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HEMOSTASIS AFTER TRAUMA (N SAILLANT, SECTION EDITOR)

A Review of Whole Blood: Current Trauma Reports

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Abstract

Purpose of Review Interest in whole blood transfusion, particularly in trauma resuscitations, has been growing over the last decade. This has led to more data from civilian trauma centers on the efficacy of whole blood compared to component therapy, the safety profile, and the hemostatic effects of cold-storage.

Recent Findings The summation of recent data suggests that whole blood is at least as effective as component therapy in trauma resuscitation although data is limited to relatively small volumes (< 6 units). The effect of leukoreduction on platelet function and other hemostatic markers appears to be small in vitro, but clinical data is lacking. There is virtually no data on massive resuscitation with whole blood (> 10 units) except for case reports.

Summary Resuscitation with whole blood appears to be safe and offers some advantages over component therapy. More clinical data is needed on the safety of whole blood in massive resuscitation and the potential hemostatic effects of whole blood transfusion.

Keywords Whole blood · Resuscitation · Trauma · Coagulopathy · Transfusion · Blood banking

Introduction

Whole blood transfusion is the administration of donated human blood with minimal post-donation processing and without the separation of components. Interest in whole blood transfusion, especially in trauma resuscitation, has been growing over the last decade. Theoretically, whole blood offers several advantages over component therapy with higher concentrations of hemoglobin, platelets, and clotting factors, all in one bag [1–3]. Whole blood is either transfused warm without preservative or stored cold with a preservative solution. Fresh warm whole blood is administered within 24 h of donation, while stored, cold whole blood is usually kept up to 14 to 28 days before use. Stored cold blood is diluted with a small amount of citrate solution with less additive solution than required to prolong the usable lifespan of packed red blood cells [4].

For use in emergencies, low-titer group O whole blood (LTOWB) was historically used and is still common today when blood typing is not practical prior to transfusion, comparable to practices with component therapy [5]. Whole blood presents a unique challenge, even with group O blood, considering the volume of antibody containing plasma in a unit and the relatively low numbers of O negative blood donors. This is mitigated by using only blood with low antibody titers, but the definition of "low" is not universal. A recent survey of US institutions showed a low titer definition ranging from < 56 to < 256, with 200 being the most commonly used cut-off [6]. Recent data support the safety of using low-titer group O but demonstrates that there is relatively small risk of isoimmunization in women with reproductive potential with the risk of becoming D alloimmunized and having a severe fetal outcome as high as 6% [7, 8].

Historical Use

Whole blood was the primary source of blood transfusion for nearly 250 years prior to the development of component

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therapy and was used extensively through several major wars dating back to the Civil War [5]. Whole blood offers several advantages in combat environments as it can be stored warm for up to 24 h, transfused fresh to injured soldiers, and prior to advances in blood banking technology, was administered without typing. It also simultaneously addresses the need for red blood cells for oxygen delivery, the need for clotting factors in plasma as well as platelets in a single unit of blood [9]. As blood banking developed with the discovery of blood types and the use of citrate for blood product storage, the Korean and Vietnam Wars became the stage for the largest whole blood transfusion programs in history. During the Vietnam War, approximately 38,000 units were transfused monthly using primarily group O, low-titer, stored whole blood [5, 10]. Reports from both wars suggested that its use was safe, even at this scale [2, 11, 12].

Despite the growing use of component therapy in the 1960s and 1970s, the military continued to use whole blood in combat-related resuscitations with more than 10,000 units of whole blood transfused during the wars in Iraq and Afghanistan [10]. Fresh whole blood is especially useful in austere environments where soldiers in hemorrhagic shock cannot be readily treated at a medical center with blood banking. A 2016 study examined 21,089 US military combat deaths in Afghanistan from 2001 to 2014, calculating the mortality adjusted for injury severity and the time period of their death [13]. When comparing those who received a blood transfusion and those who did not, the adjusted mortality was 6.8% compared to 51% ($p < 0.001$). The study also demonstrated a survival benefit for those who were transported in less than 60 min with an adjusted mortality of 25.7% vs 30.2% ($p < 0.01$). These data support that earlier blood transfusion and treatment likely save lives in combat environments, a problem that can be addressed with fresh whole blood (FWB) transfusion.

Retrospective data from the US military has supported this practice. A 2013 study examining patients treated by a US army forward surgical team (FST) compared those transfused with only packed red blood cells and fresh frozen plasma to those who received products in addition to fresh whole blood. Using propensity score matching, they found that FWB use was associated with an improved survival with an odds ratio of death of 0.11 (95% CI 0.02, 0.78) [14]. A similar study published in 2009 retrospectively compared US military combat patients who received at least 1 unit of FWB along with pRBCs and FFP to patients who received pRBCs, FFP, and/or platelets [15]. They found that crude survival at 24 h was higher in the whole blood group, 96% vs 88% ($p = 0.018$) and at 30 days, 95% vs 82% ($p = 0.002$). Using multivariate logistic regression modeling, they also found that the whole blood group had a higher odds ratio of survival compared to the control group [OR 12.4 (95% CI 1.8–80)]. Other retrospective data from military use between 2004 and 2006 did not show a benefit but did not find any safety concerns [16]. Pilot programs such as the Blood Far Forward (BFF) initiative are systemically exploring the safety and efficacy of developing training and research programs targeting whole blood use in these situations which may lead to growth of military whole blood programs [17].

Ironically, it was during the Vietnam War, where whole blood was used on a massive scale, that component therapy became the standard in civilian trauma centers [18]. One unit of whole blood can be separated into three components: one unit of packed red blood cells, one unit of plasma, and a portion of a unit of pooled platelets [19]. Breaking down whole blood into its individual components offers the advantage of targeted therapy based on patient need and the ability for longer storage [19]. These two advantages allow for greater resource utilization, especially in large systems requiring substantial donor and storage programs. This development in blood banking led to component therapy replacing whole blood at civilian medical centers throughout the world.

Civilian Interest

However, over the last decade, there has been renewed interest in whole blood programs, especially at civilian trauma centers [5]. Prospective data have examined the feasibility and safety of using LTOWB in civilian trauma (Table 1). A prospective observational study from the University of Pittsburg examined 70 hypotensive trauma patients who received 1–4 units of LTOWB and found no evidence of hemolysis compared to a matched cohort of patients who received only component therapy [21, 24••]. Additional prospective data from the same center also showed that hypotensive trauma patients who received LTOWB had a higher mean ratio of plasma/RBC (0.99 vs. 0.77, $p = 0.006$) and platelet/RBC ratio (0.72 vs. 0.51, $p < 0.0001$) than those who did not receive any whole blood [20]. In 2013, the University of Texas Health Science Center published results of a pilot trial that randomized patients to either LTOWB or conventional component therapy on arrival for their initial resuscitation with a whole blood limitation of 6 units [27]. They did not find any differences in the amount of blood products transfused between the two groups except in a subset of patients without severe brain injury who received significantly less overall blood product in the whole blood group. In an older study, a civilian center in Australia used warm, FWB (< 24 h from donation) in massive transfusion in trauma patients. In a matched cohort study, they did not find any advantage for the patients who received FWB for the utilization of blood product administrated or 30-day mortality [28]. Data on massive transfusion in civilian contexts is sparse, as many centers have been slow to raise limits placed on the maximum number of units a patient can receive. A recent case report from the US demonstrated successful

Table 1 Key recent literature on whole blood (WB) use in civilian settings

Reference	Year	Study type	Key findings
Yazer et al. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients [20]	2016	Prospective observational	No adverse events related to wb transfusion in 47 patients with maximum of 2 units
Seheult et al. Measurement of haemolysis markers following transfusion of uncrossmatched, low-titre, group O+ whole blood in civilian trauma patients: initial experience at a level 1 trauma centre. Transfusion Medicine [21]	2017	Prospective observational	No evidence of hemolysis by laboratory studies in patients receiving either group O or non-group O WB recipients
Sivertsen et al. Preparation of leukoreduced whole blood for transfusion in austere environments; effects of forced filtration, storage agitation, and high temperatures on hemostatic function [22]	2018	Diagnostic	Forced filtration of WB units reduced leukoreduction time but with significant decreases in hemostatic function
Remy et al. Effects of platelet-sparing leukocyte reduction and agitation methods on in vitro measures of hemostatic function in cold-stored whole blood [23••]	2018	In vitro randomized trial	There were multiple decreases in hemostatic function across several measurements after platelet-sparing leukoreduction. These effects worsened over time
Seheult et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients [24••]	2018	Prospective observational	There was no evidence of hemolysis in patients receiving up to 4 units of WB. There were no differences between group O and non-group O recipients
Condron et al. Massive transfusion of low-titer cold-stored O-positive whole blood in a civilian trauma setting. Transfusion [25]	2019	Case Report	Report of 69-year-old male trauma patient who received 38 units of low-titer O WB without evidence of transfusion reaction
Sheppard et al. Prehospital whole blood resuscitation prevents coagulopathy and improves acid–base status at hospital arrival in a nonhuman primate hemorrhagic shock model [26]	2019	Randomized animal model	Coagulopathy prevention was superior with WB resuscitation compared to hetastarch in a pre-hospital primate model

resuscitation of a trauma patient with nearly 40 units of low-titer group O whole blood but suggested possible platelet dysfunction [25] (Fig. 1). While these data in civilian settings are limited, whole blood appears to be safe compared to component therapy, and in certain populations, there may be some advantages. As these programs mature, we expect more comparison data on its safety and efficacy in resuscitations with conventional transfusion programs.

Hemostatic Concerns

Data from the 1990s supported the idea that fresh whole blood has superior platelet function to component therapy [29]. However, questions persist about the effect of cold storage and other processing techniques used by civilian centers on hemostatic function. First and foremost, the effect of leukoreduction on coagulation factors and platelet function is unclear [30]. Leukoreduction is used to reduce pathogens to help attenuate the risk of infectious transmission and to decrease the number of white blood cells that may contribute to a transfusion reaction or alloimmunization to HLA antigens. Initially, these processes filtered both white blood cells and platelets, but during the early 2000s, data emerged about platelet sparing filters that showed minimal effects on platelet quantity but with adequate white blood cell filtering [31]. While these data have suggested that absolute platelet numbers might be affected by filtration, subsequent studies

Fig. 1 Massive transfusion with whole blood after traumatic injury

have focused on platelet function and clot formation, rather than counts.

A 2018 study compared leukoreduced and non-leukoreduced whole blood units using rotational thromboelastometry (ROTEM), thromboelastography (TEG) platelet mapping, and impendence aggregometry to measure differences in hemostatic function [23••]. They found significant decreases across multiple hemostatic assessments in leukoreduced units. These differences were especially pronounced early after leukoreduction. For example, on day 0, median ROTEM maximum clot firmness was 58 mm in the non-leukoreduced units and 65 mm in the leukoreduced units ($p = 0.003$), but these measurements were similar by day 15. Mean platelet concentrations were also lower in the leukoreduced units at day 0 at 162 × 109/L versus 231 × 109/L ($p = 0.004$), but these differences disappeared by day 5. In addition, median AUC for platelet aggregation was significantly reduced in the leukoreduced units until day 15. Each of these measures, and others reported in this study, suggests significantly worse platelet function in vitro after leukoreduction. A 2013 study by Pidcoke et al. reported similar findings when examining pathogen reduction technology (PRT) using riboflavin and ultraviolet light on whole blood units [32]. Their data showed prolongation in PT and PTT as well as decreases in platelet aggregation after pathogen reduction therapy. However, these differences did not persist over the entire study period and all of these effects were attenuated by cold refrigeration at 4 °C versus 22 °C. Their findings that these effects are less pronounced with colder refrigeration have been supported with other in vitro and in vivo data examining stored platelet function [33–39].

A 2011 in vitro study of cold-stored whole blood from healthy volunteer donors examined coagulation properties over time using both TEG and light transmission aggregometry [40]. They found no abnormal TEG values from day 0 to day 11 with some units exhibiting changes by day 14. Aggregation levels were unchanged until after day 7 and never changed either with adenosine diphosphate and epinephrine. The authors concluded that normal coagulation was preserved in these units until at least day 11 after donation. A 2015 data from a Norwegian naval ship testing the feasibility of ROTEM to assess the hemostatic efficacy of whole blood in a relatively austere environment showed comparable results [41]. Clot firmness significantly reduced on days 10 through 14 compared to days 0 to 2 but was comparable with reconstituted whole blood samples. Lastly, a 2018 study examining a faster filtration device for use in austere environments reported more pronounced findings [22]. While they were able to reduce the filtration time compared to conventional approaches, TEG measurements after filtration showed steady functional deterioration with increases in time to clot formation, decreased speed of clot formation, and reduced maximum clot strength. There was also substantial loss of aggregation response by day 10. Consistent with other data comparing storage at 4 °C and 22 °C, aggregation was nearly completely lost by day 3 in blood stored at 22 °C.

The summation of available data on the effects of leukoreduction is relatively mixed. Hemostatic efficacy does appear to worsen over time or after forced filtration, but the clinical implications of these differences have not been established. Many of these differences are relatively small and may not have any meaningful effect in a massive resuscitation. In addition, there is substantial evidence that platelets stored cold either in whole blood or separated as a component, actually function better than platelets stored at room temperature, a benefit for cold-stored whole blood. The potential risks to hemostasis must also be weighed against the important clinical benefits of leukoreduction to patients [42]. Kristoffersen, in a 2019 review on the subject, concluded that most data suggest that platelets are highly functional after platelet-sparing leukoreduction but that additional data are needed on how long platelets retain their functionality [30].

As Holcomb and Jenkins point out in a 2018 editorial, very few of the 5000 hospitals in the USA have the capability of transfusing packed red blood cells, plasma, and platelets simultaneously [43]. Whole blood offers an opportunity to do this more efficiently, and in high quantities. Recent clinical data suggest that outcomes are as good, if not better, when compared with component therapy. Given the logistic advantages to resuscitations, the potential deleterious hemostatic effects may be outweighed by the ability to give more blood products faster, and in more appropriate ratios compatible with the data from the PROPPR trial [44]. In addition, the logistic advantages of whole blood in civilian trauma centers may also extend to the prehospital setting [8]. Data from a recent prehospital trial showed that outcomes were best for patients who received both plasma and packed red blood cells suggesting that whole blood may be beneficial in this setting as well [45]. A 2019 primate model of prehospital transfusion also reported improved coagulopathy prevention prior to hospital arrival compared to hetastarch resuscitation [26].

Our Institutional Practice

We established a whole blood program at Oregon Health & Science University (OHSU) in July 2018. We receive 20 units of low-titer O whole blood from the American Red Cross weekly. The blood is leukoreduced with a platelet sparing filter and has anti-A and anti-B titers less than 200. We receive a mixture of O positive and O negative blood and preferentially give O negative blood to females of childbearing age. We store the blood for up to 14 days, and in the unlikely cases it is not used, we convert the whole blood to PRBCs to avoid waste. During the first year of the program, we transfused 95 trauma patients and 45 non-trauma patients a mean of 6 units

each. We have no limits on whole blood use in patients and convert to 1:1:1 plasma/platelet/RBC transfusion when the supply is exhausted. One minor transfusion reaction was detected, and there were no other known major morbidities. We perform serial TEGs during massive transfusions with whole blood to guide adjunctive therapies, and we give calcium after every 4 units of whole blood routinely.

Conclusion

Going forward, more prospective clinical data are needed to define the role of whole blood in resuscitation, both in the prehospital and hospital settings, and to describe potential safety concerns. The questions surrounding coagulopathy, especially with platelet dysfunction, have not been satisfactorily answered in the clinical setting. Furthermore, what limited data are available in civilian centers are based on relatively small volumes of whole blood per patient [7]. As blood banks increase the maximum amount of blood allowed per patient, we will have a better understanding of the safety profile of whole blood use in massive transfusion as well.

Compliance with Ethical Standards

Conflict of Interest Dr. Gallaher and Dr. Schreiber have nothing to disclose.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were performed in accordance with all applicable ethical standards including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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