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Systematic or Meta-analysis Studies

How low should we go: A systematic review and meta-analysis of the impact of restrictive red blood cell transfusion strategies in oncology

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ABSTRACT

Background: Most non-oncologic clinical practice guidelines recommend restrictive allogeneic blood transfusion practices; however, there is a lack of consensus regarding the best transfusion practice in oncology. We conducted a systematic review of the literature to compare the efficacy and safety of restrictive versus liberal transfusion strategies in patients with cancer.

Methods: A literature search using MEDLINE, PUBMED and EMBASE identified all controlled studies comparing the use of restrictive with liberal transfusion in adult oncology participants up to August 10, 2015. Two review authors independently assessed studies for inclusion, extracted data and appraised the quality of the included studies. The primary outcomes of interest were blood utilization and all-cause mortality.

Results: Out of 4241 citations, six studies (3 randomized and 3 non-randomized) involving a total of 983 patients were included in the final review. The clinical context of the studies varied with 3 chemotherapy and 3 surgical studies. The overall risk of bias in all studies was moderate to high. Restrictive transfusion strategies were associated with a 36% reduced risk of receiving a perioperative transfusion (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.49–0.83). There was no difference in mortality between the strategies (RR 1.00, 95% CI 0.32–3.18). There were no differences in adverse events reported between the restrictive and liberal transfusion strategies.

Conclusion: Restrictive strategy appears to decrease blood utilization without increasing morbidity or mortality in oncology. This review is limited by a paucity of high quality studies on this topic. Better designed studies are warranted.

Introduction

Anemia in cancer patients is pervasive with studies reporting rates up to 90% [1–3]. The etiology of anemia in cancer patients is multifactorial and involves multiple different mechanisms including nutritional deficiencies, surgical blood loss and myelosuppressive effects of chemotherapy and radiation [3,4]. Numerous studies have demonstrated that anemia is a prognostic indicator of poor clinical and oncologic outcomes [5–10].

A combination of clinical studies revealing the adverse impact of anemia and animal models demonstrating optimal oxygen transport at hemoglobin levels greater than 10 g/dL has resulted in the historical trend towards liberal use of red cell transfusions to correct anemia in oncology patients [9,11,12]. Despite the liberal use of transfusion in many oncology studies, there are little data to support the efficacy of correcting anemia with transfusion [13]. In fact, there is evidence that suggests that blood transfusions are independently associated with worse perioperative and oncologic outcomes [14–17]. Furthermore, there is evidence from other subspecialty fields that a liberal blood transfusion strategy does not improve clinical outcomes over a restrictive strategy [18–20]. As such, many subspecialty societies have developed specific clinical practice guidelines that recommend restrictive red cell transfusion

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[21–23]. Evidence from institutional quality improvement initiatives has demonstrated that restrictive strategies have similar clinical outcomes while utilizing less blood [21–27].

Despite the widespread adoption of restrictive transfusion strategies seen in other fields, the oncology community has been resistant to change. This is in part because oncology patients are perceived to be different than non-oncology patients. The use of anticancer treatments such as radiotherapy and chemotherapy can lead to anemia and subsequent treatment delays if the anemia is not corrected quickly. Furthermore, the high incidence of fatigue in this patient population requires different transfusion strategies than other acutely ill populations to improve quality of life.

There is a lack of consensus regarding best transfusion practices resulting in wide variability in blood utilization [28–30]. Therefore, we conducted a systematic literature review to compare the efficacy and safety of restrictive versus liberal transfusion strategies in patients with cancer. The purpose of this review was to find, evaluate and summarize the existing literature to fill a gap in knowledge regarding restrictive transfusion strategies in oncology.

Methods

Study design, protocol and registration

We adhered to the Cochrane Collaboration methodology for conducting this review [31]. Study methodology was defined a priori and our protocol was registered online in advance (PROSPERO CRD42015019732). We report our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations for reporting (PRISMA) statement [32].

Eligibility criteria

Controlled studies comparing a liberal allogeneic packed red blood cell transfusion strategy to a restrictive allogeneic packed red blood cell transfusion strategy in adult oncology patients were considered. This included randomized and non-randomized studies. It was anticipated that the exact trigger or strategy may vary between studies. Patients could be receiving treatment with curative or palliative intent. Curative intent may involve surgical or medical treatment including chemotherapy or radiotherapy. Studies involving infants or neonates were excluded.

Data sources and search strategy

A literature search was performed with guidance from an experienced public health research librarian (HV). We searched the following databases: MEDLINE (Ovid), PUBMED (National Library of Medicine), EMBASE (Ovid) from inception until August 10, 2015. Additionally, all highly relevant studies were searched in *Scopus* (Elsevier) to determine if any unique studies were missed by the database searches. Bibliographies of the included studies were examined for highly relevant citations. Our search was restricted to adult patients and controlled studies published in English. No other restrictions were applied. The Medline search strategy is provided in Appendix A.

Study selection

The PRIMARY Excel Workbook for Systematic Reviews was used to screen titles and abstracts of items found through database searching [33]. Two reviewers (LP and JT) independently screened titles and abstracts in which they were blinded to authors and journal titles. Full texts were retrieved for relevant citations. In cases of disagreement, the reviewers reached a consensus through discussion or through third party adjudication (MLO).

Data collection

Two review authors (LP and JT) independently abstracted study characteristics and outcomes using a data extraction form. All characteristics and outcomes were reviewed together and discrepancies were resolved through discussion. In case of persistent disagreement, MLO served as an adjudicator. LP entered all data into RevMan version 5.3.19 [34] and data were verified by JT and MM. Dichotomous outcomes were collected according to number of patients affected. Study authors were not contacted for missing data.

Outcomes

The primary outcomes of interest were blood utilization and all-cause mortality. Secondary outcomes included cancer-related mortality, perioperative morbidity (infection, venous thromboembolism, pneumonia, unintended intubation, renal failure, stroke, cardiac arrest, myocardial infarction, flap failure, and prolonged ventilator use), transfusion-related adverse events, and other adverse events. We collected all outcome data reported in each study.

Quality assessment

Two reviewers (LP and JT) independently appraised the quality of the included studies. The Cochrane risk of bias tool was used to assess the randomized studies [31]. The tool judges the risk of 5 types of bias (i.e., selection, detection, performance, attrition, reporting) and other potentials to validity threats (e.g., funding, imbalanced use of co-intervention, etc.). Each potential source of bias was graded as low, unclear or high. Non-randomized studies were also independently appraised with A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) [35]. Studies were judged for the potential for bias due to confounding, selection of participants, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Each potential source of bias was graded low, moderate, serious, critical risk of bias or no information at the outcome level. An overall risk of bias judgment for each non-randomized study across all domains was determined based on the level of bias of each of the aforementioned components. Studies were only determined to be low risk if they met criteria for low risk on all domains. Otherwise they were judged to be at moderate risk of bias or higher. Disagreements were resolved through discussion.

Summary measures, synthesis of results and analysis

We performed our meta-analysis using RevMan [34]. We calculated the risk ratio for dichotomous variables and the mean difference for continuous variables. Data were synthesized using fixed effects models except when significant heterogeneity was found. We used the I^2 statistic to examine heterogeneity among the studies [36]. In the presence of significant heterogeneity ($P < 0.05$), we fit a random effects model based on the method of Der Simonian and Laird [37]. We analyzed only the available data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions chapter on missing data [36]. The patient was the unit of analysis. If insufficient data existed (<2 studies reporting on the same outcome), descriptive statistics were utilized to report outcomes.