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Major clinical findings of blood and blood component transfusion in polytrauma: a systematic review

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Abstract

Introduction: Polytrauma is a well-established cause of death in young people and adults and its burden is a global public concern, with multiple organ failure being the most common cause of mortality. Transfusion medicine is an evolving specialty with transfusion interventions, especially for bleeding patients. The age and sex of the blood component donor can affect post-transfusion results. When analyzing data from 2018, it is estimated that violence and injuries represented 19.5% of all deaths in Brazil. **Objective:** To present, through a systematic review, the main considerations for the transfusion of blood components in polytrauma in intensive care units, considering different types of trauma and previous procedures to reduce the need for massive blood transfusion. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from February to April 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, with articles dated from 2011 to 2024. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 102 articles were found. A total of 37 articles were evaluated and 16 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with a high risk of bias and 30 studies that did not meet GRADE. Most studies showed homogeneity in their results, with I^2 =16.7%<25%. Transfusion of blood components is necessary in the resuscitation of patients with major trauma. However, packaged red blood cells and platelets break down and undergo chemical changes during storage (known as storage injury) that lead to an inflammatory response when the blood components are transfused into patients. Although some evidence supports a detrimental association between transfusion and a patient's outcome, the mechanisms linking transfusion of stored components to outcomes remain unclear. For the most complete care of massive transfusions, it is imperative to review the concepts of volume/perfusion and tissue oxygenation, as well as the difference between the concepts. Still, there appears to be little or no difference in harm between whole blood transfusion therapy and blood component therapy, based on small studies with very low certainty of evidence. The blood component donor's gender, but not age, may be an important factor associated with post-injury multiple organ failure.

Keywords: Polytrauma. Transfusion. Hemocomponents. Survival. Hemostasis. Volume of Derivatives.

Introduction

Polytrauma is a well-established cause of death in young and old adults, and its burden is a global public concern [1]. Traumatic shock and subsequent post-injury multiple organ failure are potentially preventable causes of death among the severely injured, with multiple organ failure being the most common cause of mortality [2-4]. Optimizing blood and blood product transfusion is a focus of trauma care. Transfusion medicine is an evolving specialty with transfusion interventions, especially for hemorrhagic patients [5].

In this context, the age and sex of the blood component (BC) donor may affect posttransfusion

outcomes [6-14]. Blood donor characteristics are a recent focus of transfusion medicine, and improved transfusion-related outcomes are likely to be expected by patients and clinicians [15]. In this sense, external causes of multiple traumas have been estimated to account for numerous public health hospitalizations in Brazil, mainly composed of traffic accidents and homicides [2]. When analyzing data from 2018, it is estimated that violence and injuries accounted for 19.5% of all deaths in Brazil [16]. Despite the extensive human and socioeconomic impact associated with traumatic injuries, previous studies have prospectively identified predictors of mortality across the spectrum of trauma care such as emergency room, operating room, and intensive care unit phases [1,2].

Furthermore, in the United States, trauma is the leading cause of death among people aged 1 to 44 years and the third leading cause of death among others. Approximately 20% to 40% of trauma deaths occur after hospital admission and result from massive hemorrhage [8-10]. Few multicenter or randomized clinical studies confirm the practice of resuscitation with blood products, so there are many conflicting recommendations [11]. In other Western countries, it is the third leading cause of death, after cardiovascular disease and cancer, and in those under 45 years of age, it is the leading cause of death [9].

In this regard, most studies have focused on isolated stages in the spectrum of trauma or on specific types of trauma (e.g., traumatic brain injury, pelvic trauma, and penetrating torso injuries). Other reports have analyzed large databases and prognostic models [2]. However, no studies have evaluated the determinants of mortality across all stages or phases of care at the same time. Calcium is a key component of trauma resuscitation and the coagulation cascade. Recent data have highligBCed the intricate physiological reverberations of hypocalcemia in trauma patients; however, further research is needed to better guide the management of these patients [17].

In this regard, experimental clinical studies have shown that loss of up to 75% of red cell mass can be tolerated, as long as blood volume is maintained. However, volume losses of approximately 30% are fatal [10,11]. Initial attention in patients with hemorrhage should be given to maintaining blood volume and oxygen-carrying capacity. The patient should be clinically assessed to quantify blood loss, which is often difficult in a patient with hemorrhage. This is recommended by ATLS (Advanced Trauma Life Support) [11-13].

In general, there is no need for red blood cell transfusion for patients with acute trauma of Classes I and II, particularly in young patients who can adapt well to anemia due to acute loss, and should receive crystalloid solutions [14]. If more than 40% of the blood volume has been lost (class III and IV) in young patients with critically compromised organic functions, in addition to receiving crystalloid solutions, they need to restore the capacity to carry oxygen [13-17]. The Prospective Observational Multicenter Major Trauma Transfusion Trial demonstrated that physicians were transfusing patients with blood products in a 1:1:1 or 1:1:2 ratio – to plasma, platelets, and packed red blood cells [18-20].

In addition, it has been demonstrated that early plasma and platelet transfusion is associated with improved survival within 6 hours after admission (Holcomb). Among patients with severe trauma and severe hemorrhage, early administration of plasma, platelets, and RBC in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in 24-hour mortality and 30day mortality [21].

Therefore, the present study aims to present, through a systematic review, the main considerations of blood product transfusion in polytrauma in intensive care units, considering different types of trauma and previous procedures to reduce the need for massive blood transfusion.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: BCtp://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 02/24/2024. The methodological quality standards of AMSTAR-2 (Methodological Quality Assessment of Systematic Reviews) were also followed. Available at: BCtps://amstar.ca/. Accessed on: 02/24/2024.

Search Strategy and Search Sources

The literary search process was carried out from February to April 2024 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from 2011 to 2024. The descriptors (Health Sciences Descriptors – DeCS/MeSH Terms) were used: "Polytrauma. Transfusion. Hemocomponents. Survival. Hemostasis. Volume of Derivatives", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of

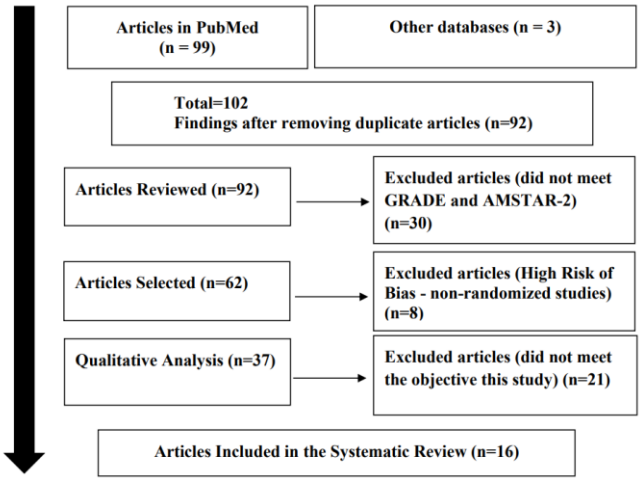
comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results

Summary of Findings

As a corollary of the literature search system, a total of 102 articles were found that were submitted to eligibility analysis and, subsequently, 16 of the 37 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies such as metaanalysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with I^2=16.7%<25%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with a high risk of bias and 30 studies that did not meet GRADE and AMSTAR-2.

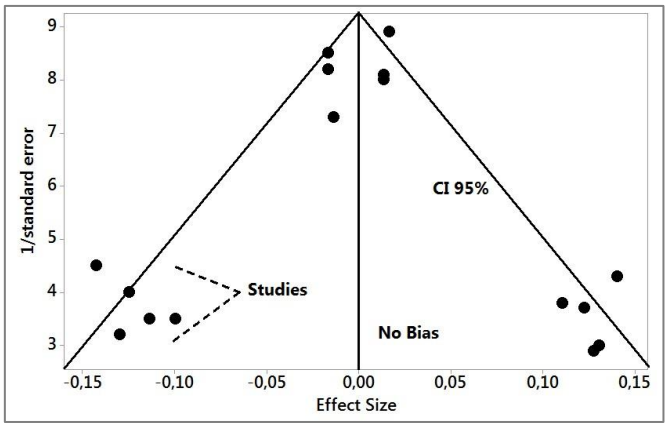
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=16 studies).



Source: Own authorship.

Major Clinical Outcomes

Based on the literature findings, a meta-analysis study by authors Geneen et al., 2022 [22], evaluated whether there is a difference in potential "all-cause" harm outcomes in whole blood transfusion (WBT) compared with blood component therapy (BC) for any bleeding patient, regardless of age or clinical condition. There was no evidence of a difference in mortality of WBT compared with BC. There may be a benefit of WBT therapy compared with BC in the non-trauma subgroup, with a reduction in the duration of oxygen dependence (1 study; n = 60; mean difference 5.9 hours shorter [95% confidence interval [CI] -10.83, -0.99] in the WBT group) and a reduction in hospital stay (1 study, n = 64, median difference 6 days shorter in the WBT group). For the remaining outcomes (organ injury, mechanical ventilation, intensive care unit admission, infection, arterial/venous thrombotic events, and hemolytic transfusion reaction), there was no difference between WBT and BC therapy, although many of these results were based on small, individual studies.

In addition, plasma resuscitation improves hyperfibrinolysis (HF) and trauma-induced coagulopathy (TIC). However, the use of other blood components to reduce TIC has not been evaluated. A study developed by the authors Stettler et al., 2021 [23], determined the effect of individual blood components and WBT in an *in vitro* model of severe TIC. A TIC solution was made with a 1:1 dilution of WBT with saline and exacerbated with

tissue plasminogen activator (tPA). The components were added in proportions equivalent to those for thromboelastographybased (TEG)-guided resuscitation. Whole blood was added in proportions equal to that transfused in injured patients. Samples (n = 9) underwent native citrate TEG and tPA challenge (75 ng/mL) with analysis of R time, angle, MA, and LY30. Statistical analyses were performed with the nonparametric Kruskal-Wallis and Dunn multiple comparisons tests. TIC solution, when compared to control, had a decrease in clot strength (MA 41 mm versus 51.5 mm, p<0.01). The addition of tPA resulted in severe coagulopathy (MA 24.5 mm versus 41 mm and LY30 52.8% versus 2.4%, p<0.03 for all). The addition of 4 U of WB improved clot strength compared to TIC + tPA (p=0.03). No individual blood component resulted in improved fibrinolysis (p>0.7). Cryoprecipitate improved R time (7.5 vs. 11.9 min, P < 0.01), angle (56.8 vs. 30.2°), and MA (49 mm vs. 36.25 mm), while platelets improved MA (44 mm vs. 36.25 mm) compared with TIC + tPA (p < 0.03 for all).

In addition, authors Amico et al, 2021 [24], tested the hypothesis that blood donor demographics are associated with post-injury multiple organ failure (MOF) status of transfused polytrauma patients. A total of 229 severely injured trauma patients with transfusion injuries were included, 68% of whom were male and with a mean age of 45 years. On average, 10 units of blood components were transfused per patient. A total of 4,379 units of blood components were donated by donors with a mean age of 46 years, 74% of whom were male. The blood components used were red blood cells (47%), cryoprecipitate (29%), fresh frozen plasma (24%), and platelets (<1%). Transfusions of red blood cells from mismatched donor-recipient sex were more likely to be associated with MOF (p=0.0012); recipients of fresh frozen plasma and cryoprecipitate were more likely to experience MOF when transfused with a male (vs. female) component (p=0.0014 and <0.0001, respectively). Donor age was not significantly associated with MOF for all blood components. In this regard, transfusion of blood components is necessary in the resuscitation of patients with major trauma. However, packed red blood cells and platelets break down and undergo chemical changes during storage (known as storage injury) that lead to an inflammatory response when blood components are transfused into patients. Although some evidence supports a detrimental association between transfusion and patient outcome, the mechanisms linking transfusion of stored components to outcomes remain unclear. One study analyzed outcomes related to trauma, hemorrhage, and blood product transfusion and grouped them according to those occurring in the short-term (≤30 days) and long-term (>30 days). A thorough understanding of these clinical implications is critical for practitioners in the evaluation and management of patients undergoing transfusion after traumatic injury [7].

Another study was designed to identify early predictors of mortality in severely injured polytrauma patients at all stages of care to better understand the physiological changes and mechanisms to improve care for this population, even when receiving blood component transfusions. A longitudinal, prospective, observational study with 200 patients was conducted between 2010 and 2013 in São Paulo, Brazil. The primary outcome evaluated 30-day mortality. The following independent early predictors of mortality were observed: arterial hemoglobin oxygen saturation, diastolic blood pressure, lactate level, Glasgow Coma Scale, crystalloid volume infused, and presence of traumatic brain injury. The results suggested that arterial oxygen saturation, diastolic blood pressure, lactate level, Glasgow Coma Scale, crystalloid volume infused, and presence of traumatic brain injury are independent predictors of early mortality [8]. Furthermore, a meta-analysis involving 30 studies was recently published on blood transfusion in polytrauma. As a result, less use of packed red blood cell transfusions was observed and fluid resuscitation was also demonstrated. A statistically significant decrease in mortality was observed in the hypotensive resuscitation group. Therefore, the significant benefits of hypotensive resuscitation regarding mortality in patients with traumatic hemorrhagic shock were demonstrated, reducing the need for blood transfusions and multiple organ dysfunction [9].

In addition, the optimal dose, timing, and relationship to red blood cells (RBCs) of blood component therapy (fresh frozen plasma (FFP), platelets, cryoprecipitate, or fibrinogen concentrate) to reduce morbidity and mortality in critically bleeding patients requiring massive transfusion are unknown. A systematic review for randomized controlled trials (RCTs) was performed in MEDLINE, the Cochrane Library, Embase, CINAHL, PubMed, and the Transfusion Evidence Library and using multiple clinical trial registries to 21 February 2017. Sixteen RCTs were identified: six completed (five in adult trauma patients, one in pediatric burns patients) and ten ongoing trials. Of the completed studies: three were feasibility trials, comparing a 1:1:1 FFP, platelet and RBC ratio to laboratory-guided transfusion practice (n = 69), early cryoprecipitate compared to standard practice (n = 41) and fibrinogen concentrate compared to placebo (n = 45); one trial compared the effect of a 1:1:1 FFP, platelet and RBC ratio to 1:1:2 on 24-hour and 30day mortality (n = 680); one compared whole blood to blood

component therapy using 24-hour blood (n = 107); one compared a 1:1 FFP to RBC ratio with a 1:4 ratio (n = 16). Data from two trials were pooled in a meta-analysis for 28-day mortality because the transfusion rates achieved were similar. The results of these two studies suggested that higher transfusion rates were associated with the transfusion of more FFP and platelets, with no evidence of a significant difference in mortality or morbidity. Based on the limited evidence available, there is insufficient basis to recommend a 1:1:1 ratio versus a 1:1:2 ratio or standard of care for adult patients with critical bleeding requiring massive transfusion [10].

Several studies were found in the literature, and among them the following were highligBCed, focusing on blood transfusion (blood component gradient) in polytrauma patients [1–5]. Furthermore, a study showed 720 military personnel with at least one traumatic amputation and a mean age of 24.3 years. Despite the severity of the injury, 94% of patients with traumatic amputation who were alive, with a stage II/III facility, survived transfer to a higher care facility [7]. In this context, transfusion is not without risks, including transfusion reaction, infection, and increased mortality. A hemoglobin level of 7 g/dL is safe in the setting of critical illness, sepsis, gastrointestinal hemorrhage, and trauma. The patient should be evaluated on a clinical basis and not solely using the hemoglobin level [8]. Another study showed that immediate preventive fibrinogen concentrate administered to trauma patients as first-line treatment of trauma hemorrhage can increase clot strength, transfusion requirements, and survival in patients who received hemostatic resuscitation according to the current standard of care [10]. Another study on burns showed the importance of red blood cell transfusions, which may lead to secondary hemochromatosis. Thus, a case was presented describing the acute development of hemochromatosis secondary to multiple transfusions in a burn patient. Therefore, secondary hemochromatosis was unavoidable [11].

It was also shown that most geriatric polytrauma patients with severe pelvic fractures are at high risk of massive transfusion. Blood extravasation on computed tomography reinforces abnormal levels of serum blood markers that help in the early identification of geriatric polytrauma patients at risk of a serious medical outcome [12]. A systematic review study revealed that components that mimic whole blood may produce survival benefits in massively transfused patients after trauma. Twenty-one studies were included in the analysis. Those who received high rates of blood components obtained greater survival benefits [13].

A transfusion study in 24 patients with acute bleeding consisted of an average of 16 to 18 units of red blood cells (ranging from 4,880 mL to 5,220 mL), fresh frozen plasma (980 mL to 1,220 mL); cryoprecipitates (an average of 10 to 15 units, i.e., 500 to 750 mL); and platelet concentrate (approximately an average of 8 to 12 units, i.e., 240 to 360 mL). As a result, the pathophysiological mechanism shown in the available medical literature was confirmed, i.e., after transfusion of a large volume of red blood cell concentrate, dilutional coagulopathy develops, caused by a sharp drop in platelet count and reduced activity of unstable coagulation factors in the patient's circulation [14].

Discussion

According to the literature review, large-volume acute bleeding is a challenge for emergency services [1,2]. In this sense, the need for chemotherapy support has led to the development of even more rational protocols for the monitored use of blood components [15-20]. In shock due to massive blood loss, the impairment of both tissue perfusion and oxygenation is critical, as are the complications resulting from shock and tissue hypoxia, as well as from side effects of therapy [21-23].

Therefore, when there is massive bleeding in an emergency room or surgical center, it is necessary to perform a massive transfusion with a replacement of at least one volume, within an interval of up to 24 hours, or to perform a replacement of 50% of the volume in three hours, or to perform the transfusion of more than 20 units of packed red blood cells [22-29]. It is important to remember that only one-third of the volume of crystalloid administered remains in the intravascular space, the remainder quickly leaks into the interstitial space, therefore, blood loss when replaced with crystalloids should maintain the proportion of 03 volumes of crystalloids for each volume of blood lost [15,29,30].

In addition, variable periods of tissue hypoperfusion determine relevant changes in microcirculation permeability, facilitating distribution to the interstitial space. This is mitigated with solutions that increase intravascular colloid osmotic pressure, using human albumin solutions or plasma expanders (low molecular weight dextrans or starches – hetastarch or pentastarch); the use of these is not free from complications such as interference with hemostasis and anaphylactic reactions [31]. Hematocrit is not a good parameter to guide the decision to transfuse or not to transfuse, as it only begins to decrease one to two hours after the onset of hemorrhage [32-37].

Conclusion

It was concluded that, based on the literature

findings, for a more complete treatment of massive transfusions, a review of the concepts of volume/perfusion and tissue oxygenation is imperative, as well as the differences that exist between the concepts. Furthermore, there appears to be little or no difference in harm between whole blood transfusion therapy and blood component therapy, based on small studies with very low certainty of evidence. Further large studies are needed to establish the overall safety of whole blood transfusion compared to blood component therapy and to assess the differences between trauma and non-trauma patients. The gender of the blood component donor, but not age, may be an important factor associated with post-injury multiple organ failure.

CRediT

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No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

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It was performed.

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