Universitat Autònoma de Barcelona

Evidencias científicas sobre las estrategias utilizadas para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos

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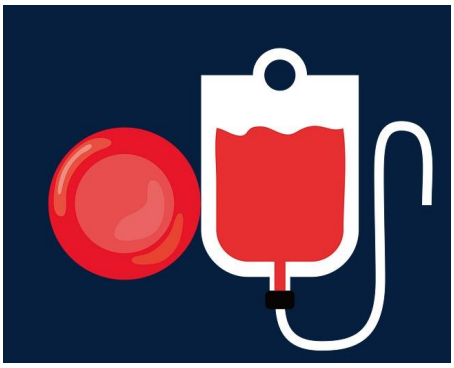

TESIS DOCTORAL

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BARCELONA, SEPTIEMBRE 2019

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AGRADECIMIENTOS

A mis directores de tesis, Xavier Bonfill y Gerard Urrútia, por acompañarme en estos años y apoyarme en el cumplimiento de esta meta académica y personal, además de ser grandes profesores y guías en este proceso.

Al Dr. Ricardo Hidalgo quién con su mentoría y sabiduría me ha apoyado en cada paso hasta alcanzar este logro.

A mis padres por su apoyo incondicional en todos los momentos difíciles de este proceso.

A toda mi familia, en especial a Mónica, Teresa, Lola que me apoyaron en todo momento.

A mi esposa por su paciencia y soporte vital para esta meta.

A los coautores de cada una de mis publicaciones, por compartir sus conocimientos, tiempo y experiencia en cada momento del proceso.

A mis pupilos, Andrés, Paula y Camila, quienes con su apoyo incondicional me recuerdan lo importante de esta meta para la construcción de nuestros sueños.
A Nadia y Solange por su ayuda incondicional en los momentos difíciles.

A todos quienes integran el Centro Cochrane Iberoamericano, por toda su ayuda desinteresada en el desarrollo de cada uno de estos trabajos de investigación.

A mis colegas y amigos de la Universidad UTE y de la Facultad de Ciencias de la Salud Eugenio Espejo, especialmente a mis jefes directos Camilo Félix, Verónica Guerra y Ricardo Hidalgo, quienes me apoyaron de múltiples maneras el desarrollo y finalización de estos trabajos.

CITA

"Investigar es ver lo que todo el mundo ha visto, y pensar lo que nadie más ha pensado".

Albert Szent-Györgyi

CONFLICTOS DE INTERÉS

El autor de este trabajo no declara conflictos en cada una de las publicaciones reportadas como parte de los requisitos para la obtención del grado de Doctor PhD en Salud Pública y Metodología de la Investigación Biomédica.

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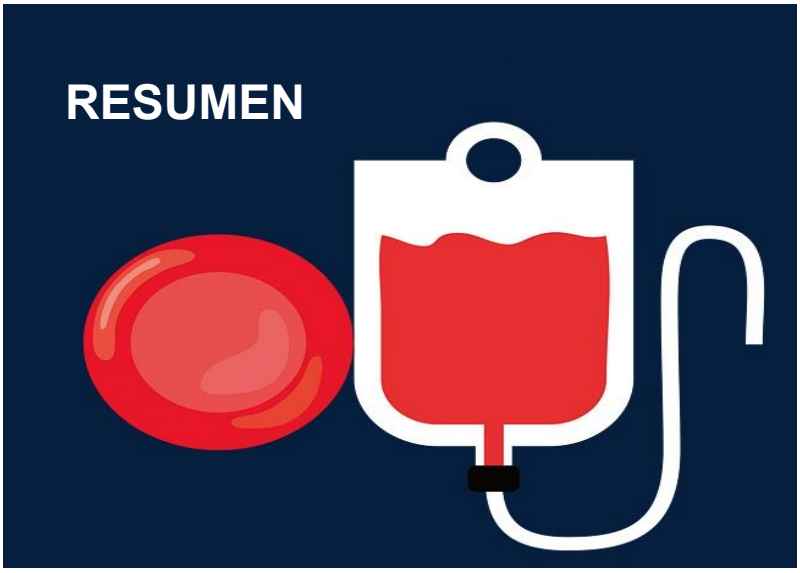
RESUMEN

1. RESUMEN

Antecedentes: la transfusión sanguínea es uno de los procedimientos más utilizados en la práctica clínica y su seguridad es un tema relevante que ha sido abordado por la mayoría de los centros investigativos de prestigio internacional. La seguridad en la transfusión sanguínea ha sido ampliamente estudiada, desde los factores de riesgo asociados a la transfusión de sangre y sus determinantes, hasta la evaluación de diversas estrategias en distintas etapas del proceso transfusional encaminadas a la prevención de posibles complicaciones. Existen discrepancias en cuanto a la efectividad y seguridad de las estrategias que se llevan a cabo para garantizar la seguridad de los pacientes que se someten, específicamente, a una transfusión sanguínea de concentrados de glóbulos rojos (CGR); por lo que resulta necesario profundizar y analizar la evidencia actual en este tema prioritario para la salud pública.

Objetivo General: Evaluar la calidad de las evidencias científicas en relación con las estrategias utilizadas para la prevención de las reacciones adversas asociadas a la transfusión de CGR.

Objetivos Específicos:

- Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de CGR.
- Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos específicamente en pacientes sometidos a procedimientos quirúrgicos cardiovasculares mayores.
- Evaluar la calidad de las guías de práctica clínica (GPCs) disponibles que incluyan recomendaciones basadas en evidencia sobre las estrategias para la prevención de reacciones adversas relacionadas con la transfusión de

concentrados de glóbulos rojos, específicamente relacionadas con el umbral de transfusión.

Métodos: Se desarrollaron tres trabajos de investigación cuyos diseños consistieron en revisiones sistemáticas de la literatura científica. El primero, evaluó la efectividad y seguridad de la transfusión de CGR leucorreducidos versus CGR no leucorreducidos. El segundo trabajo, evaluó la efectividad y seguridad de la transfusión de CGR leucorreducidos versus no leucorreducidos en pacientes sometidos a procedimientos de cirugía mayor cardiovascular. El tercer trabajo corresponde a una evaluación crítica de las GPCs que abordaron recomendaciones sobre transfusión de CGR con el instrumento AGREE II, y en el mismo trabajo se realizó un mapeo de la evidencia científica sobre el umbral de hemoglobina necesario para transfundir a un paciente en la práctica clínica. Adicionalmente, se realizó una revisión sistemática (RS) con metanálisis sobre el efecto del almacenamiento prolongado de concentrados de glóbulos rojos antes de la trasfusión (Anexo 1)

Resultados:

1.- A través de una SR que incluyó trece ensayos clínicos aleatorizados (ECA) que cumplieron con los criterios de elegibilidad, encontramos evidencia poco clara respecto a la efectividad de la transfusión de concentrados de glóbulos rojos leucorreducidos versus concentrados de glóbulos rojos no leucorreducidos para evitar: 1.- Daño agudo pulmonar asociado a la transfusión (TRALI por sus siglas en inglés), resultado obtenido a partir de un ECA que reportó datos de 1864 pacientes; 2.- Muerte por cualquier causa: resultado obtenido a partir de nueve ECAs que reportaron datos de 6485 pacientes; 3.-Infección por cualquier causa: obteniendo a partir de diez ECAs que reportaron datos de 6709 pacientes; 4.- Eventos adversos: el único evento adverso reportado fue fiebre y el resultado obtenido fue a partir de dos ECAs que reportaron datos de 634 pacientes. El análisis secuencial de los ensayos (TSA por sus siglas en inglés) determina que el tamaño de la muestra

obtenido para estos desenlaces no fue suficiente para evitar errores tipo I y II en las estimaciones, lo que indica la necesidad de conducir un número mayor de ECAs sobre este tema para obtener resultados más confiables. La calidad de la evidencia fue baja y muy baja para estos desenlaces.

2.- A través de una SR con metanálisis se encontró siete ECAs que cumplieron con los criterios de elegibilidad, encontramos evidencia clara respecto a la efectividad de la transfusión de concentrados de glóbulos rojos leucorreducidos versus concentrados de glóbulos rojos no leucorreducidos en pacientes sometidos a procedimientos de cirugía mayor cardiovascular para evitar: 1.- Muerte por cualquier causa: resultado obtenido a partir de siete ECAs que reportaron datos de 2771 pacientes; 2.-Infección por cualquier causa: resultado obtenido a partir de seis ECAs que reportaron datos de 1852 participantes. El TSA determina que el tamaño de la muestra obtenido para estos desenlaces fue suficiente para evitar errores tipo I y II en las estimaciones, es decir no hay necesidad de conducir un número mayor de ECAs sobre este tema para obtener resultados más confiables. La calidad de la evidencia para estos desenlaces fue “moderada”.

3.- En cuanto a la calidad de las GPCs sobre transfusión de concentrados de glóbulos rojos, solamente 3 de 16 GPCs fueron recomendadas por los evaluadores, debido a problemas en los diferentes dominios evaluados en el instrumento AGREE II. Los resultados (media ± DS) obtenidos en los distintos campos evaluados fueron: Alcance y objetivo (59.4% ± 19.8%), participación de los implicados (43.2% ± 22.6%), rigor en la elaboración (50% ± 25%), claridad de la presentación (74.4% ± 12.6%), aplicabilidad (19.4% ± 18.8%) e independencia editorial (41% ± 30%). Siete GPCs recomendaron una estrategia restrictiva para la transfusión de concentrados de glóbulos rojos; cuatro GPCs consideraron que una transfusión de concentrados de glóbulos rojos segura debería ser prescrita de acuerdo con el valor de hemoglobina de 7 g/dL; ocho GPCs no proporcionaron recomendaciones sobre el umbral hemoglobina necesaria para realizar transfusiones de concentrados de

glóbulos rojos, ya que mencionaron que estas transfusiones no deberían ser prescritas de acuerdo con el valor de hemoglobina únicamente.

Conclusiones:

1. No hay evidencia clara para apoyar o rechazar el uso rutinario de la transfusión de concentrados de glóbulos rojos leucorreducidos en todos los pacientes que requieren transfusión como estrategia para la prevención de reacciones adversas. La calidad de la evidencia es baja o muy baja, por lo que, se necesita más evidencia antes de poder llegar a una conclusión definitiva.

2. Encontramos evidencia que apoya el uso rutinario de leucorreducción exclusivamente en pacientes sometidos a un procedimiento quirúrgico cardiovascular importante y que requieren de transfusión de concentrados de glóbulos rojos para prevenir la muerte y la infección. En el caso de infección, las pruebas deben considerarse suficientes y concluyentes y, por lo tanto, indican que no se requiere de ensayos clínicos adicionales para demostrar su efectividad y seguridad.

3. La calidad de las GPCs que abordan la transfusión de concentrados de glóbulos rojos publicados a 2016 es heterogénea en aspectos metodológicos, sus recomendaciones, la aplicabilidad e independencia editorial. Aunque similares en contenido, varían ampliamente en términos de la valoración de la calidad de la evidencia por las serias deficiencias encontradas y la confianza en la implementación de estas en el contexto clínico. Las recomendaciones sobre el umbral de hemoglobina para transfundir concentrados de glóbulos rojos fueron heterogéneas entre las guías. Se necesitan mayores esfuerzos para proporcionar GPCs de alta calidad en la práctica clínica en relación con la transfusión de concentrados de glóbulos rojos.

1.2. Abstract

Background: blood transfusion is a common procedure applied in clinical practice, and the safety of this procedure constitutes a relevant research topic that has been studied by the most prestigious research centres around the world. Several studies on the safety of blood transfusion have focused on the risk factors associated with blood transfusion and its determinants, while others have addressed the evaluation of strategies for preventing possible complications at different stages of blood transfusion. There is disagreement in terms of the safety and effectivity levels required to guarantee overall patients' safety when they receive transfusion of packed red blood cells (PRBCs). Therefore, it is necessary to analyse current evidence in this relevant topic for public health.

Objective: to evaluate the quality of scientific evidence in relation to the strategies used to improve the safety of PRBCs transfusion in clinical practice.

Specific objectives:

- To assess the effects of leukoreduction, which is used as a strategy for the prevention of adverse reactions associated with the transfusion of PRBCs.
- To evaluate the effects of leukoreduction, which is used as a strategy for the prevention of adverse reactions associated with the transfusion of PRBCs in patients undergoing major cardiovascular surgical procedures.
- To assess the quality of available clinical practice guidelines (CPGs) that include evidence-based recommendations on strategies for preventing adverse reactions related to transfusion of PRBCs.

Methods: This paper includes four studies (systematic reviews) that systematically assess the evidence related to PRBCs transfusion. The first study evaluated the safety and effectivity of the transfusion of leukoreduced PRBCs versus non-leukoreduced PRBCs. The second study evaluated the effectivity and safety of the transfusion of leukoreduced PRBCs versus non- leukoreduced PRBCs in

cardiovascular surgery patients. The third study involves a critical appraisal of clinical practice guidelines (CPGs) about recommendations of PRBCs transfusion; this critical appraisal was performed by using the AGREE II tool. A mapping of evidence of the transfusion threshold needed in the clinical practice was also performed as part of this study. The fourth study (Annex I) is a systematic review with meta-analysis that evaluates the effects of prolonged storage of PRBCs before transfusion.

Results:

1) Unclear evidence regarding the effects of leukoreduced PRBCs transfusion vs non-leukoreduced PRBCs transfusion was found according to a systematic review that included 13 eligible studies. The effects of these interventions were focused on avoiding: a. Transfusion Related Acute Lung Injury (TRAIL) according to one study reporting 1864 patients; b. Death from any cause: according to nine clinical trials which reported data from 6485 patients; c. Infection from any cause: as reported by 10 clinical trials that included 6709 patients; d. Adverse events: fever was the only reported adverse event according to two clinical trials that included 634 patients. From the Trial Sequential Analysis (TSA) that was performed, it was found that the sample size calculated for these outcomes was not enough to avoid type I and type II errors in the estimates. The quality of evidence for these outcomes was considered low to very low.

2) According to a systematic review and meta-analysis that included seven eligible studies, there was clear evidence on the effects of leukoreduced PRBCs transfusion vs non-leukoreduced PRBCs transfusion in cardiovascular surgery patients. The effects of these interventions were focused on avoiding a. Death form any cause: obtained from seven clinical trials that reported data from 2771 patients; b. Infection from any cause: as reported by six clinical trials that reported data from 1852 patients. The TSA showed that the sample size calculated for these outcomes was not enough to avoid type I and type II errors in the estimates. The quality of evidence for these outcomes was moderate.

3) After evaluating the quality of CPGs about the transfusion of PRBCs, only three out of 16 CPGs were recommended. Results (mean ± SD) obtained from the domains that were evaluated include: Scope and Purpose (59.4% ± 19.8%), Stakeholder Involvement (43.2% ± 22.6%); Rigor of Development (50% ± 25%); Clarity of Presentation (74.4% ± 12.6%); Applicability (19.4% ± 18.8%); Editorial Independence (41% ± 30%). Seven CPGs recommended a limited strategy for PRBCs transfusion; four CPGs considered that a safe PRBCs transfusion should be prescribed according to a haemoglobin threshold of 7 g/dL. Eight CPGs did not provide recommendations on the threshold of haemoglobin needed to perform PRBCs transfusion since they mentioned that PRBCs transfusion should not be only prescribed according to the threshold of haemoglobin.

Conclusions:

1. There is not enough evidence to support or reject the regular application of PRBCs leukoreduction in all patients who require blood transfusion as a strategy to prevent adverse reactions. The quality of evidence is low to very low; therefore, more evidence is needed before making final conclusions.
2. We found evidence regarding the regular application of leukoreduction, specifically in patients who have been through important cardiovascular procedures, and who require PRBCs transfusion to prevent infection and death. This available evidence regarding the prevention of infection was enough to conclude that no further clinical trials are required to prove the effectiveness and safety of leukoreduction.
3. CPGs addressing PRBCs transfusion and published in 2016, presented heterogeneous quality in terms of methodology (recommendations, clinical applicability and editorial independence). Although the included CPGs had similar content, they presented discrepancies in regard to the quality evaluation of available evidence and in regard to their implementation in clinical settings. Recommendations about haemoglobin's threshold for PRBCs transfusion were

heterogeneous among guidelines. Further efforts are needed to generate high-quality CPGs in terms of PRBCs transfusion in clinical practice.


INTRODUCCIÓN

2. INTRODUCCIÓN

2.1. Anemia

La hemoglobina (Hb) contenida en los concentrados de glóbulos rojos, que se encuentran en la sangre, es esencial para el transporte de oxígeno. La Organización Mundial de la Salud (OMS) define la anemia como una concentración de Hb inferior a 13 g / dL en hombres e inferior a 12 g / dL en mujeres no embarazadas, y la describe como un estado clínico en el que se altera el transporte de oxígeno y puede producirse hipoxia tisular (1). La anemia no tiene una causa única, es la consecuencia de una variedad de factores. En los países de altos ingresos, la prevalencia general de anemia se estima en un 10% (2); sin embargo, esta cifra varía significativamente con los perfiles demográficos y los patrones de diagnóstico de comorbilidades (2,3). Los niños y los adultos mayores son los más comúnmente afectados por la anemia, alrededor del 90% de los recién nacidos prematuros con peso al nacer por debajo de 1.0 kg tienen anemia (4). En personas de mayor edad, las tasas vuelven a aumentar, en gran parte debido a la creciente incidencia de diagnóstico de comorbilidades.

La etiología de la anemia se puede dividir en procesos de enfermedad que perjudican la producción de glóbulos rojos y en procesos en los que se altera la vida media de los glóbulos rojos. En el primer grupo, son comunes ciertos trastornos tales como la disfunción medular adquiridos o iatrogénicos, la deficiencia nutricional y los procesos impulsados por citoquinas, y la anemia debida a enfermedad crónica. Mientras que el último grupo incluye procesos patológicos tales como el sangrado patológico y la hemólisis inmune. Cuando se produce una anemia grave, se requiere una corrección rápida, en estos casos, la transfusión de sangre es el único tratamiento viable capaz de restaurar la oxigenación del tejido.

2.2. Transfusión de Sangre

La transfusión de sangre se refiere a la infusión de concentrados de glóbulos rojos en un paciente para restaurar la oxigenación tisular y abordar afecciones agudas potencialmente mortales que puedan afectar la salud; en general, sus efectos a largo plazo tienden a ser de importancia secundaria (5). Esta infusión de formas solubles y asociadas a las células puede ser de eritrocitos, leucocitos y plaquetas (6).

A pesar de sus efectos beneficiosos, la transfusión de sangre se asocia también con un mayor riesgo de eventos adversos infecciosos y no infecciosos (7–9). La incidencia de reacciones no infecciosas a las transfusiones es mayor que la de las complicaciones infecciosas. La mortalidad asociada con los riesgos no infecciosos también es significativamente mayor y representa entre el 87% y 100% de las complicaciones mortales por transfusiones (10).

Los principales eventos adversos no infecciosos para el paciente son: la lesión pulmonar aguda relacionada con TRALI, que se considera la complicación no infecciosa más grave (11–13); la reacción febril no hemolítica a la transfusión (FNHTR por sus siglas en inglés) (14–16); y las reacciones alérgicas (17). Frecuente son la enfermedad “injerto versus huésped” asociada con la transfusión (TA-GVHD por sus siglas en inglés) (16,18,19), y la transfusión relacionada con un efecto en la inmunomodulación (TRIM por sus siglas en inglés) (20).

2.3. Transfusión de Glóbulos Rojos

El concentrados de glóbulos rojos ha sido un tratamiento común para la anemia desde la década de 1990 (21), la cual aún se practica ampliamente. Cada año, en el Reino Unido, se emiten alrededor de 1,7 millones de unidades de concentrados de glóbulos rojos (22). Esto equivale a una transfusión de

aproximadamente 36 unidades por cada 1000 habitantes por año, la cual es una cifra muy similar a la de otros países de ingresos altos (20,22). Es sorprendente, para una intervención tan generalizada, que una RS reciente concluya que faltan datos de ECAs rigurosos para respaldar los beneficios de muchas prácticas de transfusión actuales (23). De hecho, la evidencia obtenida de los ECAs indica poco o ningún beneficio de la transfusión de glóbulos rojos en los umbrales de concentración de hemoglobina del receptor más altos (comúnmente denominadas políticas "liberales" para la transfusión de glóbulos rojos) (24,25)

Las transfusiones de concentrados de glóbulos rojos también están asociadas con algunos riesgos ya descritos (26), tales como la contaminación bacteriana y viral, así como las reacciones alérgicas. El "*Serious Hazards of Transfusion*" (SHOT) es un esquema de hemovigilancia del Reino Unido que determinó que el riesgo de morbilidad relacionado con la transfusión fue de 63.5 por cada millón de componentes sanguíneos emitidos (27). Entre estos riesgos se encuentra el riesgo potencial del almacenamiento prolongado de concentrados de glóbulos rojos (28). Por lo tanto, las GPCs actualmente promueven políticas más restrictivas para la transfusión de concentrados de glóbulos rojos en varios entornos clínicos (25,29). A pesar de esto, la transfusión de concentrados de glóbulos rojos sigue siendo una intervención muy frecuente; por ejemplo, mientras que hasta el 60% de los pacientes ingresados en unidades de cuidados críticos (ICU por sus siglas en inglés) desarrollan anemia (30,31), solo del 10% al 15% tienen un historial de esta enfermedad crónica antes del ingreso en la ICU. Si no se interviniera con una transfusión de concentrados de glóbulos rojos, los valores de hemoglobina generalmente disminuirían en alrededor de 0.5 g / dL / día durante una enfermedad crítica por varias razones que incluyen una enfermedad inflamatoria asociada con enfermedad aguda, hemodiálisis, comorbilidades, sangrado y flebotomía (32). Como resultado, entre el 20% y el 50% de los pacientes en estado crítico reciben una transfusión de concentrados de glóbulos rojos, especialmente aquellos con insuficiencia orgánica múltiple.

Alrededor del 8% al 10% del suministro de sangre del Reino Unido se transfunde a los pacientes en ICU.

La transfusión de sangre es costosa, los costos directos de cada bolsa recolectada de concentrados de glóbulos rojos no son cercanos a los costos usualmente relacionados con la práctica hospitalaria de bancos de sangre y la administración segura de pacientes. En el 2008, el pago promedio de una unidad de concentrados de glóbulos rojos leucorreducidos en los EE. UU. fue de USD 223 (33). Sin embargo, si se consideran los costos de administración, así como los gastos de adquisición de la transferencia de concentrados de glóbulos rojos, el costo estimado derivado de cuatro hospitales de EE. UU. Y de Europa aumenta a USD 761 por unidad (desviación estándar +/- USD 294) (33).

2.4. Estrategias para la prevención de reacciones adversas

La principal opción de tratamiento para elevar rápidamente la concentración de Hb en pacientes con anemia sigue siendo la transfusión de concentrados de glóbulos rojos. Los concentrados de glóbulos rojos para transfusión se recogen de la donación de sangre total que posteriormente se centrifuga para concentrar las células, antes de agregar el anticoagulante y las soluciones de almacenamiento. Sin embargo, existen riesgos conocidos asociados a la transfusión de sangre, al igual que con cualquier intervención médica.

En los países con un suministro de sangre bien regulado, la seguridad de la transfusión alogénica de concentrados de glóbulos rojos ha mejorado considerablemente en los últimos 30 años, y los riesgos generales son muy bajos. Por ejemplo, en los EE. UU. el riesgo estimado por unidad de VIH es 1: 1,467,000 (34); para el virus de la hepatitis C (VHC), 1: 1,149,000 (34); y para el virus de la hepatitis B (VHB), 1: 282,000 a 1: 357,000 (35). Esto se debió principalmente a mejoras en las políticas de detección de sangre de los donantes y a la implementación de medidas de control de calidad más estrictas (36). En los países de escasos recursos, el suministro de sangre es inadecuado y puede

que no sea seguro porque a menudo no se realizan pruebas para detectar virus o patógenos. Las donaciones de sangre en 39 países no se analizan de manera rutinaria para detectar infecciones transmisibles por transfusión que incluyen el VIH, la hepatitis B, la hepatitis C y la sífilis (37). En 40 países, menos del 25% del suministro de sangre se obtiene de donadores de sangre no remunerados voluntarios, y la mayoría proviene de donantes de sangre familiares o pagados (37). La prevalencia del VIH de las donaciones de sangre en los países de bajos ingresos es del 2,3% en comparación con el 0,001% en los países de altos ingresos (37).

Se han descrito otros riesgos generales de transfusión (aunque tal vez no han sido tan difundidos) e incluyen reacciones agudas a la transfusión, sobrecarga de volumen, contaminación bacteriana, infección por patógenos transmitidos por la sangre nueva y lesión pulmonar aguda relacionada con la transfusión (38,39). Otros efectos adversos posibles incluyen la pérdida de la producción de óxido nítrico en los concentrados de glóbulos rojos, que se cree que induce la vasodilatación local y efectos inmunomoduladores o proinflamatorias variables de diferentes productos celulares en los concentrados de glóbulos rojos. En general, estos efectos dañinos de las transfusiones de concentrados de glóbulos rojos pueden manifestarse como un aumento de los riesgos de infecciones o eventos cardiovasculares, incluido el infarto de miocardio o el accidente cerebrovascular en los hospitales.

Existe también la preocupación de que el prolongado almacenamiento de concentrados de glóbulos rojos también pueda hacerlos menos eficaces y potencialmente dañinos. Sin embargo, los ensayos recientes no han demostrado daño clínico a la sangre almacenada durante aproximadamente 21 a 28 días en comparación con menos de siete a 10 días (40–43).

2.5. Leucorreducción

La transfusión de concentrados de glóbulos rojos con reducción de los leucocitos es uno de los enfoques más utilizados para la reducción de las complicaciones propias de la terapia transfusional (15,44,45). Los leucocitos (WBC por sus siglas en inglés) en los componentes sanguíneos pueden mediar las reacciones febriles a las transfusiones, estimular la aloinmunización de antígenos de leucocitos humanos (ALH) en los receptores de transfusiones y transmitir algunos agentes patógenos asociados con las células como el citomegalovirus (CMV). Por lo tanto, es aconsejable eliminar los WBC de los componentes sanguíneos transfundidles (46). La tabla 1 muestra las definiciones de reacción no infecciosa a la transfusión relacionada con los WBC.

La leucorreducción es un proceso que permite reducir los leucocitos de forma intencional en los concentrados de glóbulos rojos para reducir el riesgo de reacciones adversas. Este proceso reduce intencionalmente los glóbulos blancos en casi 99.99% de los concentrados de glóbulos rojos (47). Existen muchos métodos para llevar a cabo la leucorreducción, sin embargo, actualmente este proceso se lo realiza utilizando filtros de leucorreducción selectiva (46). De acuerdo con la Agencia de control de Drogas y Alimentos de los Estados Unidos (FDA por sus siglas en inglés), los concentrados de glóbulos rojos reducidos de WBC contienen menos de 5 × 10 ^ -6 WBC / unidad y al menos el 85% de los concentrados de glóbulos rojos originales (46), y de acuerdo al “agreement with the Council of Europe” menos de 1 × 10 ^ -6 WBC total / unidad. En general, la mayoría de los procesos de reducción de WBC de concentrados de glóbulos rojos se realizan en los centros de recolección de sangre en los primeros días después de la recolección (46).

Leucorreducción en pacientes con trauma. - La reducción de WBC en pacientes con trauma que requieren transfusión es una necesidad para el tratamiento exitoso de su condición. Sin embargo, no está claro si la leucorreducción en

concentrados de glóbulos rojos es el mejor método para proporcionar hemoderivados a pacientes con trauma (48–50). Los estudios retrospectivos han mostrado una reducción en las complicaciones infecciosas en pacientes transfundidos con sangre alogénica leucorreducida; este efecto parece ser más evidente en pacientes que reciben transfusiones masivas (> 6 unidades de concentrados de glóbulos rojos) (51).

Leucorreducción en pacientes sometidos a cirugía.- Varios estudios se han centrado en las ventajas de la reducción de WBC de los concentrados de glóbulos rojos para la transfusión en pacientes sometidos a cirugía cardíaca o a cirugía mayor (52–57); también se reportan estudios en cirugía colorrectal (53,58–62); cirugía gastrointestinal (53,56,63); y trasplante de riñón (64–66). Sin embargo, algunos de los hallazgos de estos ensayos publicados se consideran controversiales y contradictorios. Además, este enfoque se ha contrastado en pacientes con SIDA; pero, no queda claro si esta alternativa corresponde a una estrategia beneficiosa en esta población (67).

Tabla 1. Reacciones adversas no infecciosas relacionadas a la transfusión.

Términos	Definiciones	Referencias
Reacciones alérgicas	Las reacciones alérgicas son probablemente las más frecuentes, ya que ocurren en 1 a 2% de todas las reacciones que se producen después de la transfusión. Los síntomas varían desde prurito local o difuso, urticaria, eritema y enrojecimiento cutáneo, hasta reacciones alérgicas anafilácticas que ocurren a los pocos minutos de la transfusión. Las reacciones anafilactoides se encuentran entre los dos extremos del espectro. Las reacciones alérgicas no complicadas se asocian con un aumento de la histamina (aumento durante el	(17)

	almacenamiento), citoquinas, activadores de mastocitos (es decir, leucotrienos) y otras sustancias vasoactivas (C3a y C5a) producidas por los leucocitos del donante durante el almacenamiento	
Reacción febril no hemolítica (Febrile non-haemolytic transfusion reactions (FNHTR))	Las FNHTR se definen como un aumento de la temperatura de al menos 1 ° C en asociación con una transfusión o hasta 4 h después de esta, puede ir acompañado de escalofríos. Dichas reacciones se deben a los anticuerpos adquiridos contra antígenos leucocitarios donantes o citoquinas pirógenas (IL-1, IL6, IL-8 y TNF-D) producidas por los leucocitos presentes en los componentes o productos de la sangre.	(17)
Daño agudo pulmonar relacionado con la transfusión (definición clínica) Transfusion-related acute lung injury (TRALI) (clinical definition)	La definición más temprana de TRALI incluye a todos los pacientes que desarrollaron dificultad respiratoria aguda, hipoxemia moderada a grave (PaO2 30 a 50 mmHg), aparición rápida de edema pulmonar, hipotensión leve a moderada y fiebre (definida como un aumento de la temperatura corporal desde la línea de base antes de la transfusión) dentro de las 6 horas posteriores a la recepción de una transfusión de sangre que contiene plasma. La definición excluye a los pacientes que tienen una enfermedad cardíaca o respiratoria subyacente.	(39,68)

Daño agudo pulmonar relacionado con la transfusión (definición histológica) TRALI (histopathological definition)	Se evidencia por la fuga pulmonar intersticial y la histología pulmonar que mostró engrosamiento del tabique, se observa un infiltrado inflamatorio que consiste principalmente en granulocitos detectados luego de la transfusión.	(69)
Non-hemolytic febrile transfusion reaction (NHFTR)	La apoptosis de los leucocitos o la activación de los monocitos, o ambas, pueden hacer que las citocinas se acumulen en los productos sanguíneos durante el almacenamiento. Síntomas / signos: fiebre, escalofríos.	(14,16,70)
Enfermedad injerta contra huésped asociada a transfusión Transfusion-associated graft-versus-host disease (TA-GVHD)	Las células T inmunológicas viables presentes en los productos sanguíneos se introducen en un huésped inmunoincompetente que no puede destruir los linfocitos del donante. Síntomas / signos: náuseas, vómitos, anorexia, fiebre, diarrea acuosa, anomalías de la función hepática, aplasia de la médula ósea, erupción cutánea, ictericia e insuficiencia renal	(16,19)

Leucorreducción en pacientes sometidos a cirugía mayor cardiovascular.- Varios estudios se han enfocado en las ventajas de la transfusión de CGR leucorreducidos en cirugías cardiacas (54,55,57,71,72). Las cirugías cardíacas representan una gran proporción de las transfusiones sanguíneas que se administran cada año. La

taza de transfusión reportada para la combinación de cirugía de bypass coronario con válvula y otras intervenciones quirúrgicas mayores es de 7.8% a 92.8% (73).

A pesar de que las transfusiones sanguíneas son necesarias para las cirugías cardiovasculares, varios estudios han demostrado que las transfusiones sanguíneas también acarrean efectos perjudiciales. Por lo tanto, el subgrupo poblacional que ha sido sometido a cirugía cardiovascular es de gran interés para el análisis de la efectividad y seguridad de las prácticas de transfusión. Se ha demostrado que la cirugía cardíaca está relacionada al trauma de tejidos blandos, al daño isquémico de reperfusión y al contacto de la sangre con ciertas superficies; los mismos que conllevan a efectos sistémicos y a la liberación de mediadores de la inflamación. Ambas reacciones están relacionadas al desarrollo del Síndrome de Respuesta Inflamatoria Sistémica (SIRS por sus siglas en inglés), al Síndrome de Disfunción Orgánica Múltiple (MODS por sus siglas en inglés), a infecciones y a complicaciones post operatorias (74,75). Adicionalmente, la transfusión de CGR en cirugías cardiovasculares es frecuente y estas transfusiones han sido asociadas (según la dosis) con el incremento del riesgo de infecciones postoperatorias y mortalidad después de una cirugía cardiaca (76–80).

Los mecanismos de estos efectos son aún desconocidos (81); sin embargo, se ha encontrado la presencia de WBC alogénicos en el CGR, por lo que podrían cumplir un rol en la respuesta inflamatoria después de una cirugía cardíaca. Bilgin et al. demostraron que existe una gran concentración de mediadores proinflamatorios (IL-6 y IL-19) durante el periodo postoperatorio en pacientes que han sido sometidos a cirugías cardíacas con válvula y que han recibido una transfusión sanguínea que contenía WBC alogénicos comparado a pacientes que fueron sometidos a la misma intervención quirúrgica y que recibieron una transfusión sanguínea leucorreducida (82). Este resultado respalda los potenciales beneficios del uso rutinario de la transfusión de CGR leucorreducidos en cirugía cardíaca (83).

2.6. Almacenamiento de Sangre

Actualmente, las unidades de concentrados de glóbulos rojos se pueden almacenar de manera segura para transfusiones hasta por 42 días, según los estudios que han optimizado el almacenamiento al agregar nutrientes, fosfato y adenina (84–87). Cada vez es más claro que los cambios que se producen en el almacenamiento de concentrados de glóbulos rojos pueden afectar el suministro de oxígeno a través de una multitud de cambios metabólicos y fisiológicos que se producen durante el almacenamiento (88,89). Estos cambios en el almacenamiento conducen a cambios corpusculares en los concentrados de glóbulos rojos, lo que dificulta la deformación de estos. El daño oxidativo a la membrana del concentrados de glóbulos rojos, el agotamiento de 2, 3-DPG y ATP, y la canalización de fosfolípidos de la membrana contribuyen a los cambios corpusculares en estas células durante el almacenamiento (90). La suma total de este efecto en el glóbulo rojo se conoce como la "lesión de almacenamiento" (90).

Existe un interés creciente en explorar si la duración del almacenamiento de las unidades de concentrados de glóbulos rojos influye de manera independiente en los resultados clínicos (91). Los estudios en pacientes en estado crítico demostraron que la edad de la sangre transfundida puede afectar negativamente la estadía en la ICU y la supervivencia general (92–94). Estos estudios generalmente definen "nuevo" como almacenado por menos de 14 días y "viejo" como almacenado por más de 14 días. Aunque no hay un cambio específico que ocurra a los 14 días, esta es la duración del almacenamiento en la que se ha demostrado el mayor efecto sobre la mortalidad y la morbilidad.

2.7. Umbral de transfusión de glóbulos rojos

El fundamento para la transfusión de concentrados de glóbulos rojos en pacientes anémicos es probar el suministro de oxígeno a los tejidos y al miocardio, para reducir el trabajo compensatorio realizado por el corazón para aumentar el gasto cardíaco.

La transfusión de concentrados de glóbulos rojos es uno de los pocos tratamientos que pueden restaurar la oxigenación de los tejidos adecuadamente cuando la demanda de oxígeno supera la oferta (36,95). Muchos ECAs que compararon los resultados de los participantes asignados a diferentes políticas o programas de uso de concentrados de glóbulos rojos presentaron resultados después de la asignación aleatoria de participantes a los desencadenantes "restrictivos" (por lo general, los participantes se transfunden solo cuando su concentración de Hb cae a aproximadamente 7 g / dL a 8 g / dL) o desencadenantes "liberales" (participantes se transfunden a una concentración de Hb mayor de alrededor de 9 g / dL a 10 g / dL).

Históricamente, el estándar clínico ampliamente aceptado fue el de transfundir a los pacientes cuando el nivel de Hb cayó por debajo de 10 g / dL o el hematocrito cayó por debajo del 30%. Adams y Lundy propusieron por primera vez esta regla “10 / 30” en 1942, y sirvió como un activador de transfusión de concentrados de glóbulos rojos durante décadas (95,96). Sin embargo, la Conferencia de Consenso de los Institutos Nacionales de la Salud de 1988 en los EE. UU. informó que las pruebas no apoyaban un solo criterio de transfusión (97). Desde entonces, la mayoría de las guías publicadas han desaconsejado un único umbral para la transfusión de concentrados de glóbulos rojos, recomendando que se pueda utilizar un rango de valores de Hb entre 6 g / dL y 10 g / dL, dependiendo de la presencia de comorbilidad grave (98–103). Pautas de la Asociación Estadounidense de Bancos de Sangre (AABB, por sus siglas en inglés) recomiendan utilizar un umbral de transfusión restrictivo de 7 g / dL a 8 g / dL en la mayoría de los entornos clínicos (101).

2.8. La Colaboración Cochrane

Cochrane es una red global e independiente de clínicos, investigadores, pacientes y otros actores relacionados con la salud, que buscan responder al desafío de proveer evidencia generada de forma sistemática para informar las decisiones en el campo de la salud. Actualmente simplemente denominada como “Cochrane”, esta

es una organización sin fines de lucro cuyo objetivo es producir información confiable y accesible en el área de la salud, que sea libre de conflictos de intereses (p.e. intereses comerciales) (104).

La comunidad interesada en llevar a cabo este tipo de actividades ha crecido exponencialmente, desde su primera reunión anual celebrada en 1993 a la que asistieron 77 personas de nueve países, hasta los 11.000 miembros y más de 68.000 colaboradores de 130 países que conforman hoy la organización (105–107).

Uno de los principales objetivos de Cochrane (según su estrategia 2020) es producir evidencia de la más alta calidad a través de revisiones sistemáticas Cochrane y otras formas de síntesis de la evidencia para informar la toma de decisiones en el campo de la salud.

2.8.1. Revisiones sistemáticas y metanálisis

La RS es un diseño de investigación que consiste en la reunión de evidencia científica que cumple con criterios de elegibilidad establecidos para responder una pregunta de investigación específica. La RS se caracteriza por utilizar una metodología explícita y reproducible, una búsqueda sistemática de la evidencia, una evaluación de la validez de los resultados de los estudios incluidos, una presentación sistemática y síntesis de las características y resultados de los estudios incluidos (104).

Las RS son de gran utilidad para resumir los resultados de un grupo de estudios y estimar con mayor precisión y confiabilidad la efectividad de una intervención relevante para la toma de decisiones en pacientes y en la política pública. Las RS también pueden demostrar la falta de evidencia en ciertas áreas del conocimiento para guiar futuras investigaciones clínicas. Por lo tanto, este tipo de diseño es relevante para quienes toman decisiones en salud, de manera que ayuda a mejorar la práctica clínica, disminuir las variaciones en la atención en salud y tomar la mejor evidencia disponible para la aplicación de políticas públicas de salud (108).

2.8.1.1. Metanálisis

El término metanálisis se refiere a los métodos cuantitativos utilizados para resumir los resultados de una RS (109). A pesar de que los términos “revisión sistemática” y “metanálisis” se utilizan erróneamente de manera indistinta, son conceptos diferentes. El metanálisis es una técnica estadística que extrae y combina los resultados de varios estudios independientes en un único estimador (estadígrafo) para crear un resumen de resultados (104). Una revisión sistemática puede o no contener un metanálisis de los resultados según sea el caso; sin embargo, nunca un metanálisis debería ser interpretado sin el contexto de la revisión sistemática del que surgió.

El metanálisis es una técnica útil para mejorar la precisión en las estimaciones de riesgo, para generalizar los resultados a una población más grande, para cuantificar y analizar inconsistencia en los resultados y para identificar la variación entre distintos estudios (109).

Tanto las RS como los metanálisis han adquirido gran relevancia en diversos temas de salud, ambos han sido útiles para establecer una práctica basada en la evidencia y para resolver contradicciones entre resultados de diversas investigaciones independientes.

2.8.1.2. Análisis Secuencial de los Ensayos (Trial Sequential Analysis (TSA))

2.8.1.2.1. Error aleatorio en los metanálisis

Es importante definir el error aleatorio en el metanálisis, dado que algunos hallazgos metanalíticos "positivos" pueden deberse al azar (error aleatorio) en lugar de deberse a algún efecto "verdadero" de la intervención (110).

De manera similar, algunos hallazgos metanalíticos neutros o "negativos" ("no positivos") también pueden representar un "hallazgo casual" debido a la falta de poder estadístico y precisión (104,111–115)

Estos dos tipos de errores se conocen comúnmente como falsos positivos (o errores tipo I) y errores falsos negativos (o errores tipo II). En general, los metanálisis se consideran "positivos" o "negativos" sobre la base de alguna prueba estadística (estadísticas de prueba), comunicados con un valor de *p* o con el cálculo del respectivo intervalo de confianza (110)

Cuando un metanálisis incluye una pequeña cantidad de ensayos y una pequeña cantidad de pacientes, los errores aleatorios pueden causar hallazgos falsos y llevar a conclusiones espurias. A la inversa, cuando hay un gran número de pacientes, y cuando varios ensayos han confirmado los hallazgos de los ensayos anteriores, las estadísticas de las pruebas y las estimaciones del efecto de la intervención generalmente convergerán hacia la "verdad" (110).

Las figuras 1 (A) y 1 (B) ilustran ejemplos de dicha convergencia en las estadísticas de prueba. En ambas situaciones, las inferencias sobre la significación estadística son erróneas en ciertas etapas iniciales, pero eventualmente convergen al lado "verdadero" de la significación estadística.

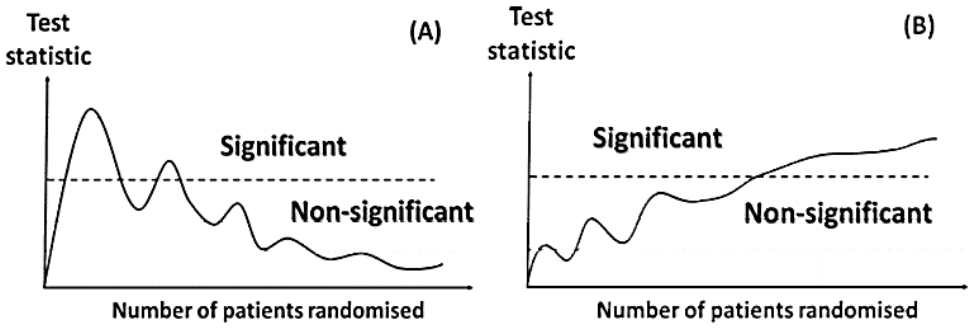

Figura 1. Ejemplos de convergencia en las estadísticas de pruebas a medida que los pacientes se incluyen y siguen hasta una medida de resultado (por ejemplo, muerte) en dos ensayos clínicos aleatorizados A y B.

2.8.1.2.2. Análisis Secuencial de los Ensayos

El análisis secuencial de los ensayos (TSA por sus siglas en inglés) es una metodología que utiliza una combinación de técnicas estadísticas, que permite

cuantificar la información requerida para estimar de manera confiable las diferencias estadísticamente significativas encontradas en los metanálisis y de esta forma tratar de disminuir la posibilidad de incurrir en un error en la interpretación de los resultados de las investigaciones clínica (110). La información requerida se cuantifica, proporcionando un valor del tamaño de muestra necesario para detectar las diferencias entre las comparaciones (information size). Los umbrales de significación estadística se ajustan y estas modificaciones se realizan de acuerdo con la fuerza cuantificada de la evidencia y el impacto de la multiplicidad, que no se toma en cuenta a los metanálisis convencionales (113,114).

Los umbrales para la inutilidad de una intervención también se pueden construir con estas estrategias y utilizando un marco estadístico similar (110).

En resumen, la TSA puede proporcionar un tamaño de la información necesaria para determinar el efecto estadísticamente significativo de un tratamiento y el umbral para la inutilidad cuando los estimativos indiquen que no hay diferencias entre los grupos comparados. Las conclusiones realizadas con el uso de la TSA muestran ser potencialmente más confiables que los que utilizan las técnicas tradicionales de metanálisis (110).

La evidencia empírica sugiere que las consideraciones de tamaño de la información y los umbrales de significación ajustados pueden eliminar los hallazgos falsos positivos tempranos debido a la imprecisión y las pruebas de significación repetidas en los metanálisis (110).

Alternativamente, uno puede penalizar el estadístico de prueba de acuerdo con la fuerza de la evidencia y el número de pruebas de significación realizadas (116,117).

Los estudios de simulación han demostrado que la penalización de las estadísticas de prueba permite un buen control del error tipo I en los metanálisis.

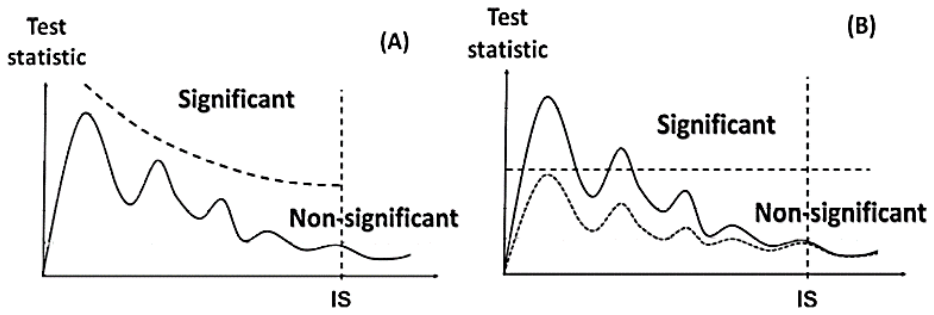

Figura 2. Ejemplos de ajuste del umbral de significación (límites de monitoreo estipulados) (A) y estadísticos de prueba penalizados (estipulados) (B) para evitar resultados falsos positivos y falsos negativos en dos metanálisis acumulativos A y B.

2.9. Guías de Práctica Clínica

Las GPC son documentos en los que se presentan recomendaciones elaboradas sistemáticamente para ayudar a la toma de decisiones por parte del personal de salud y sus pacientes (118). Estos documentos además pueden llegar a jugar un papel esencial en la elaboración de políticas de salud cuando son tomados en cuenta por parte de los tomadores de decisiones en salud (119,120).

La proliferación de documentos auto declarándose GPC ha llevado a la necesidad de introducir estándares al momento de elaborar GPC, estos han sido realizados por organismos internacionales tales como la Organización Mundial de la Salud (OMS), National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Net- work (SIGN), and Guidelines International Network (G-I-N) (121).

Estos estándares son necesarios ya que los potenciales beneficios de las GPC están estrechamente relacionados con la calidad intrínseca de las mismas. La calidad de una GPC se entiende como "*la confianza en que los sesgos potenciales del desarrollo de guías han sido resueltos de forma adecuada y en que las*

recomendaciones son válidas tanto interna como externamente y son aplicables a la práctica" (122).

Con el objetivo de evaluar la calidad de las GPC se creó el instrumento para la Evaluación de Guías de Práctica Clínica (AGREE por sus siglas en inglés) (122).

2.9.1. AGREE II

La herramienta AGREE fue originalmente publicada en el año 2003. Los objetivos de esta herramienta fueron generar un instrumento que evalúe la calidad de las GPC, proporcione una estrategia metodológica para su desarrollo y establezca información respecto a su correcta presentación (122).

Posteriormente se realizó una mejora de las propiedades métricas, de fiabilidad y validez de la herramienta, con el objetivo de facilitar la aplicación del instrumento y mejorar la confianza que los usuarios tienen en el mismo; esta versión de la herramienta es conocida como AGREE II. (123,124)

La herramienta AGREE II consta de 23 ítems que evalúan 6 dominios relevantes para determinar la calidad de las GPC. Estos dominios son alcance y objetivos, participación de los implicados, rigor en la elaboración, claridad en la presentación, aplicabilidad e independencia editorial.

2.10. Mapeo de Evidencia

El mapeo sistemático de evidencia es un tipo de metodología en la que se hace una revisión respecto a áreas de investigación amplias. Esta metodología describe la extensión y distribución de la evidencia disponible para promover el uso apropiado de la evidencia en el proceso de toma de decisiones en salud (125).

Usualmente esta aproximación sistemática permite identificar suficiente evidencia para informar a los tomadores de decisiones en salud, así como para reconocer áreas donde la evidencia está concentrada y en las que es susceptible conducir una RS. Así también, los mapeos de evidencia son importantes para reconocer brechas

del conocimiento en el cúmulo de evidencia para así priorizar investigación en esas áreas (125–127).

De acuerdo a (128), la realización de un mapeo sistemático incluye los siguientes pasos:

1. Identificar la(s) pregunta(s) de investigación.
2. Identificar los estudios relevantes.
3. Seleccionar los estudios.
4. Organizar la información obtenida de los estudios.
5. Recopilar, resumir y reportar la información obtenida.
6. Consultar a expertos en el área (paso opcional).

El mapeo sistemático también es útil para caracterizar estudios de acuerdo a la perspectiva teórica, al grupo poblacional de la investigación o al ámbito en el que los estudios fueron realizados (129). Sin embargo, es necesario considerar que los mapeos sistemáticos no incluyen un análisis de la calidad de los estudios incluidos por lo que los estudios son caracterizados netamente en base al diseño de los mismos (129).

El producto final del mapeo sistemático es, por lo general, una presentación narrativa con una mínima o limitada información estadística; puesto a que el objetivo del mapeo sistemático es sintetizar la evidencia existente de un tema al articular los conceptos claves derivados de fuentes, tales como investigaciones revisadas por pares, literatura gris y la opinión de expertos (130).

2.11. Justificación

La transfusión de concentrados de glóbulos rojos es una de las intervenciones más utilizadas en la práctica clínica para el tratamiento de los estados agudos y crónicos que producen pérdida de volumen sanguíneo en pacientes con diferentes condiciones de salud. Sin embargo, se ha cuestionado la seguridad de estas transfusiones y se las ha asociado con reacciones adversas serias

como: muerte, infección postoperatoria, daño agudo pulmonar relacionado con la transfusión y otras reacciones no infecciosas. Las estrategias para la prevención de estas complicaciones asociadas a la transfusión requieren un análisis minucioso para determinar su efectividad y seguridad especialmente para su implementación en países de escasos recursos. La evidencia disponible en relación con las variadas intervenciones en los distintos momentos del proceso salud-enfermedad sugiere efectos positivos, al punto de universalizar algunas de estas estrategias; sin embargo, para algunas de ellas aún hay insuficiente información o bien ésta es controversial.

Entre las intervenciones que pueden influir en las distintas etapas del proceso de transfusión de concentrados de glóbulos rojos está: la reducción intencional de glóbulos bancos de los derivados; la reducción del umbral para solicitar transfusiones, el tiempo corto de almacenamiento de los concentrados antes de transfundir, tamizaje de enfermedades infeccionas previo a la donación, entre otras estrategias analizadas en la literatura. Lamentablemente, existen controversias en la literatura reportada y la evidencia encontrada no es de calidad y no cuenta con tamaños de muestra necesarios para evitar conclusiones espurias. Para este trabajo de tesis doctoral, se consideraron las siguientes:

- La leucorreducción en los concentrados de glóbulos rojos, si bien es conocido en algunas regiones y países que, la leucorreducción se ha implementado de forma universal para todos los derivados sanguíneos como estándar en los bancos de sangre, es cierto también que en otros lugares su implementación es parcial, sobre todo considerando que esta estrategia es costosa y no ha demostrado de manera consistente su efectividad en todos los pacientes que se transfunden concentrados de glóbulos rojos. Es necesario este primer trabajo debido a las inconsistencias metodológicas y alta heterogeneidad encontradas en trabajos previamente publicados.

- El efecto de la leucorreducción en pacientes sometidos a procedimientos quirúrgicos cardiovasculares mayores que requieren transfusión de concentrados de glóbulos rojos: Si bien hay algunos estudios que han intentado determinar su efectividad, se hace necesario sistematizar la información existente a través de este segundo trabajo, para generar conclusiones válidas y determinar que la leucorreducción podría ser útil y segura en grupos de pacientes específicos y no en todo paciente que requiera transfusión. Este trabajo es el primero que analiza específicamente el grupo de pacientes sometidos algún procedimiento de cirugía cardíaca y cardiovascular.

- La calidad de las GPCs disponibles sobre transfusión de concentrados de glóbulos rojos: considerando la proliferación de GPCs y la importancia que éstas tienen al momento de recomendar las intervenciones más apropiadas a ser implementadas o recomendadas para esta condición específica, se hace necesario saber cómo éstas han sido desarrolladas y cuál es la validez y alcance de sus recomendaciones. Adicionalmente se quiere saber si las GPCs han evolucionado a través del tiempo logrando mejor calidad y confiabilidad. Se busca también mapear en estas guías el umbral de hemoglobina recomendado como estrategia para minimizar el número de transfusiones en cada paciente y con esto lograr que el beneficio de transfundir concentrados de glóbulos rojos supere los riesgos ya mencionados.

- La efectividad y seguridad del almacenamiento de los concentrados de glóbulos rojos: Finalmente, varios estudios reportan desenlaces desfavorables en pacientes transfundidos con concentrados de glóbulos rojos con almacenamiento prolongado, las lesiones de depósito que resultan de la degradación de las células provocan alteraciones con

potencial afectación sistémica en el individuo. Resulta necesario analizar sistemáticamente y de forma crítica la evidencia científica en relación con esta estrategia de prevención de reacciones adversas asociadas a la transfusión (anexo 1).

En este contexto se ha formulado la siguiente pregunta de investigación como hilo conductor para este trabajo de tesis, desarrollado como compendio de publicaciones:

Pregunta de Investigación:

¿Cuál es la calidad de las evidencias sobre las estrategias utilizadas para la prevención de reacciones adversas asociadas a la transfusión de glóbulos rojos?


OBJETIVOS

3. OBJETIVOS

3.1. Objetivo General

Evaluar la calidad de las evidencias científicas en relación con las estrategias utilizadas para la prevención de las reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos.

3.2. Objetivos Específicos

- Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos.
- Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos específicamente en pacientes sometidos a procedimientos quirúrgicos cardiovasculares mayores.
- Evaluar la calidad de las GPCs disponibles que incluyan recomendaciones basadas en evidencia sobre las estrategias para la prevención de reacciones adversas relacionadas con la transfusión de concentrados de glóbulos rojos, específicamente relacionadas con el umbral de transfusión.


MÉTODOS

4. MÉTODOS

4.1. Primer trabajo de investigación

El objetivo de esta RS Cochrane fue determinar la efectividad clínica de la transfusión de concentrados de glóbulos rojos en la prevención de reacciones adversas asociadas a la transfusión.

4.1.1. Criterios de inclusión de los estudios

4.1.1.1. Diseño de los estudios.

Ensayos clínicos aleatorizados controlados.

4.1.1.2. Tipo de participantes

Pacientes que requieran transfusiones sanguíneas alogénicas de concentrados de glóbulos rojos.

4.1.1.3. Tipo de intervenciones

- **Intervención**

  Transfusiones sanguíneas leucorreducidas de concentrados de glóbulos rojos. No aplicamos ninguna restricción para el tipo de leucorreducción aplicada.

- **Comparación**

  Transfusiones sanguíneas no leucorreducidas de concentrados De glóbulos rojos

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4.1.2. Tipos de desenlaces valorados

4.1.2.1. Desenlace primario

Incidencia de lesión aguda de pulmón relacionada con la transfusión (TRALI).

4.1.2.2. Desenlaces secundarios

- Muerte por cualquier causa
- Infección por cualquier causa
- Complicaciones no infecciosas (Anexo 1)
- Cualquier evento adverso, definido como "cualquier acontecimiento médico adverso que pueda presentarse durante el tratamiento con un producto farmacéutico pero que no necesariamente tenga una relación causal con este tratamiento" (131).

Tomamos la incidencia esperada para el resultado primario de esta revisión a partir del riesgo relativo informado en Nathens 2006 (48,49). Este estudio incluyó pacientes con trauma. Se definió un tamaño de muestra total de 8781 participantes necesarios para evaluar una reducción del riesgo relativo en los eventos de TRALI del 25%, a partir de una incidencia referencia en el control del 6,31% (nivel alfa del 5% y potencia del 90%).

4.1.3. Estrategia de búsqueda para la identificación de los estudios

Con el objetivo de disminuir las probabilidades de cometer un sesgo de publicación o de recogida, decidimos no restringir la búsqueda por idioma, fecha o estado de publicación.

4.1.3.1. Búsquedas electrónicas

El coordinador del Grupo Cochrane de Heridas realizó la búsqueda en las siguientes bases de datos:

- Registro especializado del Grupo Cochrane de Heridas (10/11/2015).
- Cochrane Central Register of Controlled Trials (CENTRAL, Biblioteca Cochrane) (volumen 10 of 12, 2015).
- MEDLINE (OvidSP) (1950 a semana 1 noviembre, 2015).
- Embase + Embase Classic (OvidSP) (1947 a 10/11/2015).
- LILACS (BIREME) (1982 a 10/11/2015).
- CINAHL Plus (EBSCO) (1937 a 10/11/2015).
- Clinicaltrials.gov (www.clinicaltrials.gov) (10/1/2015).
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) (10/11/2015).

Reportamos las estrategias de búsqueda en el anexo 2. Adaptamos la estrategia de Medline para las otras bases de datos. A la búsqueda en Medline añadimos la estrategia altamente sensible para la identificación de ensayos clínicos de Cochrane. Para la búsqueda en EMBASE añadimos términos de la estrategia de búsqueda y diseños de los estudios como se estila en el Centro Cochrane de Reino Unido (132).

4.1.3.2. Búsquedas en otras fuentes

Realizamos búsquedas en las siguientes páginas web (25 de noviembre de 2014)

- FDA Estados Unidos (http://www.fda.gov)
- Agencia Europea de Medicamentos (https://www.ema.europa.eu)
- Scirus (www.scirus.com)

- Asociación Americana de Bancos de Sangre (http://www.aabb.org)
- Biblioteca de la Evidencia en Transfusiones (https://www.transfusionguidelines.org)

Además, corroboramos las listas de referencias de todos los artículos incluidos.

4.1.4. Recolección y análisis de datos

Realizamos la síntesis de datos de acuerdo a los estándares de Cochrane, incluyendo el Manual Cochrane de SR (104) y las Expectativas Metodológicas para las Revisiones Cochrane de Tratamientos (MECIR) (133).

4.1.4.1. Selección de estudios

Dos revisores analizaron de forma independiente todos los estudios potencialmente relevantes identificados a través de las búsquedas de la literatura. Consultamos a un tercer revisor cuando existieron discrepancias, las cuales fueron resueltas mediante la discusión y consenso.

4.1.4.2. Extracción de datos

Dos revisores extrajeron los datos de forma independiente todos los estudios incluidos en esta revisión. Consultamos a dos revisores cuando existieron discrepancias, las cuales fueron resueltas mediante la discusión y consenso. Los datos recogidos fueron: criterios de elegibilidad, datos demográficos (sexo, edad, país), tipo de cirugía, ámbito (p.e. cirugía cardíaca, unidad de cuidados intensivos), desenlaces. Se construyó una base de datos con esta información mientras que dos autores revisaron los datos ingresados.

Contactamos a los autores de los estudios primarios cuando el documento en texto completo no estuvo disponible.

4.1.4.3. Evaluación del riesgo de sesgo

Dos revisores evaluaron la calidad de cada estudio de forma independiente utilizando una hoja simplificada de acuerdo a lo establecido en el Manual Cochrane (104). Comparamos las evaluaciones y discutimos las discrepancias entre los dos revisores, consultamos a un tercer revisor cuando existieron discrepancias para llegar a un consenso.

Para cada estudio incluido evaluamos el riesgo de sesgo (como bajo, alto o incierto) para cada uno de los siguientes aspectos:

- Generación de la secuencia de aleatorización
- Ocultamiento de la asignación al tratamiento (sesgo de selección).
- Cegamiento de participantes y personal (persona que entrega tratamiento) a la asignación del tratamiento (sesgo de ejecución).
- Cegamiento de los evaluadores de resultado a la asignación de tratamiento (sesgo de detección).
- Integridad de los desenlaces de resultado (incluidas las verificaciones de posible sesgo de desgaste a través de retiros, pérdida de seguimiento e infracciones de protocolo). Para sección de datos de desenlace incompletos, se consideró como un alto riesgo de sesgo a los ECAs en que los participantes se pierden después de la intervención de transfusión. Además, consideramos como alto riesgo de sesgo (sesgo de diseño) aquellos estudios en los que los pacientes no se transfundieron debido a la inconsistencia para determinar los criterios de

inclusión adecuadamente o cuando se realizó una asignación al azar prematura.

- Informe selectivo de resultados (sesgo de reporte).
- Otras fuentes de sesgo (otros sesgos).

4.1.4.4. Medición del efecto del tratamiento

Todos los desenlaces medidos en esta SR fueron dicotómicos. Calculamos el efecto del tratamiento mediante riesgos relativos (RRs) con intervalos de confianza (CI) de un 95%.

4.1.4.5. Unidad de análisis

La unidad de análisis fue cada paciente. Recolectamos y analizamos una medición única para cada desenlace para cada paciente.

4.1.4.6. Datos faltantes

Evaluamos los porcentajes de abandonos generales para cada ECAs incluido y para cada rama de cada ECAs, evaluamos si se había realizado un análisis por intención de tratar (ITT) o se podría realizar con la información publicada disponible. Definimos estos abandonos como el porcentaje de pacientes perdidos que recibieron una transfusión efectiva, sobre el total de pacientes transfundidos para cada brazo de los estudios incluidos.

4.1.4.7. Análisis de la heterogeneidad

Cuantificamos la heterogeneidad estadística utilizando el estadígrafo I2. El I2 describe el porcentaje de variación total entre los ECAs que se debe a la heterogeneidad en lugar del error de muestreo (134).

Consideramos los resultados de I^2 entre el 50% y el 74% como una heterogeneidad estadística moderada, mientras que un valor de ≥ 75% representa una alta heterogeneidad. Exploramos la heterogeneidad mediante un análisis de sensibilidad.

4.1.4.8. Análisis del sesgo de publicación

Realizamos un diagrama de túnel para analizar el sesgo de reporte para cada desenlace (135) que tuvo al menos 10 estudios que lo evaluaron (104).

4.1.4.9. Síntesis de los datos

Resumimos los ECAs suficientemente comparables utilizando el modelo de efectos aleatorios para adaptarse a la alta heterogeneidad, y utilizamos un modelo de efectos fijos para el análisis de sensibilidad. Realizamos un análisis principal basado en el número de participantes aleatorizados, utilizando un análisis ITT. Todos los análisis se realizaron con RevMan 2014.

4.1.4.10. Análisis de subgrupos e investigación de la heterogeneidad

No existieron datos para realizar los análisis de subgrupos propuestos para el desenlace primario (incidencia de TRALI)

- Por tipo de complicación post transfusional.
- Por tipo de técnica o material utilizado.
- Pacientes inmunosuprimidos vs. no inmunosuprimidos.
- Transfusiones masivas (> a 6 unidades de concentrados de glóbulos rojos) vs. transfusiones no masivas.

4.1.4.11. Análisis de sensibilidad

Realizamos los siguientes análisis de sensibilidad:

- Para evaluar la solidez de las estimaciones, utilizamos modelos de efectos fijos y de efectos aleatorios para todos los desenlaces y los resultados comparados.
- Realizamos un análisis de sensibilidad que comparó los ECAs con bajo riesgo de sesgo, con aquellos con riesgo de sesgo incierto o alto, según el sesgo de desgaste (104).
- Realizamos un análisis de sensibilidad basado en pacientes transfundidos para explorar la alta heterogeneidad.

4.1.4.11.1. Análisis secuencial de los ensayos

Llevamos a cabo un TSA para cada resultado dicotómico evaluado en esta SR: TRALI, muerte por cualquier causa, infección por cualquier causa y eventos adversos / fiebre. El TSA es un tipo de análisis del poder estadístico que puede ser se utilizado para investigar más a fondo la relevancia de los resultados ("fuerza de evidencia") (113). Es la contraparte de un cálculo del tamaño muestral como parte del diseño de un estudio convencional. El TSA permite a los investigadores diferenciar entre hallazgos significativos "espurios" causados por un error aleatorio en un conjunto de datos con solo un pequeño número de participantes, ECAs y un "verdadero" resultado significativo con suficiente poder estadístico. Por lo tanto, el TSA también cuenta para pruebas de significación repetidas. El tamaño óptimo de la información y los límites de gasto alfa de O'Brien-Fleming que indican el umbral de significación "real" se construyen al proporcionar los números para el nivel alfa, la potencia, el riesgo del grupo de control y la heterogeneidad entre estudios (9). El TSA se puede

realizar solo si el tamaño de la información (número de participantes) es lo suficientemente grande en comparación con el tamaño de óptimo de información, y solo si el resultado es dicotómico. Se pueden encontrar más detalles en el "Manual del usuario para el análisis secuencial de los ensayos (TSA)", proporcionado por el Centro de Investigación de Intervención Clínica de la Unidad de Ensayos de Copenhague (110).

4.1.4.11.2. Tabla del resumen de la evidencia

Utilizamos la estrategia GRADE (136) para evaluar la calidad general de la evidencia. El enfoque GRADE evalúa la calidad de un cuerpo de evidencia en función de la medida en que se puede estar seguro de que una estimación del efecto o asociación refleja el tema que se está evaluando. La calidad de un cuerpo de evidencia considera el riesgo de sesgo (calidad metodológica) dentro del estudio, si la evidencia es indirecta, la heterogeneidad de los datos, la precisión de las estimaciones de los efectos y el riesgo de sesgo de publicación (137–143). Creamos una tabla de resumen de la evidencia con la herramienta de desarrollo GRADEpro GDTGuideline (www.gradepro.org). Hemos presentado el cuerpo de evidencia en resumen de hallazgos para la comparación principal.

4.2. Segundo Trabajo de Investigación

Se realizó una SR de ECAs. El protocolo de esta SR fue registrado en PROSPERO (Número de registro: CRD42018103104). PROSPERO es un registro internacional que incluye protocolos de revisiones sistemáticas.

4.2.1. Búsqueda

Se realizaron búsquedas electrónicas en el registro especializado del grupo Cochrane de Lesiones, en el registro de ensayos clínicos Cochrane Central (CENTRAL, Cochrane Library), en MEDLINE (OVID – desde 1946 hasta el momento), EMBASE (Elsevier), LILACS, Clinical Trials register (http://www.clinicaltrials.gov),y en la plataforma de la OMS de registro de ensayos clínicos (http://apps.who.int/trialsearch/). La búsqueda más reciente se realizó el 10 de junio del 2018.

4.2.2. Criterios de inclusión y exclusión

Para que los ECAs sean incluidos en la revisión, debían cumplir con los siguientes criterios: ser un ECA con pacientes de cualquier edad quienes hayan 1) haber sido sometidos a un procedimiento quirúrgico cardiovascular, por ejemplo, cirugía de válvulas cardíacas, cirugía de revascularización coronaria o reparación del aneurisma aórtico; 2) necesidad de transfusión de concentrados de glóbulos rojos alogénico; con el objetivo de comparar la transfusión de concentrados de glóbulos rojos leucorreducidos versus concentrados de glóbulos rojos no leucorreducidos. Además, los estudios tenían que haber reportado resultados de muerte por cualquier causa e infección por cualquier causa. Se excluyeron estudios con otros diseños o estudios que incluyeran pacientes que recibieron transfusión sanguínea con otros componentes sanguíneos como parte de la intervención principal.

4.2.3. Obtención de datos

Dos revisores cribaron independientemente todas las referencias obtenidas mediante la búsqueda para incluirlas por título y resumen según los criterios de selección; después, obtuvieron los documentos a texto completo de los artículos que fueron seleccionados. Todas las decisiones de inclusión y exclusión se las

realizaron con el consentimiento de ambas partes. Los datos fueron extraídos por duplicado.

4.2.4. Evaluación de la Calidad

La evaluación de riesgo de sesgo de los ECAs incluidos fue realizada por duplicado, siguiendo el método de evaluación descrito en el Manual Cochrane para SR de Intervenciones (104).

Para establecer nuestras conclusiones sobre los efectos de la transfusión sanguínea con concentrados de glóbulos rojos leucorreducidos, desarrollamos una tabla de "Resumen de Resultados" usando GRADE para evaluar la calidad de evidencia de acuerdo a los métodos y recomendaciones descritas en el Manual Cochrane para SR de Intervenciones (104).

4.2.5. Análisis Estadístico

Se calculó el efecto total del tratamiento para muerte por cualquier causa y para infección por cualquier causa. Se utilizó como estimador el RR con un CI de 95%, y se utilizó un modelo de efectos aleatorios.

4.3. Tercer Trabajo de Investigación

Se realizó una evaluación de GPC que permitirá realizar recomendaciones sobre la transfusión de concentrados de glóbulos rojos.

4.3.1. Búsqueda

Se la realizó la búsqueda en bases de datos, entidades compiladoras de GPCs, registros de GPCs y organizaciones que desarrollan GPCs. Para la búsqueda se usó lenguaje libre tal como: "red blood cell transfusion", "blood transfusion", "anemia"

y “erythrocyte cells”. Para la búsqueda en MEDLINE a través del buscador Pubmed se combinaron términos MeSH (“blood transfusion,” “erythrocytes,” “Erythrocyte Transfusion,” “blood component transfusion,” “anemia”) y lenguaje libre como: (transfus* [tiab], transfusion requirements, PRBC, PRBCs transfusión strategy, blood loss, blood conservation, transfusion of package red blood cells, red cell transfusion, management of anemia). Adicionalmente, se usaron una serie de términos relacionados a las GPCs tal como: “practice guideline,” “consensus,” “development conference,” y “guideline”.

4.3.2. Criterios de inclusión y exclusión

Se incluyeron: (1) GPCS con recomendaciones referentes a la concentración de hemoglobina y a la transfusión de concentrados de glóbulos rojos; (2) GPCs que realizaron una búsqueda en al menos una base de datos; (3) GPCs publicadas desde el 2006 hasta octubre del 2017, sean en español o en inglés. Se excluyeron: (1) Publicaciones secundarias tal como SR o metanálisis y (2) GPCs con recomendaciones para pacientes pediátricos (< 15 años) y neonatos.

4.3.3. Obtención de datos

Dos revisores seleccionaron independientemente los artículos según el título y resumen y de acuerdo con los criterios de inclusión mencionados anteriormente. Si los artículos cumplían con los criterios de inclusión, se obtuvieron los documentos a texto completo, y fueron escrutados para determinar su elegibilidad. Dos revisores extrajeron de manera independiente la siguiente información de cada GPCs: Título, año, organización que desarrolló la guía, país de origen y financiamiento. En el caso de desacuerdo, se consultó a un tercer revisor. Un revisor extrajo las recomendaciones acerca del umbral de hemoglobina necesario para una transfusión y de los estudios individuales usados para dar las recomendaciones.

4.3.4. Evaluación de la calidad

Tres revisores con experiencia en evaluación de GPCs usaron la herramienta AGREE II para evaluar independientemente la calidad de las GPCs que fueron incluidas (122–124,144). Este instrumento fue desarrollado principalmente para quienes realizan GPCs y para investigadores; de esta manera, mediante el uso de la herramienta AGREE es posible medir los elementos principales del desarrollo e implementación de las GPCs. La herramienta AGREE (inicialmente AGREE I y ahora AGREE II) contiene 23 ítems incluidos dentro de 6 dominios (122): Alcance y objetivo, participación de los implicados, rigor en la elaboración, claridad de la presentación, aplicabilidad e independencia editorial. Además, la herramienta AGREE II contiene un ítem final dedicado a la evaluación global de la guía para así determinar hasta qué punto la guía puede ser recomendada para su uso práctico. Para evaluar los ítems dentro de los 6 dominios, se usó una escala de Likert sobre 7 puntos; esta escala varía entre “Muy en desacuerdo” a “Muy de acuerdo”. Para el último ítem de evaluación general se usó una escala de 3 puntos que varía entre “no recomendada” y “altamente recomendada”.

En caso de desacuerdo al usar la herramienta AGREE II, los tres revisores se reunieron para discutir sus resultados. Sin embargo, en el caso de que no se llegó a un acuerdo, se consultó a un cuarto revisor.

4.3.5. Análisis Estadístico

Realizamos un análisis descriptivo de las GPCs de acuerdo con el país de origen, el tipo de organización que las desarrollaron, el año de publicación y el lenguaje de las GPCs. Para establecer la calidad de cada guía, la puntuación estandarizada fue calculada en forma de porcentaje; esta puntuación se lo obtuvo al añadir todas las puntuaciones individuales de los ítems de cada dominio y estandarizando el total como porcentaje de la máxima puntuación posible:

(Puntuación obtenida – mínima puntuación posible) / (Máxima puntuación posible - mínima puntuación posible) x 100.

Una vez que la calidad de cada guía fue establecida, ésta fue comparada con las variables descriptibles anteriormente mencionadas.

El nivel de concordancia entre revisores fue evaluado mediante el coeficiente de correlación intraclase (ICC) con un intervalo de confianza de 95%. Se utilizó la prueba *t* de estudiante para comparar la puntuación entre variables diferentes (fecha de publicación y recomendaciones restringidas). Para el análisis sobre los cambios que han existido en la puntuación global a lo largo del tiempo, se categorizó la fecha de publicación en dos períodos (2006-2011 y 2012-2015). Se usó el paquete estadístico IBM SPSS (versión 22).


RESULTADOS

5. RESULTADOS

5.1. Primera Publicación

De acuerdo a los resultados obtenidos en el primer estudio (Simancas-Racines et al., 2015; Factor de Impacto (JCR): 6.7; SJR: 2.347, Primer Cuartil (Q1)) realizado para esta tesis, se incluyeron 13 ECAs que cumplieron con los criterios de inclusión previamente establecidos (48,49,54–56,60,61,63,64,67,71,145–148). 11 ECAs fueron incluidos en el metanálisis (149).

No se encontró evidencia suficiente del efecto de las transfusiones de concentrados de glóbulos rojos leucorreducidos versus las transfusiones de concentrados de glóbulos rojos no leucorreducidos en pacientes que fueron aleatorizados para los siguientes eventos:

- **Incidencia de lesión aguda de pulmón relacionada con la transfusión (TRALI):** No se encontró ninguna diferencia entre el grupo control y el grupo de tratamiento en el ECA (48) que incluyó 1864 pacientes (RR 0.96, 95% CI 0.67 - 1.36, P = 0.8). Además, TSA determinó que la población incluida correspondía únicamente al 28,5% del tamaño de información necesaria de acuerdo con el cálculo ajustado de los 6548 participantes requeridos para una adecuada estimación de los desenlaces. La calidad de la evidencia para este desenlace fue baja.

- **Muerte por cualquier causa:** se incluyeron 9 ECAs para evaluar este evento (48,54–56,60,61,64,67,71,148). Los ECAs abarcaron 6485 participantes entre los que existieron pacientes que recibieron cirugía cardiovascular, pacientes que recibieron cirugía gastro-oncológica, pacientes con trauma y pacientes con VIH. No se encontró diferencia alguna en el riesgo de muerte por cualquier causa entre los grupos tratados (8.54% versus 9.34%; RR 0.81, 95% CI 0.58 - 1.12, I^2 = 63%, P = 0.20). El TSA determinó que la población incluida correspondía al 55,3% del tamaño de información necesaria con

base en el cálculo ajustado de los 11735 participantes requeridos para una adecuada estimación de los desenlaces. La calidad de la evidencia para este desenlace fue muy baja.

- **Infección por cualquier causa:** se incluyeron 10 ECAs (48,49,54–56,60,61,64,67,71,148) con un total de 6709 participantes, estos ECAs incluyeron pacientes que recibieron cirugía cardiovascular, pacientes que recibieron cirugía gastro-oncológica, pacientes con trauma y pacientes con VIH. No se encontró diferencia en el riesgo de infección por cualquier causa entre los grupos tratados (17.7% versus 20.4%; RR 0.80, 95% CI 0.62 - 1.03; I^2 = 84%, P = 0.08). El TSA determinó que la población incluida correspondía al 60,6% del tamaño de información necesaria con base en el cálculo ajustado de los 11062 participantes requeridos para una adecuada estimación de los desenlaces. La calidad de la evidencia para este desenlace fue muy baja.

- **Eventos adversos:** el único evento adverso reportado fue fiebre. Se incluyeron 2 ECAs (54,64) en los que participaron un total de 634 pacientes que recibieron cirugía cardiovascular o cirugía gastro-oncológica. No se encontró diferencia alguna en la presencia de eventos adversos entre los grupos tratados (31.9% versus 38.7%; RR 0.81, 95% CI 0.64 - 1.02; I^2 = 0%, P = 0.07). El TSA determinó que la población incluida correspondía al 84,4% del tamaño de información necesaria con base en el cálculo ajustado de los 751 participantes requeridos para una adecuada estimación de los desenlaces. La calidad de la evidencia para este desenlace fue baja.

- **Incidencia de otras complicaciones no infecciosas:** este evento no fue analizado en ningún que fue incluido en el estudio.

Cochrane Library

Cochrane Database of Systematic Reviews

Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion (Review)

Simancas-Racines D, Osorio D, Martí-Carvajal AJ, Arevalo-Rodriguez I

Simancas-Racines D, Osorio D, Martí-Carvajal AJ, Arevalo-Rodriguez I.
Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD009745.
DOI: 10.1002/14651858.CD009745.pub2.

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[Intervention Review]

Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion

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Editorial group: Cochrane Injuries Group.
Publication status and date: New, published in Issue 12, 2015.
Review content assessed as up-to-date: 10 November 2015.

Citation: Simancas-Racines D, Osorio D, Martí-Carvajal AJ, Arevalo-Rodriguez I. Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD009745. DOI: 10.1002/14651858.CD009745.pub2.

ABSTRACT

Background

A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis. However, blood transfusions have adverse events, some of them potentially related to immune modulation or to a direct transmission of infectious agents (e.g. cytomegalovirus). Leukoreduction is a process in which the white blood cells are intentionally reduced in packed red blood cells (PRBCs) in order to reduce the risk of adverse reactions. The potential benefits of leukoreduced PRBCs in all types of transfused patients for decreasing infectious and non-infectious complications remain unclear.

Objectives

To determine the clinical effectiveness of leukoreduction of packed red blood cells for preventing adverse reactions following allogeneic blood transfusion.

Search methods

We ran the most recent search on 10th November 2015. We searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (OvidSP), Embase(OvidSP), CINAHL Plus (EBSCO), LILACS (BIREME), and clinical trials registers. In addition, we checked the reference lists of all relevant trials and reviews identified in the literature searches.

Selection criteria

Randomised clinical trials including patients of all ages requiring PRBC allogeneic transfusion. Any study was eligible for inclusion, regardless of the length of participant follow-up or country where the study was performed. The primary outcome was transfusion-related acute lung injury (TRALI). Secondary outcomes were death from any cause, infection from any cause, non-infectious complications and any other adverse event.

Data collection and analysis

At least two review authors independently performed study selection, 'Risk of bias' assessments and data extraction. We estimated pooled relative risk for dichotomous outcomes, and we measured statistical heterogeneity using I^2 statistic. The random-effects model was used to synthesise results. We conducted a trial sequential analysis to assess the risk of random errors in cumulative meta-analyses.

Main results

Thirteen studies, most including adult patients, met the eligibility criteria. We found no clear evidence of an effect of leukoreduced PRBC versus non-leukoreduced PRBC in patients that were randomised to receive transfusion for the following outcomes:

TRALI: RR 0.96, 95% CI 0.67 to 1.36, P = 0.80 from one trial reporting data on 1864 trauma patients. The accrued information of 1864 participants constituted only 28.5% of the diversity-adjusted required information size (DARIS) of 6548 participants. The quality of evidence was low.

Death from any cause: RR 0.81, 95% CI 0.58 to 1.12, I^2 statistic = 63%, P = 0.20 from nine trials reporting data on 6485 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6485 participants constituted only 55.3% of the DARIS of 11,735 participants. The quality of evidence was very low.

Infection from any cause: RR 0.80, 95% CI 0.62 to 1.03, I^2 statistic = 84%, P = 0.08 from 10 trials reporting data on 6709 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6709 participants constituted only 60.6% of the DARIS of 11,062 participants. The quality of evidence was very low.

Adverse events: The only adverse event reported as an adverse event was fever (RR 0.81, 95% CI 0.64 to 1.02; I^2 statistic= 0%, P = 0.07). Fever was reported in two trials on 634 cardiovascular surgical and gastro-oncology surgical patients. The accrued information of 634 participants constituted only 84.4% of the DARIS of 751 participants. The quality of evidence was low.

Incidence of other non-infectious complications: This outcome was not assessed in any included trial.

Authors' conclusions

There is no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death, infection, non-infectious complications and other adverse events. As the quality of evidence is very low to low, more evidence is needed before a definitive conclusion can be drawn.

PLAIN LANGUAGE SUMMARY

White blood cells reduction in packed red blood cell transfusions for preventing adverse reactions

Background

A blood transfusion is when blood is taken from one person and given to another person. Blood transfusions are given to solve life and health-threatening medical conditions on a short-term basis. However, blood transfusions have adverse events, some of them potentially related to an immune system response or due to the transmission of infectious agents (e.g. Human Immunodeficiency Virus). Leukoreduction is a process in which the white blood cells are intentionally removed from donated blood in order to reduce the risk of adverse reactions in people receiving the blood transfusion. The benefits of removing white blood cells with the intent of reducing infectious and non-infectious complications in all types of transfused patients remains unclear. Removing white blood cells is costly. The USA and UK spend tens of millions each year on the procedure. In the USA, the procedure costs approximately USD $30 for each unit of blood product. It may not be worth spending so much money if there is no clear benefit to patients.

Clinical question

What are the benefits and harms of removing white blood cells from donated blood for people receiving a blood transfusion?

Study characteristics

We searched medical journals for reports of clinical trials which examined the effects of removing white blood cells from donated blood. We were interested in finding out whether the removal of white blood cells from donated blood resulted in patients receiving a blood transfusion having few complications such as transfusion-related acute lung injury, death, infectious and non-infectious complications,

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Leukoreduced PRBCs versus non-leukoreduced PRBCs for preventing adverse reaction from allogeneic blood transfusion

Patient or population: Patients receiving RBC transfusion
Settings: Any
Intervention: Leukoreduced PRBCs
Comparison: Non-leukoreduced PRBCs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-leukoreduced packed RBCs	Leukoreduced packed RBCs				
TRALI Follow-up: mean 28 days	Study population		RR 0.96 (0.67 to 1.36)	1864 (1 study)	⊕⊕◯◯ **low**[1]	TSA yielded an inconclusive result.
	63 per 1000	61 per 1000 (42 to 86)				
Death due to any cause Follow-up: median 2.5 months	Study population		RR 0.81 (0.58 to 1.12)	6485 (9 studies)	⊕◯◯◯ **very low**[2]	TSA yielded an inconclusive result.
	93 per 1000	76 per 1000 (54 to 104)				
Infection from any cause Follow-up: mean 2.5 months	Study population		RR 0.80 (0.62 to 1.03)	6709 (10 studies)	⊕◯◯◯ **very low**[3]	TSA yielded an inconclusive result.
	204 per 1000	163 per 1000 (127 to 210)				
Adverse events Follow-up: mean 3 months	Study population		RR 0.81 (0.64 to 1.02)	634 (2 studies)	⊕⊕◯◯ **low**[4]	TSA yielded an inconclusive result.
	387 per 1000	314 per 1000 (248 to 395)				

Non-infectious complication	**Study population**		Not estimable	-	-	No trial assessed this outcome.
	Not estimable	Not estimable				

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **TRALI:** Transfusion-related acute lung injury; **RBC:** Red blood cell; **PRBC:** Packed red blood cell; **DARIS:** Diversity-adjusted required information size.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by two due to imprecision: small sample size as compared with the calculated DARIS and the wide CI overlapping zones of no effect, as well as potential harm or benefit, or both. Few events reported.
[2] Downgraded due to: high risk of bias (Six of nine included studies have high or unclear risk of bias. -1); important heterogeneity (I^2 statistic: 63%, -1); and imprecision as reflected in the wide CI and an insufficient accrued information size compared with the DARIS (-1).
[3] Downgraded due to: high risk of bias (Seven of 10 included studies were at high or unclear risk of bias, -1); important heterogeneity (I^2 statistic: 84%, -2); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)
[4] Downgraded due to: high risk of bias (All included studies evaluated were at high risk of bias, -1) and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1).

BACKGROUND

Description of the condition

Blood transfusion is the infusion of both soluble and cell-associated forms (red blood cells (RBCs), white blood cells (WBCs) and platelets) into a recipient (Vamvakas 2001). A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis; and in general, its long-term effects tend to be of secondary importance (Tsai 2010). However, blood transfusion is associated with an increasing risk of infectious and non-infectious adverse events (Wagner 2004; Hendrickson 2009; Sachs 2010). The incidence of non-infectious transfusion reactions is greater than that of infectious complications (Lavoie 2011). Mortality associated with non-infectious risks is also significantly higher and accounts for 87% to 100% of fatal complications of transfusions (Lavoie 2011).

The main non-infectious adverse events to the patient are transfusion-related acute lung injury (TRALI), which is considered the most severe non-infectious complication (Renaudier 2009; Triulzi 2009; Vamvakas 2009); non-haemolytic febrile transfusion reaction (NHFTR) (King 2004; Blajchman 2006; Hoffman 2008) and allergic reactions (Tenorio 2007). Less frequent are transfusion-associated graft-versus-host disease (TA-GVHD) (Dwyre 2008; Hoffman 2008; Rühl 2009) and transfusion-related with an immunomodulation effect (TRIM) (Vamvakas 2006).

Several approaches have been considered to prevent adverse reactions related to transfusion (Martí-Carvajal 2010; Lavoie 2011; Lindholm 2011; Tobian 2011). Transfusion of leukocyte-reduced RBC concentrates is one of those approaches (Blajchman 2010; Blumberg 2010; Mukagatare 2010). Leukocytes (WBCs) in blood components can mediate febrile transfusion reactions, stimulate human leukocyte antigen (HLA) alloimmunization in transfusion recipients, and transmit some cell-associated pathogens such as cytomegalovirus (CMV). Therefore, it is desirable to remove WBCs from transfusable blood components (Galel 2009).

Appendix 1 shows non-infectious transfusion reaction definitions related to WBCs.

Description of the intervention

Leukoreduction is a process in which the WBCs are intentionally reduced by almost 99.99% in RBC concentrates (Shapiro 2004). There are many methods to conduct this approach; however, this process is currently performed using selective leukoreduction filters (Galel 2009). According to the U.S. Food and Drug Administration (FDA), leukocyte-reduced RBC concentrates contain fewer than 5×10^6 WBCs/unit and at least 85% of the original RBCs (Galel 2009), and according to the Council of Europe $< 1 \times 10^6$ total WBC/unit. Usually, most RBC leukofiltration is performed by blood collection centres within the first few days after collection (Galel 2009).

Leukoreduction in trauma patients

Safe transfusion products are a necessity for the successful treatment of trauma patients (Tien 2007; Theusinger 2009). It is unclear if leukoreduction of RBC concentrates is the best method of providing blood products for trauma patients (Nathens 2006; Phelan 2007; Watkins 2008). Retrospective studies have shown a reduction of infectious complications in injured patients treated with leukoreduced AlloBT; this effect appears more pronounced in patients receiving massive transfusion (> 6 units of PRBC) (Friese 2008).

Leukoreduction in surgery

Several studies have focused on the advantages of leukoreduced PRBC cells for transfusion in cardiac surgery (van de Watering 1998; Dzik 2002; Wallis 2002; Bilgin 2004; van Hilten 2004; Connery 2005); colorectal surgery (Jensen 1992; Houbiers 1994; Jensen 1996; Titlestad 2001; Dzik 2002; Skånberg 2007); gastrointestinal surgery (Tartter 1998; Dzik 2002; van Hilten 2004); and renal transplantation (Sanfilippo 1985; Opelz 1997; Hiesse 2001). However, some of the findings of these published trials are considered controversial. Furthermore, this approach has been used in patients with AIDS; but, is unclear if this alternative method is beneficial in this population (Collier 2001).

How the intervention might work

Leukoreduction works through multiple mechanisms for preventing adverse reactions:

1. To prevent TRALI: avoiding the transfer of leukocytes and reducing the cellular antibody interaction complexes that damage the endothelium of the lung (Triulzi 2009; Sachs 2011).
2. To avoid post-transfusion infections through reducing some cell-associated pathogens, such as CMV (Bilgin 2004; Blajchman 2004; van Hilten 2004; Connery 2005; Friese 2008).
3. To prevent immunomodulation: donor WBCs may suppress the recipient's immune system by interacting with it, producing susceptibility to many pathological conditions including cancer recurrence and other malignancies (Blajchman 2002; Dellinger 2004; Flohé 2007).

Why it is important to do this review

This Cochrane review is important for the following reasons:

Firstly, leukoreduction is expensive. About EUR 29 million/year are spent on implementing leukoreduction (AETSA 2007). Other studies reported costs ranging from CAD $26 million to 46 million annually (CCOHTA 1998). One study estimated the total

cost of implementing leukoreduction was about USD 600 million dollars per year in USA (Shapiro 2004). It has also been reported that leukoreduction results in an increase of approximately USD 30/unit of blood product (Phelan 2007). More recently, Tsantes 2014 reported an incremental cost-effectiveness ratio (ICER) of EUR 6916 to prevent one case of febrile non-haemolytic transfusion reactions (FNHTR). Secondly, the potential role of leukoreduction for decreasing mortality and infection is controversial (AETSA 2007; Mukagatare 2010). Thirdly, several studies and meta-analyses did not report conclusive results about leukoreduction, and showed methodological inconsistencies (Vamvakas 1996; Blumberg 1998; Jensen 1998; Fergusson 2004; Blumberg 2007; Vamvakas 2007). Therefore, it is important to conduct this Cochrane review to determine the potential benefits of leukoreduction procedure in patients requiring RBC concentrates, focused on the prevention of adverse reaction.

OBJECTIVES

To determine the clinical effectiveness of leukoreduction of packed red blood cells for preventing adverse reactions following allogeneic blood transfusion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients requiring allogeneic packed RBC (PRBC) transfusion. Patients could be of any age.

Types of interventions

Intervention

- Leukoreduced PRBCs.

Comparison

- Non-leukoreduced PRBCs.

We applied no limitations to the leukoreduction procedures used.

Types of outcome measures

Primary outcomes

1. Incidence of TRALI.

Secondary outcomes

1. Death due to any cause.
2. Infection from any cause (number of patients out of the total randomised).
3. Non-infectious complications (Appendix 1).
4. Any other adverse event: "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004).

We took the information size for the primary outcome of this Cochrane review from the relative risk reported in Nathens 2006. This study included trauma patients. A total sample size of 8781 participants was defined to assess a relative risk reduction on TRALI events of 25%, from a baseline incidence in the control of 6.31% (alpha level of 5% and power of 90%).

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (10/11/2015)
2. Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (issue 10 of 12, 2015)
3. MEDLINE (OvidSP) (1950 to November week 1, 2015)
4. Embase + Embase Classic (OvidSP) (1947 to 10/11/2015)
5. LILACS (BIREME) (1982 to 10/11/2015)
6. CINAHL Plus (EBSCO) (1937 to 10/11/2015)
7. Clinicaltrials.gov (www.clinicaltrials.gov) (10/1/2015)
8. WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) (10/11/2015)

We have reported the search strategies in Appendix 2. We adapted the MEDLINE search strategy as necessary for the other databases. To the MEDLINE search strategy we added the Cochrane Highly Sensitive Search Strategy for identifying RCTs. To the EMBASE strategy we added the terms of the search strategy and study design terms as used by the UK Cochrane Centre (Lefebvre 2011).

Searching other resources

We also searched the following websites (25 November 2014):

1. US FDA (http://www.fda.gov).
2. European Medicines Agency (http://www.emea.europa.eu).
3. Scirus (www.scirus.com).
4. American Association of Blood Banks (AABB) (http://www.aabb.org).
5. Transfusion Evidence Library (http://transfusionguidelines.org).

In addition, we checked the reference lists of all relevant trials and reviews identified.

Data collection and analysis

We summarised data according to standard Cochrane methodologies, including the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011) and the Methodological Expectations for Cochrane Intervention Reviews (MECIR) (Chandler 2013).

Selection of studies

Two review authors, Daniel Simancas-Racines (DSR) and Ingrid Arévalo-Rodriguez (IAR), independently assessed for inclusion all the potential studies identified from the literature searches. We consulted a third review author, Arturo Martí-Carvajal (AMC) for any disagreements, which were resolved through discussion and consensus.

Data extraction and management

Two review authors, DSR and IAR, independently extracted data from the included trials. We consulted AMC and Dimelza Osorio (DO) in the event of any disagreements, which we resolved through discussion and consensus. Data were recorded for: eligibility criteria, demographics (age, gender and country), type of surgery, setting of the patients (i.e. cardiac surgery, intensive care unit (ICU)) outcomes. DSR recorded the data into a database. IAR and DO checked the data entered.

We contacted the trial author when a full-text article was unavailable (see Appendix 3 for details).

Assessment of risk of bias in included studies

Two review authors, DSR and IAR, independently assessed the quality of each trial using a simple form following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the assessments and discussed any discrepancies between the review authors. We consulted a third review author (AMC) to resolve any disagreement and to reach consensus.

For each included trial, we assessed risk of bias (as low, high or unclear) for each of the following domains:

- Generation of random sequence (selection bias).
- Concealment of treatment allocation (selection bias).
- Blinding of participants and personnel (person delivering treatment) to treatment allocation (performance bias).
- Blinding of outcome assessors to treatment allocation (detection bias).
- Completeness of the outcome data (including checks for possible attrition bias through withdrawals, loss to follow-up and protocol violations). For the incomplete outcome data domain, we considered as a high risk of bias RCTs that losses participants after transfusion intervention. Additionally, we considered high risk of bias (design bias) as those studies in which the patients were not transfused because inconsistency to determine inclusion criteria adequately or when a premature randomisation was done.
- Selective reporting of outcomes (reporting bias).
- Other sources of bias (other bias).

Measures of treatment effect

All outcomes in this Cochrane review were binary outcomes. We calculated the treatment effect with risk ratios (RRs) with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis was the patient. We collected and analysed a single measurement for each outcome from each patient.

Dealing with missing data

We assessed the percentages of the overall dropouts for each included trial and per each randomisation arm, and we evaluated whether an intention-to-treat (ITT) analysis had been performed or could be performed with the available published information. We defined these dropouts as the percentage of lost patients who received an effective transfusion, over the total of transfused patients reported for each arm of the included studies.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic. The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We considered I^2 statistic between 50% and 74% as a moderate statistical heterogeneity, whereas a value of $\geq$ 75% represents high heterogeneity. We explored heterogeneity using a sensitivity analysis.

Assessment of reporting biases

We created a funnel plot to assess reporting bias for each outcome (Sterne 2011) where there were data from at least 10 trials (Higgins 2011).

Data synthesis

We summarized sufficiently comparable trials using the random-effects model to accommodate the high heterogeneity, and used a fixed-effect model for the sensitivity analysis. We carried out the main analysis based on the number of randomised participants, using an ITT analysis. All the analyses were carried out using RevMan 2014.

Subgroup analysis and investigation of heterogeneity

No data were available to perform the following subgroup analyses for the primary outcome (incidence of TRALI):

1. By type of post-transfusion complication.
2. By technique or type of material used.
3. Immunosuppressed patient versus non-immunosuppressed patient.
4. Massive transfusion (> 6 units PRBCs) versus less.

Sensitivity analysis

We performed the following sensitivity analysis for the primary outcome:

1. To assess the robustness of estimates, we used both fixed-effect and random-effects models for all outcomes and compared results.
2. We conducted a sensitivity analysis comparing trials with low risk of bias, with those at unclear or high risk of bias, according to attrition bias (Higgins 2011).
3. We also conducted a sensitivity analysis based on transfused patients to explore the high heterogeneity.

Trial sequential analysis

We carried out a trial sequential analysis (TSA) for every dichotomous outcome evaluated in this systematic review: TRALI, death from any cause, infection from any cause, and adverse events/fever. TSA is a type of statistical power analysis that can be used to further investigate the relevance of results ("strength of evidence") yielded by a meta-analysis (Wetterslev 2008). It is the counterpart of a sample size calculation as part of a conventional study design. TSA allows researchers to differentiate between "spurious" significant findings caused by random error in a data-set with only small numbers of participants and trials and a "truly" significant result with sufficient statistical power. Thereby, TSA also accounts for repeated significance testing. The optimal information size and O'Brien-Fleming alpha-spending boundaries indicating the "real" significance threshold are constructed by providing the numbers for alpha level, power, control group risk and inter-study heterogeneity (Thorlund 2011). TSA can be performed only if the information size (number of participants) is large enough as compared with the optimal information size, and only if the outcome is dichotomous. Further details can be found in the "User Manual for Trial Sequential Analysis (TSA)", provided by the Centre for Clinical Intervention Research of the Copenhagen Trial Unit (Thorlund 2011).

'Summary of findings' tables

We used the GRADE approach (Guyatt 2011b) to assess the overall quality of evidence. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Balshem 2011; Brozek 2011; Guyatt 2011a; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h). We created a 'Summary of Findings' table using GRADEpro GDT Guideline Development Tool (www.gradepro.org). We have presented the body of evidence in Summary of findings for the main comparison.

RESULTS

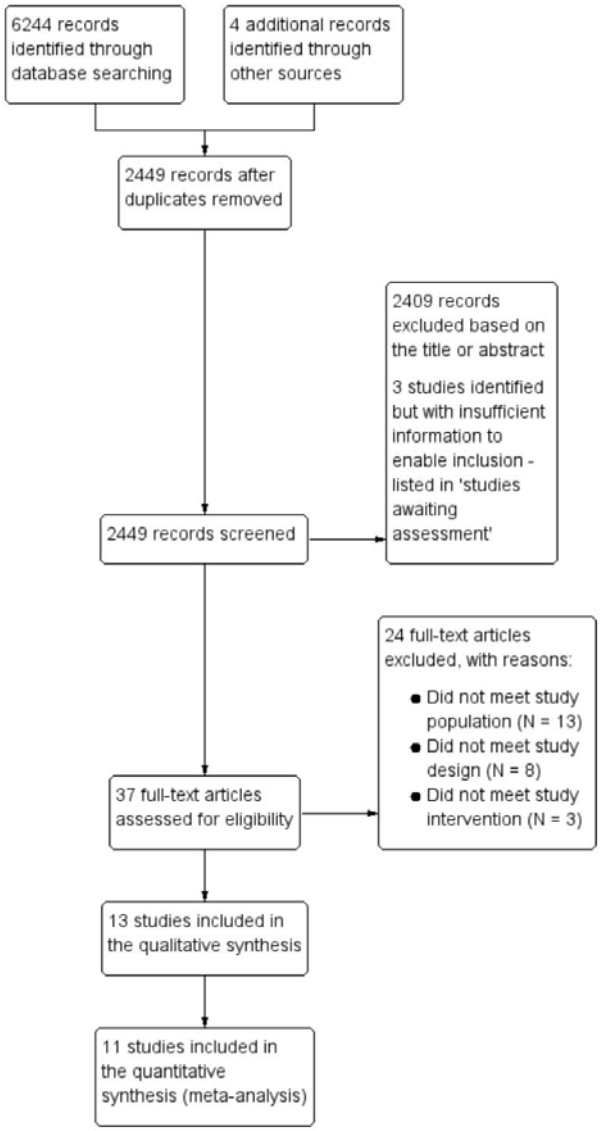
Description of studies

See the Included studies section.

Results of the search

We identified 6244 references. Thirteen RCTs met our inclusion criteria (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Boshkov 2006; Nathens 2006; Lapierre 2007; Donati 2014). See Figure 1.

Figure 1. Study flow diagram.



We did not find any ongoing trials. Three studies were classified as awaiting assessment (Zhao 2004; NCT00810810; Waghmare 2012). There is insufficient information available about these studies to enable us to decide whether or not they should be included in the review. See Characteristics of studies awaiting classification.

Included studies

Methodology characteristics

Trials were published between 1985 and 2014. They were conducted in various countries: five in the USA (Sanfilippo 1985; Tartter 1998; Collier 2001; Boshkov 2006; Nathens 2006), three in the Netherlands (van de Watering 1998; Bilgin 2004; van Hilten 2004), two in Denmark (Jensen 1996; Titlestad 2001), one in France (Lapierre 2007), one in the UK (Wallis 2002) and one in Italy (Donati 2014).

All trials had a parallel study design; 11 comparing two groups and two trials comparing three groups (van de Watering 1998; Wallis 2002). The number of trial participants ranged from 20 (Donati 2014) to 1864 (Nathens 2006), with a median of 531 participants.

In three trials participants were monitored for one month or less (Jensen 1996; Nathens 2006; Donati 2014). In 10 trials participants were monitored for between two and 15 months. In 11 trials there was an a priori sample size estimation, and one trial did not report how the sample size was derived (Sanfilippo 1985). In one trial the data used were taken from the report's abstract, and there was no information about the sample size calculation (Boshkov 2006). All trials used patients as the randomisation unit and unit of analysis. All trials reported inclusion criteria. Exclusion criteria were not reported in the Boshkov 2006 study abstract.

Patient characteristics

All 13 included trials were conducted in adults, but two trials also included patients under 18 years of age: Collier 2001 ($\geq$ 14 years) and Nathens 2006 ($\geq$ 17 years). Twelve trials reported the gender of the participants; almost 60% of the included participants were men. Five trials involved cardiac surgery patients (van de Watering 1998; Wallis 2002; Bilgin 2004; van Hilten 2004; Boshkov 2006), four trials involved gastro-oncology surgery patients (Jensen 1996; Titlestad 2001; van Hilten 2004; Lapierre 2007), one trial involved non-surgical oncology patients (Lapierre 2007), one trial involved trauma patients (Nathens 2006), one trial included HIV infected patients (Collier 2001) and one trial involved patients with sepsis, severe sepsis or septic shock requiring ICU care (Donati 2014).

Interventions

Leukoreduction definition

The extent of leukoreduction differed across the studies: two studies obtained 0.1 to 0.3 $\times$ 10^6 per unit (Bilgin 2004; Titlestad 2001). Three trials reported 5 $\times$ 10^6 leukocytes per unit of blood after leukoreduction (Collier 2001; Wallis 2002; Nathens 2006). Jensen 1996 reported 1.2 $\times$ 10^9 per unit; van de Watering 1998 reported 1.2 $\pm$ 1.4 $\times$ 10^6 per unit; Tartter 1998 reported 2 $\times$ 10^5 per unit; and Lapierre 2007 less than 2 $\times$ 10^4 per unit. Four studies did not report definitions for leukoreduction (Sanfilippo 1985; van Hilten 2004; Boshkov 2006; Donati 2014).

Type of filters

Trials were conducted using different types of filters. Two trials used "Cellselect Optima" filters (Bilgin 2004; van de Watering 1998). Four trials used "BPF4" filters for blood leukoreduction (Tartter 1998; Titlestad 2001; Wallis 2002; Nathens 2006). Jensen 1996 used "RC 100" filters and two trials used "Sepacell RZ-200B1" filters (Lapierre 2007; Donati 2014). Four trials did not report the type of filter used (Sanfilippo 1985; Collier 2001; van Hilten 2004; Boshkov 2006).

Control groups

Trials were conducted using different types of comparator groups. Five trials used "Buffy coat depleted packed cells (PCs)" as a comparison group (Jensen 1996; van de Watering 1998; Wallis 2002; Bilgin 2004; van Hilten 2004). Eight trials used "unmodified RBC transfusion" or standard RBCs as a comparison group (Sanfilippo 1985; Tartter 1998; Collier 2001; Titlestad 2001; Boshkov 2006; Nathens 2006; Lapierre 2007; Donati 2014). One trial also used "Red blood cells concentrate with plasma reduction" as a third non-leukoreduced arm (Wallis 2002).

Cointervention

Three studies described the use of platelets as co-intervention (Collier 2001; Bilgin 2004; Nathens 2006). Bilgin 2004 reported that platelets were all leukocyte-depleted by filtration; Collier 2001 did not describe the platelet leukoreduction process, and Nathens 2006 reported that all patients received apheresis platelets when platelets were required. Lapierre 2007 reported that none of the patients received platelets concentrate.

Outcomes

One trial reported on TRALI (Nathens 2006).

Nine trials reported on death from any cause (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). Boshkov 2006 reported death only for the transfused patients group.

Ten trials reported on infection from any cause (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007) the infections reported were: respiratory tract infections in six studies (Jensen 1996; van de Watering 1998; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); urinary tract infections in five studies (Jensen 1996; van de Watering 1998; Bilgin 2004; Nathens 2006; Lapierre 2007); wound infections or surgical site infections in seven studies (Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); bacteraemia or septicaemia in seven studies (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); abdominal infection in three studies (Jensen 1996; Titlestad 2001; Nathens 2006). Collier 2001 included persons infected with HIV and CMV.

Three trials reported adverse events (Collier 2001; Wallis 2002; Lapierre 2007). One trial, Collier 2001, analysed fever episodes per transfusion, but not per study participant, thus it was not included in the meta-analysis.

Donati 2014 and Sanfilippo 1985 reported only physiological outcomes. There were no relevant data to include in the analyses.

Excluded studies

We excluded 24 studies (see Characteristics of excluded studies) for the following reasons:

- Use of other blood products in the intervention groups (Gilbert 1989; Jensen 1992; Houbiers 1994; Bowden 1995; Kao 1995; Gu 1996; Nielsen 1999; Hayashi 2000; Dzik 2002; Efstathiou 2003; Connery 2005; Gu 2009).
- No transfusion in one of the study groups (Opelz 1997; de Vries 2004; Koskenkari 2005; Leal-Noval 2005; Salamonsen 2005; So-Osman 2010).
- Non-randomised clinical trial (Bracey 2002; de Vries 2003; Llewelyn 2004; Skånberg 2007), or a review article (van de Watering 2004; Vamvakas 2007).

Risk of bias in included studies

We have summarised the risk of bias in the included studies in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

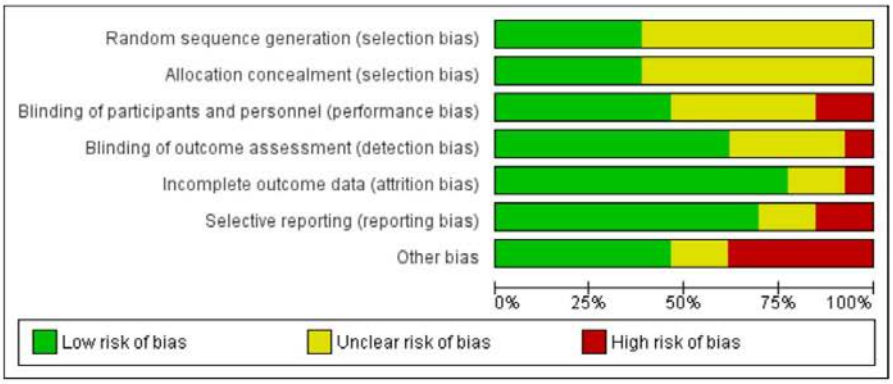
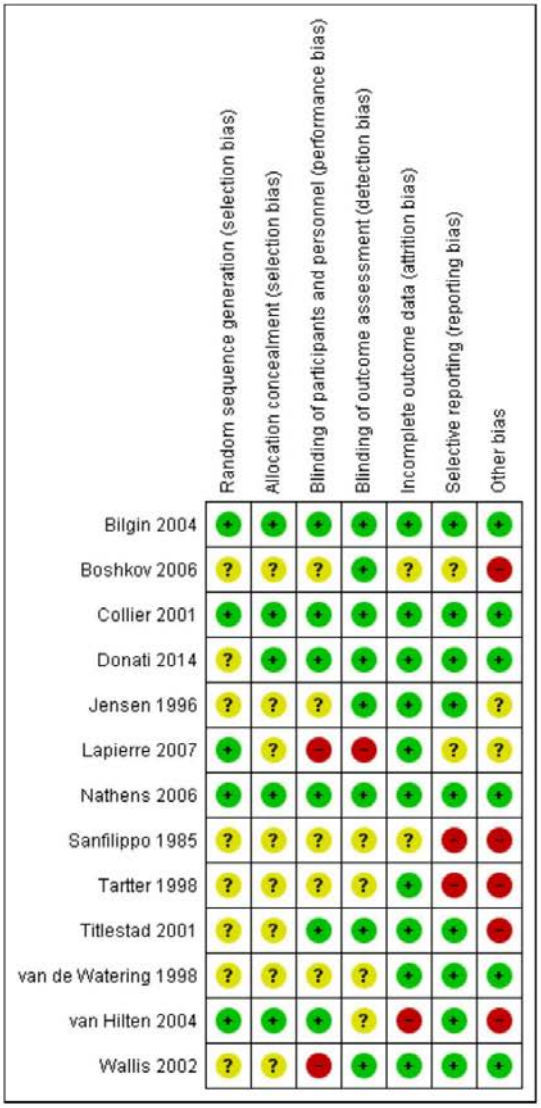


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

Random sequence generation

In five trials there was low risk of bias related to the sequence generation method (Collier 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). Eight trials had unclear risk of bias (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Wallis 2002; Boshkov 2006; Donati 2014).

Allocation concealment

In five trials there was low risk of bias related to the method of allocation concealment (Collier 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). Eight trials had unclear risk of bias (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Wallis 2002; Boshkov 2006; Lapierre 2007).

Blinding

Blinding of participants and personnel

The risk of bias arising from the lack of blinding was rated as low in six trials (Collier 2001; Titlestad 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). The risk of bias from blinding was unclear in five trials (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Boshkov 2006) and high in two studies (Wallis 2002; Lapierre 2007).

Blinding outcome assessment

Eight trials had a low risk of bias arising from the method of blinding outcome assessment (Jensen 1996; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; Boshkov 2006; Nathens 2006; Donati 2014). Four studies were at unclear risk (Sanfilippo 1985; Tartter 1998; van de Watering 1998; van Hilten 2004) and one trial was at high risk of bias (Lapierre 2007).

Incomplete outcome data

Ten trials were judged to be at low risk of bias from incomplete outcome data (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; Nathens 2006; Lapierre 2007; Donati 2014). There was unclear risk of bias in two trials (Sanfilippo 1985; Boshkov 2006), and high risk of bias in one trial (van Hilten 2004).

Selective reporting

We judged nine trials as at low risk of reporting bias (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). Two trials were at unclear risk of bias (Boshkov 2006; Lapierre 2007), and two trials were at high risk of bias (Sanfilippo 1985; Tartter 1998).

Other potential sources of bias

Six trials appeared free of other potential sources of bias and we judged these trials to be at low risk of bias (van de Watering 1998; Collier 2001; Wallis 2002; Bilgin 2004; Nathens 2006; Donati 2014). Seven trials had design bias of different kinds: inconsistency in adequately determining inclusion criteria, premature randomisation (Sanfilippo 1985; Tartter 1998; van de Watering 1998; Titlestad 2001; van Hilten 2004; Boshkov 2006) or sample size bias (Lapierre 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Leukoreduced PRBCs versus non-leukoreduced PRBCs for preventing adverse reaction from allogeneic blood transfusion

Leukoreduced PRBC versus non-leukoreduced PRBC

1. Primary outcomes

TRALI (analysis based on total randomised patients)

Overall analysis

One trial including 1864 participants showed no difference between treatment groups on TRALI (6.02% versus 6.31%) (RR 0.96, 95% CI 0.67 to 1.36; P = 0.80) (Nathens 2006). See Analysis 1.1.

Quality of evidence (TSA and GRADE)

The accrued information of 1864 participants constituted only 28.5% of the diversity-adjusted required information size (DARIS) of 6548 participants. We calculated DARIS based on a diversity of 4%; a proportion with the TRALI events of 6.3% in the control group; a relative risk reduction of 25%; an alpha of

5%; and a beta of 20% (power = 80%). With the inclusion of data from one trial, the Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. The TSA-adjusted 95% CI overlapped with no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.46 and RR 1.98, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was low (imprecision as reflected in the wide CI and only one trial with a small sample size as compared with the DARIS (-2)).

In the analysis including "only transfused patients", compared to all patients results were similar (RR 0.98, 95% CI 0.74 to 1.29; P = 0.87; Analysis 2.1). We were unable to conduct other subgroup and sensitivity analyses because only one study measured this outcome. In this study, Nathens 2006, leukoreduction was performed pre-storage.

2. Secondary outcomes

Death due to any cause

Overall analysis (total randomised patients)

The meta-analysis of nine trials including 6485 participants showed no difference between treatment groups in the risk of death from any cause (8.54% versus 9.34%; RR 0.81, 95% CI 0.58 to 1.12, I^2 statistic = 63%, P = 0.20) (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). See Analysis 1.2.

Sensitivity analysis

We conducted three sensitivity analyses; none of which were statistically significant. The RRs using the fixed-effect model were similar to that of the random effect model.

1. Including three studies with low risk of bias (Collier 2001; Bilgin 2004; Nathens 2006), compared to six studies at unclear or high risk of bias (RR 1.03, 95% CI 0.89 to 1.20; I^2 statistic = 38%, P = 0.66).
2. Including "only transfused patients", compared to all patients (RR 0.80, 95% CI 0.60 to 1.07, I^2 statistic: 60%, P = 0.13, Analysis 2.2).
3. Post-storage leukoreduction, compared with pre-storage leukoreduction (RR 0.74, 95% CI 0.53 to 1.04, I^2 statistic: 70%, P = 0.09).

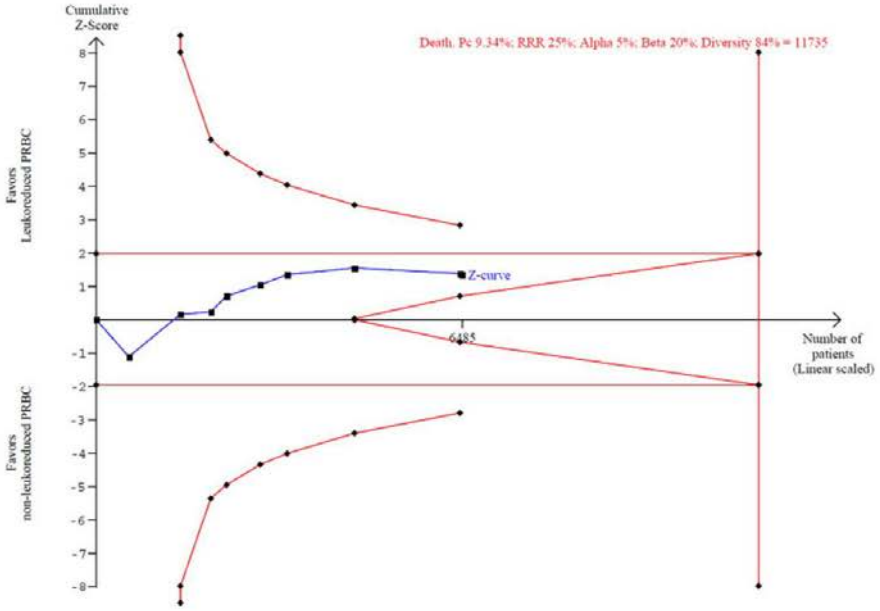
Reporting bias

We did not explore reporting biases since the meta-analysis included fewer than 10 studies (Higgins 2011).

Quality of evidence (TSA and GRADE)

The accrued information of 6485 participants constituted only 55.2% of the DARIS of 11,735 participants. DARIS was calculated based on a diversity of 84%; a proportion of death from any cause of 9.34% in the control group (median proportion of deaths in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. The TSA did not indicate futility, as the cumulative Z-curve did not cross the futility wedge (Figure 4). The TSA-adjusted 95% CI overlapped with no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.51 and RR 1.27, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was very low (high risk of bias (-1); important heterogeneity (-1); and imprecision as reflected in the wide CI and an insufficient accrued information size compared with the DARIS (-1)).

Figure 4. TSA calculated to reliably detect a 25% relative change in the incidence of death from any cause, assuming a control group event rate of 9.34% with a power of 80% at an alpha of 5%



Infection from any cause

Overall analysis (total randomised patients)

The meta-analysis of 10 trials involving 6709 participants showed no difference between treatment groups in the risk of infection from any cause (17.7% versus 20.4%; RR 0.80, 95% CI 0.62 to 1.03; I^2 statistic = 84%, P = 0.08) (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). See Analysis 1.3.

Sensitivity analysis

The RR was different when we used the fixed-effect model (RR 0.85, 95% CI 0.77 to 0.93; I^2 statistic = 84%, P = 0.0006); however, the results of TSA indicate this statistically significant result may be a spurious finding.

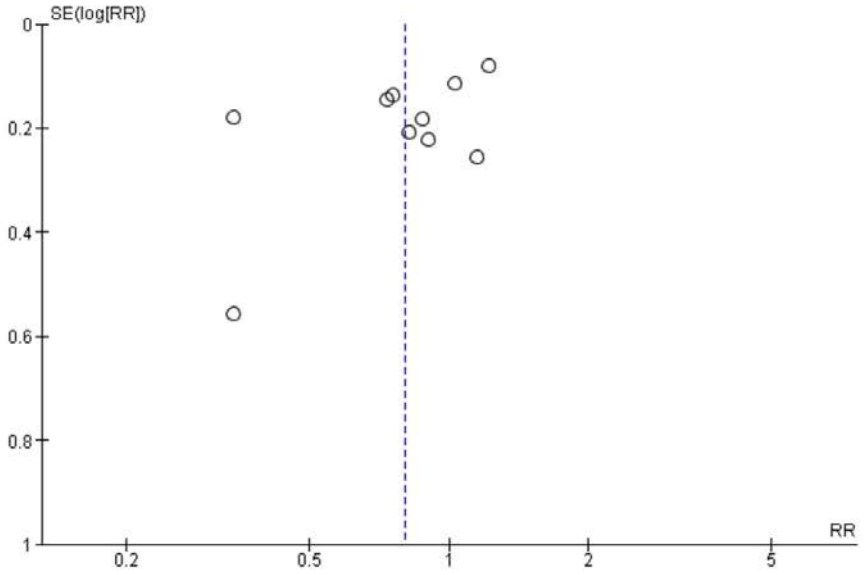
We performed three other sensitivity analyses, which showed no statistically significant differences:

1. Including three studies with low risk of bias (Collier 2001; Bilgin 2004; Nathens 2006), compared with seven studies at unclear or high risk of bias (RR 0.92, 95% CI 0.63 to 1.34; I^2 statistic = 83%, P = 0.67).
2. Including "only transfused patients", compared with all randomised patients (RR 0.76, 95% CI 0.58 to 1.00; I^2 statistic = 87%, P = 0.05, Analysis 2.3), and the heterogeneity remained high.
3. Post-storage leukoreduction, compared with pre-storage leukoreduction (RR 0.91, 95% CI 0.76 to 1.09; I^2 statistic = 65%, P = 0.32).

Reporting bias

After visual assessment of the funnel plot (Figure 5) and a formal assessment of the funnel plot asymmetry, applying the Egger's test (P = 0.09), we found no sign of reporting bias.

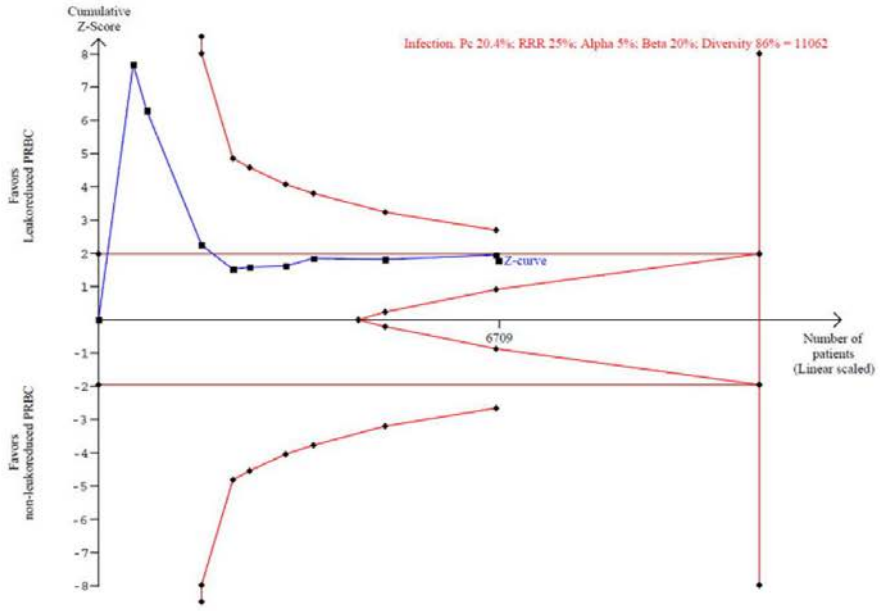
Figure 5. Funnel plot of comparison: 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main Analysis (Randomised patients), outcome: 1.3 Infection. Number of events of the total of randomised patients reported.



Quality of evidence (TSA and GRADE)

The accrued information of 6709 participants constituted only 60.6% of the DARIS of 11,062 participants. We calculated DARIS based on a diversity of 86%; a proportion of infection from any cause of 20.4% in the control group (median proportion in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. TSA did not indicate futility, as the Z-curve did not cross the futility wedge (Figure 6). The TSA-adjusted 95% CI overlapped the zone of no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.57 and RR 1.12, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was very low (high risk of bias (-1); important heterogeneity (-2); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)).

Figure 6. TSA calculated to reliably detect a 25% relative change in the incidence of infection from any cause, assuming a control group event rate of 20.4% with a power of 80% at an alpha of 5%.



Adverse events (fever)

Three trials reported adverse events. However, we excluded one trial reporting fever as a temperature increase of at least 1°C per transfusion from the meta-analysis since fever was not analysed per study participant (Collier 2001).

Overall analysis (total randomised patients)

Two trials including 634 participants showed no difference between treatment groups in adverse events (31.9% versus 38.7%; RR 0.81, 95% CI 0.64 to 1.02; I^2 statistic = 0%, P = 0.07) (Wallis 2002). See Analysis 1.4.

Sensitivity analysis

In the sensitivity analysis comparing "transfused patients" with randomised patients, there was a statistically significant difference (RR 0.75, 95% CI 0.60 to 0.94, I^2 statistic = 0%, P = 0.01, Analysis 2.4); however, the results of TSA indicate this statistically significant result may be a spurious finding.

In a sensitivity analysis of data from one study, Wallis 2002, there was no difference when comparing post-storage with pre-storage leukoreduction (RR 0.81, 95% CI 0.64 to 1.04).

Reporting bias

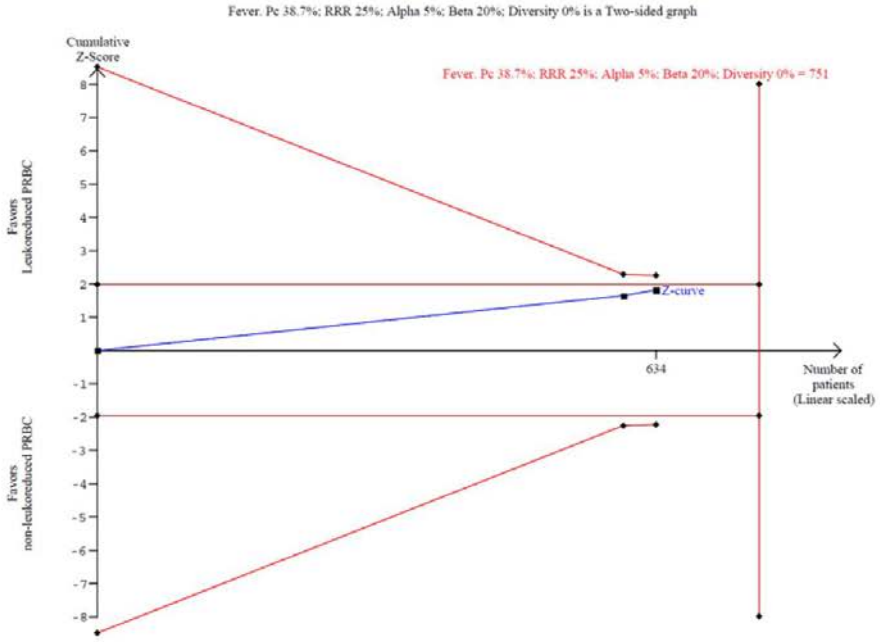
We did not explore reporting biases since the meta-analysis included fewer than 10 studies (Higgins 2011).

Quality of evidence (TSA and GRADE)

The accrued information of 634 participants constituted only 84.4% of the DARIS of 751 participants. DARIS was calculated based on a diversity of 0%; a proportion of infection from any cause of 38.7% in the control group (median proportion in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. TSA did not indicate futility, as the

Z-curve did not cross the futility wedge (Figure 7). The TSA-adjusted 95% CI overlapped with the zone of no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.68 and RR 1.05, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was low (high risk of bias (-1); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)).

Figure 7. TSA calculated to reliably detect a 25% relative change in the incidence of fever, assuming a control group event rate of 38.7% with a power of 80% at an alpha of 5%.



Non-infectious complications

The included trials did not assess this pre-defined outcome.

DISCUSSION

Summary of main results

In this systematic review we included 13 trials involving cardiovascular surgical, gastro-oncology surgery, trauma and HIV patients who were randomised to receive leukoreduced compared with non-leukoreduced PRBC transfusion. After analysis of the study data, we are unable to conclude whether or not leukoreduction of PRBC has an effect on preventing TRALI (one trial), death (nine trials), infection (10 trials) and other adverse events (fever, reported in two trials). The quality of evidence was low (TRALI

and adverse events) to very low (death and infection) due to high heterogeneity, imprecision and high risk of bias. None of the included trials reported on other non-infectious complications. The sensitivity analyses of trials at low risk of bias showed neither a beneficial or harmful effect of leukoreduction of PRBC on the pooled data regarding death, infection and adverse events.

Overall completeness and applicability of evidence

Overall completeness of evidence

We analysed 13 controlled clinical trials that met our predefined inclusion criteria. Two trials reported only physiological results and we excluded them from the meta-analyses. Only one RCT evaluated the primary outcome (TRALI). However, we obtained data from 11 trials which contributed to the effect estimates of the secondary outcomes (death from any cause, infection from any cause and adverse events/fever). We found no trials evaluating non-infectious complications other than TRALI (e.g. FNHTR). Therefore, the pre-specified objectives and outcomes of our Cochrane review were partially addressed and the results are inconclusive. Consequently, the findings of this review should be interpreted with caution until more data are available.

Applicability of evidence

This Cochrane review is complex for a variety of reasons:

Firstly, regarding the population: the identified studies enrolled patients with different health problems, including trauma, cancer, cardiac disease and HIV-infected patients. Some important patient populations were not studied at all (e.g. paediatric or obstetric patients) or were insufficiently assessed (e.g. one RCT of trauma patients). In this context, external validity may be limited due to a lack of studies analysing these populations. Furthermore, the effect of leukoreduction on some types of patients without a strong indication for leukoreduced PRBC has not been sufficiently evaluated: single-transfused patients, patients without history of FNHTR, patients who are not receiving long-term platelet transfusions and those who are not at risk of developing CMV disease.

Secondly, regarding the intervention, the included studies did not adequately report several aspects related to the transfusion of RBC that need to be considered when interpreting the results, namely: the use of leukoreduced or non-leukoreduced platelets as a co-intervention, the timing of leukoreduction (i.e. pre-storage or post-storage), the type of filter used (e.g. Cell select Optima, BPF4, RC 100, Sepacell RZ-200B1), leucocyte reduction definition (e.g. 0.1 to 0.3 $\times 10^6$ WBC/unit, 5×10^6, 2×10^5 per unit, etc.) and the type of transfusion (i.e. allogeneic or autologous).

Thirdly, regarding the outcomes: not all the included trials assessed relevant clinical outcomes. Relevant infections (e.g. CMV), non-infectious complications (e.g. TRALI, FNHTR) and any other adverse events were not sufficiently assessed or reported (Schulz 2010). The various follow-up intervals (28 days to 15 months) may represent another limitation for the assessment of outcomes.

Fourthly, regarding the costs: leukoreduction is widely implemented in clinical practice in many countries and some countries have established universal leukoreduction for blood transfusions (Laupacis 2001). However, the high costs related to this procedure deserve special attention. Even though the reintroduction of non-leukoreduced products probably provides no clinical impact, it does entail economic consequences. Changing the strategy from performing universal to selective leukoreduction would result in an important decrease in the costs (e.g. almost EUR 30 million per year in Spain (AETSA 2007)). Tsantes 2014 reported an incremental cost-effectiveness ratio (ICER) of EUR 6916 to prevent one case of FNHTR. Additionally, it is reasonable to consider other costs associated with maintaining dual inventories of leukoreduced PRBC and non-leukoreduced PRBC.

Finally, as leukoreduction of PRBC was shown to have no effect on preventing TRALI, death, infection and other adverse events reported by RCTs, these results have to be adequately interpreted within the context of current clinical practice which differs internationally and among populations. Other strategies might be more cost-effective than leukoreduction in terms of avoiding adverse events related to transfusion PRBC, such as the use of restrictive transfusion triggers (Carson 2012; Rohde 2014), that have shown effectiveness regardless of whether blood products are leukoreduced or not.

Quality of the evidence

The body of evidence available to date does not allow a definitive conclusion to be drawn about the benefits and harms of leukoreduction. The included RCTs had important methodological limitations: 1. poor and incomplete reporting of inclusion and exclusion criteria; 2. important attrition bias due to the exclusion of many patients included, but not transfused; 3. incomplete information on allocation concealment; 4. inadequate reporting of other blood components as co-interventions; and 5. incomplete reporting of clinical outcomes of interest. Additionally, some of the included trials showed important inconsistency in the estimates of effect.

Potential biases in the review process

We applied Cochrane systematic review methodology to the search for and selection of studies for inclusion in the review. However, despite our effort to include all published studies evaluating leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion, it is possible that not all relevant data were identified. The small number of trials identified in our review raises

concerns about publication bias. In order to identify this potential bias we performed a funnel plot. However, this visual method was possible only for one outcome (infection of any cause), since fewer than 10 studies assessed the other outcomes.

We contacted trial authors during the identification of trials (see Appendix 3) to clarify some questions related to the eligibility criteria, but not while we completed data extraction and analysis. We took into account only published data during these processes, considering the missing information as reporting bias.

In the review protocol we defined the main analysis based on the ITT approach (Simancas-Racines 2012). However, during the data extraction we identified an important number of patients included but not transfused. This may affect the precision of the effect estimations. In order to explore this scenario, we carried out a per-protocol analysis (only transfused patients) which did not reflect relevant differences in relation to the primary outcome (TRALI) and secondary outcomes death and infection from any cause, but the secondary outcome adverse events (fever) showed differences.

A limitation of the review was not considering the effect of buffy coat depletion in the estimations through a sensitivity analysis, because we had not planned such analysis in advance. Another limitation was not considering the subgroup analysis of the potential effect of different types of filters used in the included studies for all outcomes. We planned this analysis in the review protocol only for the primary outcome.

Agreements and disagreements with other studies or reviews

Reviews and meta-analyses on postoperative infection and death related to the leukoreduction of blood products have been carried out previously. However, as far as we know, no systematic reviews focused on non-infectious complications, such as TRALI or FNHTR, have yet been published. In the overall analysis of death from any cause, the findings of other reviews are in accordance with our results. Nevertheless, one systematic review showed a 50% reduction in the probability of postoperative infection (Blumberg 2007) and another review analysing "only patients who received transfusion" found a statistically significant reduction of 40% in postoperative infection, but a non-significant reduction in mortality (Fergusson 2004).

These two reviews have several limitations. They included studies with other blood components apart from leukoreduced PRBC cells as interventions, as well as non-randomised studies. Moreover, heterogeneity between studies was not taken into account and the risk of bias of included studies was not appropriately assessed. Furthermore, some relevant studies were not included.

AUTHORS' CONCLUSIONS

Implications for practice

There is no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death from any cause, infection from any cause, non-infectious complications and other adverse events. The quality of evidence is very low to low. Given that leukoreduction is a very expensive procedure, clinicians and policy makers may need to reconsider whether transfusing leukoreduced PRBC is suitable for all types of patients, especially for patients without a strong indication for leucocyte reduction. In countries where leukoreduction has not been universally implemented yet, selective leukoreduction is an option to be considered until better evidence on the effectiveness or harms of this procedure is available.

Implications for research

Taking into account the inconclusive evidence found in this Cochrane review, further research is needed to assess the relative efficacy, safety and cost-effectiveness of leukoreduction in different clinical settings and for different conditions. Researchers should consider that premature randomisation is an important issue because it may cause attrition bias and affect the interpretation of the results; in this case, it may affect the true effect of leukoreduced PRBC. Further research should also consider aspects of the study design (Chan 2013), such as verifying the inclusion and exclusion criteria before randomisation. Researchers should also improve the reporting of interventions and co-interventions (Schulz 2010), for example whether or not a blood transfusion includes other components or not (e.g. leukoreduced or non-leukoreduced platelets). Moreover, further studies should address all relevant outcomes (Gabriel 2012), such as death from any cause, infectious complications (e.g. risk of CMV transmission, or at least, evaluate the risk of CMV reactivation from transfused leukoreduced PRBC cells), non-infectious complications (e.g. TRALI, NHFRT) and any other adverse events related to the PRBC transfusion.

ACKNOWLEDGEMENTS

Daniel Simancas-Racines is a Ph.D. candidate at the Department of Pediatrics, Gynecology and Obstetrics, and Preventive Medicine, Universitat Autònoma de Barcelona, Spain.

We thank Ms. Marta Roqué i Figuls, Iberoamerican Cochrane Centre, for her advice on statistical analysis; Dr. Christian Gluud, Centre for Clinical Intervention Research, Denmark, for his advice on interpreting the trial sequential analyses; and Ms. Maria Victoria Leo Rosas for revising and improving the grammar and style of the review.

This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are

those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

5.2. Segunda Publicación

Por otro lado, de acuerdo con los resultados obtenidos en el segundo estudio (Simancas-Racines et al., 2019; Factor de Impacto (JCR): 2.140; SJR: 1.237, Primer Cuartil (Q1) realizado para esta tesis, se incluyeron 7 ECAs (43,54–57,71,145) con 3154 participantes) que cumplieron con los criterios de inclusión. La calidad de la evidencia de estos estudios fue “moderada” para los desenlaces infección y muerte por cualquier causa (150)**.**

El RR para infección por cualquier causa fue de 0.77 (CI 95% = 0.66 a 0.91; I^2= 0%) en la comparación de concentrados de glóbulos rojos leucorreducidos versus concentrados de glóbulos rojos no leucorreducidos. El TSA para el desenlace de infección por cualquier causa determinó que la población del estudio constituyó más del 100% del número óptimo calculado para detectar confiablemente un efecto plausible con base en el cálculo ajustado de 1315 participantes.

Hindawi
Cardiology Research and Practice
Volume 2019, Article ID 7543917, 10 pages
https://doi.org/10.1155/2019/7543917

Review Article

Leukodepleted Packed Red Blood Cells Transfusion in Patients Undergoing Major Cardiovascular Surgical Procedure: Systematic Review and Meta-Analysis

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Received 12 September 2018; Revised 21 December 2018; Accepted 23 January 2019; Published 25 February 2019

Academic Editor: Stephan von Haehling

Background. Leukocytes contained in the allogeneic packed red blood cell (PRBC) are the cause of certain adverse reactions associated with blood transfusion. Leukoreduction consists of eliminating leukocytes in all blood products below the established safety levels for any patient type. In this systematic review, we appraise the clinical effectiveness of allogeneic leukodepleted (LD) PRBC transfusion for preventing infections and death in patients undergoing major cardiovascular surgical procedures. *Methods*. We searched randomized controlled trials (RCT), enrolling patients undergoing a major cardiovascular surgical procedure and transfused with LD-PRBC. Data were extracted, and risk of bias was assessed according to Cochrane guidelines. In addition, trial sequential analysis (TSA) was used to assess the need of conducting additional trials. Quality of the evidence was assessed using the GRADE approach. *Results*. Seven studies met the eligibility criteria. Quality of the evidence was rated as moderate for both outcomes. The risk ratio for death from any cause comparing the LD-PRBC versus non-LD-PRBC group was 0.69 (CI 95% = 0.53 to 0.90; $I^2 = 0\%$). The risk ratio for infection in the same comparison groups was 0.77 (CI 95% = 0.66 to 0.91; $I^2 = 0\%$). TSA showed a conclusive result in this outcome. *Conclusions*. We found evidence that supports the routine use of leukodepletion in patients undergoing a major cardiovascular surgical procedure requiring PRBC transfusion to prevent death and infection. In the case of infection, the evidence should be considered sufficient and conclusive and hence indicated that further trials would not be required.

1. Introduction

Blood transfusion is an acute intervention implemented to solve life- and health-threatening conditions on a short-term basis [1]. Packet red blood cell (PRBC), prepared by removing plasma from whole blood, is typically used to transfuse anemia patients who require infusion of red blood cell (RBC) to restore tissue oxygenation. However, PRBC transfusion is associated with an increasing risk of infectious and noninfectious adverse events, the most common among which are nonhemolytic febrile transfusion reactions, human leukocyte antigen (HLA) alloimmunization and platelet

refractoriness observed in multitransfused patients, and transmission of leukotropic viruses. One of the strategies commonly used to prevent posttransfusion complications is leukodepletion, that is, a process by which the white blood cells (WBCs) are intentionally reduced by almost 99.99% to PRBC. According to the current standards, PRBC residual leukocytes require to be $<5\times10^6$ cells per unit according to the FDA or $<1\times10^6$ cells per unit according to the Council of Europe [2].

Several studies have focused on the advantages of leukodepleted PRBC for transfusion in cardiac surgery [3–8], colorectal surgery [4, 9–13], gastrointestinal surgery [4, 7, 14], and renal transplantation [15–17]. Cardiac surgery accounts for a large proportion of the blood transfusions administered each year. Transfusion rates have been reported from 7.8% to 92.8% for combination of coronary artery bypass graft (CABG) surgery with valve or other major surgical interventions [18].

Although blood transfusions are necessary in major cardiovascular surgery, several studies found that blood transfusions had also deleterious effects. Considering the abovementioned reasons, this subgroup of the surgical population is of special interest for the analysis of the effectiveness and safety of transfusion practices. Several studies have been showed that cardiac surgery is related with tissue trauma, ischemia-reperfusion injury, and blood surface contact. These clinical settings induce systemic effects and release of inflammatory mediators, which are supposed to play a role in the development of systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), infections, and postoperative complications [19, 20]. Additionally, in cardiac surgery, PRBC are frequently transfused and these transfusions have been found to be associated (dose-dependent) with an increased risk of postoperative infections and mortality after cardiac surgery [21–25]. It is not clear what the possible mechanisms that clarify this association could be [26] although the presence of allogeneic leukocytes in PRBC are hypothetical to play a fundamental role, probably by evolving into the inflammatory response after cardiac surgery. In support of this reasoning, Bilgin et al. found higher concentrations of proinflammatory mediators (such as IL-6 and IL-10) during the postoperative period in cardiac valve surgery patients receiving allogeneic leukocyte-containing blood transfusions compared with leukocyte-depleted blood transfusions [27]. This, in turn, would support the potential benefits of the routine use of leukodepleted PRBC transfusion in the setting of cardiac surgery to reduce infectious complications [28].

One previous review reported that there is no clear evidence supporting the effectiveness of leukodepleted PRBC for preventing transfusion-related acute lung injury (TRALI) or reducing mortality and infectious or non-infectious complications in patients undergoing any type of surgery [29]. However, a considerable heterogeneity in the pooled estimation was found due to the inclusion of different types of populations (oncology, trauma, and cardiac surgery patients) which may have prevented the detection of beneficial effects in some particularly relevant subgroups of surgical patients. Therefore, the objective of this review was to assess the effects of LD-PRBC in patients undergoing major cardiovascular surgical procedure, who are more likely to suffer significant blood loss [20] and consequently have a much higher probability to receive transfusions of blood products [18].

2. Methods

We conducted a systematic review of randomized clinical trials (RCTs). The protocol was registered in PROSPERO, an international prospective register of systematic review protocols (registration number: CRD42018103104).

2.1. Inclusion and Exclusion Criteria. To be included in the review, studies had to meet the following criteria: randomized controlled trial conducted with patients of any age undergoing a major cardiovascular surgical procedure (such as valve surgery, cardiac bypass, and aneurysm repair), requiring allogeneic PRBC, with the aim of comparing LD-PRBCs versus non-LD-PRBCs. Besides, studies had to report results on death from any cause and infection from any cause (unspecified). We excluded studies with other designs or that included patients transfused with other blood components as a principal intervention.

2.2. Search Strategy. We carried on sensitive electronic searches in the Cochrane Injuries Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (OVID 1946 to present), EMBASE (Elsevier), LILACS, Clinical Trials register (http://www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/). We ran the most recent search on June 10th, 2018 (see Supplementary material (available here) for details).

2.3. Screening, Data Extraction, and Assessment of Risk of Bias. Two review authors independently screened all titles and abstracts retrieved by the search against the selection criteria and obtained full texts when necessary. All decisions regarding inclusion and exclusion were made by consensus. Data extraction was performed in duplicate and risk of bias (RoB) assessment of the included studies, following the domain-based evaluation method described in the Cochrane Handbook for Systematic Reviews of Interventions [30].

As a support to establish our conclusions on the effects of leukodepleted PRBC, we developed a "Summary of Findings" table using the GRADE approach for assessing the quality of evidence, according to the methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions [30].

2.4. Statistical Analysis. We calculated the treatment pooled effect for death from any cause and infection from any cause by means of the risk ratio (RR) with the corresponding 95% confidence intervals (CI), using the random-effects model

approach for data pooling in the meta-analysis, which accounts for statistical heterogeneity across studies and leads to a more conservative estimate of the effect. We estimated the statistical heterogeneity in the meta-analysis by using the I^2 statistics [31]. All these analyses were carried out using RevMan 5.3 [32].

We used trial sequential analyses (TSA) to estimate the required information size for death from any cause and infection from any cause in order to reduce the risk of random errors in our conclusions and calculating the required information size for a meta-analysis. This analysis makes available an adjusted statistical threshold for benefits, harms, or futility before the required information size was reached [33, 34]. By using this method, we aimed at controlling the risk of type I and type II errors due to sparse data and repetitive testing of accumulating data [33, 35–37].

3. Results

3.1. Literature Search Results. We initially identified 7,999 records from the search strategies updated until June 2018 [23] and four more from other sources. After removing duplicates, 4,022 were manually screened, and 3,993 records were excluded for title and abstract. We reviewed the full text of 29 studies, 22 of which were excluded. Finally, only seven RCTs with 3,154 participants were included into the qualitative and quantitative analysis of this report [3, 5–8, 38, 39] (Figure 1).

3.2. Characteristics of the Included Studies. Two of the seven included studies only had abstract available [38, 39]. Three studies were carried out in the Netherlands (60%) [3, 6, 7]. All studies included adult patients, with mean ages greater than 60 years. Leukodepletion process was described only in three of the seven studies, using three different criteria ($1.2 \pm 1.4 \times 10^6$, 5×10^6, or $0.15 \pm 0.02 \times 10^6$, leukocytes per unit) [3, 5, 6].

Sample size for the transfused patients ranged from 38 to 304 (mean 189) for the leukodepleted group and 31 to 303 (mean 207) for the comparator group. In van Hilten 2004 study, we included only patients undergoing aneurysm repair, excluding gastrointestinal oncology surgery. From the van de Watering 1998 study, we included the stored-filtered (SF) group within the leukodepleted group and the packed cells (PC) group within the comparator group. Table 1 describes the main characteristics of included studies. Regarding risk of bias, most studies were assessed as "unclear risk" regarding selection bias (random sequence generation and allocation concealment) due to lack of details in the study report. Only one study was assessed as having "low risk" of bias for blinding of participants, personnel, and outcome assessors [6]. We considered the missing outcome data shown in van Hilten 2004 as having a "high risk" of bias, due to fact that losses are likely to be related to the main outcomes [7]. In addition, three studies were considered as at "unclear risk" of other bias [3, 7, 8, 38, 39].

3.3. Target Death from Any Cause. In the included studies, death was assessed at 30 days [8], 60 days [3], 90 days [5, 6], and up to twelve months [38]. Two studies did not report the follow-up time for the death from any cause outcome [7, 39]. The overall death from any cause at the last follow-up was 5.96% (79 events). The pooled RR for the comparison of LD-PRBC versus non-LD-PRBC was 0.69 (CI 95% = 0.53 to 0.90; $I^2 = 0\%$), thus showing a statistically significant reduction in the risk of death from any cause with LD-PRBS (31% relative reduction) (Figure 2).

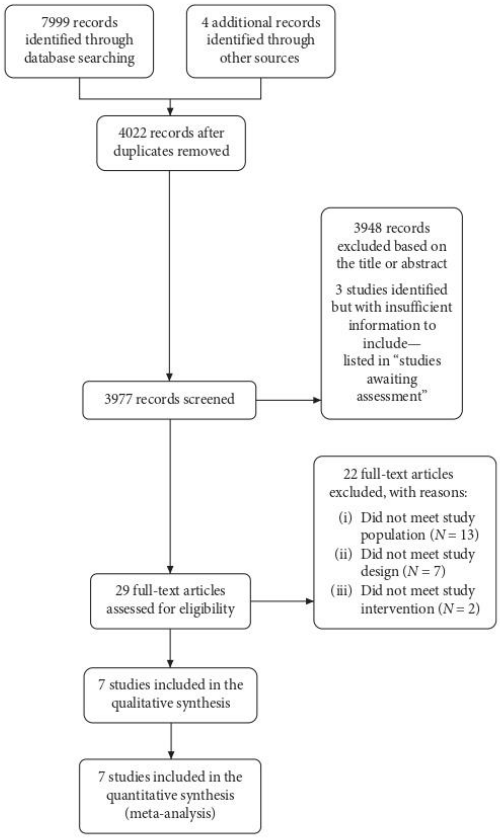

Figure 1: Flow diagram of the literature search and study selection.

We conducted TSA analysis to determine the reliability of one of the outcomes of this systematic review: death from any cause (Figure 3). TSA of LD-PRBC compared with control non-LD-PRBC indicated that the optimal information size needed to reliably detect a plausible effect was 5,187 patients. However, 2,771 (53.4%) patients had so far been collected. The cumulative z-curve of all trials crossed the traditional boundary but did not cross the trial sequential monitoring boundary. The TSA α-spending adjusted 95% CI overlapped with no effect (RR 0.49 and RR 1.02, respectively); thus, the TSA yielded an inconclusive result about the true effect of LD-PRBC in preventing death from any cause. Therefore, for death from any cause outcome,

Table 1: Characteristics of the included studies.

ID	Country	Age mean by group (LD, C)*	Male (%)	Leukodepleted group				Comparator group		Cointerventions
				Transfused patients,*n*	Type of surgery	Leukodepleted definition	Filter	Transfused patients, *n*	Comparator	
Bilgin et al. 2004 [6]	Netherlands	65.3, 66.6	53 to 57	216	Cardiac valve surgery with or without coronary artery bypass graft	$0.15 \pm 0.02 \times 10^6$ per unit	Cellselect-Optima	216	Buffy coat depleted packed cells	Platelets
Boshkov et al. 2006 [38]	USA	Unclear	Unclear	304	Coronary artery bypass graft and/or cardiac valve replacement	Unclear	Unclear	258	Standard RBC	No
Bracey et al. 2002 [39]	USA	Unclear	Unclear	170	Open-heart surgery, coronary artery bypass graft, and valve replacement	Unclear	Unclear	187	Standard RBC	Unclear
Connery et al. 2005 [8]	USA	62.9, 66	71 to 74.2	38	Coronary artery bypass graft	Unclear	Unclear	31	Standard RBC	Platelets
van de Watering et al. 1998 [3]	Netherlands	62.9, 64.4	72.2 to 73.7	287	Coronary artery bypass graft and/or cardiac valve surgery	$1.2 \pm 1.4 \times 10^6$ per unit	Cellselect-optima	294	Buffy coat depleted packed cells	No
van Hilten et al. 2004 [7]	Netherlands	66, 71	Unclear	133	Acute aneurysm surgery and elective aneurysm surgery	Unclear	Unclear	128	Buffy coat depleted packed cells	No
Wallis et al. 2002 [5]	UK	61.7, 62.4	Ratio men/women: 2.6 to 2.9	176	Coronary artery bypass graft and/or cardiac valve surgery	5×10^6 per unit	BPF4	333	Buffy coat depleted packed cells and red blood cells concentrate with plasma reduction	No

RBCs = red blood cells. *LD: leukodepleted group; C: comparator group.

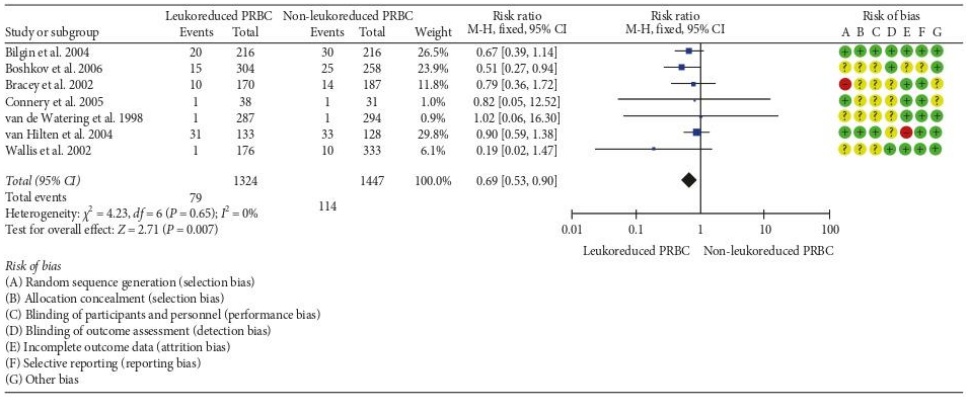

FIGURE 2: Forest plot of included studies evaluating LD-PRBC versus non-LD-PRBC in patients undergoing a major cardiovascular surgical procedure: death from any cause outcome.

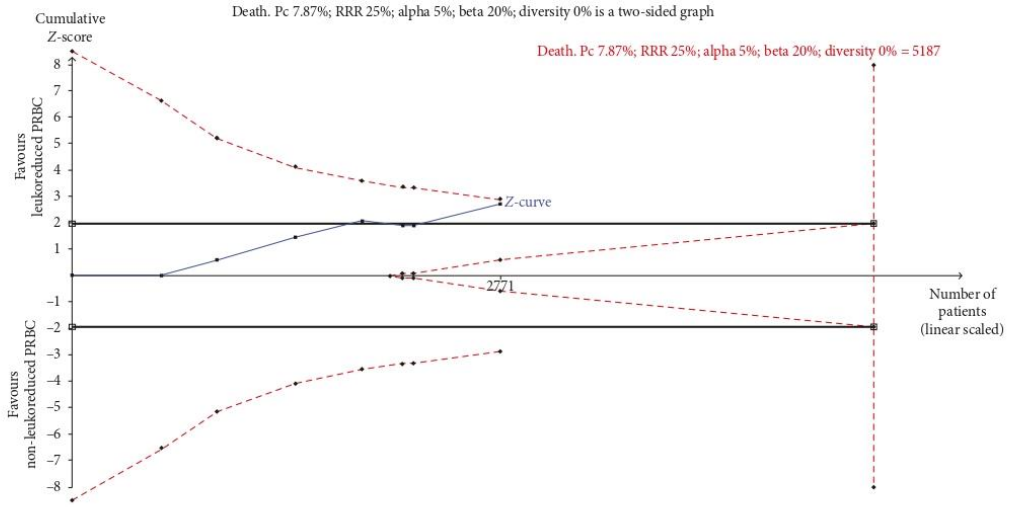

FIGURE 3: TSA calculated to reliably detect a 25% relative change in the incidence of death from any cause, assuming a control group event rate of 8.99% with a power of 80% at an alpha of 5%. Notes: DARIS: diversity adjusted required information size; Pc: event proportion in the control group; RRR: relative risk reduction in the intervention group; (a) type I error; (b) type II error; DIVERSITY: diversity (D-square). Dead: the required information size was 5,187 participants. The cumulative Z-score (blue line) did not cross the trial sequential monitoring boundaries for benefit (red lighter inward sloping line) after the seven trials.

more RCTs are needed (Figure 3). According to GRADE criteria, the quality of the evidence was moderate to low (Table 2).

3.4. Target Infection. Regarding infection, five out of seven included studies reported this outcome [3, 5–8, 38, 39]. Incidence of infection after follow-up was 19.8% (494 events). The pooled RR for the comparison of the LD-PRBC versus non-LD-PRBC group was 0.77 (IC 95% = 0.66 a 0.91; $I^2 = 0\%$), thus showing a statistically significant reduction in the risk of infection with LD-PRBS (23% relative risk reduction) (Figure 4).

We conducted TSA to determine the reliability of one of the outcomes of this systematic review: infection from any cause. TSA of LD-PRBC compared with non-LD-PRBC indicated that the optimal information size needed to reliably detect a plausible effect was 1,315 patients. However, the accumulate data of 1,852 participants constituted more than 100% of the optimal information size calculated. The cumulative z-curve of all trials crossed the traditional boundary as well as the trial sequential monitoring

Table 2: Summary of findings: GRADE criteria.

Leukodepleted packed red blood cells transfusion in patients undergoing a major cardiovascular surgical procedure
Patient or population: patients undergoing a major cardiovascular surgical procedure transfused with allogeneic packed red blood cells (PRBC)
Setting: hospital
Intervention: leukodepleted (PRBC)
Comparison: non-leukodepleted (PRBC)

Outcomes	Anticipated absolute effects* (95% CI) Risk with non-leukodepleted (PRBC)	Risk with leukodepleted (PRBC)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (grade)	Comments
Death. Number of events of the total number of transfused patients reported	79 per 1.000	**54 per 1.000** (42 to 71)	**RR 0.69** (0.53 to 0.90)	2771 (7 RCTs)	⊕⊕⊕◯ Moderate[a,b]	TSA yielded an inconclusive result.
Infection. Number of events of the total number of transfused patients reported	259 per 1.000	**200 per 1.000** (171 to 236)	**RR 0.77** (0.66 to 0.91)	1852 (5 RCTs)	⊕⊕⊕◯ Moderate[a,b]	TSA yielded a conclusive result.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio. The overall certainty in the evidence should be assessed for each important outcome using four or three categories (such as high, moderate, low, and/or very low) and definitions for each category that are consistent with the definitions used by the GRADE Working Group. [a]Downgraded because one study has high risk of bias due to attrition bias; another study has other risk of bias at high risk of bias; three studies have unclear risk of bias in generation and allocation concealment of random sequence. [b]Downgraded due to high risk of bias; one study has high risk of bias due to attrition bias; another study has high risk of bias in a random sequence; five studies have unclear risk of bias in generation and allocation concealment of random sequence.

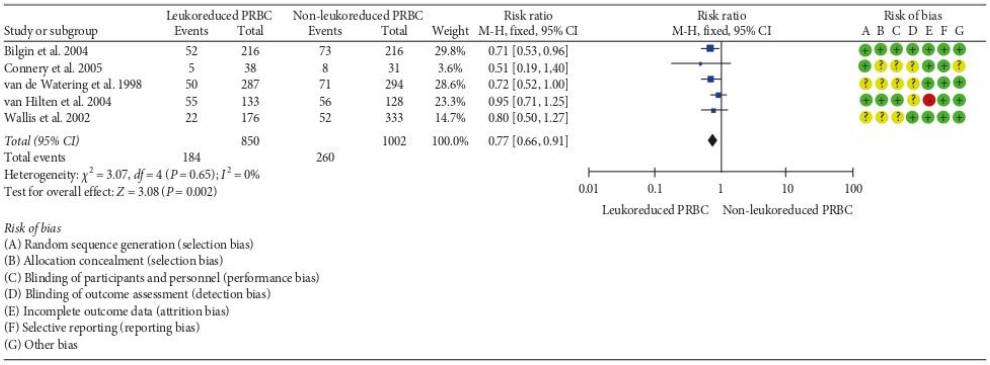

Figure 4: Forest plot of included studies evaluating LD-PRBC versus non-LD-PRBC in patients undergoing a major cardiovascular surgical procedure: infection outcome.

boundary. The TSA α-spending adjusted 95% CI, did not overlap the zone of no effect (RR 1.0), and is compatible with a potential benefit (RR 0.65 and RR 0.93, respectively); thus, the TSA yielded a conclusive result about the true effect of LD-PRBC in preventing infection from any cause. Therefore, for infection from any cause outcome, no more RCTs are needed (Figure 5). According to GRADE criteria, the quality of the evidence was moderate (Table 2).

4. Discussion

In this systematic review, we showed that patients undergoing a major cardiovascular surgery who were transfused with LD-PRBCs might benefit from a decreased risk of infections and death from any cause. The certainty for the first outcome is moderate according to the quality of the body of evidence available, but conclusive according to the TSA analysis. As for the later outcome, the certainty in the result is also moderate but not as conclusive as regarding the former result.

Several reviews and meta-analyses on postoperative infection and death related to the leukoreduction of blood products have been carried out previously [29]. However, as far as we know, no systematic reviews or meta-analysis with TSA focused specifically in patients undergoing a major cardiovascular surgery have yet been published. Nevertheless, it is important to point out that numerous studies have sought to demonstrate the benefit of leukocytes reduction from red blood cell concentrates in different scenarios.

One previously published Cochrane systematic review comparing LD-PRBC with non-LD-PRBC in all type of

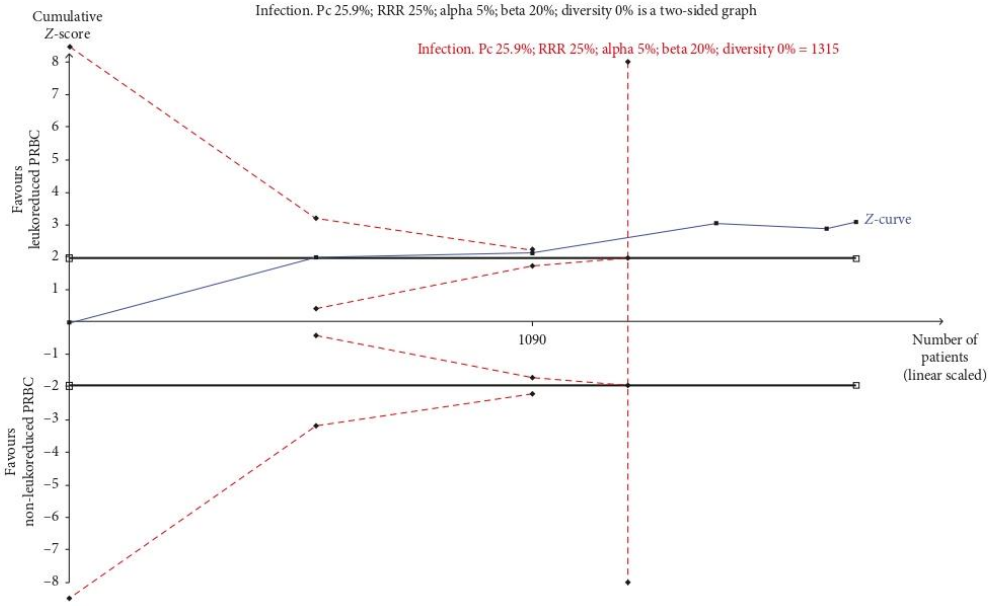

Figure 5: TSA calculated to reliably detect a 25% relative change in the incidence of infection from any cause, assuming a control group event rate of 24.6% with a power of 80% at an alpha of 5%. Notes: DARIS: diversity adjusted required information size; Pc: event proportion in the control group; RRR: relative risk reduction in the intervention group; (a) type I error; (b) type II error; DIVERSITY: diversity (D-square). Infection: the required information size was 1,315 participants. The cumulative *Z*-score (blue line) crossed the trial sequential monitoring boundaries for benefit (red lighter inward sloping line) after the second trial (1,090 participants); thus, the risk of random error in the finding can be excluded. Therefore, it is not necessarily additional testing based on the assumed intervention effect of the RRR of 25%, an alpha of 5%, and a beta of 20% with respect to this result.

surgical patients requiring transfusion, showed a non-significant decrease in the risk of infection (10 trials with 6,709 patients) and all-cause mortality (9 trials with 6,485 patients). However, these results were limited by a significant heterogeneity [29]. These findings contradict our results partially because the population included in that review was very heterogeneous which may have hidden the effect of the intervention in specific subgroups of interest. In contrast, our study was specifically focused in patients undergoing major cardiovascular surgery. This surgery has been related to a higher volume of PRBC 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 [40]. Thus, it is reasonable to assume that the potential harms of using non-LD-PRBC are higher than in other surgical scenarios.

In contrast, the findings of other systematic reviews are in accordance with our results. One systematic review showed a 50% reduction in the risk of a postoperative infection [41], and another one analyzing "only patients who received transfusion" found a statistically significant reduction of 40% in postoperative infection risk, but a nonsignificant reduction on mortality [42]. However, these two reviews have several limitations. They included studies that used other blood components apart from LD-PRBC cells as an intervention, as well as nonrandomized studies. Moreover, heterogeneity between studies was not taken into account, and the risk of bias of included studies was not appropriately assessed. Furthermore, some relevant studies were not included, and patients undergoing major cardiovascular surgery were not evaluated independently. Finally, any of the aforementioned reviews did not perform a trial sequential analysis, in order to control the risks of type I and type II errors due to sparse data and repetitive testing of accumulating data in all of calculated meta-analyses.

Applicability of this evidence to daily clinical practice is restricted for several reasons. Firstly, external validity may be limited to patients undergoing the same major cardiovascular surgery procedures that have been included in this review. Secondly, the identified studies did not adequately report several factors related to the transfusion of RBC practices that need to be considered when interpreting the results, such as the use of LD or non-LD platelets as a cointervention, the timing of LD (pre-post-storage), and the type of the filter used, among other factors. Thirdly, the number of units transfused in major cardiovascular surgery is massive in most of the cases compared with other surgical and nonsurgical transfusion clinical settings, and therefore, patients undergoing major cardiovascular surgery may suffer a posttransfusion complication is more likely. Finally,

the studies reported different definitions for infections, and the mortality was assessed in different time periods (30 days, 60 days, 90 days, and up to twelve months).

Most developed countries currently recommend universal LD-PRBC. However, high costs associated with this procedure, such as the direct costs of LD-PRBC and other associated costs (i.e., costs associated with maintaining dual inventories of leukodepleted PRBC and non-leukodepleted PRBC), merit special attention [43]. As a main strength of this report, we applied Cochrane systematic review methodology throughout all the process. However, despite our effort to include all published studies evaluating LD-PRBC for the prevention of infection and death from any cause in patients undergoing major cardiovascular surgery, it is possible that not all studies were identified. The Bilgin 2004 and Connery 2005 studies reported the use of platelets as a cointervention, which could intervene as a confounder in the analyses. The study Kremke et al. concluded that platelet transfusion of CABG is not associated with increased postoperative mortality [44]; on the contrary, the study Mangano observed a strong relationship between perioperative platelet transfusion and increased postoperative mortality [45]. The effect of platelets on major cardiovascular surgery is not yet clear; however, we have decided to include the studies with the use of platelets due to their common practice, and we recommend analyzing this variable in future studies. The small number of trials identified in our review raises concern about publication bias. However, we demonstrated by means of the TSA analysis that no additional RCTs need to be conducted in order to demonstrate the beneficial effects in terms of preventing infection complications.

5. Conclusions

There is clear evidence for supporting the routine use of leukoreduction in patients undergoing a major cardiovascular surgical procedure for preventing infection from any cause. Based on TSA analysis, it is not necessary to conduct more RCTs to assess the effects on infection complications risk reduction. The quality of the evidence is moderate for this outcome and therefore the certainty as well. As for death from any cause, a beneficial effect of LD-PRBC in patients undergoing a major cardiovascular surgical procedure was also observed, but more RCTs are needed to confirm our findings. More research could be justified specifically in those middle and low incomes countries in which LD-PRBC has not been implemented universally yet and/or where the costs of the procedure could be a barrier.

Disclosure

Daniel Simancas-Racines is a Ph.D. candidate at the Department of Pediatrics, Gynecology and Obstetrics and Preventive Medicine, Universitat Autònoma de Barcelona, Spain.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by Universidad UTE.

Supplementary Materials

Appendix 1: detailed search strategy. (*Supplementary Materials*)

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5.3. Tercera Publicación

Finalmente, de acuerdo con los resultados obtenidos en el tercer estudio (Simancas-Racines et al., 2018; Factor de Impacto (SJR): 1.093, Primer Cuartil (Q1) realizado para esta tesis, 16 GPCs fueron seleccionadas por texto completo al cumplir con todos los criterios de inclusión previamente establecidos (151).

La puntuación promedio (media ± desviación standard) de las GPCs en los respectivos dominios fue: Alcance y objetivos (59.4% ± 19.8%); participación de los implicados (43.2% ± 22.6%); rigor en la elaboración (50% ± 25%); claridad de la presentación (74.4% ± 12.6%); aplicabilidad (19.4% ± 18.8%); e independencia editorial (41% ± 30%). Adicionalmente, se realizó un mapeo de la evidencia sobre el umbral de transfusión recomendado en las GPCs incluidas, los resultados indicaron que siete GPCs recomendaron una estrategia restrictiva para la transfusión de glóbulos rojos (22,152–157); cuatro GPCs consideraron que un umbral de hemoglobina de 7 g/dl es necesario para que una transfusión de glóbulos rojos se segura (158–161). Ocho GPCs indicaron que la transfusión de concentrados de glóbulos rojos no debería prescribirse en base al umbral de hemoglobina únicamente (102,162–168).

Received: 9 February 2018 | Accepted: 24 September 2018
DOI: 10.1111/jebm.12330

ARTICLE

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Quality of clinical practice guidelines about red blood cell transfusion

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Abstract

Background: Red blood cell (RBC) transfusions are essential in health care. The quality of recommendations included in clinical practice guidelines (CPG), regarding this intervention, has not been systematically evaluated. This paper systematically assessed CPGs for RBC-transfusion, to appraise their methodological quality, to explore changes in quality over time, and to assess the consistency of the hemoglobin threshold (HT) recommendations.

Methods: We searched for CPGs that included recommendations of RBC-transfusion in generic databases, compiler entities, registries, clearinghouses and guideline developers. Three reviewers extracted data on CPGs characteristics and HT recommendations, independently appraised the quality of the studies using AGREE II and resolved disagreements by consensus.

Results: We examined 16 CPGs. Mean scores (mean ± SD) were: scope and purpose (59.4% ± 19.8%), stakeholder involvement (43.2% ± 22.6%), rigor of development (50% ± 25%), clarity of presentation (74.4% ± 12.6%), applicability (19.4% ± 18.8%), and editorial independence (41% ± 30%). Seven CPGs recommended a restrictive strategy for RBC transfusion; four CPGs gave a guarded statement considering an HT of 7 g/dL, as safe to prescribe an RBC transfusion. Eight CPGs did not provide an HT stating that RBC transfusions should not be prescribed by HT alone.

Conclusions: Only 3 out of the 16 evaluated CPGs were "recommended" by the independent evaluators. Four domains "stakeholder involvement," "rigor of development," applicability," and "editorial independence" had serious shortcomings. Recommendations about the use of an HT for RBC-transfusion were heterogeneous among guidelines. Greater efforts are needed to provide high-quality CPGs in the RBC-transfusion practice.

KEYWORDS
blood transfusion, clinical practice guidelines, red blood cells, systematic review

1 | INTRODUCTION

Blood transfusion is the infusion of both soluble and cell-associated forms like RBCs, white blood cells, and platelets into a recipient.[1] A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis.[2,3] However, RBCs and other blood components therapies have been associated with several adverse clinical events, and require physicians to be fully informed of the risks and benefits.[4,5] Several strategies for preventing adverse events caused by RBC-transfusions have been studied; however, their clinical effectiveness has not yet sufficiently demonstrated.[2,3,6–11]

About 85 million people are transfused annually, with considerable variation in the use of RBC-transfusion practices worldwide.[6] In spite of the efforts to standardize transfusion practice, as the publication of clinical practice guidelines, this variability in transfusion practices has persisted. For instance, while some CPGs have included recommendations focused on hemoglobin concentration to guide RBC-transfusion, other CPGs emphasize that transfusions should be provided in the presence of anemia symptoms and should not be based on hemoglobin concentration only.[2,5,8,9]

CPGs are defined as systematically developed statements to assist practitioner and patient decisions about appropriate health care.[12] International organizations have introduced and promote standards for the development of CPG, such as the Institute of Medicine (IOM),[13] World Health Organization (WHO),[14] National Institute for Health and Clinical Excellence (NICE),[15] Scottish Intercollegiate Guideline Network (SIGN),[16] and Guidelines International Network (G-I-N).[17] All these efforts provide resources to assist guideline developers in producing high-quality recommendations. Despite these initiatives, the quality of the CPGs and the adherence to methodological guidelines has been improved only lightly in the last decade.[18–21]

In the field of RBC-transfusion, a large body of clinical evidence has been generated; resulting in the publication of many CPGs.[22–40] These CPGs face with inconsistent recommendations that potentially result in confusion among clinicians, and the quality of the guidelines could be put to question. For these reasons, there is a need to assess the methodological quality of the CPGs in this field, to explain the variability of the recommendations. We conducted a systematic assessment of CPGs for RBC-transfusion, to appraisal their methodological quality using AGREE II tool, and to explore changes in quality over time, and to evaluate the consistency of hemoglobin concentration recommendations to guide transfusion.

2 | METHODS

2.1 | Data search

We searched for CPGs that included recommendations of RBC-transfusion in generic databases, compiler entities, registries, clearinghouses and guideline developers. We used free terms such as red blood cell transfusion, blood transfusion, anemia, and erythrocyte cells for these searches. For the MEDLINE search, via PubMed, we combined MeSH terms ("blood transfusion," "erythrocytes," "Erythrocyte Transfusion," "blood component transfusion," "anemia") and free terms (transfus* [tiab], transfusion requirements, RBC, RBCs, transfusion strategy, blood loss, blood conservation, transfusion of RBCs, red cell transfusion, management of anemia). Additionally, we used a series of terms related to guidelines as: "practice guideline," "consensus," "development conference," and "guideline." The search strategy and sources are listed in Table 1.

2.2 | Inclusion and exclusion criteria

We included (1) CPGs with recommendations related to hemoglobin concentration to guide the RBC-transfusion; (2) CPGs that performed a search in at least one database; and (3) CPGs published from 2006 until October 2017, in English or Spanish. We excluded (1) secondary publications like systematic reviews or meta-analyses and (2) CPGs with recommendations about pediatric patients (<15 years) and neonates.

2.3 | Data collection

Two reviewers independently screened abstracts using the inclusion criteria stated above. If the inclusion criteria met, we retrieved the full-text article and screened it to determine their eligibility. Two reviewers independently extracted the following data from each CPG: title, year, organization that developed the guideline, country of origin, and source of funding. In the case of disagreement, a third reviewer was consulted. One reviewer extracted the recommendation about hemoglobin threshold to guide transfusion, and the individual studies used to support the recommendation.

2.4 | Quality assessment

We used the AGREE instrument to evaluate the quality of the included CPGs.[41–44] This was developed primarily for guideline developers and researchers, to outline and measure the core elements of guideline development and implementation. The AGREE instrument (initially AGREE I, now AGREE II) contains 23 items,[41] spread over six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence, in addition to a final general item that evaluates the extent to which the guideline can be recommended for use in practice. To evaluate the items within the six domains, a 7-point Likert scale was used, ranging from "strongly disagree" to "strongly agree." For the overall assessment, we used a 3-point scale ranging from "not recommended" to "strongly recommended." Three independent reviewers, with experience in CGs assessment, applied the AGREE II instrument. In the case of disagreement, an agreement was reached by consensus. In the event of persistent disagreement, a fourth evaluator was consulted.

2.5 | Statistical analysis

We performed a descriptive analysis of the CPGs according to the country of origin, the type of organization that developed them, the year of publication and the language of the CPGs. To establish the quality of each CG, the standardized score was calculated as a percentage; this was obtained by adding all the individual points from the items of a domain, and standardizing the total as a percentage of the maximum possible score from that area: (score obtained − minimum possible score)/(maximum possible score − minimum possible score) × 100. Once the quality of each CG was established, it was compared to the aforementioned descriptive variables. The degree of agreement between the reviewers was assessed using an intraclass correlation coefficient (ICC) with a 95% confidence interval (CI). Student's *t*-test compared the scores between different variables (date of publication and restrictive recommendations). For the analysis of the change in the global score over time, the date of publication was categorized into two

TABLE 1 Searched sites for the identification of CPGs

Generic databases	Websites
MEDLINE (PubMed)	http://www.ncbi.nlm.nih.gov/pubmed/
TRIP database	http://www.tripdatabase.com
Excelencia Clínica	http://www.excelenciaclinica.net/
Compiler Entities, Registries, or Clearinghouses	Websites
National Guidelines Clearinghouse	http://www.guideline.gov/
Agency for Healthcare Research and Quality	http://www.ahrq.gov/
Biblioteca de Guías de Práctica Clínica del Sistema Nacional de Salud	http://www.guiasalud.es
Canadian Medical Association Infobase: Clinical Practice Guidelines	http://www.cma.ca
Guidelines Developers	Websites
National Institute for Health and Care Excellence	http://www.nice.org.uk
Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk
New Zealand Guidelines Group	http://www.nzgg.org.nz
Institute for Clinical Systems Improvement	http://www.icsi.org
American College of Physicians	http://www.acponline.org
International Society of Blood Transfusion	http://www.isbtweb.org/
Asian Association of Transfusion Medicine (AATM)	http://saatm.org/
Australian and New Zeland Society of Blood Transfusion	http://www.anzsbt.org.au/
British Blood Transfusion Society	https://www.bbts.org.uk/
American Red Cross	http://www.redcross.org/

periods (2006–2011 and 2012–2015). We used the statistical package IBM SPSS (version 22).

3 | RESULTS

3.1 | Guideline characteristics

The search strategy provided 615 references after eliminating duplicates. A review of the titles and abstracts identified 47 potentially eligible CPGs. From the 47 examined CPGs, only 16 fulfilled the eligibility criteria and were included (Table 2).[22–40] One of these guidelines included four chapters that give the hemoglobin threshold recommendation for different settings.[34–37] Included guidelines were published from 2008 to 2016. Six CPGs were from the United States,[23,28,29,33,40] four from the United Kingdom,[22,31,38,39] one with four chapters from Australia,[34–37] one from Canada,[24] Finland,[27] the Netherlands,[26] Singapore,[25] and Spain.[30] Twelve documents were developed by scientific societies,[22–24,27–33,39,40] and seven CPGs were developed by government agencies.[25,26,34–38] Five of 16 included CPGs, focused solely on RBC-transfusion,[22–24,31,40] while there remaining 11 gave recommendations on blood products in general.[25–30,32–39]

Eight guidelines gave recommendations for general medical patients.[24–27,30,35,38,40] The other 11 CPGs focused on specific populations: four on perioperative patients[22,28,33,34]; three on critically ill patients[23,31,36]; two on obstetric patients[37,39]; one on patients with heart disease[32]; and one on chronic kidney diseases patients.[29]

For the analysis of recommendations, each chapter of one of the CPGs included,[34–37] were considered separately due to differences in hemoglobin threshold recommendation. Seven guidelines recommended a restrictive strategy for RBC transfusion,[30–33,36,38,40] defined as the administration of blood transfusion when the hemoglobin level falls below 7 g/dL. Four CPGs had a guarded statement considering a hemoglobin threshold of 7 g/dL, as safe to indicate RBC transfusion.[22,25,26,28] The remaining eight CPGs avoid giving a hemoglobin threshold[23,24,27,29,34,35,37,39] and state that RBC transfusion should not be dictated by hemoglobin concentration alone (Table 2).

Overall, 39 clinical trials supported these recommendations. The references of included studies to base the recommendations were not possible to obtain in two guidelines.[24,27] Another two CPGs supported their recommendations in previously published guidelines[37,39] (see supplementary material for information about the evidence supporting recommendations). Only four guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate the quality of evidence and to grade the strength of recommendations.[30,31,38,40] One guideline used a modified version of GRADE,[27] 13 guidelines applied other methods to determine the quality of the evidence,[23–26,28,29,32–37,39] and 1 guideline did not explain the methodology used to assess the quality of evidence.[22]

3.2 | Quality assessment

The agreement between the three reviewers was high, with an ICC of 0.90 (95% CI: 0.81-0.96). Table 2 shows the standardized score of the AGREE II tool by domain and by guideline, as well as the overall evaluation. Additionally, Figure 1 shows the statistical summarized analysis of the total standardized score by domain.

TABLE 2 CPG characteristics and hemoglobin threshold recommendations

Guideline	Organization	Year	Hemoglobin threshold recommendation	Country and language	Methods used to assess the quality and strength of the evidence
Blood transfusion and the anesthetists. Red cell transfusion[22]	The Association of Anaesthetists of Great Britain and Ireland	2008	"The decision to transfuse should always be made on an individual patient basis. Patients should not normally be transfused if the hemoglobin concentration is >10 g/dL. A strong indication for transfusion is a hemoglobin concentration <7 g/dL" (Perioperative patients)	UK/IR, English	Grading system not stated
Clinical practice guideline: red blood cell transfusion in adult trauma and critical care[23]	The Eastern Association for Surgery of Trauma Practice Management Workgroup	2009	"The use of only Hb level as a 'trigger' for transfusion should be avoided. A 'restrictive' strategy of RBC transfusion (transfuse when Hb 7 g/dL) is as effective as a "liberal" transfusion strategy (transfusion when Hb 10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia" (Critically ill patients)	USA, English	Canadian and US Preventative Task Force grading system
Guidelines for red blood cell and plasma transfusion for adults and children. updated[24]	Guidelines for Canadian Clinical Practice Guidelines. Expert Panel	2009	"Red blood cell transfusion should not be dictated by a single hemoglobin trigger but should be based on a complete evaluation of the patient including volume status, tissue perfusion and comorbid disease" (General medical patients)	Canada, English	Modified version of the Canadian Task Force on the Periodic Health Examination grading system
Clinical blood transfusion[25]	Singapore Ministry of Health	2011	"When hemoglobin >10 g/dL, there is usually very little indication for red cell transfusion. When hemoglobin <7 g/dL, red cells transfusion may be beneficial particularly in symptomatic patients or ongoing blood loss is expected" (General medical patients)	Singapore, English	Own rating scheme used to assess the quality of the evidence
Blood transfusion guideline[26]	Dutch Institute for Healthcare Improvement	2011	"The indication for administering erythrocytes is based on medical factors and is aimed at treating or preventing the symptoms of a lack of oxygen transport capacity by the blood. Consider a transfusion if the following occurs at a Hb < 4 mmol/L: acute blood loss in a healthy individual (ASA I) < 60 years, normovolemic, blood loss at 1 location" (General medical patients)	The Nether-lands, English-Dutch	Own rating scheme used to assess the quality of the evidence
Blood transfusion: indications, administration, and adverse reactions[24]	Finnish Medical Society Duodecim	2011	"It is not possible to give single hemoglobin (Hb) value as a trigger for red cell transfusion since the requirement for a transfusion is based on anemia symptoms, the patient's age, and the underlying diseases (chronic or slowly developing anemia)" (General medical patients)	Finland, English	Rating scheme modified of GRADE 2011 by the EBM Guidelines Editorial Team
2011 update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines[28]	The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists	2011	"With hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable since this can be life-saving. Transfusion is reasonable in most postoperative patients whose hemoglobin is less than 7 g/dL, but no high-level evidence supports this recommendation" (Perioperative patients)	USA, English	The assessment was conducted according to the level of evidence recommended by the AHA/ACCF Task Force on Practice Guidelines

(Continues)

TABLE 2 (Continued)

Guideline	Organization	Year	Hemoglobin threshold recommendation	Country and language	Methods used to assess the quality and strength of the evidence
KDIGO Clinical Practice Guideline for anemia in chronic kidney disease[29]	Kidney Disease: Improving Global Outcomes (KDIGO)	2012	"We suggest that the decision to transfuse a CKD patient with nonacute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia" (Chronic kidney diseases patients)	USA, English	KDIGO grading system
The "Seville" document on consensus on the alternatives to allogenic blood transfusion[30]	The Spanish Societies of Anesthesiology, Critical Care Medicine and Coronary Units, Hematology and Hemotherapy, Blood Transfusion and Thrombosis and Hemostasis	2013	"The majority of trauma, critical and surgical patients can tolerate hemoglobin levels of 70 g/L. However, if they present acute cardiological and/or central nervous system involvement, hemoglobin levels of at least 80 g/L may be required. In any case, the decision to transfuse should be individualized for each patient" (General medical patients)	Spain, Spanish	GRADE 2008
Guidelines on the management of anemia and red cell transfusion in adult critically ill patients[31]	British Committee for Standards in Haematology	2013	"A transfusion threshold of 70 g/L or below, with a target Hb range of 70–90 g/L, should be the default for all critically ill patients, unless specific comorbidities or acute illness-related factors modify clinical decision-making" (Critically ill patients)	UK, English	GRADE 2008
Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians[32]	American College of Physicians	2013	"ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease"(Patients with heart disease)	USA, English	ACP's clinical practice guidelines grading system
Practice guidelines for perioperative blood management—an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management[33]	American Society of Anesthesiologists	2014	"A restrictive red blood cell transfusion strategy may be safely used to reduce transfusion administration" (Perioperative patients)	USA, English	ASA grading system
The National Blood Authority's Patient Blood Management Guideline: Module 2—Perioperative[34]	National Blood Authority Australia	2012	"RBC transfusion should not be dictated by a hemoglobin 'trigger' alone but should be based on an assessment of the patient's clinical status" (Perioperative patients)	Australia, English	National Blood Authority scheme
The National Blood Authority's Patient Blood Management Guideline: Module 3—Medical[35]	National Blood Authority Australia	2012	"RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on an assessment of the patient's clinical status. Direct evidence is not available in general medical patients" (General medical patients)	Australia, English	National Blood Authority scheme
The National Blood Authority's Patient Blood Management Guideline: Module 4—Critical Care[36]	National Blood Authority Australia	2012	"In critically ill patients, a restrictive transfusion strategy should be employed" (Critically ill patients)	Australia, English	National Blood Authority scheme

(Continues)

TABLE 2 (Continued)

Guideline	Organization	Year	Hemoglobin threshold recommendation	Country and language	Methods used to assess the quality and strength of the evidence
The National Blood Authority's Patient Blood Management Guideline: Module 5—Obstetrics and Maternity[37]	National Blood Authority Australia	2015	"In maternity patients who are not actively bleeding, RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on an assessment of the patient's clinical status (eg, the risk of further hemorrhage)" (Obstetric patients)	Australia, English	National Blood Authority scheme
Blood Transfusion NICE guideline[38]	National Institute for Health and Care Excellence	2015	"Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not: have major hemorrhage, or have the acute coronary syndrome, or need regular blood transfusions for chronic anemia" (General medical patients)	UK, English	GRADE
Blood transfusion in obstetrics[39]	Royal College of Obstetricians & Gynaecologists	2015	"There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be made on clinical and hematological grounds" (Obstetric patients)	UK, English	Scheme using Royal College of Obstetricians and Gynaecologists for grading recommendations
Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage[40]	American Association of Blood Banks	2016	"The AABB recommends a restrictive RBC transfusion threshold in which the transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than a liberal threshold when the hemoglobin level is 10 g/dL" (General medical patients)	USA, English	GRADE

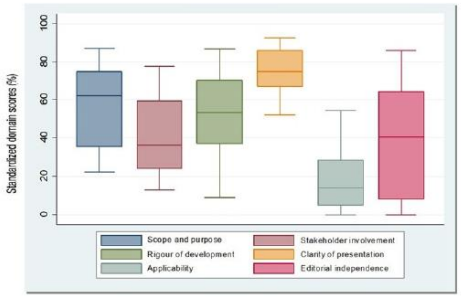

FIGURE 1 Distribution of the standardized domain scores for 16 CPGs. The top and bottom of the box represent the 75th (Q3) and 25th percentile (Q1), respectively, and the band near the middle of the box indicates the 50th percentile (median). The upper and lower ends of the whisker represent Q3 + 1.5× (interquartile range), and Q1-1.5× (interquartile range), respectively

3.2.1 | Domain 1: scope and purpose

This domain focuses on the general goal of the CPGs, considering the health condition, and the specific population for applying the guideline. The average score was 59.4% (median = 62% and a range from 22.2% to 87%; Figure 1). Five CPGs (31%) scored above 70%.[23,30,32,34,38] See Table 2 for details about Domain 1.

3.2.2 | Domain 2: stakeholder involvement

This domain assesses the working group that developed the CPGs, the involvement of stakeholders, and potential users. The average score was 43.2% (median = 40% and a range from 13% to 78%; Figure 1). Only three CPGs (18.7%) scored more than 70 on this domain.[26,29,38] See Table 3 for details about Domain 2.

3.2.3 | Domain 3: rigor of development

This domain addresses the process used to identify and summarize the evidence, the methodology to formulate recommendations, and their updates. The average score was 50% (median = 53% and a range from 9% to 87%; Figure 1). Four CPGs (25%) scored above 70% on this domain.[26,29,34,38] See Table 3 for details about Domain 3.

3.2.4 | Domain 4: clarity and presentation

This domain focuses on the wording, the structure, and the general format of the CPGs. The average score was 74.4% (median = 75% and a

TABLE 3 AGREE II domain-standardized scores

Guideline	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Overall recommendation
Blood transfusion and the anesthetists. Red cell transfusion[22]	35.2	24.1	9	53.7	8.3	0	Not recommended
Clinical practice guideline: red blood cell transfusion in adult trauma and critical care[23]	83.3	33.3	54.2	92.6	11.1	55.6	Recommended with modifications
Guidelines for red blood cell and plasma transfusion for adults and children. updated[24]	22.2	13	9	51.9	1.4	5.6	Not recommended
Clinical blood transfusion[25]	55.6	42.6	36.8	87	22.2	0	Not recommended
Blood transfusion guideline[26]	64.8	77.8	79.2	75.9	52.8	36.1	Recommended with modifications
Blood transfusion: indications, administration and adverse reactions[27]	35.2	14.8	16	68.5	0	8.3	Not recommended
2011 update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice guidelines[28]	27.8	50	45.1	64.8	9.7	33.3	Recommended with modifications
KDIGO Clinical Practice Guideline for anemia in chronic kidney disease[29]	66.7	74.1	80.6	87	34.7	72.2	Recommended

(Continues)

TABLE 3 (Continued)

Guideline	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Overall recommendation
The "Seville" document on consensus on the alternatives to allogenic blood transfusion[30]	72.2	37	37.5	75.9	13.9	41.7	Recommended with modifications
Guidelines on the management of anemia and red cell transfusion in adult critically ill patients[31]	61.1	24.1	36.8	74.1	18.1	8.3	Not recommended
Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians[32]	77.8	35.2	61.8	92.6	0	75	Recommended with modifications
Practice guidelines for perioperative blood management—an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management[33]	63	48.1	52.1	68.5	1.4	55.6	Not recommended
The National Blood Authority's patient blood management guideline[34–37]	79.6	31.1	81.9	81.5	54.2	86.1	Recommended
Blood transfusion NICE guideline[38]	87	74.1	86.8	85.2	51.4	83.3	Recommended
Blood transfusion in obstetrics[39]	59.3	13	54.2	63	18.1	38.9	Not recommended
Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage[40]	31.1	68.5	59	68.5	13.9	55.6	Recommended with modifications
Mean score (SD)	59.5 (±19.9)	43.1 (±22)	50 (±25.1)	74.4 (±12.7)	19.4 (±18.8)	41(±30)	
Median (range)	62 (22.2–87)	39.8 (13–77.8)	53 (9–86.8)	75 (52–92.6)	13.8 (0–54.2)	40.2 (0–86.1)	

range from 51% to 92.6%; Figure 1). Nine CPGs (56.2%) scored above 70% on this domain.[23,25,26,29–32,34,38] This domain scored the highest among the six domains included in the AGREE II instrument. See Table 3 for details about Domain 4.

3.2.5 | Domain 5: applicability

This domain considers the barriers and facilitators for the implementation of the CPGs, including aspects of resources and adherence to the recommendations. The average score was 19.4% (median = 14% and a range from 0% to 54.2%; Figure 1). This was the lowest evaluated domain for all the CPGs, and none of the included CPGs scored above 70% on this domain. See Table 3 for details about Domain 5.

3.2.6 | Domain 6: editorial independence

This domain assesses if funding sources influenced recommendations. The average score was 41% (median = 40% and a range from 0% to 86%; Figure 1). Four CPGs (25%) scored above 70% on this domain.[29,32,34,38] See Table 3 for details about Domain 6.

3.2.7 | Overall assessment

Three out of the 16 evaluated CPGs (18.7%) were "recommended" by the independent evaluators,[29,34,38] 6 CPGs (37.5%) were "recommended with modifications,"[23,26,28,30,32,40] and 7 CPGs (43.7%) were "not recommended" (see Table 3).[22,24,25,27,31,33,39] The three "recommended" CPGs scored ≥ 70% in the "rigor of development" domain. The seven CPGs (18.7%) "not recommended"[22,24,25,27,31,33,39] by evaluators had scores below 70% in five of the six reported domains (see Table 3).

We did not find statistically significant differences in the AGREE II global score between CPGs published in 2006-2011 and those published in the period 2012–2015 ($P = 0.49$). Additionally, those CPGs recommending restrictive strategies scored similarly in the rigor of development domain, as those that did not recommend a specific threshold ($P = 0.92$).

4 | DISCUSSION

4.1 | Summary of the main finding

In our review, we found 16 CPGs that met the eligibility criteria.[22–40] In the overall CPGs' assessment, only 3 out of the 16 evaluated CPGs (18.7%) were "recommended" by the independent evaluators,[29,34,38] 6 CPGs (37.5%) were "recommended with modifications,"[23,26,28,30,32,40] and 7 CPGs (43.7%) were "not recommended."[22,24,25,27,31,33,39]

Most of the CPGs did not describe the literature search and selection methods, and they were ambiguous regarding how the evidence was appraized and whether or not the recommendations were truly evidence-based. The domains with the highest scores were "clarity and presentation" and "scope and purpose," and the domains with the lowest scores were "applicability" and "editorial independence" (see Table 3 and Figure 1). Only four CGs[26,29,34,38] scored ≥ 70% in the domain "rigor of development," which was considered one of the most critical domains, as it refers to methodological aspects concerning how the recommendations were developed.

In the analyzed CPGs, the use of a hemoglobin threshold for RBC-transfusion was variable. Some guidelines recommended restrictive strategies, and other CPGs avoided using a hemoglobin threshold, on the basis that RBC-transfusion should not be dictated by hemoglobin concentration alone. However, when the score in the rigor of development domain, of the CPGs recommending restrictive strategies, as compared with the CPGs that avoid giving a hemoglobin threshold, we did not find statistically significant differences. Therefore, the variability in recommendations cannot be explained by differences in this domain ($P = 0.92$).

Finally, our study could not demonstrate statistical differences over time in the global score of CPGs quality (published in 2006–2011 versus 2012-2016; $P = 0.49$). However, we believe that the low number of included CPGs did not allow an adequate evaluation of the variability in the quality of RBC-transfusion CGs over time.

4.2 | The context of this review with other literature

This review represents the first systematic assessment of the quality of clinical practice guidelines focused on red blood cell transfusion recommendations. Consistently with previous CPG evaluations in other clinical areas,[45–48] the domains with the highest scores were "clarity of presentation" and "scope and purpose," whereas the domains with the lowest scores were "stakeholder involvement," "editorial independence," and "applicability." The lowest scores related to the "applicability" domain can be related to the belief that the activity of formulating recommendations was separated from the implementation processes. Our results for the domains were similar to those of previous systematic assessment done by our group, that included the evaluation of 626 CPGs.[19] Specifically, in the "rigor of development" domain our review found low quality, with an average of 46.3% compared to 68% in other similar reviews.[19]

4.3 | Strengths and limitations

Our systematic assessment has some limitations. First, although a robust set of search criteria was formulated and tested prior to full guideline identification, some CPGs might not have been adequately indexed as they were only used for institutional purposes, so we failed in their identification. We think that the quality of the CPGs not indexed in biomedical databases is probably lower compared to those indexed. Second, there is also a potential risk of selection bias because we included only studies that had been published in English or Spanish. To this extent, our assessment could be overestimating the quality of CPGs in RBC-transfusion. Third, the AGREE II[41–44] instrument has undergone some revisions since the development of the original AGREE instrument.[41] A 7-point scale is used instead of a 4-point scale for evaluating the items in the domains. This may have been a limitation in assessing the quality of the CPGs because the only well-defined points in the scale are 1 and 7. We found that the evaluators had difficulty in distinguishing between 3, 4, and 5 Likert values, which may

have introduced a potential risk of reporting bias. However, the agreement among reviewers using the AGREE II instrument was high, with an ICC of 0.97.

On the other hand, we recognize some strengths of this systematic assessment. First, we are the first to assess the quality of development of clinical practice guidelines focused on red blood cell transfusion recommendations using methodological instruments that are widely recognized and accepted. Second, the uses of extensive search strategies, covering both indexed and gray literature and the use of expert appraisers who completed training and calibration to assess the quality of CPGs.

In conclusion, our findings show that much remains to be done to reach excellence in the area of CPGs on RBC-transfusion. Only three out of the 16 evaluated CPGs were "recommended" by the independent evaluators. Four domains ("stakeholder involvement," "rigor of development," "applicability," and "editorial independence") had serious shortcomings. The domains: "scope and purpose" and "clarity of presentation" were the more precisely reported.

Moreover, our study could not demonstrate statistical differences over time in the global score of CPGs quality (published in 2006-2011 versus 2012-2016; $P = 0.49$). Also, the recommendations about hemoglobin threshold for RBC-transfusion was variable among the CPGs analyzed.

Clinical practice guidelines users should be aware of the low quality reported in this study. Meanwhile, developers should adhere to rigorous methods, like those provided in handbooks from institutions, such as the Scottish Intercollegiate Guidelines Network (SIGN) or the National Institute for Health and Care Excellence (NICE).[15] Additionally, guideline developers should use checklists to optimize methods for the development and reporting of CPG, such as the GIN-McMaster Guideline Development Checklist (GDC)[49,50] and AGREE II,[42–44] respectively. Moreover, to improve communication among users and developers, GRADE methodology is highly recommended, as it is a widely implemented rigorous system.

Regarding research strategies, additional efforts should be made to develop and consolidate networks, to improve the evaluation and synthesis of the available evidence in the RBC-transfusion field. Researchers, who wish to identify knowledge gaps, and policymakers, looking to endorse adequate CPG development, should work together to ensure the adherence to recommendations related to RBC-transfusion, and minimize the heterogeneity in clinical practice.

AUTHOR CONTRIBUTIONS

D S-R, XB, and P A-C conceived the idea for this research and designed the study. D S-R and IS searched the literature. D S-R, NM, I A-R, and RB reviewed the published work and participated in data extraction. IG and D S-R conducted the statistical analysis. All authors participated in data interpretation. D S-R, NM, I A-R, and RB wrote the first draft of the report. P A-C and XB contributed to the review and approved the final manuscript. All other authors commented on the draft and approved the final version.

FUNDING SOURCES

This work was supported by Universidad UTE. Facultad de Ciencias de la Salud Eugenio Espejo. PA-C was supported by a Miguel Servet investigator contract from the Instituto de Salud Carlos III (CPII15/0034).

CONFLICTS OF INTEREST

None

ACKNOWLEDGMENTS

Daniel Simancas-Racines is a PhD student at the Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine of Universitat Autònoma de Barcelona. The authors acknowledge Maria Victoria Leo Rosas, Andrea Cervera and Susana Hidalgo for their assistance with the edition of this paper. The authors acknowledge Iván Solà for reviewing the Search strategy.

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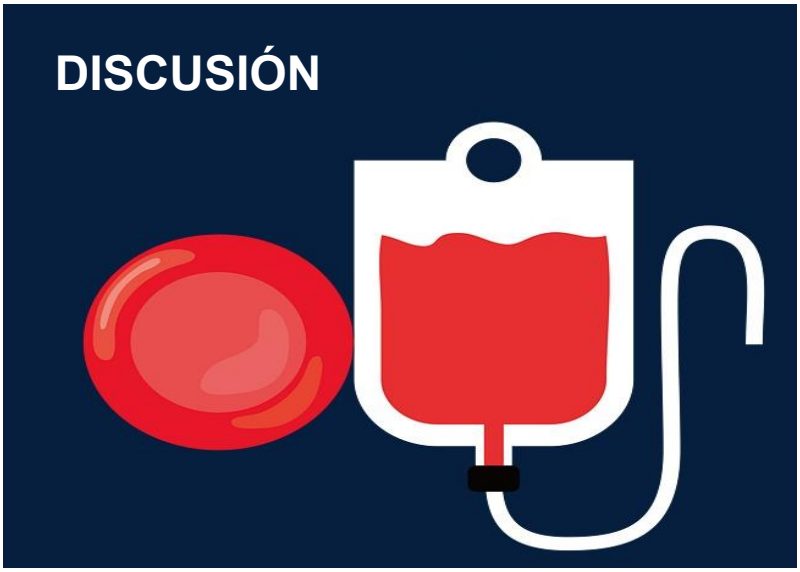
How to cite this article: Simancas-Racines D, Montero-Oleas N, Vernooij RWM, et al. Quality of clinical practice guidelines about red blood cell transfusion. *J Evid Based Med*. 2019;12:113–124. https://doi.org/10.1111/jebm.12330


DISCUSIÓN

6. DISCUSIÓN

6.1. Estructura general del trabajo de tesis

En este trabajo de tesis doctoral se han integrado tres investigaciones con objetivos independientes, pero relacionados tanto en aspectos clínicos como con las metodologías utilizadas en cada una de ellas.

El aspecto clínico común en este trabajo fue la transfusión de componentes sanguíneos, especialmente la investigación se centra en la efectividad de las estrategias utilizadas para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos, ya que esta es una de las intervenciones de mayor importancia para la prestación de servicios sanitarios.

Dado que esta intervención es común en la práctica clínica, se han identificado varias estrategias utilizadas para mejorar la seguridad del paciente sometido a transfusión de componentes sanguíneos y resulta oportuno identificar y clasificar las mejores alternativas disponibles para la toma de decisiones informada.

Para esto, es necesario afirmar con cierto grado de certeza y confiabilidad la relación entre la implementación de estas estrategias sanitarias utilizadas para mejorar la seguridad del paciente y la reducción real de la incidencia de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos.

Para cumplir con todos los objetivos trazados en este trabajo de tesis doctoral se utilizó la metodología de revisión sistemática de la literatura, efectuando búsquedas exhaustivas de todas las investigaciones primarias que respondiesen a cada una de las preguntas de investigación específicas propuestas previamente. Adicional a esto, se incorporaron escalas ampliamente difundidas y validadas que permiten el análisis crítico de la evidencia científica encontrada en el momento de esta investigación.

En este contexto, la pregunta de investigación planteada como hilo conductor para este trabajo de tesis, desarrollado como compendio de publicaciones fue: ¿Cuál es la calidad de las evidencias científicas sobre las estrategias utilizadas para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos?, la cual fue desarrollada a través de tres objetivos:

1. Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos.
2. Evaluar la efectividad de la leucorreducción como estrategia para la prevención de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos en pacientes sometidos a procedimientos quirúrgicos cardiovasculares mayores.
3. Evaluar la calidad de las GPCs disponibles que incluyan recomendaciones basadas en evidencia sobre las estrategias para la prevención de reacciones adversas relacionadas con la transfusión de concentrados de glóbulos rojos.

Adicionalmente, se propuso investigar el efecto de la transfusión de concentrados de concentrados de glóbulos rojos frescos comparado con el almacenamiento prolongado en la reducción de reacciones adversas asociadas a esta intervención (anexo 1).

6.2. Discusión derivada de las publicaciones

6.2.1. "Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion"

En nuestra primera SR titulada "Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion" (169) incluimos 13 ECAs (48,49,54–56,60,61,63,64,67,71,145–148) que aleatorizaron a pacientes con enfermedad cardiovascular, cirugía gastro-oncológica, trauma, e infectados con VIH a recibir

transfusión de concentrados de glóbulos rojos leucorreducidos o concentrados de glóbulos rojos no leucorreducidos. Después de analizar los datos no fuimos capaces de concluir si la leucorreducción tiene un efecto significativo en la prevención de TRALI (un estudio) (48), muerte (nueve ECAs) (48,54–56,60,61,64,67,71,148), infección (10 ECAs) (48,49,54–56,60,61,64,67,71,148) u otros eventos adversos (p.e. fiebre, dos ECAs) (54,64).

Los motivos por los cuales no se logró construir evidencia precisa y confiable sobre la leucorreducción fue que, al analizar la calidad de la evidencia por cada desenlace se demostró que esta fue baja para TRALI y para otros eventos adversos, mientras que para los desenlaces de muerte e infección fue muy baja; la deficiencia en la calidad se debe a la alta heterogeneidad, imprecisión y alto riesgo de sesgo.

El análisis de sensibilidad de los estudios calificados con bajo riesgo de sesgo no demostró un efecto beneficioso ni perjudicial para los concentrados de glóbulos rojos leucorreducidos cuando se los compara con concentrados de glóbulos rojos no leucorreducidos, en los desenlaces de muerte, infección y otros eventos adversos analizados. Debido a que los desenlaces planteados para esta revisión fueron parcialmente abordados por los estudios incluidos y los efectos de esta estrategia fueron no concluyentes, estos resultados deben ser interpretados con precaución.

Respecto a la validez externa de los hallazgos de esta SR, se ve reducida debido a que poblaciones importantes no fueron consideradas por los estudios primarios (p.e. pacientes pediátricos y población en estado de gestación). Así también, el efecto de la leucorreducción de concentrados de glóbulos rojos en pacientes sin una indicación fuerte de leucorreducción no fue suficientemente evaluado: pacientes con transfusión única, pacientes sin historia de reacción febril no hemolítica asociada a transfusión o aquellos que no están en riesgo de desarrollar infección por citomegalovirus (CMV).

Los desenlaces de interés clínico no siempre fueron abordados por los estudios incluidos. Datos sobre las infecciones, complicaciones no infecciosas (p.e. TRALI o reacción febril no hemolítica asociada a transfusión), eventos adversos no relacionados a la fiebre, no fueron analizados o en algunos casos ni siquiera reportados por los autores. Además, existió mucha variación en los seguimientos de los pacientes en los estudios incluidos (desde 28 días hasta 15 meses).

Por tanto, los ECAs incluidos y analizados en esta SR no han podido demostrar que la transfusión de concentrados de glóbulos rojos leucorreducida comparada con la transfusión de concentrados de glóbulos rojos no leucorreducida logre prevenir reacciones adversas como TRALI, muerte, infección y otros efectos adversos.

En relación con similares estudios publicados en la literatura sobre este tema, cabe mencionar que se han realizado algunas revisiones y metaanálisis sobre infección postoperatoria asociados con la trasfusión de concentrados de glóbulos rojos leucorreducidos. Sin embargo, hasta donde sabemos, no hay SR centradas en complicaciones no infecciosas, como TRALI o FNHTR que hayan abordado directamente estos desenlaces. En el caso del análisis de mortalidad, otros estudios concuerdan con nuestros resultados (89,170). Nuestros resultados son discordantes respecto con el desenlace de infección, una SR mostró una reducción del 50% en la probabilidad de infección postoperatoria (170) y otra revisión que analizó "solo pacientes que recibieron transfusión" encontró una reducción estadísticamente significativa del 40% en la infección postoperatoria (89).

Estas dos SR tienen varias limitaciones: Incluyeron estudios con otros componentes sanguíneos que no sean células concentrados de glóbulos rojos leucorreducidas como intervenciones (p.e. plaquetas), así como estudios no aleatorios con alto riesgo de sesgo de selección de los participantes. Además, no se tuvo en cuenta la alta heterogeneidad entre los estudios al momento de realizar las conclusiones y tampoco se evaluó adecuadamente el riesgo de sesgo de los estudios incluidos.

Adicionalmente, las SR y metanálisis dejaron de incluir estudios relevantes para la pregunta de investigación planteada. En este sentido en nuestro trabajo consideramos todos estos problemas metodológicos y las limitaciones de esta evidencia al momento de la toma de decisiones informada.

Otras estrategias tales como el uso de puntos de corte de hemoglobina restrictivos al momento de decidir la transfusión a un paciente han sido estudiadas por otros trabajos y han demostrado ser costo-efectivos. Es decir, con algún grado de certeza se puede saber que mientras menos transfusiones reciba el paciente o si se logra que un paciente no sea transfundido, se reducirían las probabilidades de desarrollar reacciones adversas relacionadas a esta intervención (25,29,171).

Respecto a los costos, la leucorreducción es un procedimiento costoso, algunos países han adoptado esta estrategia como estándar de transfusión, universalizándola a pesar de no contar con evidencia científica concluyente. Aproximadamente 29 millones de euros / año se gastan en implementar la leucorreducción según el informe de la Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (172). Otros estudios informaron costos que van desde CAD $ 26 millones a 46 millones anuales (173). Un estudio estimó que el costo total de implementar la leucorreducción era de aproximadamente USD 600 millones de dólares por año en EE. UU. (47). También se ha informado que la leucorreducción produce un aumento de aproximadamente USD 30 / unidad de producto sanguíneo (50). Más recientemente, (174) informó una relación costo-efectividad incremental (ICER) de EUR 6916 para prevenir un caso de reacciones de transfusión febril no hemolítica (FNHTR).

En los países de recursos económicos limitados se debería analizar el impacto presupuestario en salud que provoca implementar una estrategia que no ha demostrado tener un impacto clínico importante. Una alternativa a esto podría ser realizar leucorreducción selectiva y no universal y de esta manera lograr disminuir los costos de esta intervención.

6.2.2. "Leukodepleted "Packed Red Blood Cells Transfusion in Patients Undergoing Major Cardiovascular Surgical Procedure: Systematic Review and Meta-Analysis"

En nuestra segunda SR titulada "Leukodepleted "Packed Red Blood Cells Transfusion in Patients Undergoing Major Cardiovascular Surgical Procedure: Systematic Review and Meta-Analysis" (150) incluimos siete ECAs (43,54–57,71,145) que incluyeron a pacientes adultos con necesidad de procedimientos de cirugía mayor cardiovascular y que requieren transfusión de concentrados de glóbulos rojos.

Después de analizar los datos fuimos capaces de demostrar que los pacientes que han sido sometidos a procedimientos de cirugía mayor cardiovascular y que han recibido una transfusión sanguínea con concentrados de glóbulos rojos leucorreducidos comparados con aquellos pacientes que recibieron concentrados de glóbulos rojos no leucorreducidos podrían tener menor riesgo de infecciones y muerte.

Al analizar la calidad de la evidencia por desenlace, determinamos que, tanto para el riesgo de infecciones como para la mortalidad, la certeza de la evidencia es "moderada". Además, de acuerdo con los resultados del análisis TSA encontramos que, para el desenlace de infección, los resultados fueron "conclusivos" y no se requiere de nuevos estudios para demostrar su efectividad.

En relación con los hallazgos de este segundo trabajo y otras investigaciones sobre el tema, podemos señalar que en esta misma tesis en el primer trabajo no se logró demostrar el efecto de la reducción de leucocitos de los concentrados de glóbulos rojos para prevenir reacciones adversas asociadas a la transfusión, en este caso para los desenlaces de infección (10 ensayos clínicos con 6709 pacientes) (48,49,54–56,60,61,64,67,71,148) y en el caso de muerte (9 ensayos clínicos con 6485 pacientes) (48,54–56,60,61,64,67,71,148).

Nuestro segundo trabajo no concuerda con los hallazgos del primer trabajo y si logra determinar un efecto importante de la leucorreducción en concentrados de glóbulos rojos para prevenir muerte e infección. Las causas de esta discrepancia radican en la heterogeneidad clínica del primer trabajo al incluir pacientes con una variedad importante de patologías, en este caso se incluyó a pacientes con problemas oncológicos, con problemas cardiovasculares, trauma, HIV, en cambio en el segundo trabajo se incluyeron específicamente pacientes que requieren cirugía mayor de tipo cardiovascular encontrando el efecto antes mencionado.

Varios estudios y metanálisis no informaron resultados concluyentes sobre la leucorreducción y mostraron inconsistencias metodológicas (89,170,175–177). Por lo tanto, es importante realizar esta revisión Cochrane para determinar los beneficios potenciales del procedimiento de leucorreducción en pacientes que requieren concentrados de glóbulos rojos, centrados en la prevención de reacciones adversas.

Por otro lado, existen SR en las cuales se han encontrado resultados similares a los nuestros (144). Sin embargo, estas revisiones han tenido ciertas limitaciones como incluir estudios en los cuales se usaron otros componentes sanguíneos (p.e. plaquetas) como parte de la transfusión, o incluir estudios no aleatorizados. Además, ninguna SR incluyó un análisis TSA.

Los estudios identificados en estos trabajos no han reportado de manera adecuada ciertos factores como el uso de plaquetas leucorreducidas y no leucorreducidas como co-intervención, el tiempo de leucorreducción (pre-post almacenamiento) y el tipo de filtro que se usa para el procedimiento de leucorreducción. Además, no se mencionan las complicaciones post-transfusionales en las unidades de cirugía cardiovascular y los estudios incluidos reportaron distintas definiciones para los desenlaces de infección y muerte especialmente en los periodos de seguimiento de los pacientes.

La aplicabilidad de esta evidencia científica en la práctica clínica diaria es limitada a pacientes que han sido sometidos a los mismos procedimientos de cirugía cardiovascular a los que han sido realizados en los pacientes incluidos en esta revisión. Sin embargo, es importante señalar que a diferencia de la leucorreducción universal, la relación costo efectividad al dirigir los esfuerzos a esta población en particular podría tener el impacto clínico necesario para lograr reducir la incidencia de reacciones adversas asociadas a la transfusión de concentrados de glóbulos rojos.

6.2.3. "Quality of clinical practice guidelines about red blood cell transfusion"

Nuestra tercera SR titulada "Quality of clinical practice guidelines about red blood cell transfusion" (169) es la primera evaluación sistemática que se realiza sobre la calidad de GPCs que formulan recomendaciones en relación a la transfusión de concentrados de glóbulos rojos.

En esta SR identificamos 16 GPCs que cumplieron con los criterios de elegibilidad (22,102,160–168,152–159). Tres de las 16 GPCs (18.7%) que fueron de evaluadas de manera independiente fueron "recomendadas" por los evaluadores (22,164,165); seis GPCs (37.5%) fueron "recomendadas con modificaciones" (102,152,154,157,160,161); y siete GPCs (43.7%) fueron "no recomendadas" (153,155,158,159,162,163,168).

La mayor parte de GPCs no describen detalladamente la estrategia de búsqueda utilizada y tampoco reportan adecuadamente la sección de métodos. Además, fueron ambiguas al describir cómo evaluaron la evidencia utilizada y si las recomendaciones fueron realmente basadas en evidencia o no.

Los dominios de la herramienta AGREE II que recibieron el puntaje más alto fueron "Alcance y objetivos" y "Claridad de la presentación", mientras que los dominios que

recibieron el puntaje más bajo fueron “Aplicabilidad” e “Independencia editorial”. Es importante señalar que al no tener claro la aplicabilidad de la evidencia se hace difícil la implementación de estas GPCs dentro de los servicios de salud. En cuanto a la independencia editorial llama mucho la atención los bajos puntajes dada la importancia de la transparencia en los procesos de generación de recomendaciones clínicas.

Nuestros hallazgos demuestran que aún falta mucho por hacer para mejorar el desarrollo de las GPCs que abordan el tema de transfusión de concentrados de glóbulos rojos. Además, nuestro estudio no pudo demostrar una diferencia estadística significativa en la calificación global de la calidad de GPCs cuando se compara las GPCs publicadas entre el 2006-2011 versus las publicadas entre el 2012-2016; ($p = 0.49$).

Adicionalmente, las recomendaciones acerca del punto de corte de concentración de hemoglobina necesaria para iniciar una transfusión de glóbulos rojos fue variable entre las distintas GPCs que fueron evaluadas.

Es importante señalar que, esta revisión representa la primera evaluación sistemática de la calidad de las guías de práctica clínica centradas en las recomendaciones de transfusión de glóbulos rojos. Sin embargo, esta misma metodología se ha aplicado a otras evaluaciones de GPCs en otras áreas clínicas de interés, y los resultados concuerdan con los de este trabajo en cuanto a detectar las deficiencias de la GPCs evaluadas en los dominios de metodología utilizada, aplicabilidad de las recomendaciones e independencia editorial de los involucrados. (178–181).

Adicionalmente, uno de los estudios más importantes en este campo incluye 626 GPCs evaluadas (182), mostró similares resultados que nuestro trabajo de investigación, con excepción del dominio "rigor de desarrollo", donde nuestra revisión encontró baja calidad, con un promedio de 46.3% en comparación con 68%

en otras evaluaciones de trabajos similares, pero en diferentes áreas del conocimiento clínico (182).

6.3. Discusión general del trabajo de tesis

En este proyecto de tesis doctoral nos propusimos investigar un tema de gran interés para la práctica clínica, el área de la medicina transfusional es sin duda un campo vital para mejorar la práctica clínica y por sobre todo tiene grandes retos en cuanto a la mejora de la seguridad del paciente transfundido.

Asegurar la calidad de las transfusiones de sangre, incluyendo las estrategias de transfusión de concentrados de glóbulos rojos es una tarea crucial y muchas organizaciones han emitido sus recomendaciones para lograrlo. La OMS ha estimado que las causas para realizar transfusiones de concentrados de glóbulos rojos a nivel global varían sustancialmente dependiendo de si se trata de países desarrollados o en vías de desarrollo. En los países desarrollados, la mayor cantidad de este tipo de transfusiones está relacionada con cirugías (34%); mientras que, en países en vías de desarrollo con complicaciones relacionadas al embarazo (37%) (183).

Independientemente del contexto clínico, existe un consenso global de que es necesario asegurar la calidad de la sangre que se transfunde. Algunas medidas para mejorar esta calidad y/o disminuir los efectos adversos asociados con esta terapia son la leucorreducción, el trigger de transfusión, el almacenamiento de derivados sanguíneos, el fraccionamiento, etc. (183,184)

Las reacciones adversas relacionada a la transfusión de glóbulos rojos son muy diversas y cada una tiene investigaciones sobre su causalidad y posibles estrategias para contrarrestar o minimizar los posibles daños a los pacientes (24,25).

Existen discrepancias en cuanto a la efectividad y seguridad de las estrategias mencionadas anteriormente que se utilizan para la prevención de reacciones adversas asociadas a la transfusión sanguínea de concentrados de glóbulos rojos.

Por tanto, el objetivo de esta tesis doctoral es evaluar la calidad de la evidencia que existe en relación con esta intervención (24,130,171).

Para este proyecto de tesis, el objetivo fue evaluar las estrategias que se utilizan para prevenir reacciones adversar luego de la transfusión de concentrados de glóbulos rojos, en este sentido una de las estrategias es la leucorreducción, para esto, desarrollamos dos trabajos.

El primer trabajo de esta tesis doctoral fue una SR donde evaluamos la efectividad y seguridad de la transfusión de concentrados de glóbulos rojos leucorreducidos versus concentrados de glóbulos rojos no leucorreducidos. Luego nos propusimos desarrollar el segundo trabajo que evaluó la efectividad y seguridad de la transfusión de concentrados de glóbulos rojos leucorreducidos versus no leucorreducidos, específicamente en población sometida a procedimientos de cirugía mayor cardiovascular específicamente.

Los hallazgos de estos dos trabajos difieren entre sí, principalmente por la población que se incluye, pero es fundamental señalar que hemos logrado precisar que uno de los problemas de la leucorreducción es que esta estrategia se la realiza de forma no selectiva, por el contrario muchos países han implementado la leucorreducción de forma universal y estandarizada (172,173). Esto provoca seria heterogeneidad tanto clínica como estadística en los diferentes análisis reportados en la literatura.

Adicional a estos dos primeros trabajos, y dado que son las GPCs los instrumentos donde se generan recomendaciones clínicas sobre las estrategias de que se utilizan para la prevención de las reacciones adveras asociadas a la transfusión de glóbulos rojos, analizamos críticamente todas las GPCs publicadas que abordan preguntas

clínicas sobre transfusión de CGR, La metodología que utilizamos fue el instrumento AGREE II (122, 123,124), que es ampliamente aceptado por la comunidad científica como un mecanismo de apoyo y evaluación para mejorar la calidad e estas guías. Adicional a esto, quisimos mapear una de las más importantes estrategias que se han investigado en la actualidad, el umbral de hemoglobina necesario para realizar una transfusión.

Los hallazgos son concluyentes en señalar los problemas metodológicos detectados, así como también las inconsistencias en cuanto a la aplicabilidad e independencia editorial de estos documentos. Cuando analizamos las recomendaciones sobre el umbral de hemoglobina, no encontramos acuerdos entre las guías y muchas de ellas no reportan esta estrategia dentro de sus recomendaciones.

Es importante especificar los detalles de los hallazgos de estos trabajos incluidos en este proyecto de tesis doctoral. Es así como, no se pudo establecer la efectividad de la reducción de leucocitos de transfusión de concentrados de glóbulos rojos como estrategia para la prevención de reacciones adversas asociadas a la transfusión de estos componentes en todo tipo de pacientes que requieran esta intervención.

Los ECAs detectados y evaluados en esta RS revelaron una importante heterogeneidad clínica que se tradujo al análisis, en heterogeneidad estadística en los metanálisis realizados. Esto, junto con el alto riesgo de sesgo, afectó la calidad de la evidencia encontrada.

Así mismo, se pudo establecer que existe ausencia de evidencia concluyente al momento de los análisis para apoyar la universalización de esta estrategia como estándar de transfusión y como estrategia para la prevención de reacciones adversas asociadas, especialmente en aquellos países de escasos recursos donde la leucorreducción no ha sido implementada aún.

Para tratar de detectar y explicar las fuentes de heterogeneidad clínica y estadística encontrada en el primer trabajo de esta tesis, decidimos realizar un segundo trabajo de investigación para analizar el impacto que podría tener la leucorreducción en un grupo específico de pacientes que generalmente requieren trasfusión de concentrados de glóbulos rojos, estos son los pacientes sometidos a procedimientos de cirugía mayor cardiovascular.

La pertinencia de estudiar este tipo de pacientes en especial, radica del hecho que algunas teorías apuntan a un posible mecanismo adicional de reacciones adversas provocado por el paso de los leucocitos a través de los equipos de circulación extracorpórea con la consecuente liberación de histamina y los efectos sistémicos posteriores relacionados a esta molécula (82).

Como resultado de esta investigación logramos obtener conclusiones más precisas y confiables comparadas con las previamente obtenidas en el primer trabajo de investigación de esta tesis doctoral, es decir, luego de este segundo trabajo podemos decir con cierta precisión y confianza que la reducción de leucocitos de los concentrados de glóbulos rojos como estrategia para la prevención de muerte e infección en pacientes sometidos a procedimientos de cirugía mayor cardiovascular resulta ser efectiva y segura. Además, hemos demostrado que no se requieren estudios adicionales para llegar a conclusiones más precisas y confiables.

Esta información debería ser tomada en cuenta por las autoridades sanitarias al momento de implementar esta estrategia como estándar de seguridad en este tipo específico de pacientes, para que con cierto grado de certeza y confianza lograr mejorar la seguridad de los pacientes en el campo de la medicina transfusional.

Adicional a estos trabajos mencionados, debíamos investigar sobre otras estrategias que podrían ayudar a mejorar las prácticas transfusionales en los pacientes que requieren esta vital intervención. Por tanto, nos propusimos explorar

y evaluar la calidad de las GPCs que incluyan preguntas clínicas sobre transfusión de concentrados de glóbulos rojos, dada la importancia de estas publicaciones como herramientas de toma de decisión en la práctica diaria (182). Este tipo de investigaciones se enmarca en una línea específica que ha dado lugar a varios trabajos de tesis doctoral de la UAB (178–181).

Por ello, nos propusimos analizar si las recomendaciones de estas GPCs incluyen a una de las estrategias que más plausibilidad biológica y especificidad ha demostrado, en este caso nos referimos a la reducción del umbral de hemoglobina con el cual se decide transfundir a un paciente específico.

Los hallazgos de este trabajo permiten demostrar la baja calidad metodológica con la cual se publican las GPC en este campo, problemas con la aplicabilidad de este tipo de documentos que podrían tener los usuarios. Específicamente, logramos mapear las discrepancias que existen entre los clínicos y elaboradores de las guías al momento de recomendar el umbral de transfusión necesario para transfundir a los pacientes que requieren esta intervención.

Finalmente, nos propusimos investigar el almacenamiento corto versus prolongado de CGR como otra de las estrategias que se han propuesto para mejorar la seguridad de los pacientes sometidos a transfusión de CGR para prevención de reacciones adveras asociadas a la transfusión de este tipo de componente sanguíneo (Anexo 1).

Los resultados de este trabajo demostraron la ausencia de evidencia conclusiva y de calidad respecto a la implementación de esta estrategia como estándar en la práctica transfusional, es decir no se logró demostrar si el corto almacenamiento de concentrados de glóbulos rojos podría implementarse como estrategia con impacto clínicos para mejorar la seguridad de los pacientes en la práctica transfusional.

En relación con el desarrollo de estos trabajos, se puede mencionar que este trabajo de tesis utilizó herramientas para la evaluación de dos tipos diferentes de estudios (GPCs, y estudios primarios) en el campo de la práctica transfusional de concentrados de glóbulos rojos, con el fin de evaluar la calidad de la evidencia que es utilizada en el contexto clínico de manera habitual en el cuidado de los pacientes.

Es así como, para la evaluación de los estudios primarios se utilizó el Riesgo de Sesgo de las Revisiones Cochrane (104); para el análisis de las guías se utilizó la herramienta AGREE II (122, 123,124).

En este sentido, es importante señalar que el enfoque sistemático de evaluación de la calidad de la evidencia no se había realizado previamente en el campo de las transfusiones, debido en parte al limitado avance en los métodos para una adecuada valoración crítica de la evidencia científica en esta área clínica especifica del conocimiento en salud y de la metodología de la investigación biomédica.

Estas metodologías ahora más desarrolladas, permiten saber que las revisiones sistemáticas son insumos para la elaboración de GPCs y pueden llegar a ser documentos que pueden llegar a jugar un papel esencial en la elaboración de políticas de salud cuando son tomados en cuenta por parte de los tomadores de decisiones (119, 118, 120).

Estas herramientas han sido realizadas y consensuadas por organismos internacionales tales como la Organización Mundial de la Salud (OMS), National Institute for Health and Clinical Excellence (NICE) (22), Scottish Intercollegiate Guideline Net- work (SIGN), and Guidelines International Network (G-I-N) (121).

Con el objetivo de evaluar la calidad de las GPC nuestro proyecto de tesis realizó la Evaluación de Guías de Práctica Clínica (AGREE por sus siglas en inglés) (122, 123, 124).

6.4. Fortalezas y limitaciones

A continuación, presentaremos las fortalezas y limitaciones, así como las posibles aplicaciones de los resultados de este trabajo en el ámbito de la investigación científica y en la práctica transfusional.

6.4.1. Fortalezas

Las fortalezas del presente trabajo de tesis fueron:

- Aplicar la metodología de las SR Cochrane en cuanto a las estrategias de búsqueda reproducibles y a la selección independiente de los estudios incluibles en los trabajos previstos para esta tesis.

- Hemos logrado realizar a través del segundo trabajo un análisis de un grupo específico de pacientes que requieren transfusión de concentrados de glóbulos rojos y demostrar la fuente de heterogeneidad clínica y estadística que se encontró en el primer trabajo al juntar varias poblaciones en un solo metaanálisis.

- Es el primer trabajo de investigación en el campo transfusional que logra incorporar en sus análisis el TSA que nos permite corregir posibles errores en la interpretación de los resultados al no considerar y corregir las estimaciones por error tipo 1 y error tipo 2.

- Dentro de la evaluación sistemática de las GPCs:

    - Primero, somos los pioneros en evaluar la calidad del desarrollo de las GPCs sobre transfusión de concentrados de glóbulos rojos utilizando instrumentos metodológicos ampliamente reconocidos y aceptados por la comunidad científica.

- En segundo lugar, el uso de estrategias de búsqueda extensas, que abarcan tanto la literatura indexada como la gris, y el uso de evaluadores expertos que completaron el entrenamiento y la calibración para evaluar la calidad de los GPCs nos da confianza en los hallazgos del tercer trabajo de esta tesis.
- Somos pioneros en el campo de la medicina transfusional en realizar un mapeo de evidencia científica sobre las recomendaciones del umbral de hemoglobina necesario para recomendar una transfusión de concentrados de glóbulos rojos.

6.4.2. Limitaciones

Las limitaciones de los estudios que integran este trabajo de tesis fueron:

- A pesar de nuestro esfuerzo por incluir todos los estudios publicados que evalúan la leucorreducción para la prevención de reacciones adversas asociadas a las transfusiones de sangre alogénica, es posible que no se haya podido identificar toda la evidencia relevante. Sin embargo, para identificar este potencial sesgo, realizamos un "funnel plot" en la SR de leucorreducción en todos los pacientes con necesidad de transfusión. Este método visual solo fue posible para un desenlace (infección por cualquier causa), ya que en este caso si logramos identificar al menos los 10 ECA (48,49,54–56,60,61,64,67,71,148) necesarios para este análisis. Para el desenlace de muerte no fue posible realizar los análisis confirmatorios respecto al sesgo de publicación.

- En el protocolo del primer trabajo, definimos que el análisis principal estaría basado en el enfoque intención a tratar (ITT); sin embargo, durante la extracción de datos se identificó un número importante de pacientes incluidos, pero no transfundidos, esto podía afectar sustancialmente la precisión de las estimaciones del efecto. Para explorar este escenario,

realizamos un análisis por protocolo (solo pacientes transfundidos) que no reflejó diferencias relevantes en relación con el resultado primario (TRALI) y los resultados secundarios muerte e infección por cualquier causa, pero los efectos adversos del resultado secundario (fiebre) si mostró diferencias.

- A pesar del pequeño número de ECAs identificados en algunos de nuestros trabajos, específicamente en la SR de leucorreducción en pacientes con cirugía cardiovascular mayor, que podría generar preocupación sobre el sesgo de publicación, realizamos un análisis de TSA demostrando que no es necesario realizar ECAs adicionales para mejorar la precisión y confianza respecto con los resultados obtenidos para el desenlace de infección.

- Una limitación de la SR Cochrane fue no considerar el efecto de la "capa leucocitaria" en las estimaciones a través de un análisis de sensibilidad específico, ya que este efecto podría disminuir la cantidad de leucocitos en una proporción inferior a la leucorreducción. Por tanto, resulta ser una intervención diferente a la planteada en la pregunta de investigación de este trabajo de tesis.

- Otra limitación fue no considerar el análisis de subgrupos del efecto potencial de los diferentes tipos de filtros utilizados en la leucorreducción y descritos en los estudios incluidos, para todos los resultados tanto primarios como secundarios. Se planificó este análisis en el protocolo de revisión solo para el resultado primario TRALI, dejando por fuera desenlaces importantes como muerte e infección.

- A pesar de estas limitaciones y dado que los resultados del primer trabajo de todas formas fueron no concluyentes, estas omisiones no deberían haber afectado los resultados del presente estudio.

- La aplicabilidad a la práctica clínica de la evidencia de esta disertación podría estar restringida por varias razones:

    - En primer lugar, la validez externa puede limitarse a los pacientes que se sometan a los mismos procedimientos detallados en nuestras revisiones.

    - En segundo lugar, los ECAs identificados no informaron adecuadamente varios factores relacionados con la transfusión de concentrados de glóbulos rojos que deben tenerse en cuenta al interpretar los resultados, como el uso de plaquetas leucorreducidas o no, como las co-intervenciones, el momento de la leucorreducción (pre-post almacenamiento), el tipo de filtro utilizado, entre otros factores.

    - En tercer lugar, el número de unidades transfundidas en cirugía cardiovascular es masivo en la mayoría de los casos en comparación con otros entornos clínicos de transfusión quirúrgica y no quirúrgica y, por lo tanto, los pacientes que se someten a cirugía cardiovascular pueden sufrir una complicación posterior a la transfusión, de forma más probable.

    - Finalmente, los estudios informaron diferentes definiciones para las infecciones y la mortalidad se evaluó en diferentes períodos de tiempo (30 días, 60 días, 90 días y hasta doce meses).

    - Cabe recalcar que estas barreras para la aplicabilidad clínica de los resultados de esta disertación no se debieron a fallos metodológicos de los diseños de nuestro estudio, sino más bien, a las deficiencias de los estudios primarios analizados.

- Por otra parte, nuestra evaluación sistemática de GPCs tiene algunas limitaciones.

- Primero, aunque se formuló y probó un conjunto sólido de criterios de búsqueda antes de la identificación de las GPCs, es posible que algunas GPCs no se hayan incluido en nuestro tercer estudio de este trabajo de tesis. Sin embargo, creemos que la calidad de las GPCs no indexadas en bases de datos biomédicas probablemente tengan una menor calidad en comparación con las indexadas.

- En segundo lugar, también existe un riesgo potencial de sesgo de selección porque solo incluimos estudios que se habían publicado en inglés o español. En este sentido, nuestra evaluación podría estar sobreestimando la calidad de las GPCs en transfusiones de concentrados de glóbulos rojos.

- Además, encontramos que los evaluadores tuvieron dificultades para distinguir entre los valores 3, 4 y 5, que pueden tener un potencial riesgo de sesgo de notificación. Para corroborar si esta limitación tuvo un efecto en el resultado final de los evaluadores realizamos un análisis del acuerdo entre los revisores que utilizaron el instrumento AGREE II y este fue alto, con un ICC de 0.97, lo que demuestra que esta limitación podría no influir en el resultado global de nuestro estudio.

6.5. Implicaciones para la práctica clínica

- Se podrían identificar las siguientes implicaciones para la práctica clínica como parte de los estudios incluidos en este trabajo de tesis:
    - No existe evidencia clara para apoyar o rechazar el uso rutinario de la leucorreducción en todos los pacientes que requieren transfusión de concentrados de glóbulos rojos para prevenir el TRALI, muerte por cualquier causa, infección por cualquier causa, complicaciones no

infecciosas y otros eventos adversos. La calidad de la evidencia para dichos desenlaces fue baja y muy baja. Dado que la leucorreducción es un procedimiento muy costoso, los clínicos y los responsables de la formulación de políticas pueden tener que reconsiderar si la transfusión de concentrados de glóbulos rojos leucorreducidos es adecuada para todos los tipos de pacientes, especialmente para aquellos que no tienen una fuerte indicación de reducción de leucocitos. En los países donde la leucorreducción en concentrados de glóbulos rojos no ha sido implementada aún de forma universal, la reducción de leucocitos en los concentrados de glóbulos rojos de forma selectiva podría ser una opción que debería considerarse hasta que se encuentre disponible más y mejor evidencia en relación con la efectividad y la seguridad de este procedimiento.

- Por otro lado, existe evidencia clara para apoyar el uso rutinario de la leucorreducción en pacientes que se someten a cirugía mayor cardiovascular para prevenir la infección y muerte por cualquier causa. La calidad de la evidencia es moderada para este desenlace, lo cual hace confiables los resultados de este trabajo de investigación.

- Finalmente, los usuarios de GPCs sobre transfusión de concentrados de glóbulos rojos deben ser conscientes de la baja calidad de metodológica, poca aplicabilidad y falta de declaración de conflictos de intereses, antes de implementar o adaptar estos documentos a la práctica clínica. Los responsables de la formulación de políticas, que desean respaldar el desarrollo adecuado de GPCs, deben trabajar para garantizar el cumplimiento de las recomendaciones relacionadas con la transfusión de concentrados de glóbulos rojos y minimizar la heterogeneidad en la práctica clínica evidenciado a través de nuestro trabajo de investigación.

6.6. Implicaciones para la investigación

- Se podrían identificar las siguientes implicaciones para la investigación como parte de los estudios incluidos en este trabajo de tesis:
    - Al demostrar que la evidencia encontrada en nuestro primer trabajo de investigación resulta ser no concluyente, se necesita más investigación para evaluar la efectividad, la seguridad y los costos de la leucorreducción en diferentes contextos clínicos y para diferentes condiciones de salud (172,173).

    - Los investigadores en futuros trabajos de investigación deberían considerar que, la asignación al azar prematura a transfusión sanguínea es un problema importante detectado en nuestros estudios parte de esta tesis, dado que podría provocar en los ECAs un sesgo de desgaste (104) y afectar la interpretación de los resultados, al incluir participantes que no se ha confirmado adecuadamente la necesidad de transfusión (24,25); en este caso, puede afectar el efecto real de la leucorreducción en los concentrados de glóbulos rojos, especialmente en el análisis por intensión a tratar (185).

    - Las futuras investigaciones también deben considerar aspectos del diseño del estudio (186), como la verificación de los criterios de inclusión y exclusión antes de la asignación al azar. Los investigadores también deben mejorar el reporte de las intervenciones y las cointervenciones (187), dado que resultan ser factores fundamentales en el análisis global.

    - Además, estudios adicionales deben abordar todos los resultados relevantes (188), como muerte por cualquier causa, complicaciones infecciosas (p.e. CMV), complicaciones no infecciosas (por ejemplo, TRALI, (39,68,189) NHFRT (14,16,157)) y cualquier otro tipo de

reacción adversa asociada a la transfusión de concentrados de glóbulos rojos.

- Para el desenlace de infección por cualquier causa en pacientes que fueron sometidos a cirugía cardiovascular y recibieron transfusión de CGR leucorreducidos, según el análisis TSA (39,68,189), no es necesario realizar más ECAs para evaluar los efectos en la reducción del riesgo de complicaciones por este desenlace. Se podría justificar más investigación específicamente en otros desenlaces (p.e. muerte por cualquier causa), especialmente en aquellos países de ingresos medios y bajos en los que la leucorreducción de concentrados de glóbulos rojos no se ha implementado universalmente todavía y / o donde los costos del procedimiento podrían ser una limitación.

- Por otro lado, los desarrolladores de GPC deben adherirse a métodos rigurosos, como los que se proporcionan en los manuales de instituciones como la Scottish Intercollegiate Guidelines Network (SIGN) (121) o el Instituto Nacional de Excelencia en Salud y Atención (NICE) (22). Además, los desarrolladores de guías deben usar listas de verificación para optimizar los métodos de el desarrollo y la presentación de informes de GPC, como la “GIN-McMaster Guideline Development Checklist” (119, 118, 120, 121) y AGREE II (122, 123, 124), respectivamente.

- Además, para mejorar la comunicación entre los usuarios y los desarrolladores de GPCs, la metodología (137,138) GRADE es altamente recomendada, ya que es un sistema riguroso y ampliamente aceptado por la comunidad científica. Así también, se deben realizar esfuerzos adicionales para desarrollar y consolidar redes que permitan mejorar la evaluación y la síntesis de la evidencia disponible en el campo de transfusión de concentrados de glóbulos rojos.

- Los investigadores que deseen identificar las brechas de conocimiento y los responsables de la formulación de políticas que deseen respaldar el desarrollo adecuado de GPC deben trabajar juntos para garantizar el cumplimiento de las recomendaciones relacionadas con la transfusión de concentrados de glóbulos rojos y minimizar la heterogeneidad en la práctica clínica.


CONCLUSIONES

7. CONCLUSIONES

- No hay evidencia clara para apoyar o rechazar el uso rutinario de la leucorreducción en concentrados de glóbulos rojos en todos los pacientes que requieren transfusión como estrategia para la prevención reacciones adversas. La calidad de la evidencia es baja o muy baja, por lo que, se necesita más evidencia antes de poder llegar a una conclusión definitiva.

- Encontramos evidencia que apoya el uso rutinario de leucorreducción exclusivamente en pacientes sometidos a un procedimiento de cirugía mayor cardiovascular y que requieren de transfusión de concentrados de glóbulos rojos para prevenir la muerte y la infección. En el caso de infección, las pruebas deben considerarse suficientes y concluyentes y, por lo tanto, indican que no se requiere de ensayos clínicos adicionales para demostrar su efectividad y seguridad.

- La calidad de las guías de práctica clínica que abordan la transfusión de concentrados de glóbulos rojos publicadas a 2016 es heterogénea en aspectos metodológicos, sus recomendaciones, la aplicabilidad e independencia editorial. Aunque similares en contenido, varían ampliamente en términos de la valoración de la calidad de la evidencia por las serias deficiencias encontradas y la confianza en la implementación de estas en el contexto clínico. Las recomendaciones sobre el umbral de hemoglobina para transfundir glóbulos rojos fueron heterogéneas entre las guías. Se necesitan mayores esfuerzos para proporcionar GPCs de alta calidad en la práctica clínica en relación con la transfusión de glóbulos rojos.

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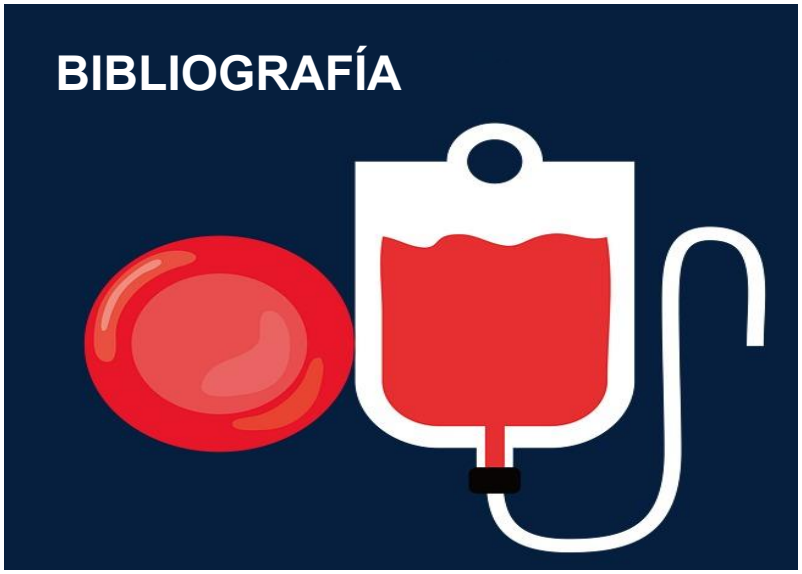

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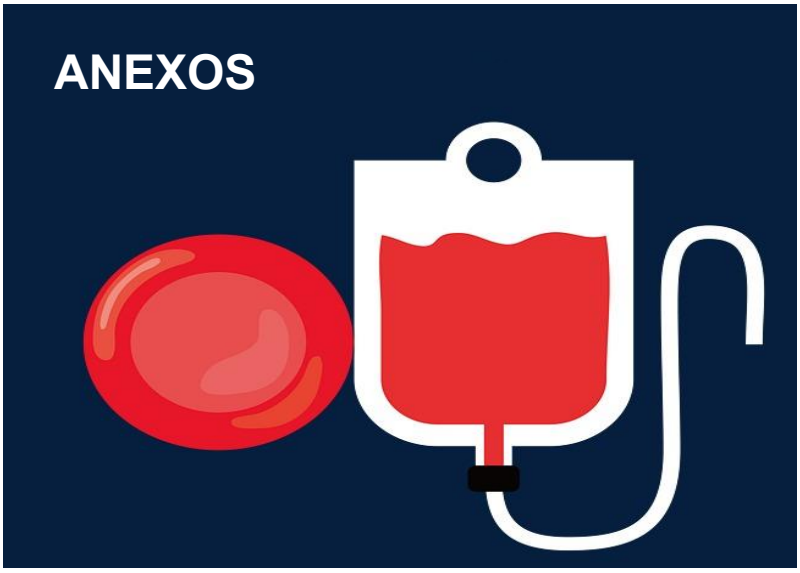
ANEXOS

9. ANEXO

9.1. Anexo 1: Prolonged storage of packed red blood cells for blood transfusion

Cochrane Library
Cochrane Database of Systematic Reviews

Prolonged storage of packed red blood cells for blood transfusion (Review)

Martí-Carvajal AJ, Simancas-Racines D, Peña-González BS

Martí-Carvajal AJ, Simancas-Racines D, Peña-González BS.
Prolonged storage of packed red blood cells for blood transfusion.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD009330.
DOI: 10.1002/14651858.CD009330.pub2.

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[Intervention Review]

Prolonged storage of packed red blood cells for blood transfusion

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Editorial group: Cochrane Injuries Group.
Publication status and date: New, published in Issue 7, 2015.

Citation: Martí-Carvajal AJ, Simancas-Racines D, Peña-González BS. Prolonged storage of packed red blood cells for blood transfusion. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD009330. DOI: 10.1002/14651858.CD009330.pub2.

ABSTRACT

Background

A blood transfusion is an acute intervention, used to address life- and health-threatening conditions on a short-term basis. Packed red blood cells are most often used for blood transfusion. Sometimes blood is transfused after prolonged storage but there is continuing debate as to whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood.

Objectives

To assess the clinical benefits and harms of prolonged storage of packed red blood cells, in comparison with fresh, on recipients of blood transfusion.

Search methods

We ran the search on 1st May 2014. We searched the Cochrane Injuries Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCO Host) and two other databases. We also searched clinical trials registers and screened reference lists of the retrieved publications and reviews. We updated this search in June 2015 but these results have not yet been incorporated.

Selection criteria

Randomised clinical trials including participants assessed as requiring red blood cell transfusion were eligible for inclusion. Prolonged storage was defined as red blood cells stored for $\geq$ 21 days in a blood bank. We did not apply limits regarding the duration of follow-up, or country where the study took place. We excluded trials where patients received a combination of short- and long-stored blood products, and also trials without a clear definition of prolonged storage.

Data collection and analysis

We independently performed study selection, risk of bias assessment and data extraction by at least two review authors. The major outcomes were death from any cause, transfusion-related acute lung injury, and adverse events. We estimated relative risk for dichotomous outcomes. We measured statistical heterogeneity using I^2. We used a random-effects model to synthesise the findings.

Main results

We identified three randomised clinical trials, involving a total of 120 participants, comparing packed red blood cells with ≥ 21 days storage ('prolonged' or 'older') versus packed red blood cells with < 21 days storage ('fresh'). We pooled data to assess the effect of prolonged storage on death from any cause. The confidence in the results from these trials was very low, due to the bias in their design and their limited sample sizes.

The estimated effect of packed red blood cells with ≥ 21 days storage versus packed red blood cells with < 21 days storage for the outcome death from any cause was imprecise (5/45 [11.11%] versus 2/46 [4.34%]; RR 2.36; 95% CI 0.65 to 8.52; I^2: 0%, P = 0.26, very low quality of evidence). Trial sequential analysis, with only two trials, shows that we do not yet have convincing evidence that older packed red blood cells induce a 20% relative risk reduction of death from any cause compared with fresher packed red blood cells. No trial included other outcomes of interest specified in this review, namely transfusion-related acute lung injury, postoperative infections, and adverse events. The safety profile is unknown.

Authors' conclusions

Recognising the limitations of the review, relating to the size and nature of the included trials, this Cochrane Review provides no evidence to support or reject the use of packed red blood cells for blood transfusion which have been stored for ≥ 21 days ('prolonged' or 'older') compared with those stored for < 21 days ('fresh'). These results are based on three small single centre trials with high risks of bias. There is insufficient evidence to determine the effects of fresh or older packed red blood cells for blood transfusion. Therefore, we urge readers to interpret the trial results with caution. The results from four large ongoing trials will help to inform future updates of this review.

PLAIN LANGUAGE SUMMARY

Prolonged storage of packed red blood cells (storage of 21 days or more) in comparison with fresh cells on recipients of blood transfusion

Review question

We reviewed the clinical benefits and harms of prolonged storage of packed red blood cells (storage of 21 days or more) in comparison with the use of fresher packed red blood cells on recipients of blood transfusion.

Background

Blood transfusion is used to try to solve life- and health-threatening conditions on a short-term basis. Packed red blood cells are most often used for blood transfusion. Sometimes blood is transfused after prolonged storage of these cells but there is continuing debate as to whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood.

Study characteristics

We identified three studies, involving a total of 120 participants, comparing packed red blood cells stored for ≥ 21 days versus < 21 days.

Key results

The results of the studies for the outcome death from any cause were uncertain due to the small number of participants who contributed information. We could not exclude an effect on death with either longer or shorter storage. None of the trials considered the other outcomes of interest in this review, namely transfusion-related acute lung injury, postoperative infections, and adverse events. The safety profiles of the two approaches are unknown.

Quality of evidence

The level of confidence in the results of this review is very low. The studies have limitations in the way they were designed and executed. Moreover, the limited number of people included in the studies led to imprecise results. We are aware of four large ongoing trials in this area which will help us to better understand the effects of storage on red blood cells in relation to outcomes for patients.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Long-stored (older) PRBC (≥ 21 days of storage) compared with short-stored (fresh) PRBC (< 21 days of storage) for patients requiring blood transfusion

Patient or population: patients requiring blood transfusion (children with malaria and adults with a traumatic injury)
Settings: intensive care unit
Intervention: Long-stored (older) PRBC (≥ 21 days of storage)
Comparison: Short-stored (fresh) PRBC (< 21 days of storage)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short-stored (fresh) PRBC (< 21 days of storage)	Long-stored ('older') PRBC (≥ 21 days of storage)				
Death from any cause	Study population		RR 2.36 (0.65 to 8.52)	91 (2 studies)	⊕◯◯◯ **very low**[1]	Dhabangi 2013 (children with malaria) Schulman 2002 (adults with a traumatic injury)
	43 per 1000	103 per 1000 (28 to 370)				
	Low					
	43 per 1000	101 per 1000 (28 to 366)				
Transfusion-related acute lung injury - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Postoperative infections - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Post-injury coagulopathy - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.

Multiple organ failure post-injury - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Adverse event (Hyperkalaemia) - not measured	See comment	See comment	Not estimable	-	See comment	No trial assessed this outcome.
Adverse event (Metabolic acidosis) Follow-up: 12 months	See comment	See comment	Not estimable	22 (1 study)	⊕○○○ **very low**[2,3]	"No acid-base parameter changed significantly between the pre- and posttransfusion periods either within each group or comparing changes between the groups" (Walsh 2004).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small sample size and low event rate (91 participants with 7 events).
[2] The one trial had high risk of bias.
[3] Small sample size (22 participants) and no reported event rate of this outcome.

BACKGROUND

Transfusion of blood is the process of transferring blood cells from one person into the circulatory system of another (Sullivan 2007; Giangrande 2000). It is a very common procedure for a number of acute and chronic conditions. A blood transfusion is a costly intervention, implemented to solve life- and health-threatening conditions, and in general its long-term effects tend to be of secondary importance (Tsai 2010). This potentially life-saving intervention is, however, associated with adverse events, categorised as immune or non-immune hazards (Hendrickson 2009) (Appendix 1). Formerly, whole blood was transfused. During the last 30 years, packed red blood cells have been most often used for blood transfusion. Packed red blood cells were introduced to reduce the immunisation hazards of whole blood and to preserve leucocyte-rich and thrombocyte-rich blood products for more targeted use for people lacking these components.

Many clinical studies have suggested a general association between transfusion and morbidity (Dunne 2004; Leal-Noval 2001; Leal-Noval 2003; Malone 2003; Mynster 2000; Vamvakas 1999; Vamvakas 2002; Vamvakas 2006) and mortality (Ho 2003; Robinson 2005; Spinella 2009). One critical question that needs to be answered is, "Are the short- and long-term effects of blood transfusion intrinsic to the process or are they exaggerated by *blood storage*?" (Tsai 2010). However, specific concern has been expressed as to whether use of blood transfusion may contribute to adverse outcomes in people receiving transfusions, because of a cellular and biochemical phenomenon called the '*storage lesion*' of red cells (Bosman 2008; Lelubre 2009; Tinmouth 2006; Zimrin 2009). This is a very controversial issue in clinical medicine (Zimring 2013).

What is blood storage?

All blood transfusion services store collected red blood cells in a specific additive medium, which includes anti-coagulants and nutrients. Most current red blood cell storage solutions are composed of dextrose, phosphate, adenine, and citrate (Hess 2006). Use of these solutions allows units (or bags) of red blood cells to be stored for a period of time prior to transfusion at 2°C to 6°C in blood banks, which considerably facilitates inventory management at national, regional, and hospital levels. The development of blood storage systems has allowed donation and transfusion to be separated in time and space (Zimrin 2009).

Peyton Rous was the first person to store red blood cells (Zimrin 2009). In 1915, Rous and Turner developed the first red blood cell storage solution, a mixture of citrate and glucose, for storing rabbit red blood cells for use in a heterophil agglutination test for syphilis (Hess 2006). Historically, the shelf-life of red blood cells was established based on biochemical standards and survival studies, conducted largely in healthy volunteers and not in patients. The typical recovery of red blood cells post transfusion was 75% to 89% and the percentage of haemolysis was 0.1% to 0.4% (Hess 2006).

An extensive review of the history of red blood cell storage solution has been published (Hess 2006). For details of red blood cell storage solutions and a glossary, see Appendix 2 and Appendix 3, respectively.

Definition of red blood cell storage lesion

Red blood cell storage lesion is the name given to all of the biochemical and biomechanical changes that occur within the red blood cell and the supernatant (including plasma and the storage media) during conventional blood bank storage (Hess 2010; Hess 2010a). During storage, red blood cells lose potassium, diphosphoglycerate, adenosine 5′-triphosphate (ATP), lipids and membranes, while becoming more rigid and demonstrating reduced oxygen off-loading. Stored units become more acidotic and the suspending fluid has higher concentrations of free haemoglobin and biologically-active lipids, and contains greater quantities of negatively-charged microvesicles with pro-inflammatory and procoagulant activity (Hess 2006). The components of the red blood cell storage lesion are metabolic, enzymatic, oxidative, and physiologic (Hess 2010; Hess 2010a). This results in changes in red blood cell metabolism, shape, and rheology; loss of membrane carbohydrates, lipids and proteins; and alterations in secretion, oxygen delivery, and adhesion (Hess 2010a). Details of these changes are shown in Appendix 4.

Definition of prolonged storage

There is no consensus on the duration of storage that is considered to be 'prolonged' (Flegel 2014; Triulzi 2010). Donated red blood cells can be stored for as long as 42 days at 2°C to 6°C (Hebert 2005; Yap 2008). Duration of storage has been described as "the number of calendar days between the day of collection of the red blood cell unit and the day of transfusion" (Gauvin 2010). However, there is no consensus on what is meant by prolonged storage or 'older' red blood cells. Data from observational clinical studies reporting transfusion of 'older' red blood cells describe a wide range from 14 days to 24 days (Zimrin 2009). The data from an extensive narrative review of randomised controlled trials of the transfusion of 'older' red blood cells report a wider range of 5 to 20 days (Zimrin 2009).

Storage and trauma patients

Haemorrhagic shock is the second most frequent cause of death in trauma patients (Tien 2007). It has been shown to be responsible for 30% to 40% of trauma mortalities (Theusinger 2009). Several observational studies have been conducted in critical care and intensive care unit patients to assess the impact of red blood cell stor-

age (Keller 2002; Leal-Noval 2008; Murrell 2005; Offner 2002; Spinella 2009; Wienberg 2008b; Zallen 1999). The transfusion of blood and its components is critical in the management of traumatic haemorrhage and other conditions, but is itself associated with adverse outcomes (Greer 2010; Theusinger 2009). Some of the clinical consequences associated with the transfusion of 'older' packed red cells include multi-organ failure (Spinella 2009; Zallen 1999), infections (Offner 2002), mortality (Purdy 1997; Spinella 2009; Weinberg 2008a; Wienberg 2008b), renal failure (Wienberg 2008b), pneumonia (Vandromme 2009; Wienberg 2008b), and deep vein thrombosis (Spinella 2009). Recently, a retrospective study reported red blood cell storage is not associated with an increasing risk of death in critically ill people (Aubron 2014).

Storage and non-trauma patients

Serious complications and mortality after cardiac surgery have been associated with the prolonged storage of transfused red cells (Basran 2006; Koch 2008; Leal-Noval 2003; Vamvakas 2000; Watering 2006; Yap 2008).
Gauvin 2010 described an association between the length of storage of transfused red blood cells and multiple organ dysfunction syndrome in paediatric intensive care patients.
Studies of red blood cell storage in colorectal and biliary surgery have reported an increase in the risk of postoperative infections (Edna 1994; Edna 1998; Mynster 2000; Mynster 2001).

Potential adverse events induced by storage

Transfusion of red blood cells after prolonged storage may produce harmful effects that could be mediated by several pathways (Hod 2010). The following storage-induced potential adverse events have been both suggested and reported, which may underlie why patients receiving 'older' blood have a longer stay in intensive care units (Murrell 2005).

1. Cardiac arrhythmia induced by hyperkalaemia (Hess 2010).
2. Transfusion-related acute lung injury due to the alteration of erythrocyte phospholipids and generation of platelet activating factor (Hess 2010; Goldberg 2012).
3. Reduction in the efficacy of transfused blood components by reducing their flow, functional capacity, and survival (Hess 2010a).
4. Contaminating bacteria and infection (Hess 2010a; Hod 2011).
5. Immunosuppression (Purdy 1997).
6. Multiple organ failure post-injury (Gauvin 2010; Offner 2002).
7. Reduction of cerebral oxygenation in patients with severe traumatic brain injury (Leal-Noval 2008).
8. Post-injury coagulopathy (Maani 2009).
9. Thrombosis (Sweeney 2009; Zimrin 2009) and adverse effects on global coagulation status (Aucar 2009; Bosman 2008).
10. Immune haemolytic transfusion reaction (Zimrin 2009).
11. Postoperative infections risk (Edna 1994; Edna 1998).

See Appendix 3 for glossary.

Why it is important to do this review

This Cochrane Review was conducted for the following reasons:

- *First*, it has been difficult to establish whether there are significant clinical implications in transfusing red blood cells after prolonged storage (Hess 2010a; Qu 2015; Sparrow 2015; Van De Watering 2013). There is an active debate on whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood (Glynn 2010). An association between the duration of storage of transfused red blood cells and morbidity and mortality in adult patients is considered by some to be an established fact but by others to be a myth (Almac 2007; Lelubre 2009). In one opinion in cardiac surgery, transfusion of 'older' blood is inherently more fraught with complications and poorer outcomes (Koch 2008). However, Yap 2008 reported that the age of transfused red cells is not associated with early mortality and morbidity after cardiac surgery.

- *Second*, there is uncertainty as to the true clinical impact of prolonged storage of red blood cells on microcirculation and tissue oxygenation in critically ill patients (Frenzel 2009).

- *Third*, observational clinical studies (prospective and retrospective) are the source of most of our knowledge on "the importance of the question of whether or not storage of red blood cell affects clinical outcomes" (Stowell 2010). However, such studies with observational design are not able to correctly assess the benefits and harms of intervention (Deeks 2003; Jakobsen 2013).

- *Fourth*, patients receiving 'older' blood seem to have a significantly longer stay in intensive care units (Murrell 2005).

- *Fifth*, there is a need to assess the methodological quality of randomised clinical trials on the duration of storage of red blood cells for transfusion in a variety of clinical settings (Bennett-Guerrero 2009; Hebert 2005; Schulman 2002).

- *Sixth*, a recent meta-analysis on "the purported deleterious effects of 'old' (versus 'fresh') red blood cells did not report the risk of bias of the included randomised clinical trials, did not use the I^2 statistic to quantify the statistical heterogeneity, did not consider risks of random error with current methodology (Brok 2008; Brok 2009; Thorlund 2011; Wetterslev 2008; Wetterslev 2009) and was conducted by just one author. All of these factors may have led to bias (Vamvakas 2010).

OBJECTIVES

To assess the effects of prolonged compared with shorter storage of packed red blood cells for red blood cell transfusion.

The focus is packed red blood cells, as they are the most frequently transfused blood product. For this review, prolonged storage is defined as storage of 21 days or more. We chose this threshold since it is the chronological midpoint in storage duration for additive solution units (42 days) (Bennett-Guerrero 2009).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials, irrespective of publication status (trials might be unpublished or published as an article, an abstract or a letter), language of publication, country where the study took place, or period of follow-up. We included randomised clinical trials conducted in a hospital or community setting or both. We did not apply any limits with respect to the period of follow-up. We excluded randomised clinical trials conducted without definition of the term 'prolonged storage', or where the definition was unclear.

Types of participants

Any participant requiring a red blood cell transfusion. No limitation was applied on the age of participants.
We included randomised clinical trials in which participants received either only long-stored or only short-stored blood products. We excluded randomised clinical trials where patients received a combination of short- and long-stored blood products.

Types of interventions

Intervention

- Red blood cells stored for ≥ 21 days in a blood bank.

Comparison

- Red blood cells stored for < 21 days in a blood bank.

Types of outcome measures

Primary outcomes

Clinical effectiveness outcomes

1. Death from any cause.
2. Transfusion-related acute lung injury.
3. Adverse events: number and type of adverse events defined as patients with any untoward medical occurrence not necessarily having a causal relationship with the treatment. We reported on adverse events that lead to treatment discontinuation and those that have not lead to treatment discontinuation separately. We have defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that at any dose results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, or is a congenital anomaly/birth defect, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events were considered non-serious.

Secondary outcomes

1. Postoperative infections.
2. Postinjury coagulopathy defined by arbitrary thresholds in standard laboratory parameters as follows: 1) prothrombin time more than 18 seconds; (2) activated partial thromboplastin time more than 60 seconds; (3) prothrombin time/activated partial thromboplastin time > 1.5 (1.6) control values; (4) international normalised ratio (INR) > 1.2 (prothrombin time); (5) international normalised ratio > 1.5 (prothrombin time); (6) quick value of more than 70% (prothrombin time) (Stahel 2009).
3. Multiple organ failure post-injury.

Safety outcomes

1. Hyperkalaemia.
2. Metabolic acidosis.

See Appendix 3 for definitions.

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (10/05/2014);

2. Cochrane Central Register of Controlled Trials, *The Cochrane Library* (issue 4, 2014);
3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) 1946 to 10/05/2014;
4. Embase Classic+Embase (OvidSP) 1947 to 10/05/2014;
5. CINAHL Plus (EBSCOHost) (1937 to 10/05/2014);
6. ISI Web of Science:Science Citation Index Expanded (SCI-EXPANDED) 1970 to 10/05/2014;
7. ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) 1990 to 10/05/2014;
8. LILACS (http://lilacs.bvsalud.org/) (10/05/2014);
9. Clinicaltrials.gov (www.clinicaltrials.gov) 10/05/2014;
10. WHO Clinical Trials Search Portal (http://apps.who.int/trialsearch/) (10/05/2014).

We adapted the MEDLINE search strategy illustrated in Appendix 5 as necessary for each of the other databases. We used search filters, a modified version of the 'Cochrane Highly Sensitive Search Strategies, for identifying randomized trials in MEDLINE and Embase (Lefebvre 2011).

We performed a further search in June 2015. Those results have been added to Studies awaiting classification and will be incorporated into the review at the next update.

Searching other resources

We also searched the following websites:

- Transfusion Evidence Library (http://transfusionguidelines.org);
- NHS Evidence (http://www.evidence.nhs.uk);
- American Association of Blood Banks (http://www.aabb.org).

In addition, we checked the reference lists of identified material for relevant trials.

Data collection and analysis

Selection of studies

Arturo Martí-Carvajal and Daniel Simancas independently assessed for inclusion all the potential studies identified by the search strategy. We contacted the authors of one trial (Dhabangi 2013), in order to clarify details in order to decide whether the trial should be included or excluded.

Data extraction and management

Arturo Martí-Carvajal, Barbra Peña-González and Daniel Simancas independently extracted data from the selected trials using a standardised data extraction form (Zavala 2006). We extracted the following data: eligibility criteria, demographics (age, gender, country), storage duration (days), reason for transfusion, setting of the patients (i.e. cardiac surgery, intensive care unit), outcomes. We did not contact any trial author regarding missing data, because there was no need to do so.

Assessment of risk of bias in included studies

Arturo Martí-Carvajal and Daniel Simancas independently assessed the quality of each trial using a simple form following the domain-based evaluation as described in the *Cochrane Handbook* (Higgins 2011). We compared the assessments and discussed any discrepancies between the review authors. We resolved disagreements through discussion and consensus.

The definitions of each classification are given below.

Generation of randomisation sequence (checking for possible selection bias)

- Low risk: any truly random process (e.g. random number table, computer random number generator).
- High risk: any non-random process (e.g. odd or even date of birth, hospital or clinic record number).
- Unclear: the trial was described as randomised but the method used for the allocation sequence generation was not described.

Allocation concealment (checking for possible selection bias)

- Low risk: e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes.
- High risk: open random allocation, unsealed or non-opaque envelopes, alternation, date of birth.
- Unclear: the trial was described as randomised but the method used to conceal the allocation was not described.

Blinding or masking (checking for possible performance bias)

- Low risk: participants, carers/personnel and/or outcome assessors blinded from the knowledge of which intervention the participant received, or the lack of blinding could not have affected the results;
- High risk: participants, carers/personnel and/or outcome assessors were not blinded from the knowledge of which intervention the participant received, and this could have affected the results;
- Unclear: the blinding of participants, carers/personnel and/or outcome assessors was not reported.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention

effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on the observed effect size; missing data have been imputed using appropriate methods.

- High risk (any one of the following): reason for missing outcome data likely to be related to the true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in the observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomised not stated, no reasons for missing data provided); the study did not address this outcome.

Selective reporting bias

- Low risk (any one of the following): the study protocol is available and all the pre-specified (primary and secondary) outcomes were reported in the final report, or the study protocol was not available but it was clear that the published reports included all expected outcomes.
- High risk (any one of the following): not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk: insufficient information available to permit judgement of 'Low risk' or 'High risk'.

Other biases

We described for each included study any important concerns about other possible sources of bias (baseline imbalance, sponsorship bias, confirmation bias, bias of the presentation data, etc.)

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias;
- Unclear risk: the trial may or may not be free of other components that could put it at risk of bias;
- High risk of bias: there are other factors in the trial that could put it at risk of bias.

Measures of treatment effect

Binary data was available for death from any cause and measured using the risk ratio (RR) with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We would have used the following procedures (and will apply these for future updates, if possible). We would have noted levels of attrition and explored the impact of high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes we would have carried out analysis, as far as possible, on an intention-to-treat basis (i.e. we would have attempted to include all participants randomised to each group in the analyses). The denominator for each outcome in each trial would have been the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We conducted a meta-analysis on death from any cause. We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We considered there to be significant statistical heterogeneity if $I^2 > 75\%$ and moderate statistical heterogeneity if the I^2 was between 50 and 74% (Higgins 2011).

Assessment of reporting biases

Only three trials were available, so publication bias was not explored.

We would also have attempted to assess whether trials included in the review are affected by publication bias, by using a funnel plot to graphically illustrate variability between trials. If asymmetry were detected, we would have explored causes other than publication bias (e.g. selective outcome reporting, poor methodological quality in smaller studies, true heterogeneity) (Higgins 2011). In future updates we will construct a funnel plot, provided we have ten or more randomised clinical trials for each comparison (Sterne 2011).

Data synthesis

We carried out statistical analysis with Review Manager software (RevMan 2011) using the random-effects model.

Trial Sequential Analysis

Trial sequential analysis (TSA) was applied, as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To minimise random errors, we calculated the required information size (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Thorlund 2009; Wetterslev 2008). The required information size calculation should also account for the heterogeneity or diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009). We planned to conduct our meta-analysis using the following assumptions: the required information size would have been based on the event proportion in the control group; assumption of a plausible RR reduction of 20% on the RR reduction observed in the included trials with low risk of bias; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis (Wetterslev 2009). The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial has been published in a year, trials were added alphabetically according to the last name of the first author. On the basis of the required information size, trial sequential monitoring boundaries were constructed (Thorlund 2011; Wetterslev 2008). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential alpha-spending monitoring boundary is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential beta-spending boundaries.
We conducted TSA for exploring the effect of the intervention on death from any cause.

Subgroup analysis and investigation of heterogeneity

Meta-analysis of two small trials involving 91 participants showed no important heterogeneity.
We would have used the following procedures (and will apply these for future updates, if possible). We had anticipated clinical heterogeneity in the effect of the intervention and we had proposed to conduct the following subgroup analyses.

1. Age
2. Type of storage duration definition
3. Medical versus surgical indications
4. By using arbitrary cut-off points of units transfused:
    - one unit
    - two units
    - three or more units

Sensitivity analysis

We would also have conducted sensitivity analysis according to the methods outlined in the *Cochrane Handbook* (Higgins 2011). In future updates, if sufficient trials are identified, we will conduct a sensitivity analysis comparing: trials with 'low risk of bias' versus those at 'high or unclear risk of bias' in the domain allocation concealment.

Summary of findings tables

We used GRADE (Guyatt 2011) to assess the quality of the body of evidence. The summary of findings was constructed using GRADEpro software (GRADEpro 2008). The GRADE approach appraises the quality of a body of evidence, based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Balshem 2011; Brozek 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g).
Summary of findings for the main comparison shows the body of evidence for the outcomes reported by the included trials i.e., death from any cause and metabolic acidosis. However, we included other unreported outcomes to show the lack of evidence.
We would have used (and will apply in future updates, if possible) the principles of the GRADE system to assess the quality of the body of evidence associated with other outcomes of interest to this review.

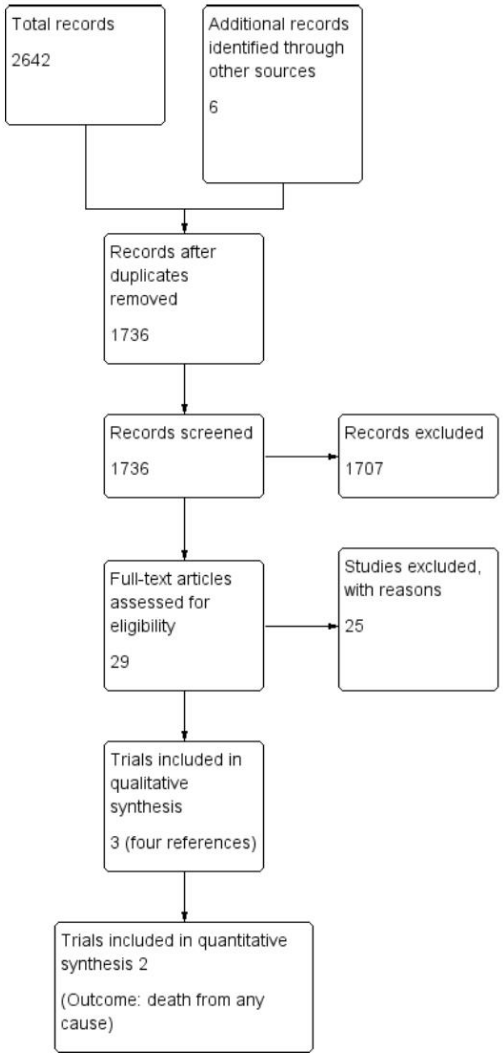
RESULTS

Description of studies

Results of the search

We identified 2642 references of which 912 were duplicates (Figure 1). From the 29 full text papers we accessed to determine eligibility, we found three randomised clinical trials that met our inclusion criteria (Dhabangi 2013; Schulman 2002; Walsh 2004). These trials were published between 2002 and 2013, and were conducted in Uganda (Dhabangi 2013), the United States of America (Schulman 2002), and the United Kingdom (Walsh 2004). The Characteristics of included studies table shows a detailed description of the included trials.

Figure 1. Study flow diagram.



We also identified four ongoing studies (Characteristics of ongoing studies).
Ten study reports from an updated search in June 2015 have been added to Studies awaiting classification.

Included studies

Clinical characteristics

One trial was conducted in adults (Walsh 2004), and one in children (Dhabangi 2013). One trial did not report the age of the participants (Schulman 2002). Two trials reported the gender of the participants (Dhabangi 2013; Walsh 2004). Trials involved people with malaria (Dhabangi 2013), critically ill people with anaemia (Walsh 2004), and people with a traumatic injury (Schulman 2002).

Intervention characteristics

- Packed red cell blood storage definition

1. Long-stored ('older') blood cell use: trials met the criteria of long-stored ('older') blood cells if they were stored for ≥ 21 days (Dhabangi 2013; Schulman 2002; Walsh 2004).
2. Short-stored (fresh) blood cell use:
trials were conducted using different definitions for short-stored (fresh) blood cells: 1 to 10 days (Dhabangi 2013), ≤ 5 days (Walsh 2004) and ≤ 11 days (Schulman 2002).

- Intervention and comparator groups

The intervention and comparator groups differed across the trials. Dhabangi 2013 compared a short storage arm (1-10 days) versus a long storage arm (21-35 days). No information was supplied as to whether the transfused blood was leukodepleted. Schulman 2002 compared leukodepleted packed red blood cells stored for ≥ 21 days since collection, with leukodepleted packed blood cells stored for ≤11 days; participants were transfused within 24 hours of hospitalisation. Walsh 2004 compared 2 units of leukodepleted packed red blood cells stored for ≥ 21 days since collection, with 2 units of leukodepleted packed red blood cells stored for ≤ 5 days.

Outcome characteristics

Data were available for two of our defined outcomes: death from any cause (Dhabangi 2013; Schulman 2002) and incidence of metabolic acidosis (Walsh 2004).

Methodology characteristics

All the trials had a parallel-study design and compared two groups. Each was conducted in a single centre. These trials randomised 127 participants, of which there were outcome data for 113 participants. The duration of follow-up in one trial was 24 hours (Dhabangi 2013). Another trial followed participants for 12 months (Walsh 2004). One trial did not report the follow-up period (Schulman 2002). All trials were conducted without a priori sample size estimation (Dhabangi 2013; Schulman 2002; Walsh 2004) and used participants as both the units of randomisation and analysis (Dhabangi 2013; Schulman 2002; Walsh 2004). All three trials reported inclusion criteria (Dhabangi 2013; Schulman 2002; Walsh 2004). Two trials reported exclusion criteria (Dhabangi 2013; Walsh 2004).

Excluded studies

We excluded 25 studies: eleven trials for having overlapping 'fresh' and 'older' storage criteria, two trials for comparing packed red blood cells versus whole blood, two trials where no information was provided on the duration of storage, one retrospective study, one case series, one case cross-over study and seven observational studies. See Characteristics of excluded studies.

Ongoing trials

We found four ongoing trials (ACTRN12612000453886; ISRCTN08118744; NCT00458783; NTR2662). The Characteristics of ongoing studies table shows full details.

Risk of bias in included studies

The risk of bias in the included trials is summarised in Figure 2 and Figure 3, and detailed in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Three studies are included in this review.

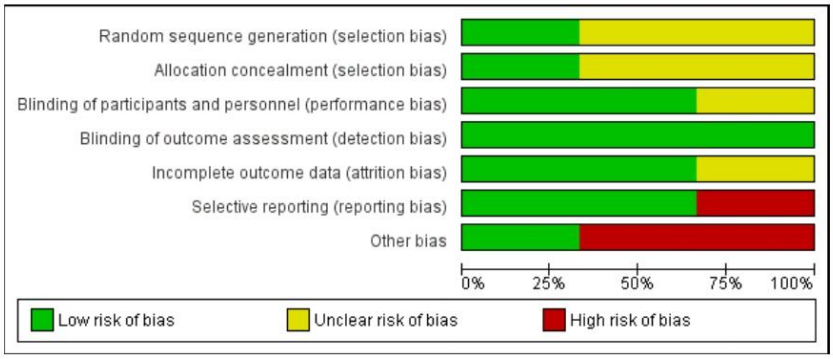
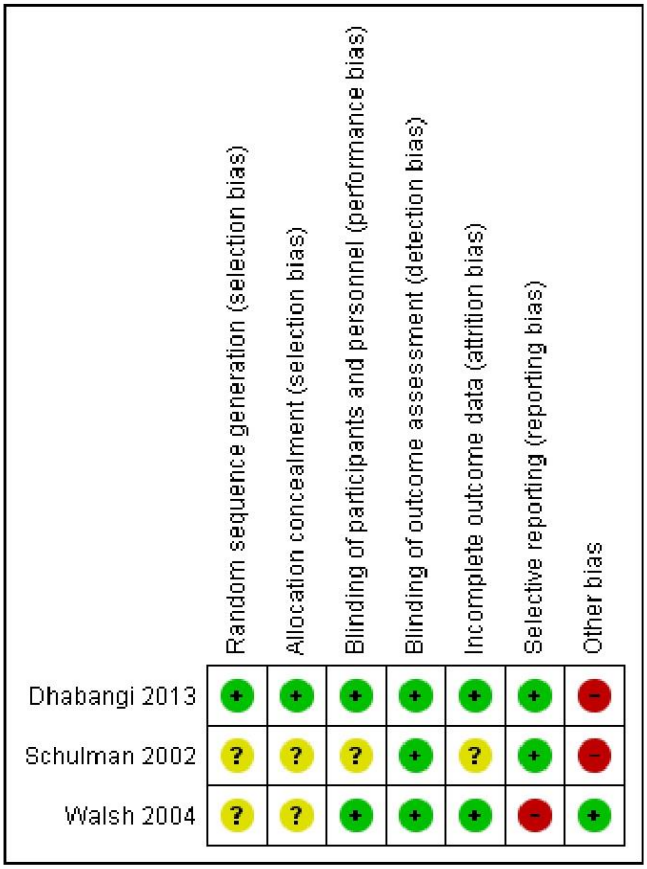


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of the randomisation sequence

One trial was rated as low risk of bias (Dhabangi 2013). The risk of bias arising from the method of generation of the randomisation sequence was rated as unclear risk in two trials (Schulman 2002; Walsh 2004).

Allocation concealment

One trial was rated as low risk of bias (Dhabangi 2013). The risk of bias arising from the method of allocation concealment was unclear in two trials (Schulman 2002; Walsh 2004).

Blinding

We judged all trials to be of low risk of bias in relation to the method of blinded outcome assessment (Dhabangi 2013; Schulman 2002; Walsh 2004).

We judged the risk of bias arising from blinding of the participants and personnel as low in two trials (Dhabangi 2013; Walsh 2004). The risk of bias from blinding was unclear for one trial as insufficient information was provided on which to make a judgement (Schulman 2002).

Incomplete outcome data

The risk of bias arising from incomplete outcome data was low in two trials (Dhabangi 2013; Walsh 2004). This domain was rated as unclear in one trial (Walsh 2004).

Selective reporting

Risk of reporting bias was rated as low as in two trials (Dhabangi 2013; Schulman 2002). This domain was rated as high in one trial, because all the outcomes reported were physiological measurements (Walsh 2004).

Other potential sources of bias

One trial was rated as low risk in this domain (Walsh 2004). One trial had bias in the presentation of data and was rated as high risk (Schulman 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Long-stored ('older') PRBC (≥ 21 days of storage) compared with short-stored (fresh) PRBC (< 21 days of storage) for patients requiring blood transfusion

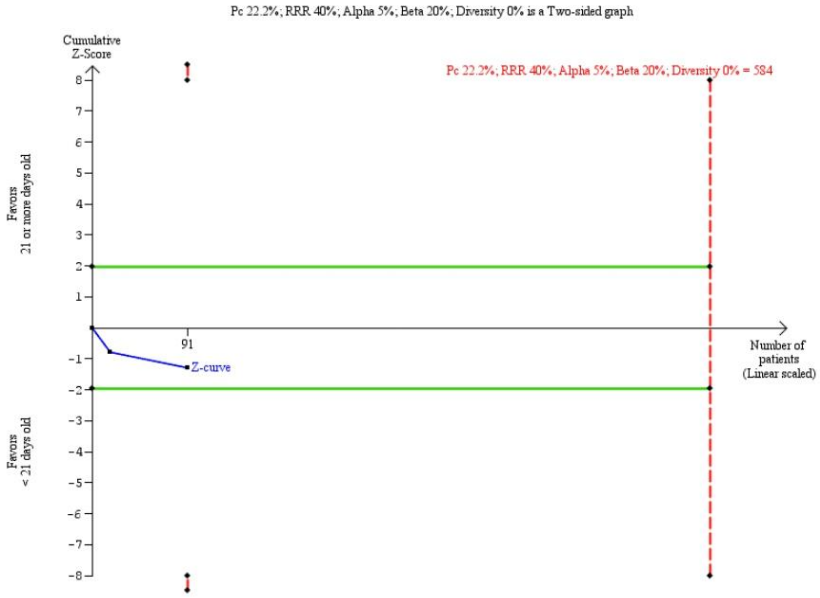
The included trials did not assess the following pre-defined outcomes in this Cochrane Review: multiple organ failure post injury, transfusion-related acute lung injury, postoperative infections, hyperkalaemia, coagulopathy and post-injury coagulopathy.

Primary outcomes

Death from any cause

Meta-analysis of two trials showed no difference in the risk of death among participants receiving packed red blood cells with longer or shorter storage duration (5/45 (11.11%) versus 2/46 (4.34%); (RR 2.36; 95% CI 0.65 to 8.52; I^2: 0%, very low quality of evidence) (Dhabangi 2013; Schulman 2002). See Analysis 1.1. Trial sequential analysis shows that, based on two trials, we have convincing evidence that packed red blood cells with < 21 days of storage are not able to induce a 20% RR reduction of death from any cause compared with red blood cells with ≥ 21 days of storage (Figure 4).

Figure 4. Trial sequential analysis on death from any cause in two trials of < 21 day old versus ≥ 21 day old packed red blood cells. Trial sequential analysis of two trials of < 21 day old versus ≥ 21 day old packed red blood cells on death from any cause based on the diversity-adjusted required information size (DARIS) of 584 patients. This DARIS was calculated based upon a proportion of patients with death from any cause of 22.2% in the control group; a RRR of 40% in the experimental intervention group; an alpha (α) of 5%; and a beta (β) of 20%. The cumulative Z-curve (blue line) did not cross the conventional alpha of 5% (green line) after two trials. It implies that there is a random error. The cumulative Z-curve did not reach the futility area, which is not even drawn by the program. Presently, only 2.91% (17/584) of the DARIS has been obtained. Had we calculated the DARIS based on a more realistic RRR such as 20% or less, the obtained evidence would represent a much smaller part of the DARIS.



Secondary outcomes

Metabolic acidosis

One trial (29 participants) reported no important changes in pH and HCO_3^- from the baseline period (2.5 hrs; mean of five measurements) to the post-transfusion period (5 hrs; mean of five measurements). There was no difference in pH values comparing packed red blood cells with ≤ 5 days of storage (median 0.02 [interquartile range (IR) -0.01 to 0.05]) with packed red blood cells with ≥ 21 days of storage (median -0.02 [IR -0.06 to 0.01]). There was no difference in HCO_3^- ([actual], mmol/L) values comparing packed red blood cells with ≤ 5 days storage (median -0.85 [IR -1.44 to -0.53]) with ≥ 21 days of storage (median -0.29 [IR -0.90 to 0.07]) (Walsh 2004).

DISCUSSION

Summary of main results

We identified three randomised clinical trials involving 120 participants. These trials were conducted in Uganda, the USA, and the UK. One trial was conducted in children (Dhabangi 2013), one in adults (Walsh 2004), and the other trial did not report the age of the participants (Schulman 2002). Over 60% of the participants were male in the one trial reporting this variable (Walsh 2004). Trials involved people with malaria, critically ill people with anaemia, and people with a traumatic injury. One trial had low risk of bias (Dhabangi 2013), the other two trials had a high risk of bias (Schulman 2002; Walsh 2004). All trials were underpowered. Furthermore, they were conducted in a single centre.

Meta-analysis of two trials on the outcome death from any cause found no difference between 'fresher' red blood cells (< 21 days) compared with 'older' packed red blood cells (≥ 21 days) (Dhabangi 2013; Schulman 2002). One trial reporting metabolic acidosis showed no difference between 'fresh' packed red blood cells (< 21 days) compared with 'older' packed red blood cells (≥ 21 days of storage) (Schulman 2002).

None of the trials reported data on two of the review's pre-planned primary outcomes: transfusion-related acute lung injury and post-operative infections. There was no information about safety and so adverse events may be underestimated. Furthermore, included trials did not address coagulopathy, post-injury coagulopathy, multiple organ failure post-injury, hyperkalaemia, or quality of life.

Overall completeness and applicability of evidence

This Cochrane Review provides inconclusive evidence on the clinical effectiveness and safety of prolonged storage of red blood cells compared with fresh red blood cells for blood transfusion. This conclusion is based on three small single centre trials with inadequate information provided by trial reports on patient-important outcomes. These methodological issues have a negative impact on effectiveness trials (Hopewell 2010). We feel those issues are particularly relevant to consider as further work on the topic is planned. In this regard, it has been suggested that trials should adopt an agreed set of core outcomes for each medical condition to enable generation of information that is relevant and trustworthy for patients, and to enable decisions that improve patient-important outcomes (Basch 2012; Clarke 2007; Selby 2012). The meta-analysis assessing the effect of interventions on death from any cause included participants with different characteristics, i.e. children with malaria and people with a traumatic injury (Dhabangi 2013; Schulman 2002). In the future when more studies are included in this review, the review will include data from people with additional different characteristics which will make the results more relevant across all populations.

Quality of the evidence

GRADE assessments were conducted on the pre-specified outcomes. None of the trials were graded as providing strong evidence because of small sample size, lack of measurement of important clinical outcomes in the included trials (reporting bias), high risk of selection bias, or bias in the presentation of data, sample bias or design bias. Our assessment of the risk of bias of the included studies has been described previously and is summarised in the Risk of bias in included studies table and Figure 2 and Figure 3. See Summary of findings for the main comparison for the complete rationale for the ratings.

Potential biases in the review process

Systematic reviews are predisposed to have a 'significance-chasing bias' (Ioannidis 2010). This includes publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias (Ioannidis 2010). We tried to reduce the risk of such biases affecting the results of this review by completing a thorough search for studies. Selective outcome reporting bias operates through suppression of information on specific outcomes and has similarities to publication bias, in that 'negative' results remain unpublished (Ioannidis 2010). This review found that one out of the three included trials has high risk of selective outcome reporting (Walsh 2004), because it only reported physiological measurements.

Agreements and disagreements with other studies or reviews

Despite differences in the methodology, this review has the same findings as Frenzel 2009 who pointed out the uncertainty about the true clinical impact of the role of prolonged storage of red blood cells on the microcirculation and tissue oxygenation in critically ill patients. In addition, Yap 2008 suggested that age of transfused red cells is not associated with early mortality and morbidity after cardiac surgery. Furthermore, this systematic review has addressed the queries on need to assess the methodological quality of trials and the duration of storage of red blood cells for transfusion in any clinical setting. The debate on whether transfusion of 'older' blood is as beneficial as transfusion of 'fresher' blood, as described by Glynn 2010, continues.

AUTHORS' CONCLUSIONS

Implications for practice

Recognising the limitations of the review, relating to the size and nature of the included trials, this Cochrane Review provides no

evidence to support or reject the use packed red blood cells stored for more or less than 21 days. These results are based on three small single centre trials at high risk of bias. There is insufficient evidence to determine the effects of 'fresher' or 'older' packed red blood cells for blood transfusion. Therefore, we urge readers to interpret the trial results with caution. The results from four large ongoing trials will help to inform future versions of this review.

Implications for research

Currently, four larger trials are being conducted in different clinical settings to assess the impact of prolonged storage of packed red blood cells for blood transfusion (ACTRN12612000453886; ISRCTN08118744; NCT00458783; NTR2662). These trials will contribute substantially to our understanding of the effects of these different approaches to transfusion. Any further studies should be well-designed, high-quality randomised trials which explicitly define 'short' and 'long' storage periods, and measure patient-important outcomes such as mortality from any cause, transfusion-related acute lung injury, postoperative infections, coagulopathy, post-injury coagulopathy, multiple organ failure post-injury and harms outcomes (hyperkalaemia and metabolic acidosis) as recommends the Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI) (Basch 2012; Cohen 2013). The results of these ongoing trials could change the conclusions of this Cochrane Review.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to the Cochrane Injuries Group's editors, and peer reviewers, for their comments, which have improved the quality of this systematic review.

This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

9.2. Anexo 2. Estrategias de búsqueda del primer artículo

Cochrane Injuries Group Specialised Register

"blood transfusion" AND (leuk* OR leuc* OR plasmapheresis OR cytapheres OR apheresis)

Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library)

#1MeSH descriptor Blood Component Removal explode all trees
#2MeSH descriptor Leukocyte Reduction Procedures explode all trees
#3MeSH descriptor Cytapheresis explode all trees
#4(plasmapheresis or cytapheres* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis) #5(Leukoreduc* or leukodeplet* or leukofilt* or leukocyte-reduc* or leucoreduc* or leucodeplet* or leucofilt* or desleucotizat*) #6buffy coat-depleted
#7leukocyte count or leukocyte free or leucocyte count or leucocyte free
#8((Blood or white blood cell* or WBC or plasma) NEAR/3 (reduc* or deplet* or replete* or remov* or filtrat* or filter* or cytapheresis)) #9((leukocyte* or leucocyte*) NEAR/3 (reduc* or deplet* or replete* or remov* or filtrat* or filter*))
#10(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11MeSH descriptor Blood Transfusion explode all trees
#12((allogenic or allogeneic) NEAR/3 blood transfusion*)
#13(blood component* NEAR/3 transfusion*)
#14((erythrocyte* or leukocyte* or platelet* or CONCENTRADOS DE GLÓBULOS ROJOS or red blood cell* or WBC or white blood cell* or thrombocyte* or blood) NEAR/ 3 Transfusion*)
#15(#11 OR #12 OR #13 OR #14)
#16(#10 AND #15)

Medline (OvidSP)

1.exp Blood Component Removal/
2.exp Leukocyte Reduction Procedures/
3.exp cytapheresis/
4.(plasmapheresis or cytapheres* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucaphere- sis).ab,ti.

5.(Leukoreduc* or leukodeplet* or leukofilt* or leukocyte-reduc* or leucoreduc* or leucodeplet* or leucofilt* or desleucotizat*).mp. 6.buffy coat-depleted.ab,ti.
7.(leukocyte count or leukocyte free or leucocyte count or leucocyte free).ab,ti.
8.((Blood or white blood cell* or WBC or plasma) adj3 (reduc* or deplet* or replete* or remov* or filtrat* or filter* or cytapheresis)).ab,ti. 9.((leukocyte* or leucocyte*) adj3 (reduc* or deplet* or replete* or remov* or filtrat* or filter*)).ab,ti.
10.or/1-9
11.exp Blood Transfusion/
12.((allogenic or allogeneic) adj3 blood transfusion*).ab,ti.
13.(blood component* adj3 transfusion*).ab,ti.
14.((erythrocyte* or leukocyte* or platelet* or package red blood cells or red blood cell* or WBC or white blood cell* or thrombocyte* or blood) adj3 Transfusion*).ab,ti.
15.or/11-14
16.10 and 15
17.randomi?ed.ab,ti.
18.randomized controlled trial.pt.
19.controlled clinical trial.pt.
20.placebo.ab.
21.clinical trials as topic.sh.
22.randomly.ab.
23.trial.ti.

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24.17 or 18 or 19 or 20 or 21 or 22 or 23 25.(animals not (humans and animals)).sh. 26.24 not 25
27.26 and 16

Embase + Embase Classic (OvidSP)
1. exp Blood Component Removal/
2. exp Leukocyte Reduction Procedures/
3. exp cytapheresis/

4. (plasmapheresis or cytapheres* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucaphere- sis).ti,ab.
5. (Leukoreduc* or leukodeplet* or leukofilt* or leukocyte-reduc* or leucoreduc* or leucodeplet* or leucofilt* or desleucotizat*).ti,ab. 6. buffy coat-depleted.ti,ab.
7. (leukocyte count or leukocyte free or leucocyte count or leucocyte free).ti,ab.
8. ((Blood or white blood cell* or WBC or plasma) adj3 (reduc* or deplet* or replete* or remov* or filtrat* or filter* or cytapheresis)).ti,ab. 9. ((leukocyte* or leucocyte*) adj3 (reduc* or deplet* or replete* or remov* or filtrat* or filter*)).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp blood transfusion/
12. ((allogenic or allogeneic) adj3 blood transfusion*).ti,ab.
13. (blood component* adj3 transfusion*).ti,ab.
14. ((erythrocyte* or leukocyte* or platelet* or package red blood cells or red blood cell* or WBC or white blood cell* or thrombocyte* or blood) adj3 Transfusion*).ti,ab.
15. 11 or 12 or 13 or 14
16. 10 and 15
17. exp Randomized Controlled Trial/
18. exp controlled clinical trial/
19. placebo.ab.
20. randomi?ed.ti,ab.
21. *Clinical Trial/
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animal/ not (exp human/ and exp animal/)
26. 24 not 25
27. 16 and 26

CINAHL Plus (EBSCO)

S1 (MH “Blood Component Removal+”)
S2 (MH “Cytapheresis+”)
S3 TX plasmapheresis or cytapheres* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis S4 TX

Leukoreduc* or leukodeplet* or leukofilt* or leukocyte-reduc* or leucoreduc* or leucodeplet* or leucofilt* or desleucotizat

S5 TX buffy coat-depleted

S6 TX leukocyte count or leukocyte free or leucocyte count or leucocyte free

S7 TX (Blood or white blood cell* or WBC or plasma) N3 (reduc* or deplet* or replete* or remov* or filtrat* or filter* or cytapheresis) S8 TX (leukocyte* or leucocyte*) N3 (reduc* or deplet* or replete* or remov* or filtrat* or filter*)

S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

S10(MH “Blood Transfusion+”)

S11 TX (allogenic or allogeneic) N3 blood transfusion*

S12 TX blood component* N3 transfusion*

S13 TX (erythrocyte* or leukocyte* or platelet* or package red blood cells or red blood cell* or WBC or white blood cell* or thrombocyte* or blood) N3 Transfusion*

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S14 S10 or S11 or S12 or S13 S15 S9 and S14

S16 (MH “Clinical Trials”) S17 PT clinical trial*

S18 TX clinical N3 trial*

S19 TI ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*) or (tripl* N3 blind*)) or TI ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*)) or AB ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*)) or AB ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*))

S20 TX randomi?ed N3 control* N3 trial*

S21 (MH “Placebos”)

S22 TX placebo*

S23(MH “Random Assignment”)

S24 TX random* N3 allocat* -

S25 MH quantitative studies -

S26 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 -

S27 S15 and S26 Limiters - Exclude MEDLINE records

LILACS

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) AND (Medicina Transfusional or la transfusión or As transfusões or blood transfusion or Transfusión Sanguínea)

Clinicaltrials.gov

(leuk* OR leuc* OR plasmapheresis OR cytapheres OR apheresis) [DISEASE] AND transfusion [TREATMENT]

WHO Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/)

Condition: leuk* OR leuc* OR plasmapheresis OR cytapheres OR apheresis
Recruitment status: ALL