Systematic Review

Ways To Enhance Blood Transfusion Safety: A Systematic Review

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Abstract

AIM: Blood product administration is a vital and possibly life-threatening issue that may increase the risk of clinical damage in patients. This review aims to provide a comprehensive review of the ways to improve blood transfusion safety.

METHOD: In order to conduct this systematic review, electronic databases, including PubMed/MEDLINE, EMBASE, Web of Science, Cochrane CENTRAL, Scopus, and Google Scholar, were searched for data of the last 30 years using keywords including patient safety, blood transfusion, risk management, safety management, and transfusion reaction. The inclusion criteria set for the selection of quantitative articles were articles written in English and published in peer-reviewed journals during the mentioned period. In this study the publications are reviewed in line with the PRISMA guide checklist.

RESULTS: Among 6105 articles found during the initial search, 16 articles were finalized for further investigation. Fifty percent of the included articles discussed the use of modern technology including patient identification system, barcode technology, portable computer systems, and databases. Moreover, 31% of the studies evaluated the use of alternative methods for transfusion of blood products including mediastinal blood transfusion, the use of autologous blood in adult patients, the use of cord blood in children, the use of hemoglobin-based oxygen carrier-201, and the injection of fresh whole blood. About 18% of articles drew attention to indications and thresholds as an essential factor increasing patient safety.

CONCLUSION: It was concluded from this study that the use of technology leads to fewer human errors and complications caused by these errors. In addition, some alternative methods can be used in a cost-effective way to reduce serious adverse events caused by common strategies.

Keywords: Blood transfusion, patient safety, systematic review

Introduction

Blood product administration is an important and vital issue for most patients. However, it can be life threatening and may increase the risk of clinical damage in patients. Blood transfusion is continuously monitored by the hospital administration and accredited by the government and professional health organizations (McQuilten et al., 2018). However, blood transfusions have always been a point of concern for blood recipients and healthcare providers. Transfusion of blood products in the intensive care unit (ICU) is common. Scientists estimated that 15% to 53% of critically ill patients receive transfusions during their critical care stay. Blood transfusion in the ICU is primarily done to increase the oxygen-carrying capacity that has been reduced by anemia (Kashefi et al., 2018; Pirenne & Yazdanbakhsh, 2018; Tsai & Tarn, 2019). Although blood transfusion is a common procedure in the ICU, it is not without complication in the general wards (Bagwe et al., 2017; Moncharmont et al., 2019; Shamshirian et al., 2020; Sharif et al., 2020). Blood transfusion and the occurrence of complications induced by it are also common in the general wards of the hospitals and are not limited to ICUs (Moncharmont et al., 2019; Sharif et al., 2020). The etiology of anemia in the ICU is multifactorial and may be associated with blood loss due to trauma, surgery, hemorrhage, iatrogenic disease, nutritional deficiencies of iron, folate, or vitamin B, cell hemolysis, coagulopathies, and erythropoietin deficiencies (Kashefi et al., 2018; Koch et al., 2013; Piccin et al., 2020).

Blood transfusion is considered a necessary but dangerous treatment method. If the proper protocols and measures are not followed before, during, and after the transfusion, the reactions can be fatal (Raval et al., 2020). Blood transfusion is common in both ICU and general wards. Although blood transfusion might lead to fewer complications in the ICU compared to general wards, it still may induce complications affecting patient safety. Recently, scientists analyzed 125 data sets representing 25 different countries included in the International Hemovigilance Network Database and determined the rate...
of adverse reactions induced by blood transfusion. According to this estimation, out of 660 transfusion-adverse events per 100,000 individuals, nearly 3% of them were classified as severe (Bennett et al., 2017; Silvergleid et al., 2018).

Transfusion-related complications can be broadly categorized as acute or delayed reactions based on time of occurrence, and can be further divided into two categories of noninfectious and infectious complications. Acute complications happen within minutes to 24 hours following the transfusion, while delayed complications may occur days, months, or even years after the blood transfusion (Park et al., 2008). The American Association of Blood Banks (AABB) uses the term “non-infectious serious hazards of transfusion” to categorize noninfectious complications. Transfusion-related infections are less common because of advances in the blood screening process, so that the risk of contracting an infection from transfusion has decreased 10,000-fold since the 1980s (Machado et al., 2019). According to previous studies, blood transfusion-related mortality was 0.26 deaths per 100,000, and nearly 60% of deaths were caused by transfusion-associated circulatory overload (TACO), transfusion-related lung injury (TRALI), and transfusion-associated dyspnea (TAD) (Bennett et al., 2017; Silvergleid et al., 2018). Although the rates of complications and mortality induced by blood transfusion are considerable, these complications can be prevented since many of them are related to the process of transfusion (Raval et al., 2020).

Noninfectious serious hazards of transfusion are up to 1000 times more likely than infectious hazards (Sharma et al., 2011). Despite improvements in blood screening tests and other related medical advances, there has been no progress in preventing serious noninfectious hazards of transfusion (Azizi et al., 2014). Therefore, patients are far more likely to experience a serious noninfectious hazard of transfusion than an infectious complication (Sharma et al., 2011). In a retrospective study done from 2010 to 2012, adverse effects of blood transfusion were only seen in 34 out of 9183 transfused blood products (0.4%). In the aforementioned study, the most common adverse effects were discomfort and restlessness (0.16%), dyspnea (0.16%), rigors (0.13%), fever (0.08%), chest pain (0.06%), and rash or urticaria (0.04%) (Azizi et al., 2014). Despite the increase in blood transfusion safety measures, some acute complications still occur in patients during and after blood transfusions. The type, severity, and degree of the disease, gender, blood group type, genetics, and immune system status are among the factors that challenge patient safety during and after transfusion (Delaney et al., 2016). It is noteworthy that despite the significant complications of blood transfusions, a comprehensive study has not yet been conducted on the complications after blood transfusions and on the measures that should be taken to prevent these complications. A systematic review on this matter can help healthcare providers be aware of blood transfusion complications and their effects on patients. It may also help discover new guidelines and policies on blood transfusion and patient safety. Therefore, this study was conducted to provide a comprehensive review of ways to improve the safety of blood transfusion.

Research Question
1. What are the ways to increase patient safety and reduce blood transfusion-induced complications?

Method

Study Design
This systematic review was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Data were collected using a checklist and methodology flowchart and then were analyzed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009).

Search Strategy
Study data in the electronic databases, including PubMed/MEDLINE, EMBASE, Web of Science, Cochrane CENTRAL, Scopus, and Google Scholar, from the last 30 years were systematically searched using the following keywords: patient safety, blood transfusion, risk management, safety management, and transfusion reaction. The reference lists of the extracted studies were also screened to check for additional eligible studies. An example of the search strategy in PubMed, based on MeSH terms, is given in the following (Table 1).

("Patient Safety"[Mesh]) AND "Blood Transfusion"[Mesh]

(patient safety [Title/Abstract]) AND (blood transfusion [Title/Abstract])

The inclusion criteria for the selection of quantitative articles were that the articles were written in English and published in peer-reviewed journals, and published during the last 30 years. All quantitative studies were reviewed. The inclusion criteria for randomized controlled trials (RCTs) and non-randomized studies (NRSSs) were based on the PICO (Participant, Intervention, Comparison, Outcome) framework:

P: All patients who have undergone blood transfusion

I: Interventions that are related to different aspects of patient safety in the blood transfusion from pre to post-transfusion

C Usual care or different interventions

O Transfusion outcome, such as reducing medical errors

Non-English language studies, duplicate publications, and those that were not related to the aim of the study were excluded. Studies whose full text was not accessible were also excluded.

Study Selection
According to the inclusion criteria defined for this study, two of the reviewers (N.H.M and J.N) independently reviewed the title and abstract of all articles retrieved from databases. Then, the full text of those articles that potentially met these criteria was reviewed and screened. Any disagreements between researchers (N.H.M and J.N) were resolved by the senior researcher.
A total of 6105 articles were found in the initial search. After removing duplications, 4148 articles were also excluded due to their irrelevance to the aim of the study. In the next step, the full text of 334 articles was carefully reviewed according to the inclusion and exclusion criteria. Eventually, 16 articles underwent further evaluation. The data extracted from these finalized articles are shown in Table 2.

### Study Characteristics

The details of the characteristics of included studies are given in Table 2. The studies differed with regard to geographical location and their design. Six articles were published in the United States, and in other countries such as the United Kingdom (Davies et al., 2006), India (Gupta & Gupta, 2016), Spain (Uriz et al., 2011), Italy (Bennardello et al., 2009), Australia (Miller et al., 2013), the Netherlands (de Gast-Bakker et al., 2013), Afghanistan (Auten et al., 2015), Austria (Amato et al., 2017), Kenya (Hassall et al., 2015), and China (Liu et al., 2015), one study each. The design of these articles was different and included RCT (n = 3) (de Gast-Bakker et al., 2013; Jahr et al., 2008; Liu et al., 2015), cross-sectional (n = 2) (Bennardello et al., 2009; Harm et al., 2014), prospective and retrospective cohort (n = 6) (Amato et al., 2017; Auten et al., 2015; Deleon et al., 2016; Gupta & Gupta, 2016; Rheel et al., 2015; Uriz et al., 2011), and quasi-experimental designs (n = 5) (Body et al., 1999; Davies et al., 2006; Hassall et al., 2015; Miller et al., 2013; Whitehurst et al., 2012). The total sample size of each study varied from 150 to 3491 patients.

Out of 16 studies, one was on enhancement of the event-reporting system (Whitehurst et al., 2012); six were on the use of computerized methodologies for improving patient safety during the blood transfusion process (Bennardello et al., 2009; Davies et al., 2006; Gupta & Gupta, 2016; Harm et al., 2014; Miller et al., 2013; Uriz et al., 2011); and three were on allogenic (Hassall et al., 2015) and autologous (Body et al., 1999; Rheel et al., 2015) blood transfusions. The remaining studies (n = 6) implemented different interventions for improving transfusion safety, such as the platelet pathogen inactivation (Amato et al., 2017), restrictive transfusion (de Gast-Bakker et al., 2013; Deleon et al., 2016), the Peri-operative Transfusion Trigger Score of Emergency (Potts-E) (Liu et al., 2015), and the...
hemoglobin-based oxygen carrier-201 (HBOC-201) as an alternative method to safely reduce and/or eliminate perioperative transfusion and ultimately the early use of fresh, whole blood in a resource-limited setting (Auten et al., 2015).

Among the included articles, 50% (8 out of 16) discussed the use of modern methods and yielded that the use of technology leads to increased immunity in transfusions of blood products. Among these articles, three studies set up and used databases and electronic systems to report errors and complications, evaluate quality indicators, and record patients’ serology test results (Gupta & Gupta, 2016; Harm et al., 2014; Whitehurst et al., 2012). In addition, four studies examined the use of modern devices to match patient information accurately, including the patient identification system based on biometric data, barcode technology, and portable computer systems.

It is noteworthy that one study used modern technology to inactivate pathogens in blood products (Amato et al., 2017).

Moreover, approximately 31% of the studies (5 out of 16) evaluated the use of alternative methods for transfusion of blood products and examined patient safety during the use of these methods. These methods included mediastinal blood transfusion, the use of autologous blood in adult patients, the use of cord blood in children, the use of HBOC-201, and the injection of fresh whole blood (Auten et al., 2015; Body et al., 1999; Hassall et al., 2015; Jahr et al., 2008; Rhee et al., 2015).

In addition, about 18% of articles (3 out of 16) considered attention to indications and thresholds as an important factor increasing patient safety. In these studies, hemoglobin level was considered as an indicator to decide on the transfusion time of blood products (de Gast-Bakker et al., 2013; Deleon et al., 2016; Liu et al., 2015).

Bias Assessment Results
In this systematic review, the study design of three studies was RCT. The overall risk of bias in one of them (33.33%) was judged as being of some concern and in two (66.67%) as being high risk. The details on the assessment of these studies are given in Table 3.

Discussion
This systematic review aimed to present factors reducing patient safety during blood transfusion and ways of improving patient safety. For this purpose, electronic databases, including PubMed/MEDLINE, EMBASE, Web of Science, Cochrane CENTRAL, Scopus, and Google Scholar, were systematically searched from 1990 to the end of 2020 using the following keywords: patient safety, blood transfusion, risk management, safety management, and transfusion reaction. Half of the retrieved studies focused on using technology to improve safety in blood transfusion (Amato et al., 2017; Bennardello et al., 2009; Davies et al., 2006; Gupta & Gupta, 2016; Harm et al., 2014; Miller et al., 2013; Uriz et al., 2011; Whitehurst et al., 2012). One of the main risk factors mentioned in these studies
Table 2. Categories of Transfusion Safety Interventions and Their Impact

| First Author/Year        | Country  | Design                  | Objective                                                                 | Duration   | Population/Sample | Intervention                                      | Comparison                           | Findings                                                                                                                                                                                                 | Outcome                                                                                                                                                                                                 |
|--------------------------|----------|-------------------------|---------------------------------------------------------------------------|------------|------------------|---------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Whitehurst/2012          | USA      | Quasi-experimental      | To address the problem of unstructured or ambiguous voluntarily reported adverse-event data. | 2008–2011  | Monthly average report rates and completion times | Design of the enhanced SRS patient portal       | Before and after implementation of SRS | The monthly average number of inpatient transfusion SRS reports was statistically different from post-implementation, decreasing from 102.1 ± 14.3 to 91.6 ± 11.2 (p < .001) | Standardization of patient safety data can enhance adverse event reporting, aggregation, and analysis |
| (Whitehurst et al., 2012) |          |                         |                                                                           |            |                  |                                                    |                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                         |
| Anshu Gupta/2016         | India    | Two-year retrospective study | To study the usefulness of monitoring of the National Accreditation Board for Hospitals and Healthcare Providers (NABH) core indicators in blood transfusion and in the maintenance of hemovigilance. | 2011–2012  | Four core indicators in a blood storage unit of a National Accreditation Board for Hospitals and Healthcare Providers | Monitoring of NABH core indicators                   | -                      | The mean usage of blood and blood products was low (85.41%) in the year 2011 as compared to that in the year 2012 (97.38%). In the year 2011, the mean wastage was 14.58%. The number of transfusion reactions was nil. 99.5% of the total blood transfusions were satisfactory. | Monitoring of NABH core indicators results in the enhancement of quality and safety in blood transfusion services, reducing the incidence of transfusion reactions |
| (Gupta & Gupta, 2016)    |          |                         |                                                                           |            |                  |                                                    |                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                         |
| Sarah K. Harm/2014       | USA      | Cross-sectional         | To evaluate the utility of a centralized transfusion service model in preventing the transfusion of incompatible units in patients with sickle cell disease (SCD). | Over 20 years | 150 patients with SCD | Centralized Recipient Database                    | -                      | 66 (44.0%) of 150 were alloimmunized. In 42 (63.6%) of these patients, 1 or more antibodies evanesced. Of the patients with evanesced antibodies, 28.6% received transfusions at various non-index hospitals 20 or more times after the antibody evanesced. | A centralized database can help identify patients with SCD who have evanesced alloantibodies and prevent issuing incompatible RBC units. |
| (Harm et al., 2014)      |          |                         |                                                                           |            |                  |                                                    |                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                         |
| Francesco Bennardello/2009 | Italy   | Cross-sectional         | To identify patients who are candidates for the transfusion of blood components and to guarantee the traceability of the transfusion, the Securblood system (BBS srl) was introduced. | 2007–2008  | 7282 blood components transfusion | The Securblood system                             | -                      | Overall, 1777 patients were transfused. In this year of experience, no transfusion errors were recorded and each blood component was transfused to the right patient. We recorded 33 blocks of the terminals (involving 0.6% of the transfused blood components) which required the intervention of staff from the Service of Immunohematology and Transfusion Medicine (SIMT). Most of the blocks were due to procedural errors. | The Securblood system guarantees complete traceability of the transfusion process outside the SIMT and eliminates the possibility of mistaken identification of patients or blood components |
| (Bennardello et al., 2009) |          |                         |                                                                           |            |                  |                                                    |                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                         |

(Continued)
### Table 2. Categories of Transfusion Safety Interventions and Their Impact (Continued)

| First Author/Year          | Country | Design                          | Objective                                                                 | Duration | Population/Sample | Intervention | Comparison | Findings                                                                 | Outcome                                                                 |
|-----------------------------|---------|---------------------------------|---------------------------------------------------------------------------|----------|-------------------|--------------|------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Body Simon C/1999           | USA     | Quasi-experimental              | To examine the efficacy and safety of shed mediastinal blood (SMB)         | 1991–1993| 617 patients      | SMB transfusion | No SMB     | Patients transfused with SMB had significantly lower volumes of RBC      | SMB is ineffective as a blood conservation method and may be associated    |
| (Body et al., 1999)         |         |                                 | transfusion in preventing allogenic red blood cell (RBC) transfusion.      |          |                   |              |            | transfusion than those not receiving SMB (0.86 ± 1.50 vs. 1.08 ± 1.65 units; p < .05). However, multivariable analysis showed that SMB transfusion was not predictive of postoperative RBC transfusion. In patients who did not receive allogenic RBC transfusion, there was a significantly greater frequency of wound infection in the SMB group (3.6% vs. 0%; p = .02). | with a greater frequency of wound infection | 02 |
| Amanda Davies/2006          | UK      | Quasi-experimental              | To extend the evaluation of an electronic system involving bar code technology and handheld computers. | -        | 50 sample collections | Bar code technology | Before vs after implementation of bar code technology | Significant improvements were found following the introduction of the electronic system, including from 8% to 100% in checking that the blood group and unit number on the blood pack matched the compatibility label and the pack was in date (p ≤ .0001). Similar significant improvements were found in blood sample collection, the collection of blood from blood refrigerators, and the documentation of transfusion. Staff found the system easy to operate and preferred it to standard procedures. | A bar code patient identification system improved transfusion practice, although areas for improvement were identified | ≤ .0001 |
| (Davies et al., 2006)       |         |                                 |                                                                          |          |                   |              |            |                                                                          |                                                                          |
| Uríz María Jose/2011        | Spain   | Retrospective study             | To assess adequacy of transfusion traceability and compliance with proper identification procedures after introducing an electronic identification system (EIS) for transfusion safety. | 2002–2005| 11,000 blood components | New portable computerized system (EIS) | Before vs after EIS | Only 48% of the medical records were free of inaccuracies. After the implementation of the EIS (2005–2008), traceability was always above 99%. Percentage of monthly compliance from 2006 to 2008 was always above 93%, showing a significant trend to increase (p < .05). The mean compliance in this period was higher in the Transfusion Service (97.8 ± 0.7 SD) than in the ward (94.9 ± 2.4 SD, p < .001). Compliance in the ward was lowest when the system was first implemented (87.9% in April 2006) after which it progressively increased. No errors in ABO transfusions were registered. | After implementation of the EIS, traceability and compliance reached very high levels, linked to an improvement in transfusion safety. | < .001 |
| (Uríz et al., 2011)         |         |                                 |                                                                          |          |                   |              |            |                                                                          |                                                                          |
| Rhee, P/2015                | USA     | Multi-institutional retrospective study | To assess outcomes in trauma patients receiving whole blood autotransfusion (AT) from hemothorax. | 2007–2012| 272 patients      | AT           | No-AT      | Patients who received AT had significantly lower packed red blood cell (p = .01) and platelet requirements (p = .01). Cost of transfusions (p = .01) was significantly lower in the AT group compared with the No-AT group. | The autologous transfusion of the patient’s shed blood collected through chest tubes for hemothorax was found to be safe without complications | = .01 |
| (Rhee et al., 2015)         |         |                                 |                                                                          |          |                   |              |            |                                                                          |                                                                          |
Table 2.
Categories of Transfusion Safety Interventions and Their Impact (Continued)

| First Author/Year | Country | Design | Objective | Duration | Population/Sample | Intervention | Comparison | Findings | Outcome | p |
|-------------------|---------|--------|-----------|----------|-------------------|--------------|------------|----------|---------|---|
| Dehghan Nayeri et al. | Transfusion Safety | | | | | | | | | |
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## Table 2. Categories of Transfusion Safety Interventions and Their Impact (Continued)

| First Author/Year | Country   | Design                  | Objective                                                                 | Duration     | Population/Sample | Intervention                                      | Comparison                           | Findings                                                                                     | Outcome                                                                                     |
|-------------------|-----------|-------------------------|---------------------------------------------------------------------------|--------------|-------------------|-------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Miller, k/2013    | Australia | Quasi-experimental      | To establish whether the use of two-dimensional (2D) barcode technology combined with patient identification software designed to assist in blood administration improves the bedside administration of transfusions. | 2006–2011    | 60 transfusion episodes | 2D barcode and patient safety-software          | Infants aged ≤3 months vs Infants aged >3 months | There was significant improvement in administration practice. Positive, verbal patient identification improved from 57% (51/90) to 94% (79/80). Similarly, the cross-referencing of the patient’s identification with the patient’s wristband improved from 36% (32/90) to 94% (79/80), and the cross-referencing of patient ID on the compatibility tag to wristbands improved from 48% (43/90) to 99% (79/80). Importantly, the 2D barcode technology and patient safety-software saw 100% (80/80) of checks being conducted at the patient bedside, compared with 76% (68/90) in the preimplementation audits. | 2D barcode technology and patient safety-software significantly improves the bedside check of patient and blood product identification in an Australian setting |
| De-Xing Liu/2015  | China     | RCT                     | To evaluate whether the scheme can be used safely and effectively for emergency patients. | 2013–2014    | 72 patients       | Peri-operative Transfusion Trigger Score of Emergency group | Before vs after the technology’s implementation | There were no statistical differences in utilization rates of autologous blood of the two groups; the utilization rates of allogeneic RBC, total allogeneic RBC and total RBC were 48.48%, 51.5%, and 75.7% in POTTS-E group, which were lower than those of the control group (84.3%, 84.3%, and 96.8%) p < .05 or p < .01. Per capita consumption of intraoperative allogeneic RBC, total allogeneic RBC and total RBC were 0 (0, 3.0), 2.0 (0, 4.0), and 3.1 (0.8, 6.0) in POTTS-E groups were all lower than those of control group (4.0 [2.0, 4.0], 4.0 [2.0, 6.0] and 5.8 [2.7, 8.2]), p < .05 or p < .001. | POTTS-E scores scheme is safe, reasonable, and practicable and has the value for carrying out multicenter and large sample clinical researches |
| Gast-Bakker/2013  | Netherlands | RCT         | To investigate the safety and effects of a restrictive red blood cell (RBC) transfusion strategy in pediatric cardiac surgery patients. | 2009–2012    | 107 patients      | restrictive transfusion                          | Control group                        | In the restrictive transfusion group, mean volume of transfused RBC was 186 (±70) mL per patient and in the liberal transfusion group 258 (±87) mL per patient, (95% CI 40.6–104.6), p < .001. Length of hospital stay was shorter in patients with a restrictive RBC transfusion strategy: median 8 (IQR 7–11) vs. 9 (IQR 7–14) days, p = .047. All other outcome measures and incidence of adverse effects were equal in both RBC transfusion groups. Cost of blood products for the liberal transfusion group was 438.35 (±203.39) vs. 316.27 (±189.96) euros (95% CI 46.61-197.51) per patient in the restrictive transfusion group, p = .002. | restrictive RBC transfusion policy (threshold of Hb 8.0 g/dL) during the entire perioperative period is safe, leads to a shorter hospital stay and is less expensive |

(Continued)
### Categories of Transfusion Safety Interventions and Their Impact (Continued)

| First Author/Year | Country       | Design              | Objective                                                                 | Duration | Population/Sample | Intervention          | Comparison     | Findings                                                                                                  | Outcome                                                                 |
|-------------------|---------------|---------------------|---------------------------------------------------------------------------|----------|-------------------|-----------------------|----------------|---------------------------------------------------------------------------|------------------------------------------------------------------------|
| Jahr, Jonathan    | USA           | RCT                 | To study the ability of hemoglobin-based oxygen carrier-201 (HBOC-201) to safely reduce and/or eliminate perioperative transfusion. | 6 weeks  | 693 patients      | HBOC-201              | Hb 10.8 g/dL (6.8 mmol/L) vs Hb | A total of 59.4% of patients in the H arm avoided PRBC transfusion. Adverse events (8.47 vs. 5.88), and serious adverse events (SAEs) (0.36 vs. 0.25) per patient were higher in the H versus R arms (p < .001 and p < .01) with MW = 0.561 (95 CI 0.528–0.594). H+ versus R− had identical (0.14) serious adverse events/patient and a MW = 0.519 (95% confidence limit 0.481–0.556), whereas the incidence was higher (0.63 vs. 0.47) for HR versus R+ with a MW = 0.605 (95% confidence limit 0.550–0.662). Age (>80 years), volume overload and under-treatment contributed to this imbalance | HBOC-201 eliminated transfusion in the majority of subjects. The between arms (H vs. R) safety analysis was unfavorable and likely related to patient age, volume overload, and under-treatment and was isolated to patients that could not be managed by HBOC-201 alone. However, patients <80 years old with moderate clinical need may safely avoid transfusion when treated with up to 10 units of HBOC-201. |
| Auten, Jonathan   | Afghanistan   | A retrospective analysis | To analyze the safety of fresh, whole blood used in a resource-limited setting. | 2010–2012 | 354 battle injuries | early fresh whole-blood transfusion | 8.0 g/dL (5.0 mmol/L). | The group receiving fresh, whole blood was noted to have higher ISSs and lower blood pressure, pH, and base deficits on arrival. Traumatic coagulopathy was significantly less common in the group receiving fresh, whole blood (odds ratio, 0.01; 95% confidence interval, 0.00–0.18). Multivariable models found no other significant differences between the treatment groups. | The early use of fresh, whole blood in a resource-limited setting seems to confer a benefit in reducing traumatic coagulopathy. |

SRS = safety reporting system; NABH = National Accreditation Board of Hospitals and Healthcare Providers; SCD = sickle cell disease; SIMT = service of immunohematology and transfusion medicine; SMB = shed mediastinal blood; PI = pathogen inactivation; PC = platelet concentrates; RCC = red cell concentrates; HBOC = hemoglobin-based oxygen carrier-201; PRBC = packed red blood cell; EIS = electronic identification system; AT = auto transfusion.
was that human errors that significantly reduced blood transfusion safety (Miller et al., 2013; Ugwu et al., 2020; Uríz et al., 2011). The other half of the included studies were on using alternative methods and products, and hemoglobin thresholds, as a transfusion indicator (Auten et al., 2015; Body et al., 1999; de Gast-Bakker et al., 2013; Deleon et al., 2016; Hassall et al., 2015; Jahr et al., 2008; Liu et al., 2015; Rhee et al., 2015).

As demonstrated in Table 2, some of the analyzed studies suggested that using a central database and computer systems could help increase the patient safety and prevent the complications of blood transfusion (Bennardello et al., 2009; Harm et al., 2014). The results of a study by Harm et al. (2014) on the safety of blood transfusion in patients with sickle cell disease showed that using a central database that involved patients’ history and serology test results could help in improving the safety of transfusion and in preventing the onset of delayed hemolytic transfusion reaction in these patients (Harm et al., 2014). Bennardello et al. (2009) suggested that using a “secure blood” system containing patients’ previous transfusion data could prevent ABO blood group errors. One of the key strengths of a secure blood system is identification of patients using their fingerprints or wristband barcodes. In particular, it can be very beneficial in unconscious patients who cannot be identified (Bennardello et al., 2009). In line with the results of this study, Vesga, Miguel A. and Maria Azkarate (2021)(Vesga & Azkárate, 2021) concluded that utilizing modern devices, including computer systems, patient information databases, and wristband barcodes, led to higher safety and efficacy during blood component transfusion.

One of the extracted articles was on pathogen inactivation technology; it assessed the efficacy of this technology for other blood components (Amato et al., 2017). This study illustrated that the technology had no significant effect on transfusion safety. These findings contrast with the results of a review study done by Luca Galli1 et al. who concluded that using pathogen inactivation technology was associated with higher safety in terms of inactivation of most clinically relevant pathogens, reduction of the risk against unknown pathogens, and inactivation of residual lymphocytes in the product (Galli & Bruschi, 2020). Further studies should be conducted in order to support or reject the efficacy of this technology in this regard.

In terms of hemoglobin thresholds and other transfusion indicators, three studies were retrieved. One of them aimed to evaluate whether or not the scheme called “Transfusion Trigger Score of Emergency” could be safely used for the identification of the trigger point of blood transfusion in emergency patients (Liu et al., 2015). It was concluded that this scheme increased the safety of transfusion compared with doctors’ experience-based assessment for starting the RBC transfusion. Two other articles compared the effect of a restrictive and a liberal transfusion strategy on patient safety and health outcomes (de Gast-Bakker et al., 2013; Deleon et al., 2016). Although the hemoglobin thresholds, as a starting point of transfusion (Hb 7.0 g/dL and 10.0 g/dL vs. Hb 10.8 g/dL and 8.0 g/dL), and the study population (adults vs. pediatric) were different in these two studies, both studies revealed that the
restrictive RBC transfusion policy was safer, led to shorter hospital stay, and induced less complications. Contrary to the results of this study, Curley et al. 2014 and Desjardins et al. (2012) yielded that there was no sufficient evidence confirming the best strategy (restrictive or liberal). This discrepancy can be attributed to the differences in the number of included articles, so further systematic reviews are necessary to determine the optimal transfusion strategy.

Considering alternative methods and products, two studies analyzed the transfusion of autologous shed blood collected through the chest tube. In a study by Rhee et al. (2015) it was concluded that transfusion of patient’s shed blood collected through a chest tube was safe, lowered the need for allogeneic transfusions, and decreased the hospital costs. These findings are in contrast with the results of a study by Body et al. (1999) who reported that transfusion of shed mediastinal blood after cardiac surgery was not effective and increased the risk of infection. On the other hand, Rhee et al. (2015) demonstrated that the risk of infection was rare following transfusion of shed mediastinal blood. Further studies might be needed on this matter. In addition to what is mentioned above, there are some other challenges and achievements in patient safety during the transfusion of specific blood products. Jah et al. (2008) studied hemoglobin-based oxygen carrier-201 (HBOC-201) efficiency and its side effects. Their results showed that HBOC-201 had many negative effects on patient safety and was unsafe for transfusion, especially in older patients.

Another alternative method was cord blood transfusion, which was addressed in an article by Hassall et al. (2015). They analyzed the safety and efficacy of allogeneic umbilical cord red blood cell transfusion in children with severe anemia (Hassall et al., 2015).

It was revealed that transfusion of sedimented red blood cells from umbilical cord donations was safe and it was associated with no serious adverse events. Bianchi et al. (2018) published a systematic review, which is in line with the results of this study (Bianchi et al., 2018). They revealed that despite various drawbacks, including cord blood contamination by maternal blood, this practice was safe and could reduce the exposure to allogeneic adult RBCs. Furthermore, the whole-blood transfusion was another recommended method that was analyzed in one of the included articles (Auten et al., 2015). In the aforementioned study, it was demonstrated that early use of fresh whole blood, particularly in a resource-limited setting, was safe and reduced the risk of some complications, such as traumatic coagulopathy. Malkin et al. (2021) conducted a systematic review on this issue. They revealed that administration of fresh whole blood was a safe method and carried significant logistic benefits. Further high-quality studies are suggested in this regard.

**Conclusion and Recommendations**

Different approaches used for enhancing safety of blood transfusion were reviewed. Based on the findings, it can be concluded that human errors regarding blood transfusion can be decreased by using technology and computers. In addition, it also suggested that some alternative blood transfusion methods be used in a cost-effective way, without any serious adverse events. However, high-quality research on these methods is needed. An awareness of these advantages and limitations is recommended for healthcare providers and policymakers while implementing new systems during a vital process like blood component transfusion. Based on the analysis, it is argued that by using technology and computers, we can reduce the human errors and the issues caused by these errors.

More information about this systematic review according to the PRISMA 2020 Checklist is provided in Supplementary Table 1.

**Availability of Data and Materials** All data generated or analyzed during this study are included in this published article.

**Ethics Committee Approval:** This study has been approved by the Ethics Committee of High Institute for Education and Research in Transfusion on May 20, 2020 (MedicineIR.TMI.REC.1399.004).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – N.H.M., N.D.N.; Design – N.H.M., N.D.N.; Supervision – N.D.N.; Data Collection and/or Processing – N.H.M., J.N.; Analysis and/or Interpretation – N.H.M., N.D.N., J.N.; Writing Manuscript – N.H.M., J.N., A.D.; Critical Review – N.H.M., J.N.

**Declaration of Interests:** The authors declare that they have no competing interests.

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| Section and Topic | Item # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Location where item is reported |
|------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| **TITLE**        |       |                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Title            | 1     | Identify the report as a systematic review.                                                                                                                                                                                                                                                                                                   | Page 1                          |
| **ABSTRACT**     |       |                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Abstract         | 2     | See the PRISMA 2020 for Abstracts checklist.                                                                                                                                                                                                                                                                                                  | Page 1                          |
| **INTRODUCTION** |       |                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Rationale        | 3     | Describe the rationale for the review in the context of existing knowledge.                                                                                                                                                                                                                                                                  | Page 2-4                        |
| Objectives       | 4     | Provide an explicit statement of the objective(s) or question(s) the review addresses.                                                                                                                                                                                                                                                         | Page 4                          |
| **METHODS**      |       |                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Eligibility criteria | 5     | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.                                                                                                                                                                                                                                  | Page 4-5                        |
| Information sources | 6     | Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.                                                                                                      | Table 1                         |
| Search strategy  | 7     | Present the full search strategies for all databases, registers, and websites, including any filters and limits used.                                                                                                                                                                                                                          | Table 1                         |
| Selection process| 8     | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                                            | Page 6                          |
| Data collection process | 9     | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.            | Page 6                          |
| Data items       | 10a   | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                                    | Page 7-8                        |
|                  | 10b   | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.                                                                                      | Page 7-8                        |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8                          |
| Effect measures  | 12    | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.                                                                                                                                                   | Table 2                         |
| Synthesis methods| 13a   | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).                                                                                                       | Page 7-8                        |
|                  | 13b   | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.                                                                                                                                                                                             | Page 6-7                        |
|                  | 13c   | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                                                                                                                                                    | Page 6-7                        |
|                  | 13d   | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.                                               | Page 6-7                        |
|                  | 13e   | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).                                                                                                                                                | Page 6-7                        |
|                  | 13f   | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                                                                                                                                               | Page 6-7                        |

(Continued)
| Section and Topic | Item # | Checklist item                                                                                                                                                                                                 | Location where item is reported |
|------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting bias assessment | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                     | Page 8                          |
| Certainty assessment | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                       | Table 3                         |
| **RESULTS**      |        |                                                                                                                                                                                                             |                                 |
| Study selection  | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                 | Page 7–8                        |
|                  | 16b    | Cite studies that might appear to meet the inclusion criteria, but were excluded, and explain why they were excluded.                                                                                         | Page 7–8                        |
| Study characteristics | 17     | Cite each included study and present its characteristics.                                                                                                                                                   | Page 7–8                        |
| Risk of bias in studies | 18     | Present assessments of risk of bias for each included study.                                                                                                                                               | Page 7–8                        |
| Results of individual studies | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Page 7–8                        |
| Results of syntheses | 20a    | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.                                                                                                    | Page 7–8                        |
|                  | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Page 7–8                        |
|                  | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                              | Page 7–8                        |
|                  | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                   | Page 7–8                        |
| Reporting biases | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                      | Page 7–8                        |
| Certainty of evidence | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                          | Page 7–8                        |
| **DISCUSSION**   |        |                                                                                                                                                                                                             |                                 |
| Discussion       | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                             | Page 8–10                       |
|                  | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                             | Page 8–10                       |
|                  | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                       | Page 8–10                       |
|                  | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                              | Page 8–10                       |
| **OTHER INFORMATION** |        |                                                                                                                                                                                                             |                                 |
| Registration and protocol | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.                                                              | Title page                      |
|                  | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.                                                                                                                | Not applicable                   |
|                  | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.                                                                                                               | Not applicable                   |
| Support          | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.                                                                               | Title page                      |
| Competing interests | 26     | Declare any competing interests of review authors.                                                                                                                                                         | Title page                      |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data-collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Title page                      |