REVIEW ARTICLE / PREGLEDNI ČLANAK

THE USE OF WHOLE BLOOD TRANSFUSION IN EMERGENCY MEDICINE: A NARRATIVE REVIEW

PRIMJENA TRANSFUZIJE PUNE KRVI U HITNOJ MEDICINI: NARATIVNI PREGLED

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Abstract

Whole blood was the first human blood product to be transfused in modern medicine, seeing widespread use during the final months of World War I. With the advent of blood component therapy and the concept of using intravenous crystalloid fluids for initial resuscitation of hemorrhagic shock in trauma, whole blood transfusion had been forgotten as a therapeutic possibility during the larger part of the 20th century. Owing to the successful military use of whole blood in the early 1990s, extending to the early 2000s, whole blood has resurfaced as a lucrative therapeutic option for civilian trauma in the early 2010s, with approximately 25 % of level I trauma centers in the United States using whole blood transfusions in 2020. However, a large part of the developed world is still hesitant on the benefits of using whole blood both in prehospital and in-hospital trauma resuscitations, owing to the relative scarcity of high-quality evidence (especially randomized controlled trials) on its effectiveness and safety when compared to the current standard of care - blood component therapy. With recently published prospective studies demonstrating either noninferiority or marginal superiority of whole blood transfusion to blood component transfusion, interest in the use of whole blood has once again increased. This narrative review aims to present the history, technical aspect and current evidence for the use of whole blood in both the military and civilian trauma settings in a concise, succinct manner and inform the reader on the contexts and situations in which whole blood transfusion might provide the greatest benefit, both logistics and cost-wise and mortality-wise.

Key words: blood; blood transfusion; emergency medicine; emergency medical services; military medicine

Sažetak

Puna krv je bila prvi krvni pripravak koji je korišten za transfuziju u modernoj medicini, a široko se primjenjivala tijekom posljednjih mjeseci Prvog svjetskog rata. S razvojem terapije krvnim komponentama i uvođenjem intravenskih kristaloidnih otopina za početnu reanimaciju hemoragijskog šoka u traumi, transfuzija je pune krvi bila gotovo zaboravljena kao terapijska mogućnost tijekom većeg dijela 20. stoljeća. Zahvaljujući uspješnoj vojnoj primjeni pune krvi od ranih 1990-ih do početka 2000-ih godina, transfuzija pune krvi ponovno je postala terapijska opcija u civilnoj traumatologiji početkom 2010-ih, a oko 25 % trauma centara razine I u Sjedinjenim Američkim Državama koristilo ju je u 2020. godini. Ipak, velik dio razvijenog svijeta i dalje je skeptičan prema prednostima primjene cijele krvi u izvanbolničkoj i bolničkoj reanimaciji bolesnika s traumom, ponajprije zbog relativnog nedostatka visokokvalitetnih dokaza (osobito randomiziranih kontroliranih studija) o njezinoj učinkovitosti i sigurnosti u usporedbi s standardom skrbi – terapijom krvnim komponentama. Uz nedavno objavljene prospektivne studije koje

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pokazuju jednako dobre ili bolje ishode s transfuzijom pune krvi u odnosu na transfuziju krvnih komponenti, interes za primjenu pune krvi ponovno je porastao. Ovaj pregledni članak ima za cilj prikazati povijest, tehničke aspekte i aktualne dokaze o primjeni cijele krvi u kontekstu vojne i civilne traume na sažet i jasan način te informirati čitatelja o okolnostima i situacijama u kojima transfuzija cijele krvi može pružiti najveću korist – kako s logističkog i financijskog aspekta, tako i u pogledu smrtnosti.

Ključne riječi: hitna medicina; hitna medicinska služba; krv; transfuzija krvi; vojna medicina

Introduction

History of whole blood transfusion

Whole blood was historically the first type of blood product transfused to patients in order to prevent or treat hypovolemic shock caused by hemorrhagic trauma. During World War I, a physiologist named Walter Cannon laid out a theory on the mechanism of hypovolemic shock and proposed whole blood transfusion as a potentially effective intervention for its prevention (1). The theories of Cannon and several other authors were considered sensible enough to implement citrated whole blood transfusions by the United States Army during the final months of World War I (2). Since the first instances of whole blood transfusions, there were logistical limitations to their usage: during World War I, citrated whole blood was stored in Robertson bottles, filled with glucose, which enabled a maximum of 5 days of storage time before the glucose ran out and the quality of the whole blood declined (2). During World War II, this limitation was removed with the advent of Baxter bottles, which contained acid citrate dextrose - a solution which could be autoclaved, extending the safe and sterile storage time of whole blood to approximately 21 days (3). Further safety of blood transfusions was enabled by the implementation of plastic bags instead of Baxter bottles as the principal containers of blood products. Plastic bags, unlike bottles, were less prone to breaking and could withstand the high flow velocities during emergency transfusions with a lower incidence of air embolism (4). With time, owing to the advantages of using plastic bags for blood storage and the advent of technologies that allowed for the separation of whole blood into individual components (red blood cells, plasma and platelets), component therapy overtook whole blood transfusion as a primary treatment modality for hemorrhagic shock. During the Vietnam War, owing to the aforementioned logistical difficulties related to storage of whole blood, as well as a perceived high incidence of post-transfusion hepatitis, whole blood and blood component transfusions were replaced by intravenous crystalloid fluid therapy in the management of hemorrhagic shock. Further encouraged by the experimental work of Shires et al. (5), resuscitation of patients with hemorrhagic shock using primarily crystalloid infusions (with a ratio of infused crystalloid fluid volume to transfused blood product volume of 3:1) was recommended not only for military purposes, but also for civilian trauma management, finding its way into the first Advanced Trauma Life Support (ATLS) guidelines (6). However, these recommendations were often misapplied, which resulted in patients receiving up to 10 liters of intravenous crystalloids before being administered any blood products, leading to renal failure, interstitial edema, acute respiratory distress syndrome (ARDS) and, most importantly, severe coagulopathy. Miller at el. observed an increased bleeding tendency in patients receiving massive transfusions in the Vietnam War, successfully reduced by the administration of whole blood instead of crystalloids (7). During the 1980s and early 1990s, ATLS guidelines became the norm for the management of civilian trauma. Therefore, the strategy for the management of hemorrhagic shock in trauma suggested by the guidelines - administration of a 2 liter initial bolus of intravenous crystalloid fluids followed by administration of red blood cells and subsequent administration of plasma and/or platelets if the bleeding persisted, was the dominant treatment strategy during the aforementioned time period (4). The paradigm began to change in 1993, owing to a shark attack in Mogadishu, Somalia.

The shift in trauma care began in 1993, as emerging evidence pointed to the potential benefits of reintroducing whole blood transfusion.

Due to a shortage of blood component products, a US Army medical team stationed in Mogadishu opted for collection and use of whole blood for the treatment of a shark attack victim with bilateral lower extremity amputations. A stockpile of 120 units of whole blood was gathered and stored and was subsequently crucial in early resuscitation of military personnel during the Battle of Mogadishu, which occurred exactly 30 days following the shark attack incident (8). Following the battle, a review of the trauma resuscitation protocols endorsed by the US Army was conducted and use of whole blood transfusions was recommended by the Army's "Emergency War Surgery" manual (9). Following these changes, whole blood resurged as a standard of care during the war in

Iraq. In 2004, US Army forces stationed in Baghdad began using ABO type-specific whole blood for the resuscitation of traumatic hemorrhage and found a higher success rate of reversing shock and coagulopathy compared to component therapy with red blood cells and plasma. Following their experience, a massive transfusion guideline was developed, recommending whole blood transfusion as first line therapy for hemorrhagic traumatic shock, with the transfusion of blood components (packed red blood cells, platelets and plasma) in a 1:1:1 ratio allowed until whole blood is available (10). In 2011, Nessen et al. published data from the war in Afghanistan, demonstrating improved survival in hemorrhagic shock patients receiving warm fresh whole blood when compared to those receiving blood component therapies (11). This and other publications led to the inclusion of whole blood transfusion as a viable resuscitation strategy for hemorrhagic shock in combat situations in the 2014 Tactical Combat Casualty Care (TCCC) guidelines (12).

The early 2010s also marked the advent of whole blood transfusion in the context of civilian trauma resuscitation. In 2011, owing to collaboration between the North Atlantic Treaty Organization (NATO) and the Norwegian Naval Special Operations Command (NNSOC), a research network was established, with the goal of investigating optimal strategies for the treatment of trauma in austere, challenging or resource scarce environments. The research network was named THOR - Trauma Hemostasis and Oxygenation Research.

It is important to note that, when discussing "whole blood" as a concept, there are three different modalities of its storage and use: warm fresh whole blood, cold fresh whole blood and cold stored whole blood. More detail on these is provided in the "technical aspects of whole blood collection, storage and transfusion" paragraph. In the paragraphs regarding the evidence for use of whole blood, the type of whole blood according to storage method is defined for each individual study, as well as the information if the whole blood used was low-titer type O or ABO type-specific. This research network focused on applying concepts acquired and tested in the context of combat casualties to civilian trauma, publishing a protocol on the collection and prehospital use of whole blood in austere environments (13). The group also published literature reviews and their own retrospective data on the safety of transfusing low-titer type O Rh positive whole blood with regards to isoimmunization (14). Following the efforts of the THOR group, other researchers started investigating the use of whole blood in civilian trauma more intensively, yielding a wealth of studies that shall be discussed and presented in the "evidence for the use of whole blood for civilian trauma management" paragraph of this manuscript.

The aim of this narrative literature review is to evaluate and present the evidence on the efficiency and safety of using whole blood transfusion for the management of hemorrhagic shock, with a major focus on hemorrhage caused by traumatic injury, while also providing a technical background and information essential to understanding the nuances of whole blood transfusions.

The authors deem a cohesive narrative literature review with a primarily educational goal and structure necessary, as current research has demonstrated that, while whole blood transfusion has been accepted by the emergency medicine community in recent years, its implementation is mostly nominal. According to data from 2020, approximately 1 in 4 level I trauma centers in the United States use whole blood transfusions for the resuscitation of traumatic hemorrhagic shock (15). According to a study by Hanna et al, who conducted a nationwide analysis of whole blood use in civilian trauma in the United States, only a small fraction of patients with traumatic hemorrhagic shock receive whole blood transfusions in the first 24 hours in addition to blood component transfusions (280 of 8494 or just 3.3 % of patients in their study). Furthermore, of the 280 patients that received whole blood transfusions, 266 received only 1 unit of whole blood and 14 received 2 units of whole blood (16).

Although whole blood transfusion is increasingly recognized as a superior approach for hemorrhagic shock, its adoption in civilian trauma care remains limited and inconsistently implemented.

This data demonstrates extreme caution and hesitation in the use of whole blood transfusions for civilian trauma, despite the nominal implementation rate of 25 % among the level I trauma centers.

Therefore, this article may serve as a succinct, educational and straightforward review of the available literature, with the aim of informing providers on the benefits, flaws, effectiveness and overall safety of using whole blood transfusions when compared to the current norm, which is blood component therapy.

Technical aspects of whole blood transfusion

Each year, countless patients rely on blood, blood components, and plasma derivatives to increase their chances of surviving trauma. As of 2019, the European Commission (EC) had reported data for 25 countries that collected more than 17 million donations of whole blood and blood components, such as red blood cells, plasma, and platelets. The collection of blood and plasma derivatives solely relies on human donors, making it a limited and invaluable resource. In numerous countries, whole blood (WB) collections form the fundamental pillar of the blood supply system (17). Ensuring an adequate

supply of blood, blood components, and plasma for patients in need of transfusions, while maintaining safety standards and preventing the transmission of infectious diseases, is a top priority for national health authorities, such as the European Commission (EC), Food and Drug Administration (FDA), European Directorate for the Quality of Medicines & HealthCare (EDQM) and other (18). Every nation encounters obstacles in establishing a sustainable and adequate supply of blood and blood products, all the while maintaining the highest standards of quality and safety. These efforts are crucial to address both well-known and emerging threats to public health. Current practice in civilian aspects is that whole blood transfusion is not indicated when component-specific treatment is available, such as using red blood cells to treat anemia or using fresh frozen plasma to treat coagulopathy in trauma (19). Initiating early blood transfusion and implementing massive transfusion protocols (MTP) in the prehospital setting can effectively prevent the development of coagulopathy. By administering blood products promptly, this proactive approach aims to address coagulation issues at an early stage, ensuring better outcomes for patients (20).

Ensuring a safe and sufficient blood supply is a global challenge, while early better trauma outcomes.

On the other hand, Black et al. stated that in both out-of-hospital and deployed hospital settings, the United States military has adopted whole blood as a standard of care. Recent studies in civilian contexts also indicate an increasing use of whole blood as an alternative approach to trauma resuscitation, moving away from the conventional component therapy (21). Speaking about other advantages of WB, some of which will be discussed later in the paper, the following benefits should be considered simplified transfusion process, cost-effectiveness, balanced composition of blood components, improved coagulation, less complex storage requirements, veritable replication of blood lost by hemorrhage, fewer transfusion reactions [e.g Transfusion Related Acute Lung Injury (TRALI)] (22-25).

The collection of whole blood is a critical procedure characterized by the need for standardization in order to prioritize safety and optimize efficiency. Donor eligibility is determined through comprehensive screening, considering medical history, health status, and potential risk factors. Ensuring informed consent is an ethical imperative, securing voluntary and willing participation from healthy donors – preferring those with blood type O, with a lower antibody titer (26). The systematic whole blood collection process commences with proper donor preparation, followed by venipuncture performed by skilled healthcare professionals. The collection phase typically spans 8-15 minutes, yielding approximately 450 - 500 milliliters of whole blood. Observed practice in existing studies is that 450 mL ± 10 % of WB is collected in bags containing a 1:7 ratio of anticoagulants to blood. (26-27). The types and impact of anticoagulants shall be explained later in this paragraph. In their publications, Siversten et al, Strandenes et al, Schubert et al and other authors had exclusively used FDA-approved blood bag systems containing a platelet sparing, whole blood leukoreduction filter - Imuflex WB-SP collection set, containing 70 mL of citrate-phosphate-dextrose (CPD) (28-30). Furthermore, an additional blood sample was obtained using blood collection K2- EDTA tubes from each donor to conduct baseline measurements of the complete blood count (CBC).

When discussion anticoagulants for whole blood, studies mostly mention citrate-phosphate-dextrose (CPD), which had already become the most frequently used anticoagulant for this purpose in the 1950s and still is despite the development of CPD supplemented with adenine (CPDA-1). Some articles mention citrate–phosphate-double dextrose (CP2D) as the anticoagulant of use, but it didn't take root in standard practice. The frequency of use and selection of a particular anticoagulant are dependent on its shelf life, in order to optimize the quality of stored whole blood. A comparison of the anticoagulants mentioned above was published by Meledeo et al in 2019, demonstrating a slight increase in clotting time measured by thromboelastography over time, irrespective of the anticoagulant-preservative solution used. However, the use of CPDA-1 resulted in a significantly longer storage time, up to 35 days, and CPD stored WB could be stored for a maximum of 21 days in the same storage conditions of 2 – 4°C (27). Currently, there is no commercially available collection set that includes an in-line platelet-sparing filter along with CPDA-1 as an additive. Dumont et al. discussed the factors taken into account when selecting an anticoagulant for whole blood, including the viability of red blood cells residing in whole blood with regards to shelf-time (31).

Thromboelastometry analyses were developed with the aim of detecting alternations in the coagulation status of blood samples, with its principles applicable to testing the hemostatic properties of stored WB. A point-of-care device utilizing rotational thromboelastometry (ROTEM) can provide analysis of the viscoelastic properties of whole blood samples, such as clot formation and dissolution (e.g. coagulopathy) (35). There is evidence that point-of-care ROTEM analysis can be performed under demanding operational conditions, with a relatively low rate of erroneous readings (36). Time to first clot formation (R), rate of clot formation (α), and maximum clot strength (MA) are the most commonly performed measurements when testing of the hemostatic properties of whole blood testing is concerned (30).

Leukoreduction (LR) is considered an additional measure that could enhance the safety of whole blood use. LR effectively lowers the risk of human leukocyte antigen

(HLA) alloimmunization, incidence of febrile reactions, and viral transmission. However, it was posited that leukoreduction might have an effect on the number and function of platelets inside whole blood. Pidcoke et al. observed a gradual decrease in the number of platelets during storage (37). Morris et al also observed the effects of preforming leukoreduction and found decreased platelet aggregation compared to non-leukoreduced (NLR) blood. However, performing leukoreduction at 4 hours following whole blood collection did not lead to a reduction in platelet function (28). Similar results were demonstrated in studies conducted by Remy et al and Sieltz et al, that showed delayed clot development, growth, and formation in LR WB over a 30-day time frame (38-39). It is possible to successfully perform leukoreduction by using the Imuflex WB-SB filter, which was prescribed by the FDA in 2012 (40).

Pidcoke et al. observed non-leukoreduced WB (NLR WB) stored at 4°C and found a 33 % decline in the number of platelets until the end of the viable storage period.

The rate of decline in platelet count in WB stored at 4°C was higher compared to WB stored at room temperature, but the overall clotting ability was maintained during the 21 day shelf life (37). A study by Slichter et al. performed on cold stored NLR WB showed a reduction in platelet count by 25 – 30 % during the 22-day shelf time (41).

During each transfusion, providers should be cautious of pathogens which are the cause of transfusion-transmitted infections. A major logistical challenge is the development of a method of pathogen inactivation (PI) methods that does not damage WB units. Leukodepletion (LD), or leukocyte depletion, is one of most important methods of PI used in order to reduce the risk of transmission of intraleukocytic pathogens (e.g., human T-lymphotropic virus type 1, prions, cytomegalovirus). There are WB LD filters commercially available for this purpose that achieve results adequate for meeting FDA requirements for both in vitro and in vivo evaluations (32). Other methods of PI include using riboflavin for the reduction of pathogen activity (33). Pidcoke et al. performed measurements of platelet numbers in WB after using

riboflavin and UV-B illumination for PI. They concluded that there is no significant difference between controls and WB treated with riboflavin and UV-B illumination (37).

However, a study by demonstrated a sharp decline in platelet count inside pathogen-reduced WB during storage, with platelet counts falling below 150 x $10^{\wedge 9}$/L from day 3 onwards (34).

Military and combat use of whole blood

Following the historical developments and the implementation and popularization of the use of whole blood transfusions in the setting of military trauma, more studies have been conducted in order to more precisely define the contexts in which whole blood may yield the most beneficial outcomes.

A case series by Fisher et al. described the accessibility and transportation possibilities of low titer group O whole blood in combat missions and feasibility of starting transfusion therapy at the point of injury. Out of 15 casualties described, only one patient died in the resuscitative surgical center and 2 died before arrival to hospital (42).

A retrospective study by Spinella et al. lowed two groups of hemorrhaging trauma patients in the military setting, the first of which received warm fresh whole blood + red blood cells + plasma and the second received red blood cells, plasma and apheresis platelets. 100 patients were analyzed in the first group and 254 in the second group. The group that received whole blood + red blood cells + plasma had an increased 24-hour (96 % vs 88 %, p = 0.018) and 30-day (95 % vs 82 %, p = 0.002) survival when compared to the second group (43).

A prospective study by Nessen et al. compared the outcomes of patients from US army forward surgical teams with and without use of fresh whole blood in addition to red blood cells and fresh frozen plasma. When the outcomes of patients who received massive blood transfusion (10 units of red blood cells or equivalent in fresh whole blood) were compared between the two groups, a significantly lower mortality rate was observed in patients who received fresh whole blood (8.16 % vs 26.67 % p = 0,025). Furthermore, there was no difference in mortality between patients who received unmatched type O fresh whole blood (6.7 %) versus type-specific fresh whole blood (6.1 %) (11).

Early fresh whole blood transfusion near injury sites improves survival in military trauma and shows promise for civilian use.

A retrospective review of combat casualties by Perkins et al. showed similar 4-hour and 30-day survival between patients who received fresh whole blood and those who received apheresis platelets. Patients who received fresh whole blood had also received less units of plasma (8 vs 12, p < 0.001) and cryoprecipitate (0 vs 10, p < 0.001). Also, a lower proportion of patients in the whole blood group received recombinant factor VIIa (55 % vs 70 %, p = 0.02). There was no significant difference in observed adverse events except for acute respiratory distress syndrome (ARDS), which was more common in the fresh whole blood group (18.8 % vs 7.4 %, p = 0.002) (44).

A large study (n=1111) by Gurney et al. compared patients who received fresh whole blood and those that did not, but had received at least one unit of red blood cells in Role 2 environments. Following an adjusted analysis, the authors found an increased association with mortality in critical patients who did not receive fresh whole blood [hazard ratio (HR) = 2.8; 95 % CI 1.2 – 6.4, p = 0.017] (45).

Whole blood transfusion in trauma may lower mortality, reduce additional blood product use, massive transfusions, and complications like like transfusion related acute lung injury.

An important consideration for the use of fresh whole blood transfusions in the military setting is the potential reduction physical performance of whole blood donors following the donation process. Strandenes et al. tested physical performance of participants before and 2-6 minutes following the donation of 450 mL of whole blood. They reported no significant difference in physical performance test scores or VO2 max (46). Conversely, a randomized, double-blinded study by Eliassen et al. demonstrated a reduction in absolute VO2 max by 11.2 % ($p < 0.05$) and reduced exercise tolerance time for an average of 92 seconds ($p < 0.05$) when compared to baseline following donation of whole blood (47).

Another important question regarding the feasibility of using whole blood transfusions in the military setting is the effectiveness of its utilization and the rate of blood product waste. Vanderspurt et al. analyzed blood product utilization during US military operations in Iraq, Syria and Afghanistan. They found a utilization rate of 17.4 % for blood component products vs 14.3 % for low-titer O type whole blood (LTOWB), demonstrating no significant difference in utilization or waste rates between these two types of blood products (48).

Finally, it is important to note that in 2021, the Committee on Tactical Combat Casualty Care updated its guidelines on fluid therapy of hemorrhagic shock in combat settings, suggesting cold stored low-titer group O whole blood as preferred the resuscitation fluid for combat casualties, with the possibility of using fresh low-titer group O if cold stored LTOWB is not available (49).

The use of whole blood transfusions in the management of civilian trauma

As it was mentioned in the "introduction" paragraph, clinical investigations and considerations on using whole blood transfusion in the context of management of civilian trauma date back to 2011 and the establishment of the Trauma Hemostasis and Oxygenation Research (THOR) network, borne from the collaboration between the North Atlantic Treaty Organization (NATO) and the Norwegian Naval Special Operations Command (NNSOC). Following the establishment of the THOR network, medical investigators from two large countries (United States of America and Norway) diverted their attention to the efficiency, safety and possibilities of implementation of whole blood transfusions into their medical systems. Following the intensification of their research efforts and an increase in the interest regarding whole blood transfusions, a solid throughput of literature has been established. The most important studies researching the implementation of whole blood in the aforementioned medical systems shall be discussed in this paragraph.

Prehospital transfusion of blood or plasma within the first minutes post-injury can be a critical determinant of survival in hemorrhagic trauma.

Before discussing the literature, it is important to explain the two main environments in which whole blood may be implemented and the rationale for doing so. The first environment is the prehospital emergency service. A study by Shackelford et al. analyzed data on combat casualties of the United States Army in Afghanistan between 2012 and 2015. The authors analyzed data on patients who were evacuated from the point of injury and suffered either a traumatic limb amputation or traumatic hemorrhagic shock, defined by a systolic blood pressure < 90 mmHg or a heart rate > 120 beats per minute. Data on 502 patients was included in the final analysis and it was found that patients with traumatic hemorrhage who received prehospital blood product transfusions had a significantly lower rate of 30-day mortality when compared to patients who did not receive prehospital transfusions (11 % vs 23 %, $p = 0.04$). The hazard ratio for mortality in patients who received prehospital transfusions was 0.39 [95 % confidence interval (CI) 0.16-0.92, $p = 0.03$]. A reduced risk of mortality was observed in patients who received an initial blood product transfusion in 15 minutes or less following pickup from the point of injury by the medical evacuation vehicle (HR 0.17; 95 % CI 0.04-0.73, $p = 0.02$) (50). Pusateri et al. conducted a post-hoc analysis of the Prehospital Air Medical Plasma (PAMPer) and Control of Major Bleeding After Trauma (COMBAT) trials, both of which examined the effects of prehospital plasma transfusions on the mortality of patients with traumatic hemorrhagic shock. The analysis included 626 patients with a median age of 42 years and demonstrated a statistically significant reduction in mortality associated with prehospital plasma transfusion [hazard ratio (HR) 0.65; 95 % CI 0.47-0.90, $p = 0.01$] following adjustment for patient age and injury severity. Furthermore, patients who did not receive prehospital plasma transfusions had an increased risk of mortality (HR 2.12; 95 % CI 1.05-4.30, $p = 0.04$) if the duration of the transport to a hospital facility exceeded 20 minutes. There was no observed increase in mortality in relation to duration of prehospital transport in patients who received prehospital plasma transfusions (51). These studies demonstrate a significant mortality benefit to prehospital transfusions of blood products, especially if applied early during the prehospital transport or in situations where

transport takes longer than 20 minutes. Due to these time-sensitive requirements and conditions, whole blood, owing to its logistical simplicity of containing red blood cells, plasma and platelets in a single bag, presents as a compelling blood product of choice for the prehospital arena.

The feasibility of implementing whole blood in the prehospital setting was extensively studied by a group of Norwegian investigators. Bjerkvig et al. conducted a survey of 13 helicopter emergency medical services (HEMS) and 7 search and rescue (SAR) services in Norway regarding their blood product inventories and preferences for specific products or components (52). They found that 20 % of the services participating in the survey carried low titer group O whole blood as part of their regular blood product inventory. Among the services that did not have LTOWB as part of their regular inventory, 88 % expressed a desire to implement it in the future. The main challenges in obtaining and implementing LTOWB in the HEMS setting were lack of LTOWB donors, concerns of potential waste of blood products due to a low number of annual transfusions, lack of "hard" evidence on the efficiency of LTOWB in the HEMS settings and LTOWB not being available as a blood product in their local blood bank. The authors also surveyed the blood banks providing the HEMS services with LTOWB and found that blood product waste was indeed a significant problem, with half of the blood banks reporting a waste rate of > 75 %. One blood bank reported a waste rate of only 26.4 %, due to utilizing unused LTOWB returned by the HEMS services for in-hospital massive transfusions.

Another Norwegian study, by Sunde et al. analyzed data on prehospital transfusions from the HEMS base in Bergen during a period of 5 years (2015 - 2020). They found that 48 patients received LTOWB during the aforementioned period, with no severe adverse events, transfusion reactions or major logistical challenges reported. This study also demonstrated impressive efficiency of blood product use, with 0 instances of blood product waste reported during the 5 year period due to sending unused LTOWB units for in-hospital use (53).

Successful implementation of LTOWB in a prehospital system in the United States was described by Sayre et al, who reported their emergency medical ambulance service transfusing 51 units of LTOWB into 39 patients during a 1-year period, with an average cost of $ 1138 per patient transfused. The authors also reported no waste of blood products, as all of the units issued by the associated hospital were either used in the field or returned for in-hospital use (54). Levin et al. described the use of LTOWB for the management of traumatic hemorrhagic shock in Israel by the Israel

Defense Forces Airborne Combat Search and Rescue Unit. They reported transfusing 33 units of LTOWB to 27 patients over a 2,5-year period. However, their study also demonstrated the perils of using LTOWB in a system with a low incidence of transfusions and no developed program for the return of unused units of LTOWB for in-hospital use - the waste rate of LTOWB during the 2,5-year period was 98 %, due to the factors listed above (55).

The literature comparing prehospital administration of whole blood to blood component therapy with regards to patient important outcomes is relatively scarce. Williams et al conducted a prospective observational study of transfusion therapy in trauma patients both in the prehospital HEMS and the in-hospital emergency department. During a period of 8 months, they enrolled 350 patients who received either blood component therapy or LTOWB. While there was no difference in survival between patient groups in the unadjusted analysis, a significant association between survival and receiving LTOWB was found following adjustment for patient age, prehospital physiology and severity of injury [odds ratio (OR) 2.19; 95 % CI 1.01-4.76,; p = 0.047]. There was also a significant reduction in the need for blood product transfusions following initial management in the emergency department (ED) observed in the LTOWB group (OR 0.47; 95 % CI 0.23-0.94, p = 0.033) (56).

Braverman et al did a retrospective analysis of a single institution trauma registry, extracting data on patients who received prehospital blood product transfusions. Data on 538 patients was analyzed and the patients were divided into two groups: those who received prehospital LTOWB transfusions and those who received no transfusions in the prehospital setting. Patients who received prehospital LTOWB had a significantly lower rate of early mortality, defined as death in the trauma bay (0 % vs 7 %, p = 0.04) (57).

Braverman et al. recently conducted another registry analysis, extracting data from two level I trauma center registries and collecting data on patients who underwent transfusions. Data on 1562 patients was included in the analysis and the patients were divided into those who received prehospital LTOWB and those who did not. There were no significant differences in mortality or length of stay between groups. Patients who received prehospital LTOWB had a lower need for massive transfusion protocols (MTPs) (22.6 % vs 32.4 %, p = 0.01) (58).

The rationale for using whole blood in-hospital is based on the idea that whole blood is logistically simpler to collect, store and transfuse while also being potentially cheaper than blood component therapy. The logistical simplicity and straightforwardness of acquiring and using whole blood has led to several authors advocating for the use of whole blood in small rural hospitals, as well as designing protocols for the establishment of emergency whole blood donor pools, also called "walking blood banks", in rural areas that are underserved regarding the acquisition and transport of blood component products (59-60).

The volume of literature on whole blood in the emergency department or the trauma bay is significantly larger when compared to the literature on prehospital use of whole blood.

Most of the in-hospital data on the safety and efficiency of whole blood comes from the United States, where whole blood had begun to resurge as a viable blood product for transfusion therapy of hemorrhagic shock in trauma since 2016, when a number of trauma centers, including Mayo Clinic, implemented it in their protocols (61). However, one of the first studies on the effects of whole blood transfusion on mortality was conducted in Australia in 2011, when Ho et al compared the outcomes of patients requiring massive transfusion who received more than 10 packs of red blood cells to those who received warm fresh whole blood. They found 30-day or 8-year survival benefit associated with receiving whole blood (HR 1.05; 95 % CI, 0.41-2.65, p = 0.93) (62). One of the earliest studies on the effectiveness and safety of whole blood transfusions in the United States was a randomized controlled trial from 2013 conducted by Cotton et al (63). In the study, severly injured patients with traumatic hemorrhagic shock were randomized to receive either whole blood transfusions or red blood cells and plasma in a 1:1 ratio. Both groups received a unit of platelets for every 6 units of whole blood or red blood cells + plasma transfused. The primary outcome was the average transfusion volume received in each patient group and those were not significantly different amongst a total of 107 patients divided into two groups. However, following the exclusion of patients with traumatic brain injury from the analysis, the group randomized to whole blood transfusions received less units of red blood cells (median 3 vs 6, p = 0,02), plasma (4 vs 6, p = 0.02), platelets (0 vs 3, p = 0,09), and total blood products (11 vs 16, p = 0.02) during the 24-hour period following admission to the trauma bay.

Two more randomized controlled trials examining the effectiveness and safety of whole blood in the emergency department were planned: the Pragmatic Prehospital Group O Whole Blood Early Resuscitation (PPOWER) trial and the Evaluation of a Transfusion Therapy Using Whole Blood in the Management of Coagulopathy in Patients With Acute Traumatic Hemorrhage (T-STORHM) trial. The PPOWER trial was terminated in 2021 due to slow enrollment, financial considerations and the global COVID-19 pandemic (64), while the T-STORHM trial is still in the patient recruitment phase (65). Until the results of the T-STORHM trial are published, large prospective trials represent the highest quality of evidence available.

One of the largest prospective trials is a recent study conducted by the Shock, Whole Blood, and Assessment of Traumatic Brain Injury (SWAT) Study Group, enrolling 1051 patients with traumatic hemorrhagic shock from 7 different trauma centers (66). The results of the study demonstrated no significant difference in 4-hour, 24-hour or 28-day mortality between patients who received LTOWB and those who received blood component therapy. However, a subgroup analysis that included patients with an elevated prehospital probability of mortality demonstrated a significant reduction in risk of 4-hour [relative risk (RR) 0,52; 95 % CI 0,32-0,87, p = 0,01] and 28-day mortality (RR 0,70, 95 % CI 0,51 to 0,96, p = 0,03).

Other prospective trials include the one conducted by Siletz et al, comparing the effects of a combination of whole blood and blood component transfusion to transfusion utilizing only blood components on transfusion requirements of trauma patients with hemorrhagic shock (67). 60 patients in total were enrolled in the study, with the results showing no statistically significant difference in the average volume of transfusions received, mortality, complication rates or the number of intensive care unit or hospital-free days between groups.

Another prospective trial, published by Shea et al. compared the rates of survival between trauma patients with a requirement for massive transfusion who received LTOWB versus those who received blood component therapy transfusion. A total of 66 patients were enrolled in the study and the results demonstrated no significant difference in mortality between groups (21 % in the blood component group vs 16 % in the LTOWB group, p = 0.518). Following a multivariable logistic regression analysis, a significantly decreased risk of 24-hour mortality was found in patients who received whole blood transfusions (OR 0.81; 95 % CI 0.69-0.96, p = 0,017) (68). Similarly, a prospective observational trial by Duchesne et al. comparing outcomes between trauma patients with active hemorrhage who received whole blood transfusion versus those who received blood component therapy found no statistically significant association in the reduction of in-hospital mortality with receiving whole blood instead of blood components (HR 1.25; 95 % CI 0.60-2.58, p = 0.55). However, patients transfused with whole blood received significantly fewer units of red blood cells (p < 0.001) and plasma (p = 0.04) and also had a lower incidence of acute respiratory distress syndrome (ARDS) (p = 0.03), with significantly less days spent on mechanical ventilation (p = 0.03) (69).

A number of retrospective studies comparing whole blood to blood component therapy were also published, with most of them demonstrating no significant difference in mortality between groups (70-73) and some of them demonstrating a survival benefit associated with the use of whole blood when compared to blood component transfusion therapy (74-75).

Similar to prehospital application of blood product transfusions, time seems to be a relevant factor affecting clinically important outcomes in emergency department whole blood transfusions. A retrospective analysis of the American College of Surgeons' Trauma Quality Improvement Program (TQIP) database from 2017 to 2019

performed by Hosseinpour et al. found that transfusion of whole blood after more than 30 minutes following patient admission to the trauma bay was associated with an increased adjusted odds ratio of 24-hour mortality [adjusted odds ratio (aOR) 2.07, p = 0.015] and in-hospital mortality (aOR 1.79, p = 0.025), demonstrating the need for early application of whole blood in the resuscitation of traumatic hemorrhagic shock (76).

A meta-analysis by Crowe et al. synthesized the results of 12 studies comparing balanced blood component transfusion therapy to whole blood transfusion for the resuscitation of trauma patients and found no significant association of 30-day mortality with whole blood transfusions (OR = 0.79; 95 % CI 0.48–1.31) (77).

The results of the trials evaluating the effectiveness and safety of whole blood published until now and the trials comparing tranfusions of a 1:1:1 ratio of plasma, platelets and red blood cells to other ratios led to the Eastern Association for the Surgery of Trauma (EAST) to recommend the use of either blood component products transfused in a 1:1:1 ratio or whole blood for damage control resuscitation in patients with severe traumatic hemorrhage (78).

With the available literature comparing blood component therapy to whole blood transfusions demonstrating either no difference or a reduced mortality rate with the use of whole blood, another important question that arises is the cost-effectiveness of whole blood versus the current standard of care, i.e. blood component therapy. Based on the data from America's Blood Centers, a single unit of whole blood in 2017 cost $ 151,51, while the combined price of a single unit of red blood cells + fresh frozen plasma + platelets was $ 628,19 (79). A recent study by Ciaraglia et al. the comparing costs of LTOWB transfusion versus blood component transfusions found that the implementation of LTOWB transfusions reduced the mean annual cost for all blood products by 17.3 %. Furthermore, LTOWB tranfusions were significantly associated with a lower cost per patient and cost per patient per mL of transfused blood product when compared with blood component therapy at 4 hours, 24 hours and overall (p < 0.001) (80).

Conclusion

Whole blood transfusion for the treatment of hemorrhagic shock is a century-old concept that has resurged in recent years, attracting increased interest from trauma researchers. While the data for the effectiveness of whole blood transfusions in both the prehospital and hospital settings is relatively scarce, the available literature demonstrates either noninferiority or superiority of whole blood transfusions regarding mortality when compared to blood component transfusions. These results need to be tested in a well-designed, large multicenter randomized controlled trial in order to more definitely establish the role of whole blood in the resuscitation of traumatic hemorrhagic shock. In the case of more convincing positive evidence for its use surfacing in the future, the already lucrative concept of using whole blood (which, in addition to potential survival benefits offers logistical simplicity and cost-effectiveness) for trauma resuscitations may become more widespread and accepted, as current surveys on its use in the United States demonstrate a great degree of hesitance.

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