

Effectiveness of using the post-storage filter compared to pre-storage filter used for leukoreduction of blood components in the clinical outcomes of patients: a systematic review protocol

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ABSTRACT

Objective: This review will aim to synthesize the best available evidence on the effectiveness of leukocyte reduction comparing post-storage and pre-storage filters regarding transfusion reactions, bacterial infection, length of stay, and mortality.

Introduction: Transfusion is a relevant therapy, but it is not risk-free. Leukocyte reduction can be performed either by apheresis or by pre- or post-storage filters in order to reduce the risk of transfusion reactions, transmission of some diseases, alloimmunization, and platelet refractoriness, in addition to the length of stay and the use of antibiotics.

Inclusion criteria: Studies comparing the transfusion of leukocyte reduction through post-storage filter with pre-storage filters in patients of any age who received the transfusion and the clinical outcomes resulting from the transfusion will be considered for inclusion. Studies in Portuguese, English, and Spanish will be considered, with no publication time limit.

Methods: The research sources will include MEDLINE (PubMed), CINAHL (EBSCO), PsycINFO (APA), Scopus (Elsevier), The Cochrane Library (J. Wiley), Web of Science Core Collection (Clarivate Analytics), Embase (Elsevier), LILACS (VHL), and gray literature sources. The selection of titles and abstracts will be carried out by two independent reviewers, and the critical evaluation of the studies will be based on JBI tools. The data of interest for the review question will be extracted using JBI SUMARI. A narrative synthesis will be performed as well a meta-analysis and risk assessment of publication bias if possible.

Systematic review registration: PROSPERO: CRD42020192202.

Keywords: clinical outcomes; leukocyte reduction; post-storage filter; pre-storage filter; transfusion

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Introduction

Transfusion is a relevant therapy for treating patients, especially those who are critically ill, to obtain biological responses, such as increased tissue oxygenation, bleeding prevention, or bleeding cessation.¹⁻⁴ Alloantigens and metabolically active cells capable of proliferating and producing response

modifiers that affect the recipient are introduced during the transfusion. In addition, there is a release of inflammatory mediators by the degradation of leukocytes, such as cytokines, interleukins (IL) 1-6, and tumor necrosis factor, as blood components are collected, processed, and stored. At the same time, the recipient will respond to the transfusion by producing immunological mediators, which further influence clinical response.⁵

Despite the advances in transfusion medicine, this therapy can still cause significant morbidity and mortality conditions due to the risks related to the procedure, whether they are failures in the process

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during the blood cycle due to incorrect indication, inappropriate use of the blood components, or aspects inherent to the recipient themselves.¹⁻⁴ Blood components are products generated in blood services from whole blood: red blood cells (RBCs), platelet concentrates (PCs), fresh frozen plasma, and cryoprecipitate.^{3,4,6}

Transfusion reactions (TRs) are among the morbidity and mortality conditions related to the use of blood components. According to Agence Nationale de Sécurité du Médicament et des Produits de Santé, it is estimated that the expected rate of TRs is three to five reactions for every 1000 transfusions performed.⁷ Studies also indicate that RBCs and PCs are responsible for the majority of TRs.^{8,9} The main TR associated with the presence of mediators released by leukocyte degradation is the febrile non-hemolytic transfusion reaction (FNHTR). Furthermore, alloimmunization to human leukocyte antigen (ALO-HLA), transfusion-related acute lung injury (TRALI), as well as graft versus host disease (GVHD), and transmissible diseases, including cytomegalovirus (CMV), have been found, however, less frequently.⁷⁻¹⁰ Another relevant point is that transfusion immunomodulation, which involves the effects of transfusions on the immune system, can cause undesirable clinical events, such as an increase in postoperative bacterial infections and recurrence of malignant diseases (eg, intestinal neoplasia), reactivation of latent and asymptomatic infections, and increased morbidity and mortality.¹¹⁻¹³

Leukocyte reduction is one of the procedures used to remove leukocytes through the use of filters or apheresis to avoid TRs and transfusion immunomodulation. A pre-storage filter (leukocyte removal filter) is used during donation (in-line) or in separating the blood components (from the “bench”) within 48 hours after collection. The post-storage filter is used at the bedside during transfusion. The leukocyte reduction of RBC should contain less than 5×10^6 leukocytes per unit, while the PC should contain 5×10^6 leukocytes per pool unit, or 0.83×10^6 per unit. Fresh frozen plasma does not need leukocyte reduction, since there are too few leukocytes to cause harm.¹⁴

Leukocyte reduction can mitigate the risks of TRs such as FNHTR, transmission of some viruses, ALO-HLA, and platelet refractoriness. Platelet refractoriness is defined as inadequate platelet increase after transfusion of recent (≤ 48 hours)

ABO-type compatible platelets, in at least two transfusions, preferably consecutive.¹⁵ Some studies suggest other clinical benefits of leukocyte reduction, such as reduced length of stay and use of antibiotics, in addition to improving platelet transfusion efficiency.^{11,15,16}

Countries in Europe, such as Germany, the United Kingdom, Ireland, and Portugal, among others, have adopted leukoreduction since 1990 to prevent TR complications and transmission of Variant Creutzfeldt-Jakob Disease (vCJD).^{17,18} Canada has implemented the same method to prevent transfusion immunomodulation.¹⁹

Some of the benefits of leukocyte reduction with the use of the pre-storage (in-line or “bench”) filter are: avoiding the accumulation of cytokines, which are synthesized during the storage of cells; avoiding the hemolysis of red cells, and the interruption of filtration caused by cell remains resulting from the storage of concentrated red blood cells; and ensuring the quality control of leukocyte reduction of products intended for transfusion. The post-storage filter (bedside) does not eliminate the mediators produced by the degradation of leukocytes, such as cytokines, interleukins, and tumor necrosis factor, which are responsible for unfavorable clinical outcomes of the receptors.^{7,11,20}

Some studies comparing the use of blood components subjected to pre- and post-storage filtration have shown that pre-storage leukoreduction is beneficial for reducing TRs, infection, and postoperative mortality, particularly in patients with cancer, transplants, or hematological diseases.²⁰⁻²² However, other studies have shown no difference between pre- and post-storage procedures.^{23,24}

Preliminary research conducted in PROSPERO, The Cochrane Library, and JBI Evidence-based Practice Database identified two reviews that analyzed the effects of leukocyte reduction. One of the systematic reviews published in 2015 analyzed the effectiveness of leukoreduction on the outcomes presented by the transfused population, which were: TRALI, death from any cause, infection, non-infectious complications, and adverse events. This review did not identify clear evidence to support or reject the use of leukocyte reduction for all patients undergoing transfusion, mainly due to the low quality of the evidence produced.²⁵ The most recent review, published in 2018 analyzed the effectiveness of leukocyte reduction for the outcome of

death and infection, specifically for patients undergoing cardiac surgery, and identified that the leukocyte reduction process was effective in preventing infection from any cause as well as inpatient mortality.²⁶

It should be noted that the two reviews did not identify the filter (pre- or post-storage) used to perform the leukocyte reduction of blood components. The analysis of this information is important to improve patient safety. Thus, the present systematic review will synthesize the best available evidence on the effectiveness of using the post-storage filter in comparison to the pre-storage filter in leukocyte reduction of blood components for the following clinical outcomes: TRs, bacterial infection, length of stay, and hospital death of patients undergoing transfusion.

Review question

What is the effectiveness of leukocyte reduction comparing post-storage filter (bedside) and pre-storage filters (“bench” or in-line) regarding the occurrence of TRs and bacterial infection, in addition to the length of stay and death of patients?

Inclusion criteria

Participants

This review will consider studies that include patients of any age, gender, and race who received leukodepleted blood-component transfusion.

Intervention

This review will consider for inclusion studies that used a post-storage filter (bedside) of any brand and type to remove leukocytes.

Comparator

Studies that report the use of a pre-storage filter (“bench” or in-line) of any brand and type to remove leukocytes will be considered.

Outcomes

The following outcomes will be considered: length of stay, TRs, bacterial infection, and hospital death.

The length of stay will be considered as the days the patient stayed in the hospital. Transfusion reactions will be defined by the type of reaction (immediate [within 24 hours after the transfusion] and late [24 hours after the transfusion]) and the diagnosis of

the confirmed reaction (ALO-HLA, FNHTR, or TRALI). Infection will be defined as the occurrence of bacterial infection confirmed by laboratory examination. Hospital death will be identified as this event confirmed, from any cause, after receiving a leukocyte reduction transfusion.

Types of studies

The following study designs will be considered for inclusion in the review: experimental or quasi-experimental studies, including randomized or non-randomized clinical trials, prospective or retrospective cohort studies, case-control and cross-sectional observational studies, and case reports or case series.

Studies published in Portuguese, English, and Spanish will be included. No time limit will be considered for the review.

Methods

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of effectiveness.²⁷ The review project was registered with PROSPERO (CRD42020192202).

Search strategy

The search strategy will aim to locate published and unpublished studies using the three steps recommended in the *JBI Manual for Evidence Synthesis*.²⁷ A generic and limited initial search in PubMed and CINAHL was conducted to identify the publications on the subject, followed by the analysis of the words contained in the title and abstract, as well as index terms or keywords. A second, more specific search, using the identified keywords and index terms from the initial search, will be conducted in all databases included in this review. Finally, a referenced search will be done using the bibliographic references of the articles found, as well as searches for studies in the gray literature, including government websites, societies and groups of specialists, as well as a digital library of theses and dissertations.

The index terms and initial keywords used were: (transfusion OR blood transfusion) AND (blood component removal OR leukocyte removal procedures OR leukocyte reduction OR leukoreduction OR leukodepletion OR leukoreduction filtration OR leukocyte reduction filtration OR leukocyte reduction procedures OR post-LR OR postLR OR post LR OR post-SLR OR postSLR OR post SLR) AND

(pre-storage OR prestorage OR pre storage OR prestorage leukoreduction OR prestorage leucoreduction OR in line filter OR inline filter OR in-line filter OR universal leukocyte reduction OR universal leucocyte reduction OR universal leukoreduction OR universal prestorage leukoreduction OR universal leukodepletion OR pre-LR OR ULR) OR (post storage OR poststorage OR post-storage OR post-storage filter OR bedside filter OR poststorage leukoreduction) AND (death OR mortality OR transfusion reaction OR delayed transfusion reaction OR acute transfusion reaction OR length of stay OR hospital stay OR stay length OR infection).

The search strategy containing the identified keywords and index terms will be adapted for each information source included. The initial strategy conducted is described in Appendix I. A librarian with experience in systematic health reviews will assist in refining the specific search strategies for each database. The research sources will include MEDLINE (PubMed), CINAHL (EBSCO), PsycINFO (APA), Scopus (Elsevier), The Cochrane Library (Wiley), Web of Science Core Collection (Clarivate Analytics), Embase (Elsevier), and LILACS (VHL).

The search for unpublished studies (gray literature) will include the Health Surveillance Agency (Anvisa: Agência Nacional de Vigilância Sanitária), Pan American Health Organization (PAHO), World Health Organization (WHO), Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular), American Association of Blood Banks (AABB), Digital Library of Theses and Dissertations, AllTrials, and RIAT (Restoring Invisible and Abandoned Trials).

The reviewers will contact the authors of the studies included in the analysis if additional information is needed.

Study selection

After the search, the identified bibliographic references will be grouped and imported into EndNote online V.X9.3 (Clarivate Analytics, PA, USA), and the duplicate articles will be removed.

The titles and abstracts of the studies will be examined in the first stage of the systematic review, with those pertinent to the review question selected for full text retrieval. The evaluation will take place based on the inclusion criteria and will be conducted

by two reviewers independently. Any divergences between the reviewers in the study selection process will be resolved through consensus or consultation with a third reviewer.

The selection results will be reported in full in the final systematic review and presented in the form of a flowchart using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method.²⁸ Justifications for exclusion occurring in the full-text reading phase will be available in the final review.

Assessment of methodological quality

The JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) will be used to develop the systematic review. Eligible studies will be critically evaluated by two independent reviewers for methodological quality using standardized JBI critical assessment tools.²⁷ Any differences between reviewers will be resolved by consensus or via a third reviewer. Studies will not be excluded based on methodological quality. If possible, sensitivity or group analyses will be carried out at the synthesis stage, depending on the methodological quality of the studies.

The critical evaluation of the studies will be based on questions related to their risk of bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to establish the quality of the evidence, and a full explanation will be provided in the review.²⁹ The results of the critical evaluation will be reported in narrative form and tables.

Data extraction

Data will be extracted from the studies included in the review by two independent reviewers using a standardized JBI data extraction tool. The extracted data will include details on population, study design, interventions, and relevant results according to the review question and objective.

Any differences between reviewers will be resolved by consensus or through consultation with a third reviewer. Authors of papers will be contacted to request missing or additional data when necessary.

Data synthesis

The studies will, whenever possible, be grouped into statistical meta-analyses using JBI SUMARI³⁰ to

estimate a summary average effect according to the selected outcomes (length of stay, TRs, bacterial infection, and hospital death). Effect sizes will be expressed as odds ratio (for dichotomous data) and differences from weighted post-intervention means (for continuous data), with a 95% confidence interval calculated for the analysis. The appropriateness of meta-analyses will be based on the clinical, methodological, and statistical homogeneity of the studies. The statistical heterogeneity will be evaluated by visual inspection of the forest plots and using the χ^2 and I^2 standard tests. The χ^2 tests with p-values less than 0.05 or I^2 greater than 50% will indicate meta-analysis is not appropriate. Sub-group or sensitivity analyses will be carried out according to the different designs and methodological quality of the studies, if applicable. The statistical analyses will be carried out with the support of a professional statistician and the model to be used (random or fixed effects) will be defined according to the number and characteristics of the studies included and their results.³⁰ Whenever meta-analyses are appropriate, the random effect model will be used if at least five studies were included; in the case of less than five studies, the fixed effect model will be applied.³⁰

A funnel graph will be generated in Microsoft Excel (Redmond, Washington, USA) to evaluate the publication bias if 10 or more studies were included for the meta-analysis. Statistical tests for funnel graph asymmetry will be performed when appropriate. When a meta-analysis is not possible, the results will be presented in narrative form, including tables and figures.

Assessing certainty in the findings

The GRADE approach to evaluating evidence will be followed. A Summary of Findings will present the following information when appropriate: absolute risks for the pre-storage filter group and the post-storage filter group, relative risk estimates, and a ranking of the quality of evidence—based on bias risk, directivity, heterogeneity, accuracy, and publication risk of the review results. The outcomes reported in the review will be the length of stay, presence of TRs, bacterial infection, and hospital death.

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Appendix I: Search strategy

MEDLINE (PubMed)

Date searched: January 17, 2021.

Search	Query	Records retrieved
#1	"blood transfusion"[Mesh] OR "blood transfusion" [tw] OR "blood transfusion" OR transfusion [tw] OR transfusion OR (blood NEAR 5 transfusion)	194,265
#2	"blood component removal" [Mesh] OR "blood component removal" [tw] OR "blood component removal" OR leukoreduction [tw] OR leukoreduction OR "Leukocyte Reduction Filtration" [tw] OR "Leukocyte Reduction Filtration" OR "Leukocyte Reduction Procedures"[Mesh] OR "Leukocyte Reduction Procedures" [tw] OR "Leukocyte Reduction Procedures"	25,301
#3	#1 AND #2	11,433
#4	"post storage" [tw] OR "post storage" OR "bedside filter" [tw] OR "bedside filter" OR poststorage [tw] OR poststorage OR post-storage [tw] OR post-storage OR post-LR [tw] OR post-LR OR postLR [tw] OR postLR OR "post LR" [tw] OR "post LR" OR "poststorage leukoreduction" [tw] OR "poststorage leukoreduction" OR post-SLR [tw] OR post-SLR OR postSLR [tw] OR postSLR OR "post SLR" [tw] OR "post LR"	317
#5	pre-storage [tw] OR pre-storage OR "pre storage leukoreduction" [tw] OR "pre storage leukoreduction" OR "pre storage leucoreduction" [tw] OR "pre storage leucoreduction" OR "inline filter" OR "in line filter" OR "in-line filter" OR prestorage [tw] OR prestorage OR preSLR [tw] OR preSLR OR "pre storage" [tw] OR "pre storage" OR pre-LR [tw] OR pre-LR OR "prestorage leukoreduction" [tw] OR "prestorage leukoreduction" OR "prestorage leucoreduction" [tw] OR "prestorage leucoreduction" OR "universal leukocyte reduction" [tw] OR "universal leukocyte reduction" OR "universal leucocyte reduction" [tw] OR "universal leucocyte reduction" OR "universal leukoreduction" [tw] OR "universal leukoreduction" OR "universal leucoreduction" [tw] OR "universal leucoreduction" OR ULR [tw] OR ULR OR "universal prestorage leukoreduction" [tw] OR "universal prestorage leukoreduction" OR "universal leukodepletion" [tw] OR "universal leukodepletion" OR "universal leucodepletion" [tw] OR "universal leucodepletion"	1120
#6	#4 OR #5	1369
#7	#3 AND #6	277
#8	Death [Mesh] OR death [tw] OR death OR mortality [Mesh] OR mortality [tw]	2,029,535
#9	"transfusion reaction" [Mesh] OR "transfusion reaction" [tw] OR "transfusion reaction" OR "delayed transfusion reaction" [tw] OR "delayed transfusion reaction" OR "acute transfusion reaction" [tw] OR "acute transfusion reaction"	16,766
#10	"stay length" [tw] OR "stay length" OR "hospital stay" [tw] OR "hospital stay" OR "length of stay" OR "length of stay"[Mesh] OR "length of stay" [tw]	175,607
#11	Infection [tw] OR Infection OR Infection [Mesh]	3,547,169
#12	#8 OR #9 OR #10 OR #11	5,319,563
#13	#7 AND #12	116
#14	#7 AND #12 Filters: Language	113
	Limited to English, Portuguese, Spanish language	