General Anesthesia

Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials

[La transfusion de sang réduit en leucocytes peut diminuer les infections postopératoires : deux méta-analyses d'études randomisées et contrôlées]

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Purpose: To evaluate the efficacy and effectiveness of red blood cell leukoreduction in reducing postoperative infection, mortality and cancer recurrence, two meta-analyses of randomized controlled trials (RCTs) were conducted.

Methods: A systematic search of the scientific literature was conducted. The pooled relative risk ratio (RR) of developing an adverse postoperative outcome with either leukoreduced or non-leukoreduced blood was calculated using a random effects model. To better estimate the efficacy of leukoreduction, a second analysis of transfused patients only was conducted.

Results: Ten RCTs met inclusion criteria and eight provided separate data for patients randomized and transfused. The mean percentage of patients randomized but not transfused was 34%. For postoperative infection, the overall pooled RR was 0.76 [(95% confidence interval (CI): 0.54–1.08] for the "all patients randomized" analysis. For the "only patients transfused" analysis, the pooled RR became clinically and statistically significant (RR = 0.60 (95% CI: 0.38–0.93). For mortality, the pooled RR for the "all patients randomized" analysis was 0.71 (95% CI: 0.45–1.13) and 0.61 (95% CI: 0.36–1.04) for the "only patients transfused" analysis. When analyzing either all patients randomized or all patients transfused, there was no statistically significant difference in cancer recurrence rates (one study only).

Conclusion: We demonstrated that patients who were transfused leukoreduced red blood cells might benefit from a decrease in postoperative infections. A decrease in mortality may have been realized if more patients had been enrolled in the various randomized trials. Including all patients randomized, regardless of whether or not they were actually transfused diluted the observed clinical benefit of leukoreduction.

Objectif : *Dans le but d'évaluer l'efficacité de la réduction leucocytaire à diminuer l'infection postopératoire, la mortalité et la récurrence du cancer, nous avons réalisé deux méta-analyses d'études randomisées et contrôlées (ERC).*

Méthode : *Une recherche systématique des publications scientifiques a été réalisée. Le risque relatif (RR) de subir des complications postopératoires avec du sang réduit ou non en leucocytes a été calculé au moyen d'un modèle à effets aléatoires. Afin de mieux estimer l'efficacité de la réduction leucocytaire, une seconde analyse des patients transfusés a été faite.*

Résultats : *Dix ERC répondaient aux critères d'inclusion et huit portaient sur des patients randomisés et transfusés. Le pourcentage moyen de patients randomisés mais non transfusés était de 34 %. Le RR global d'une infection postopératoire était de 0,76 [(intervalle de confiance de 95 % (IC) : 0,54–1,08] pour l'analyse où «tous les patients sont randomisés». Dans l'analyse des «seuls patients transfusés», le RR est devenu cliniquement et statistiquement significatif (RR = 0,60 (IC de 95 % : 0,38–0,93). Le RR de mortalité dans l'analyse de «tous les patients randomisés» était de 0,71 (IC 95 % : 0,45–1,13) et de 0,61 (IC 95 % : 0,36–1,04) dans l'analyse des «seuls patients transfusés». Les analyses de tous les patients randomisés et de tous les patients transfusés n'ont pas montré de dif-*

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férence statistiquement significative de récurrence du cancer (une étude seulement).

Conclusion : *Les patients qui reçoivent du sang réduit en leucocytes sont moins susceptibles d'avoir des infections postopératoires. Une baisse de la mortalité aurait pu être réalisée si plus de patients avaient participé aux diverses études randomisées. Quand on inclut tous les patients randomisés, peu importe qu'ils aient été transfusés ou non, on observe une dilution des avantages cliniques de la réduction leucocytaire.*

THE immunosuppressive effects of allogeneic blood were first reported following improvements in renal allograft survival in 1973.[1] Since then, many clinical studies have been conducted to further elucidate the immunomodulatory effects of blood including its potential association with an increased risk of cancer recurrence, postoperative infections and mortality. Since donor leukocytes are hypothesized to mediate these adverse effects of allogeneic blood, leukoreduction could be effective in inhibiting transfusion-related immune suppression.[2]

However, two systematic reviews concluded that the effectiveness of leukoreduction in preventing postoperative infections, cancer recurrence and postoperative mortality in patients undergoing curative cancer surgery remained largely unproven.[3,4] There were a number of methodological concerns identified in the meta-analyses and in subsequent narrative reviews.[5,6] Both meta-analyses analyzed all patients randomized regardless of whether they received an intervention. This is commonly referred to as an intention-to-treat analysis. While considered the most conservative analytical approach, it may not reflect the true efficacy of leukoreduction. This is of significant concern in these particular trials as many investigators opted to prematurely randomize patients. As a consequence, a significant proportion of patients never received a blood transfusion, either leukoreduced or non-leukoreduced, and in some cases did not undergo surgery. When the lack of exposure to interventions is not considered in the planning of the study, then the relative risk ratio (RR) of adverse postoperative outcomes does not reflect the efficacy of treatment but rather an inadequate attempt to assess its effectiveness.[7] Efficacy is a measure of the benefit resulting from a treatment evaluated under ideal conditions whereas effectiveness refers to whether the observed benefit transfers well to the real-world population. Given that many countries have implemented universal leukoreduction and countries such as the United States and Japan are contemplating such a decision, an accurate reflection of both its efficacy and effectiveness has substantial ramifications.

In this updated meta-analysis, we therefore chose to present an analysis of only transfused patients, which best reflects the evidence of efficacy of leukoreduction in decreasing postoperative infections, cancer recurrence and death while also presenting an effectiveness analysis that included all randomized patients.

Methods

Identification of trials

A systematic search of the published scientific literature using the Medline electronic database was conducted for the dates January 1966 to May 2003 inclusive. All citations containing the terms *leukoreduction, leucoreduction, leucocyte removal, white blood count (WBC) removal, white cell removal, removal of WBCs, removal of leucocytes, white cell filtration, WBC filtration, leucocyte filtration, reduction of white cells, leucocyte-reduced, WBC-reduced, WBC depletion, and leucocyte depletion combined with any of the terms clinical trials, randomized controlled trials,* and *meta-analysis* were identified. The search was limited to studies evaluating the adult, human population.

All citations were manually reviewed and included if they consisted of a randomized, controlled clinical trial comparing leukoreduced allogeneic red blood cell (RBC) transfusions to non-leukoreduced allogeneic RBC transfusions in patients undergoing surgery. Full journal articles, letters, abstracts, and monographs were all included. At least one study arm of the trial must have consisted of patients randomized to receive leukoreduced allogeneic RBCs with the control arm consisting of patients receiving standard non-leukofiltrated allogeneic RBCs. Patients randomized to receive only autologous blood in either study arm were excluded. The outcomes evaluated in each study were clinical evidence of postoperative infection, cancer recurrence, and death. Studies that evaluated non-clinical outcome measures such as laboratory markers without clinical assessment were also excluded. The bibliographies of the selected citations and all systematic and narrative review articles were examined to identify any relevant references not identified in the original search.

Data abstraction

Three investigators (M.P.K., D.F., P.C.H.) abstracted the following information on standardized data abstraction forms: study design, randomization and blinding protocols, study population characteristics, sample size, withdrawals, type of filter, patients trans-

TABLE Study characteristics

Year	*Country*	*Surgical*	*Type of filter*	*Type of control*	*Blinding*	*Time of randomization*	*Proportion randomized but NOT transfused†*
1992[14]	Denmark	Colorectal	Bedside	Whole blood	No*	Preoperation	47%
1994[10]	Netherlands	Colorectal	Pre-storage	Buffy coat-depleted	No	Preoperation	‡
1996[11]	Denmark	Colorectal	Bedside	Buffy coat-depleted	No*	Preoperation	56%
1997[12]	Netherlands	Cardiac	Pre- & post-storage	Buffy coat-depleted	No	Preoperation	5%
1998[15]	USA	Gastrointestinal	Pre-storage	Standard	No	Preoperation	73%
2001[13]	Denmark	Colorectal	Pre-storage	Buffy coat-depleted	Patient, investigators, and physicians	Preoperation	55%
2002[16]	Netherlands	Mixture	Pre-storage	Buffy coat-depleted	‡	Need for transfusion	‡
2002[17]	USA	Cardiac	Pre-storage	Standard	‡	‡	17%
2002[18]	UK	Cardiac	Post-storage	Standard & Buffy coat-depleted	Outcome assessors	Preoperation	14%
2002[19]	USA	Mixture	Pre-storage	Standard	No	Need for for transfusion	2%

*Publications report that physicians performing follow-up examinations were blinded, however it is unclear whether they evaluated presence/absence of outcome on every patient. †Based on patients randomized and eligible as defined in publication. ‡Not reported.

fused, postoperative infections, cancer recurrence, deaths, amount of RBC units transfused, and mean preoperative and postoperative hemoglobin concentrations. Any interobserver discrepancies were resolved by consensus.

Data analysis

The RR of developing an adverse postoperative outcome with either leukoreduced or non-leukoreduced RBC transfusions was calculated for each study. Where clinically appropriate, data from studies were combined to estimate the pooled RR and 95% confidence intervals (CIs) using a DerSimonian and Laird random effects model.[8]

Two different analyses were performed: one evaluating all patients randomized to receive either leukoreduced or non-leukoreduced blood and the other evaluating only patients that received a transfusion. The second analysis was conducted to better estimate the true effect of leukoreduction. As the hypothesized benefits of leukoreduction can only be realized in patients that receive a transfusion, it seemed reasonable to exclude patients from analysis that do not undergo surgery or do not receive a transfusion. Excluding these patients from analysis is predicated on the assumption that the decision not to transfuse or operate was independent of treatment arm allocation. A summary RR was calculated for each analysis. A RR less than one indicates that more adverse events occurred in patients that received non-leukoreduced than leukoreduced blood and vice-versa for a RR greater than one. The same analytic methods were performed for the sub-group analyses of type of filter and type of surgery.

Results

Overview

The search strategy identified 729 citations. Manual review of the abstracts from each citation excluded 616 citations deemed irrelevant to the objective of our study, leaving 113 citations for full publication retrieval. Another 102 studies were excluded because they evaluated a leukofilter as part of the cardiopulmonary bypass circuit (n = 33), evaluated a blood product different from leukoreduced RBCs (n = 17), did not evaluate clinical outcomes (n = 21), did not study adult, human patients undergoing surgery (n = 5), evaluated leukoreduction in a non-surgical setting (n = 9), did not include leukoreduced RBCs in study arm (n = 3), or were review articles (n = 14).

Eleven randomized controlled trials were identified that compared leukoreduced allogeneic RBC transfusions to non-leukoreduced allogeneic RBC transfusions with respect to the risks of postoperative infection, cancer recurrence, or mortality in patients undergoing surgery.[9–19] One study evaluated patients

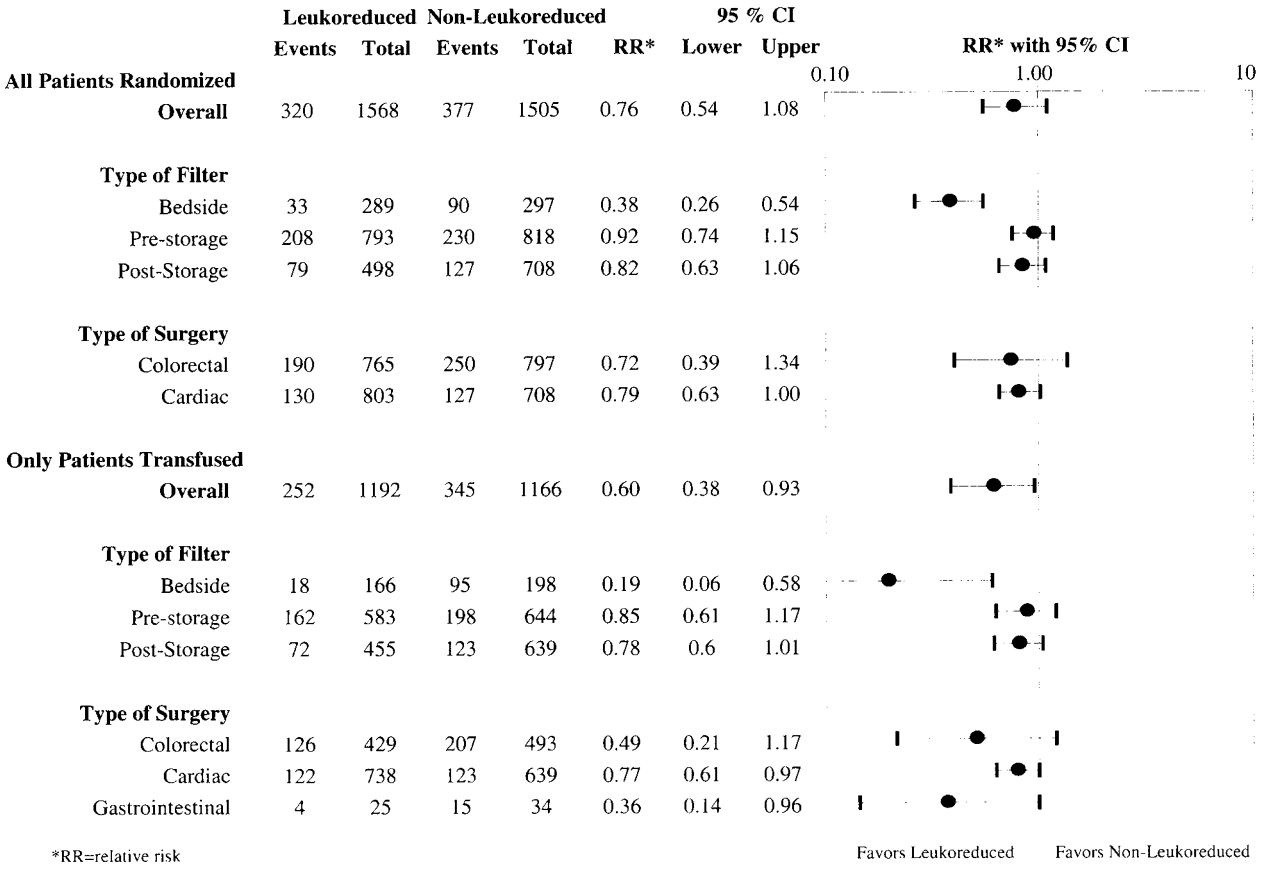

FIGURE 1 Meta-analysis for postoperative infection.

undergoing surgery for burn trauma.[9] It was excluded *a posteriori* as it was determined to be a distinct patient group from the other surgical populations. Thus, ten studies remained for analysis[10–19] (Table). Five studies provided postoperative infection data for all patients randomized and all patients transfused[10–13,18] while two studies provided data only for patients transfused.[14,15] Four studies provided mortality data for all patients randomized as well as all patients transfused.[11–13,18] Three studies presented data only for patients randomized[16,17,19] and one study presented mortality data only for patients transfused.[10] In the eight trials that provided separate data for patients randomized and transfused, the mean percentage of patients randomized but not transfused was 34% (range 2%–73%).

In four studies, patients randomized to receive either the leukoreduced or standard blood product were analyzed according to the group they were allocated regardless of whether or not they actually received the right product.[10,11,18,19] In one study, patients were analyzed according to the product they received (leukoreduced or standard blood product) and not according to the group to which they were randomized.[12] In another study, patients that received the wrong blood product were excluded from the analysis.[13] Analysis of protocol deviations was not specified in the four remaining studies.[14–17]

Postoperative infection

In the "all patients randomized" analysis, a total of 3073 patients were analyzed (Figure 1). The overall pooled RR was 0.76 (95% CI: 0.54–1.08). In the subgroup analyses, the use of a bedside filter was found to be both clinically and statistically significant (RR = 0.38, 95% CI: 0.26–0.54). The pre- and post-storage filters were found to be less effective and did not reach statistical significance (RR = 0.91, 95% CI: 0.71–1.17

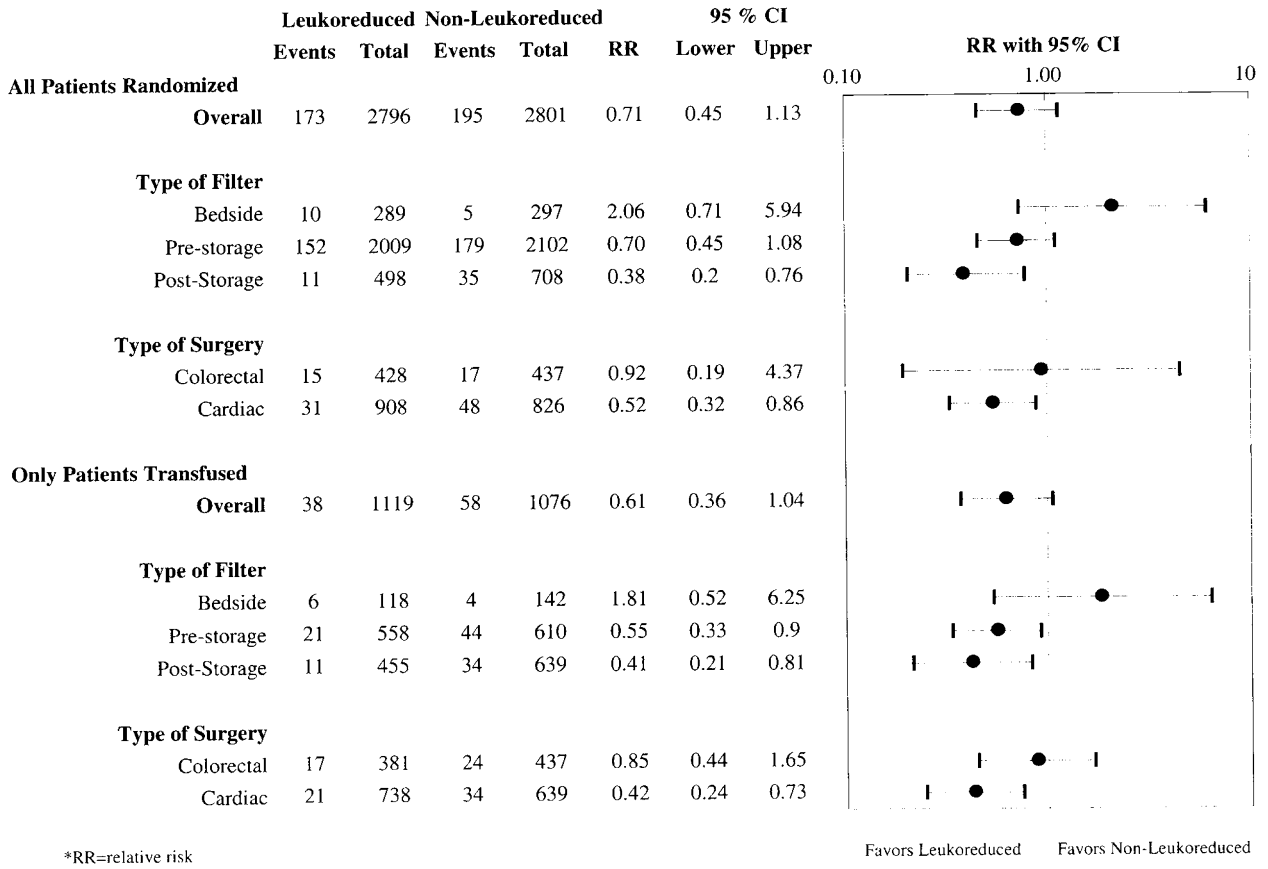

FIGURE 2 Meta-analysis for mortality.

and RR = 0.82, 95% CI: 0.63–1.06 respectively). No difference in effects was seen between colorectal and cardiac surgery, however, the effect in the cardiac subgroup was found to be statistically significant (RR = 0.82, 95% CI: 0.63–1.00).

In the "only patients transfused" analysis, outcome data from two additional studies were available.[14,15] In total, 2,358 patients were analyzed. The summary risk ratio for the aggregated data was 0.60 (95% CI: 0.38–0.93). Thus, the efficacy of leukoreduction was documented in the transfused population but not in the randomized population. As with the analysis of all randomized patients, leukoreduction appeared most effective in the bedside filter subgroup and cardiac surgery subgroup (Figure 1).

Cancer recurrence

One randomized controlled trial evaluated cancer recurrence in patients who received standard allogeneic RBCs *vs* leukoreduced blood.[10] Supplemental information was provided in a separate publication of the same study subjects.[20] When analyzing all patients randomized, there was no statistically significant difference in cancer recurrence rates between the patient group that received leukoreduced RBCs and the group that received standard buffy-coat depleted packed RBCs at the five-year follow-up point (27.9% *vs* 27.8%, $P > 0.05$.) Likewise, when analyzing only the patients who were transfused, there was no statistically significant difference in recurrence rates between the two groups (28.4% *vs* 31.2%, $P > 0.05$.)

Mortality

Perioperative mortality data were provided in eight clinical trials.[10–13,16–19] Operative mortality was defined as death within 30 days of surgery in three studies,[10,11,13] within 60 days for one study,[12] within three months for one study,[18] and one study defined in-hos-

pital mortality up to a specific study cut-off date, thus, patient follow-up time was dependent upon date of trial entry.[19] Two studies did not report a definition of operative mortality.[16,17] For mortality, the pooled RR for all patients randomized was 0.71 (95% CI: 0.45–1.13). The results were similar for the "only patients transfused" analysis (RR = 0.61 (95% CI: 0.36–1.04). Mortality decreased with pre- and post-storage filters but not with bedside filters in the "only patients transfused" group (Figure 2).

Discussion

By outlining results that best describe efficacy and effectiveness in this meta-analysis, we demonstrated that patients who were transfused leukoreduced RBCs might benefit from a decrease in postoperative infections. This benefit was not observed in all patients randomized in the published studies. A comparable decrease in mortality may have been realized if more patients had been enrolled in the various randomized trials. In effect, including all patients randomized, regardless of whether or not they actually received a blood product diluted the observed clinical benefit of leukoreduction. Practically, the premature point of randomization affected the interpretation of study results, as the results did not reflect the true effect of leukoreduction. We argue that the intention-to-treat principle remains preserved when patients that are inappropriately randomized are removed from the analysis.[7]

The protective effects of leukoreduced blood were most evident in the cardiac surgery subgroup, where a decreased risk of infection and mortality was seen in both the "only patients transfused" and "all patients randomized" groups. The reason for increased effectiveness in cardiac surgery may be related to the higher volume of RBCs transfused per patient compared to colorectal and gastrointestinal surgery as well as the fact that the leukocytes are transfused to an already activated inflammatory system caused by cardiopulmonary bypass. By transfusing leukocytes to an activated inflammatory response system, the release of cytokines and free radicals may induce organ damage and, consequently, death. Thus, in addition to an immunosuppressive effect of non-leukoreduced RBCs there is a potential pro-inflammatory effect. Given the many limitations of the reported trials and this analysis, caution would suggest that further studies in a variety of patient populations would ensure that the results were accurate and generalizable.

It is interesting to note that although the bedside filter decreased the risk of infection, it also appeared to be associated with an increased number of deaths compared to the pre- and post-storage filters. Since the results regarding the bedside filter originated from a single study, it is plausible that the trend towards increased mortality or decreased infection was related to the small sample size rather than a true harmful effect in the case of mortality or a beneficial effect with respect to postoperative infection.[11] The effectiveness of bedside filters compared to pre-storage filters has not been evaluated in head-to-head clinical trials. Animal studies have shown that pre-storage filtration is superior to bedside filters for the prevention of tumour growth and alloimmunization.[21,22] In addition, laboratory evidence shows that pre-storage leukoreduction removes leukocytes before they breakdown and release potentially harmful substances such as cytokines.[23,24] Thus, it is reasonable to postulate that pre-storage filters should confer a greater clinical benefit than bedside filters.

Only one study examined cancer recurrence in patients who received either leukoreduced or standard RBCs. No difference in recurrence rates was noted in either group, although more studies are required before making a definitive statement regarding this issue.

With premature randomization employed in the included trials, any beneficial effect of leukoreduction was diluted by the number of patients who were not transfused. Given this study design limitation, the most accurate measure of the intervention's efficacy would require limiting the analysis to patients that actually received a transfusion. However, the primary concern in counting events only in patients who were transfused would be a potential bias introduced due to the un-blinded design of the studies. A biased result would occur if clinicians consider the type of product that will be administered when deciding to transfuse a given patient. For instance, transfusing leukoreduced products to patients not requiring transfusion could result in a greater beneficial effect, as "healthier" patients would be included in the leukoreduction study arm. Our report was not able to detect such subtle but plausible biases. Although highly unlikely, this should be considered a limitation of this meta-analysis. Furthermore, although both randomization groups were more or less matched for demographic characteristics in all the trials, such information was not available for the transfused groups in all trials. However, of the eight trials that provided separate data on all patients randomized and transfused, four provided baseline differences in the "transfused only" groups.[11,13–15] For the four trials that did not provide baseline data for those transfused, this information is largely irrelevant for two as the proportion not transfused was very low.[12,19] In the four trials that provided data, there were no large differences between treat-

ment arms in the vast majority of baseline measurements. This supports our belief that patients were properly randomized to each arm of the trial and were not differentially excluded from receiving a transfusion based on treatment allocation.

The other limitations of this meta-analysis arise from limitations of the individual studies including an inconsistency in definition of outcome measures among the reported clinical trials such as what constitutes a postoperative infection and the time frame outcomes are reported. Inappropriate cross-over as well as exclusion of patients when the wrong blood was received was also identified as a concern in two studies.[12,13] Because this limitation in study analysis was attributable only to 23 patients and unlikely to affect the aggregate results of this meta-analysis, we treated the patients as randomized to the blood products they received.

Large double-blinded clinical trials randomizing patients at the point of transfusion would best address the issue of whether leukoreduced blood transfusions are superior to standard, non-filtered blood. Ironically, in countries that adopted a universal leukoreduction program, randomized trials are no longer feasible. In such countries, effectiveness is best determined by conducting large before and after studies.[25–27]

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