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The Reemerging Role of Whole Blood in Modern Trauma Care: Is the Whole Greater than the Sum of its Parts?

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Abstract

Hemorrhage is the leading cause of potentially preventable deaths in both military and civilian trauma patients. Early hemorrhage control and resuscitation with blood products have been shown to improve survival in hemorrhaging trauma patients. While the use of balanced component therapy continues to be the standard of care for resuscitation, whole blood transfusion in adjunct to component therapy is increasingly becoming the modality of choice for resuscitation of civilian trauma patients across the United States. Whole blood resuscitation offers several advantages including higher hematocrit, platelet and factor concentrations, lower additive volumes, and faster times to balanced transfusion of equivalent volumes of red blood cells, plasma, and platelets, making it logistically easier to administer. Multiple retrospective and prospective studies have shown that whole blood in adjunct to component therapy is associated with improved

outcomes in trauma patients. Multiple prospective trials are currently in progress, evaluating the impact of pre-hospital and in-hospital transfusion of whole blood in trauma patients. There has been a recent upward trend in the number and proportion of trauma centers using whole blood. However, civilian practice management guidelines are yet to formally offer recommendations on the role of whole blood in resuscitation. This review will focus on the current evidence, ongoing trials, advantages, and risks of whole blood transfusion in the resuscitation of hemorrhaging trauma patients.

Key Words: Whole Blood, Resuscitation, Hemorrhage, Civilian Trauma

Introduction

In the United States, injuries resulting from trauma rank as the fourth leading cause for mortality.[1] Hemorrhage is responsible for up to 30% of fatalities linked to trauma, resulting in the death of approximately 50,000 individuals and leading to a loss of two million years of life on an annual basis.[2] Despite the advancements in resuscitation strategies, hemorrhage continues to be the principal cause of preventable fatalities amongst trauma patients.[3] Exsanguination typically results in fatality within the initial six hours post-injury, commonly occurring between the second and third hour.[4]

While balanced component therapy (CT, characterized as a 1:1:1 ratio of packed red blood cells [pRBC], fresh frozen plasma [FFP], and platelets) remains the conventional treatment for resuscitating hemorrhaging trauma patients, the preference for utilizing whole blood (WB) transfusion in combination with CT is progressively gaining traction as standard management for resuscitating civilian trauma patients.[5] The aim of this study is to review the historical aspects, current evidence, ongoing trials, advantages, and risks of whole blood transfusion in the resuscitation of hemorrhaging trauma patients.

Whole Blood: Back to the Future

Although transfusion of whole blood in civilian trauma patients is a relatively new concept, its use in military medicine dates back to World War I.[6] Later, US Forces during World War II implemented 'Field Blood Banks' that gathered freshly donated whole blood, either to be used immediately or distributed quickly to areas close to the site of injury for emergency resuscitation.[7] This practice was effective during the Korean War, when Group O whole blood was the primary choice and Group O low titer (with anti-A and anti-B titers under 1:200 in saline dilution) was reserved for non-Group O recipients.[8,9] This knowledge from the Korean War had an impact on the resuscitation strategy in the Vietnam conflict. In 1965, the decision was made to only use low-titer Group O whole blood.[10]

Crystalloids and colloids replaced blood during and after the Vietnam era as the primary initial resuscitative approach for hemorrhagic shock due to the risks of infectious disease transmission with blood products, and research indicating the need for 1-2 L of crystalloids to resuscitate the interstitial compartment or 'third space'.[11] This led to the overuse of crystalloids and dilutional coagulopathy, and eventually the disappearance of whole blood from blood banks in civilian practice. Subsequent studies demonstrated that a crystalloid-based resuscitation approach, as compared to the use of whole blood, results in an increase in inflammation and vascular permeability.[12]

The recent conflicts in Iraq and Afghanistan sparked renewed interest in transfusing whole blood for patients with life-threatening traumatic bleeding. This strategy was supported in 2014 by the US Tactical Combat Casualty Care Committee.[13] A 2022 survey showed 16% of children's hospitals using this strategy, and a similar approach has been adopted in prehospital settings in Norway, Israel, and the US. It is now the preferred resuscitative product for patients with traumatic hemorrhagic shock.[14]

Cold-stored versus warm-stored whole blood

There are two types of whole blood: warm-stored and cold stored. Warm fresh whole blood (WFWB) may be stored at room temperature (20°C) for up to 8 h, and subsequently at 4°C for 16 h.[15] WFWB is transfused within 24–48 h after collection and considered to have full hemostatic function, especially when given early in resuscitation, and is shown to be superior to Cold-stored whole blood (CWB).[16] A recent study revealed that WFWB resuscitation was associated with a significant reduction in 6-hour mortality versus non-warm fresh whole blood (OR= 0.27 ;95% confidence interval 0.13-0.58) in combat casualties, with a dose-dependent effect (odds ratio=0.15, P=0.024).[17] Currently, the use of WFWB is mostly limited to situations when other blood products are unavailable, either in austere remote situations, or where blood bank inventories (particularly of platelet concentrates) are depleted.[18]

On the other hand, CWB can be stored at 1–6°C for up to 21 days if the anticoagulant is Citrate-phosphate-dextrose solution (CPD), or 35 days if the anticoagulant contains adenine (e.g. CPDA-1).[19] An important concern regarding cold-stored whole blood is how long the platelets maintain their function.[20] Because of the risk for bacterial contamination, whole blood is preferably stored at 4 °C in the civilian patient setting. Even if morphological changes occur during storage of refrigerated platelets, it has been suggested that these changes may be favorable for platelet function.[21] Although CWB has been approved by the FDA and may be stored up to 25 days, programs that have implemented utilizing WB as a standard of care, specify that RBC and PLT efficacy may be compromised after the 21st day, so storage duration must be limited to 14-21 days.[22,23]

Low Titer Group O Whole Blood (LTOWB) as an Adjunct to Component Therapy

Low Titer Group O Whole Blood (LTOWB) is unseparated blood, collected from a donor with "low" IgM and/or IgG anti-A and anti-B and can either be stored or given fresh. There is no universally accepted definition of LTOWB, and the Association for the Advancement of Blood and Biotherapies (AABB) states that low titer may be defined by institutions. LTOWB provides physiologic benefits when compared to conventional CT, including increased hematocrit concentrations, augmented platelet counts, heightened factor concentrations, and a lower amount of additive solution when compared to a volume equivalent of reconstituted WB.[24] Table 1 compares the composition of whole blood with reconstituted whole blood using component products.

LTOWB may offer advantages over CT for several reasons: 1) it reduces donor exposures. 2) It maintains the blood's oxygen carrying capacity by replacing lost red blood cells, as well as platelets. 3) It is far easier and faster to administer than traditional multiple blood CT. 4) More concentrated product compared to reconstituting whole blood with conventional components. 5) It provides cold stored platelets that have improved *in vitro* and perhaps *in vivo* hemostatic function compared to room temperature platelets in this patient population. 6) It provides greater availability of platelets where they might otherwise not have been available. 7) It reduces the incidence of ABO mis-transfusion during the resuscitation. 8) It gives a longer shelf life for stored platelets compared to room temperature storage.[25–30]

The improved outcomes and decreased blood product requirements associated with WB transfusion in civilian trauma patients became evident after a prospective study conducted by Cotton and colleagues.[31] During the past decade, multiple high-level studies have shown that the use of WB as an adjunct to CT in the resuscitation of hemorrhaging civilian trauma patients is not only safe and feasible, but also associated with improved 24-hour and in-hospital mortality, decreased major complications, and decreased overall transfusion requirements in hemorrhaging trauma patients with varying injury and shock severities.[17,32–35] Additionally, a recent study has demonstrated that transfusion of WB after 30 minutes of was progressively associated with increased adjusted odds of 24-hour mortality (second 30-minute: aOR:2.07, p=0.015; second hour: aOR:2.39, p=0.010) and in-hospital mortality (second 30-minute: aOR:1.79, p=0.025; second hour: aOR:1.98, p=0.018).[36] They suggest that every minute delay in WB transfusion is associated with a 2% increase in odds of 24-hour and in-hospital mortality among hemorrhaging trauma patients.[36]

A meta-analysis carried out in 2023 has showed that transfusion with WB + CT was associated with lower 24-h mortality versus CT and transfusion with WB was associated with a lower volume of red blood cells transfused at both 6 and 24 h.[37] With the emergence of whole blood in trauma resuscitation, cost-related comparisons are of significant importance to providers, blood banks, and hospital systems throughout a country. A study in 2023 revealed that after the initiation of the WB transfusion in pre-hospital settings the mean annual cost for all blood products decreased by 17.3% and the average net difference in cost related to component blood products and LTOWB was over $927,000.[38]

Whole Blood in Patients with Traumatic Brain Injuries

Although the use of WB in resuscitation of hemorrhaging trauma patients is highly recommended, its role in the management of patients with both hemorrhagic shock and traumatic brain injuries is still controversial. While isolated traumatic brain injury carries a relatively low mortality, the presence of both hemorrhagic shock and TBI doubles mortality.[39] TBI exacerbates the cardiovascular decompensation that occurs during hemorrhagic shock by decreasing blood pressure regulation and reducing cardiovascular compensatory mechanisms. Animal studies have shown improved mortality and neurologic

recovery with WB resuscitation compared to CT.[40] Additionally, in a recently conducted prospective observational study by Brill et al., sub-analysis of patients with TBI, defined as head AIS greater than or equal to 3, WB use was associated with improved survival.[34] The most recent study by Hatton et al. demonstrated that, in patients with concomitant hemorrhagic shock and TBI, WB transfusion was associated with decreased overall mortality and TBI-related mortality when compared to CT alone.[41]

Potential Risks and Practical Issues

The use of LTOWB in trauma patients is associated with a range of risks and limitations. These include the potential for hemolysis in non-Group O recipients, RhD sensitization in individuals with RhD-negative status, and wastage of blood products in times of critical shortages.[25] Strategies have been devised to minimize these risks, including selective use of blood from donors with low titers of anti-A and anti-B antibodies, cold storage to improve platelet hemostatic function and prolong shelf-life, leukocyte-reduction with a platelet-sparing filter to reduce the risk of graft versus host disease, and male or never-pregnant female donors to decrease the incidence of transfusion-related acute lung injury.[42–44] Studies by Harrold et al. and Morgan et al. have found no adverse transfusion reactions or evidence of hemolysis when LTOWB was administered to injured adults and children, including those with non-Group O blood.[45–47] Cold storage of whole blood platelets was once thought to impair their function, but more recent *in vitro* studies suggest that cold-stored platelets not only remain functional but may in fact be superior to those stored.[23,42,48]

Ongoing Trials

There are multiple ongoing clinical trials assessing the effect of LTOWB on the outcomes of hemorrhaging trauma patients. Trauma Resuscitation with Low-Titer Group O Whole Blood or Products (TROOP) is a randomized clinical trial led by the University of Alabama at Birmingham. The goal of this clinical trial is to compare the effectiveness of unseparated whole blood (LTOWB) and the separate components of whole blood (including PRBC, FFP, platelets, and cryoprecipitate) in critically injured patients who require large-volume blood transfusions. Type O Whole Blood and Assessment of Age During Prehospital Resuscitation Trial (TOWAR) is a multi-center, pre-hospital randomized trial utilizing 10 level-1 trauma centers designed to determine the efficacy and safety of LTOWB resuscitation as compared to standard of care resuscitation in patients at risk of hemorrhagic shock and to appropriately characterize the hemostatic competency of whole blood relative to its age. Shock, Whole Blood and Assessment of TBI (SWAT) is a multicenter, prospective, observational cohort study led by University of Pittsburgh aiming to evaluate patient centered outcomes associated with early whole blood resuscitation practice as compared to component resuscitation in poly-trauma patients with hemorrhagic shock and further characterize outcome benefits in those with traumatic brain injury.[49].

Summary

The use of LTOWB is increasingly common in both military and civilian settings and may represent the ideal early resuscitation intervention after injury. Exploring the potential advantages of Group O low titer CWB as an alternative to individual components could be beneficial in reducing the impact of exsanguination due to time efficiency and possible efficacy and safety advantages. High-level prospective, multicenter studies are warranted to support the pragmatic use of LTOWB as a standard of care.

Table 1: Composition of Whole Blood Compared with Reconstituted Whole blood using Component Products[24]

Variable	Whole Blood (1 unit)	Components (1 unit of pRBC, 1 unit of plasma, 1 unit of platelets, 1 unit of cryoprecipitate)
Product Volume, ml	570	675
Hematocrit, %	38-50	29
Platelet count	150,000 – 400,000	88,000
Factor activity, %	100	65
Fibrinogen, mg	1000	750

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