. 3. A forest plot compared the all-cause mortality, recurrent myocardial infarction (MI), revascularization, heart failure exacerbation between restrictive and liberal blood transfusion. df, degrees of freedom; M–H, Mantel-Haenszel; CI, confidence interval; SD, standard deviation.
cause mortality (RR = 0.95; 95% CI = 0.81 to 1.11; I² = 27%), overall morbidity (RR = 1.06 (0.93–1.21); I² = 58%), and recurrent MI (RR = 1.05 (0.82–1.36); I² = 6%). They included surgical and medical patients, adults or children, in different settings, including trauma, critical care, and perioperative settings. All of these factors will change the effect size. We only included the RCTs that included adult patients with ACS, and we also included the recent study by Ducrocq et al. 2021.14

Ducrocq et al., 2021 included 668 patients comparing RBT versus LBT in patients with AMI and Anemia.4 The primary outcomes were - all-cause mortality, reinfarction, stroke, and emergency revascularization prompted by ischemia. They reported the primary outcome in 11.0% of the patients in the RBT group versus 14.0% in the LBT group (hazard ratio 0.77, 95% confidence interval 0.50–1.18, p < 0.05 for noninferiority, p = 0.22 for superiority), all-cause mortality: 5.6% vs. 7.7% (p > 0.05), recurrent MI: 21.1% vs. 31.1%, emergency revascularization: 1.5% vs. 1.9%, Acute heart failure 3.2% vs. 1.9%. They concluded that RBT was noninferior to the LBT. The study did not have sufficient power to evaluate the superiority of either strategy.

On the other hand, Deharo et al., 2020 compared the benefits and risk of blood transfusion versus no transfusion in patients with AMI and anemia.13 They included 12,547 patients, and blood transfusion was used in 489 (3.9%) patients. They reported that the patients who received transfusion had a higher rate of death or MI (29.9% vs. 8.1%, p < 0.01), suggesting the potential risk of harm in patients who received a blood transfusion. The RCT by Deharo et al., 2020 is different from the included RCTs in our meta-analysis as Deharo, and his colleague compared blood transfusion to no transfusion.13 The indication for transfusion was not prespecified because this study is post hoc analysis from anticoagulation with otamixaban and ischemic events in non-ST segment elevation acute coronary syndromes trial (TAO randomized clinical trial).13 This finding should not be applied clinically as it was interpreted as a generated hypothesis only. Our study included RCTs that compared RBT versus LBT, and all the outcomes were prespecified in the protocols prior to commencing each respective trial. Our study had several strengths but also some limitations. Firstly, the reported outcomes were derived from a small number of RCTs, and as a result, more RCTs are needed before making clinical recommendations based on these studies. A larger ongoing RCT (Myocardial Ischemia and Transfusion; MINT trial; NCT02981407) will include 3500 participants and has the same clinical design.

The primary outcome will be a 30-day composite of all-cause mortality or nonfatal MI. Secondly, our results have wide confidence intervals due to limited trial data that could be included. Finally, the assessment of publication bias using the funnel plot is not reliable for less than ten included studies, as reported by Egger et al. Therefore, in the present meta-analysis, we could not examine the possibility of publication bias.15

5. Conclusions

The result of our meta-analysis suggests that RBT compared with LBT is not associated with reduced all-cause mortality, rates of recurrent MI, revascularization, or heart failure exacerbations when compared to liberal blood transfusion in patients with AMI and anemia. Our results are believed to be reassuring to healthcare providers during times of significant nationwide shortage of blood products. However, Larger RCTs are needed before recommending the appropriate transfusion strategy in this patient population.

Author contribution

BA, EK, and BM searched the scientific literature. BA and SB conducted the statistical analyses. BA, BM, EK, and AR participated in data interpretation, drafted the report, and conceived the study. AK and MH revised the paper.

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Conflict of interest

None declared.

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For this article, no studies with human participants or animals were performed by any of the authors. All studies conducted were in accordance with the ethical standards indicated in each case.

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