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Leukocyte filtration and postoperative infections

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ABSTRACT

Background: Leukocyte filtration has been hypothesized to reduce the risk of postoperative infections by alleviating the immunosuppressive effect of whole blood. However, the literature regarding the clinical efficacy of leukocyte filtration remains conflicted. This meta-analysis investigates the impact of allogeneic and autologous leukocyte-filtered blood transfusions on the incidence of postoperative infections in adult surgical patients.
Methods: A comprehensive literature search of PubMed, Google Scholar, and Cochrane Central Registry of Controlled trials (1966-2016) was completed for all published randomized controlled trials. Postoperative infections under "as-per-protocol" (APP) and "intention-to-treat" (ITT), length of stay, and mortality were analyzed.
Results: Sixteen randomized controlled trials involving 6586 randomized (ITT) patients (4615 APP patients) in various clinical settings were evaluated. The leukocyte-filtered blood group demonstrated an overall 26% risk reduction in postoperative infections when analyzed by APP (relative risk [RR] = 0.74; 95% confidence interval [CI, 0.60-0.92]; $P = 0.007$) and a 22% risk reduction when analyzed by ITT (RR = 0.78; 95% CI [0.65-0.94]; $P = 0.009$). Leukocyte-filtered blood was also associated with a significant reduction in length of stay (standardized difference of mean [SDM] = −0.74; 95% CI [−1.32 to −0.15]; $P = 0.014$) and all-cause mortality (RR = 0.74; 95% CI [0.57-0.95]; $P = 0.018$).
Conclusions: Leukocyte-filtered blood transfusions are associated with significantly lower postoperative infection rates in both the APP and ITT populations. Leukocyte filtration also shortens length of stay and decreases all-cause mortality in surgical patients and should be considered in all surgical patients.

Introduction

The American Red Cross has reported that a total of 15 million red blood cell (RBC) units are transfused annually.[1] Surgical patients account for two-thirds of these RBC transfusions.[2] Though transfusions are essential in saving lives, multiple studies have reported numerous findings of adverse effects, ranging from the transmission of infectious disease to deleterious transfusion-related immunomodulation (TRIM).[3-5] With modern blood banking technology, the transmission of infectious diseases has been vigilantly managed and concerns are substantially minimized overall.[6] Most transfusion-related morbidity and mortality consist of noninfectious complications, the greatest of concern being the immunosuppressive effect of TRIM.[7] The immunosuppressive effect of transfusions were first demonstrated by

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Opelz *et al.* [8] in a prospective study of 148 cadaver donor transplant recipients in which rejection rates were compared based on blood transfusion status. The result of this study revealed that renal allograft rejection was improved in recipients receiving 10 or more transfusions as opposed to those who did not receive transfusions (66% *versus* 29%, $P < 0.001$).[8] The author inferred from these findings that blood transfusions result in an immunosuppressive effect of the transfused host's immune system.[8] Historically, the immunosuppressive effect of blood transfusions was an often used means to limit rejection in renal transplants until cyclosporine and other immunosuppressives were introduced.[8]

TRIM has also been observed in surgical patient groups in which an increased number of postoperative infections are observed in patients receiving RBC transfusions. A prospective observational study by Tartter *et al.* [9], involving 168 colorectal cancer patients, sought to identify perioperative determinants of infectious complications. Using multivariate analysis, these authors reported that 24 of 168 patients developed infectious complications and observed that blood transfusion was an independent significant risk factor for infection ($P = 0.01$).[9] A meta-analysis of 21 randomized controlled trials (RCTs) involving 131,512 patients by Hill *et al.* [10] (1992) demonstrated a three-fold increase in postoperative infections in transfused patients compared to nontransfused patients (OR = 3.45; 95% confidence interval [CI, 1.42-15.15]; $P < 0.05$).

The presence of leukocytes in the transfused products appears critical to produce the TRIM effect.[11] A prospective study involving 80 orthopedic surgery patients by Innerhofer *et al.* [12] observed impaired T-cell-mediated immunity in patients who were transfused with leukocyte containing RBCs. These findings were continued by Lee *et al.* [13] who reported persistent donor leukocytes in humans for up to 1.5 y after blood transfusion. Unsurprisingly, various other benefits associated with leukocyte-filtered blood have also been reported, including prevention of recurrent febrile nonhemolytic transfusion reactions (FNHTR), alloimmunization in transplantation, and transmission of cytomegalovirus.[14]

European countries (i.e., Germany, the United Kingdom, and the Netherlands) and Canada have implemented a universal leukocyte filtration policy, reaping benefits of decreased FNHTR incidences and cost savings due to decreased length of hospital stay.[15-17] Despite implementation in these countries, the association between leukocyte filtration and postoperative infection remains controversial.[18-21] The most recent Cochrane review by Simancas-Racines *et al.* [21] included 10 RCTs involving 3557 surgical and nonsurgical patients transfused with allogeneic blood and yielded no difference in infection risks (RR = 0.76; 95% CI [0.58-1.00]; $P = 0.05$) when leukocyte-filtered blood was used. Bilgin *et al.* [22] conducted an RCT involving 496 patients undergoing valve surgery and reported lower postoperative infection rates (33.8% *versus* 24.3%, $P = 0.032$) with the use of leukocyte-filtered blood. Conversely, Nathens *et al.* [23] conducted an RCT involving 324 trauma patients and reported no difference in infection rates (36.0% *versus* 30.3%, $P = 0.321$) with the use of leukocyte-filtered blood.

The current meta-analysis provides a comprehensive review of all published studies in surgical patients, in which leukocyte-filtered blood transfusions were provided to determine the impact on postoperative outcomes, including postoperative infection rates, length of stay, and mortality.

Materials and methods

Study selection

A comprehensive search of all published RCTs comparing patients receiving leukocyte-filtered and nonleukocyte-filtered blood transfusions was conducted using PubMed, Google Scholar, Cochrane Central Registry of Controlled Trials (1966-2016). Additional citations were searched using references retrieved from prior publications (Fig. 1). The last search was conducted on January 10, 2016, and only articles conducted in English were considered. Keywords searched included combinations of "leuk(c)oreduced," "leuk(c)odepleted," "leuk(c)ocyte filtered," "white cell reduced," "leuk(c)ocyte reduced," "leuk(c)ocyte depleted," "leuk(c)ocyte depleting," and "transfusions." The inclusion criteria were limited to RCTs in adult surgical populations (>18 y), comparing leukocyte-filtered and nonleukocyte-filtered blood, and reporting the incidence of postoperative infections (surgical and nonsurgical site infections) with sample size. Studies which did not include postoperative infections as an outcome were excluded. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[24]

Data extraction

Articles retrieved from searches were assessed for eligibility and data pertaining to patients, interventions, comparison groups, outcomes, and methodology were abstracted. The primary clinical outcome of interest was the incidence of postoperative infection. Secondary outcomes were hospital length of stay and all-cause mortality.

Statistical analysis

For each trial, RR with a 95% CI for the incidence of postoperative infections and mortality was calculated. SDM with 95% CI was calculated for LOS. Meta-analysis of the pooled data was performed using Comparative Meta-analysis software version 3 (CMA v 3; Biostat, Englewood, NJ). For individual studies reporting zero events in any group, a continuity correction factor of 0.5 was adopted to calculate the RR and variance. Both fixed-effect and random-effect models were considered, depending on the heterogeneity of the included studies. To assess the heterogeneity between studies, both Cochrane's Q statistic and I^2 statistic were used. Heterogeneity was considered statistically significant when $P < 0.05$ or $I^2 > 50$. If heterogeneity was observed, data were analyzed using a random-effect model. In the absence of heterogeneity, a fixed-effect model was assumed.

For all outcomes, publication bias was the first qualitatively assessed using a funnel plot, and further quantitatively