Confusion surrounding trauma resuscitation and opportunities for clarification

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BACKGROUND: In the absence of low-titer group O whole blood, conventional components are often transfused to hemorrhaging trauma patients in a ratio designed to replicate whole blood. However, there is still confusion surrounding how conventional components should be used to support traumatically injured bleeding patients, particularly concerning how platelets should be counted in a ratio-based approach and when the resuscitation can switch from a ratio-based to a laboratory-guided approach.

CASE REPORT: A traumatically injured patient, who was resuscitated with 10 units of red blood cells (RBCs), 6 units of plasma, 2 units of apheresis platelets, and 5 pools of cryoprecipitate is described. After hemostasis was achieved, and in the setting of an international normalized ratio of 1.2, the clinical team requested 4 additional units of plasma because "the patient was not resuscitated with a 1:1 ratio of RBCs to plasma." This case illustrates that misconceptions surrounding resuscitation with conventional components may lead to unnecessary transfusions in patients with normal laboratory values who have achieved hemostasis.

CONCLUSIONS: This report provides clarification as to how conventional components can be used for trauma resuscitation and why there is no need to transfuse additional plasma-containing components to achieve a desired ratio when the patient is no longer bleeding and laboratory values are within normal limits. Furthermore, each dose of platelets is suspended in roughly the equivalent of 1 additional unit of plasma that should also be considered in the cumulative dose of plasma administered when using a ratio-based approach.

Although use of low-titer group O whole blood (LTOWB) is increasingly being adopted by civilian trauma centers,[1–3] those without access to this product continue to rely on massive transfusion protocols (MTPs) designed to provide conventional components (i.e., red blood cells [RBCs], plasma, platelets, and often cryoprecipitate) in a ratio designed to replicate whole blood (WB).[4] In spite of widespread adoption of such MTPs, a case is presented that illustrates the ongoing confusion surrounding how conventional components should be used to support traumatically injured bleeding patients. Specific points of confusion include how platelets should be counted in a ratio-based approach and when the resuscitation can be switched from a ratio-based to a laboratory-guided approach.

CASE REPORT

A middle-aged man (age 45-65) was admitted to the emergency department (ED) following a motor vehicle collision. Transfusion of 1 unit of RBCs was initiated in the air ambulance. Upon arrival at the ED, he was intubated and sedated, tachycardic (heart rate, 115), hypotensive (blood pressure, 82/28), and was actively bleeding from both upper and lower extremities with tourniquets in place for hemostasis. The MTP was activated, resulting in the rapid provision of 6 units of RBCs and 4 units of plasma (Fig. 1).[5] This MTP is designed to achieve a 1:1 ratio of plasma:RBCs by

ABBREVIATIONS: ED = emergency department; HD = hospital day; ICU = intensive care unit; LTOWB = low-titer group O whole blood; MTPs = massive transfusion protocols; WB = whole blood.

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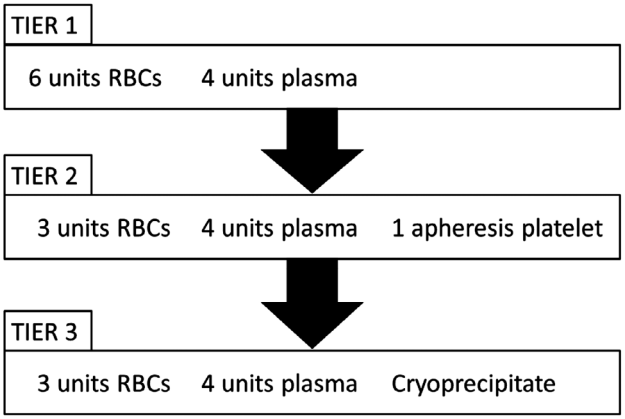

Fig. 1. Graphic representation of the MTP tiers and contents. Tier 1 is sent to the bedside upon MTP activation. Subsequent Tiers 2 and 3 are provided sequentially as needed.

the end of Tier 3, if all of the supplied blood components are transfused. The MTP includes apheresis platelets that are suspended in plasma in Tier 2.

The patient's initial laboratory studies demonstrated a hemoglobin concentration of 9.8 g/dL (reference range, 13.7-16.5 g/dL), platelet count of $153 \times 10^3/\mu L$ (reference range, 145-357 $\times 10^3/\mu L$), INR 1.2 (reference range, 0.9-1.2), and fibrinogen concentration of 157 mg/dL (reference range, 200-393 mg/dL). At this institution, laboratory values are monitored frequently during trauma resuscitation according to an emergency hemorrhage panel protocol.[6] Thromboelastography is not used.

The patient was quickly moved from the ED to the operating room for exploratory laparotomy. The time course and cumulative number of blood components transfused are shown in Fig. 2A, B. The emergency hemorrhage panel laboratory tests were obtained throughout the resuscitation, and the trends in his laboratory parameter response to component transfusions are shown in Fig. 3A-D.

During surgery, bleeding from liver lacerations was controlled with hemostatic agents and packing. Additionally, he underwent orthopedic and vascular surgery for upper and lower extremity open fractures and vascular injuries. Approximately 2.5 hours after his initial presentation, the bleeding was controlled and he was transferred to the intensive care unit (ICU). Heretofore, the patient had received 10 RBC units, 6 plasma units, 2 apheresis platelet units, and 5 cryoprecipitate pools (each containing 5 individual units). Laboratory studies, performed in the ICU 5 hours after initial presentation, demonstrated a hemoglobin concentration of 9.6 g/dL, platelet count of $120 \times 10^3/\mu L$, INR of 1.2, and fibrinogen concentration of 281 mg/dL.

Shortly after the patient was admitted to the ICU, the trauma surgery service attending physician requested four units of plasma because "the patient was not resuscitated with a 1:1 ratio of RBCs to plasma." The transfusion service attending physician declined to fill this plasma order because the patient's INR was normal and the patient was no longer bleeding, thus transfusing these 4 additional plasma units solely to increase the plasma:RBC ratio would only have conferred risk to the patient without hemostatic benefit. Further, the ratio was already nearly 1:1 when the plasma contributed from the apheresis platelet transfusions was included in the total number of units of plasma transfused.

The patient had an uneventful postoperative course and was discharged on Hospital Day (HD) 53. During the remainder of his hospital stay, he was transfused an additional 6 units of RBCs: 2 on HD 3 in setting of abdominal washout and closure, 1 each on HD 4 and HD 5 for anemia related to ongoing oozing from lower extremity injuries, and 2 on HD 15 during debridement and flap closure for an open lower extremity wound.

The patient described herein has provided consent for the writing of this case report. Unique characteristics and protected health information have been removed to protect the identity of the patient. This case report is presented for educational purposes only and did not require human subject review per the local institutional review board.

DISCUSSION

Historically, resuscitation protocols focused on the early and aggressive use of crystalloids because they were inexpensive, sterile, and easily transported at room temperature. It is now clear, however, that reliance on saline to resuscitate trauma patients is deleterious[7] and that the early administration of blood components is important in reducing mortality.[8–12]

The concept of ratio-based resuscitation has become the de facto standard of care in military and civilian trauma situations. Centers without LTOWB can attempt to replicate WB by transfusing conventional components in a 1:1:1 ratio that mimics WB, that is, for every RBC unit transfused, a plasma unit, and the equivalent of a WB-derived platelet unit is transfused (Fig. 4A). However, reconstituting WB in a 1:1:1 ratio using conventional components results in a product that is more dilute and has a lower concentration of clotting factors, platelets, fibrinogen, and hemoglobin compared to WB.[13]

Although studies have demonstrated the importance of early administration of blood components, the optimal ratio to apply when using conventional components remains unclear. The PROPPR trial compared 1:1:1 (plasma:platelet:RBC) to 1:1:2 in trauma patients who were predicted to require a massive transfusion.[14] While the study's time points were perhaps not ideal for measuring outcomes in bleeding trauma patients, it is important to recognize that there was no difference in mortality at 24 hours or at 30 days between the patients in these two groups, although

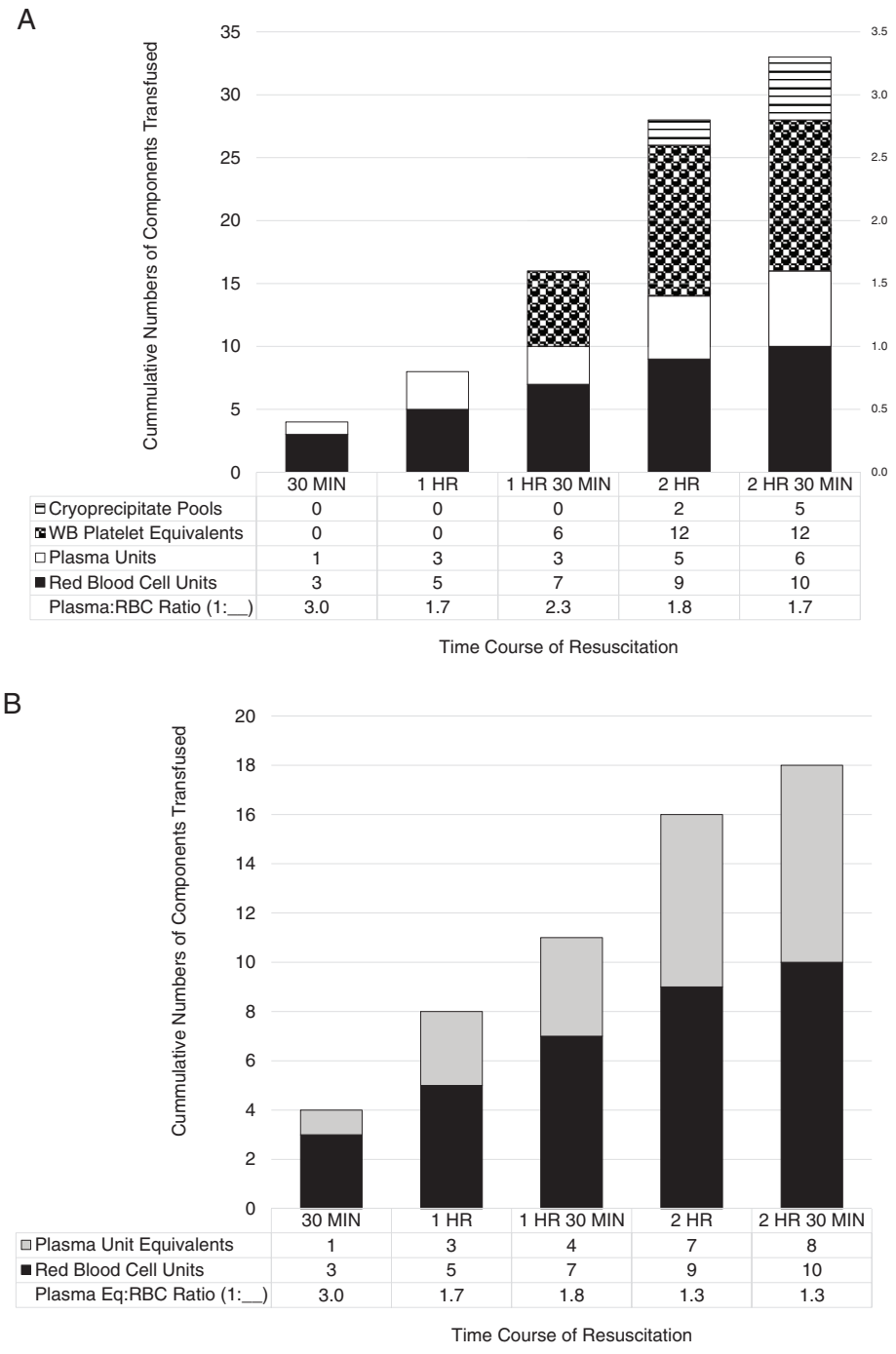

Fig. 2. (A) Graphic representation of cumulative numbers of blood components transfused over the course of the resuscitation. In this image, apheresis platelets are converted to the equivalent of six WB-derived platelet concentrates per apheresis unit transfused. (B) Graphic representation of ratio of plasma equivalents (includes plasma derived from apheresis platelets) to RBCs.

death secondary to hemorrhage and the time to surgical hemostasis favored the higher ratio (1:1:1) group.

Perhaps more important than the final ratio is how that ratio is achieved. A subanalysis of the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study found an association between the early administration of plasma (within the first 3-6 transfusion units and within 2.5 hr of admission) with reduced 24-hour and 30-day mortality compared to patients who receive delayed plasma transfusion but who nevertheless eventually achieved a balanced ratio by the end of their resuscitation (i.e., patients who did not receive early administration of plasma but

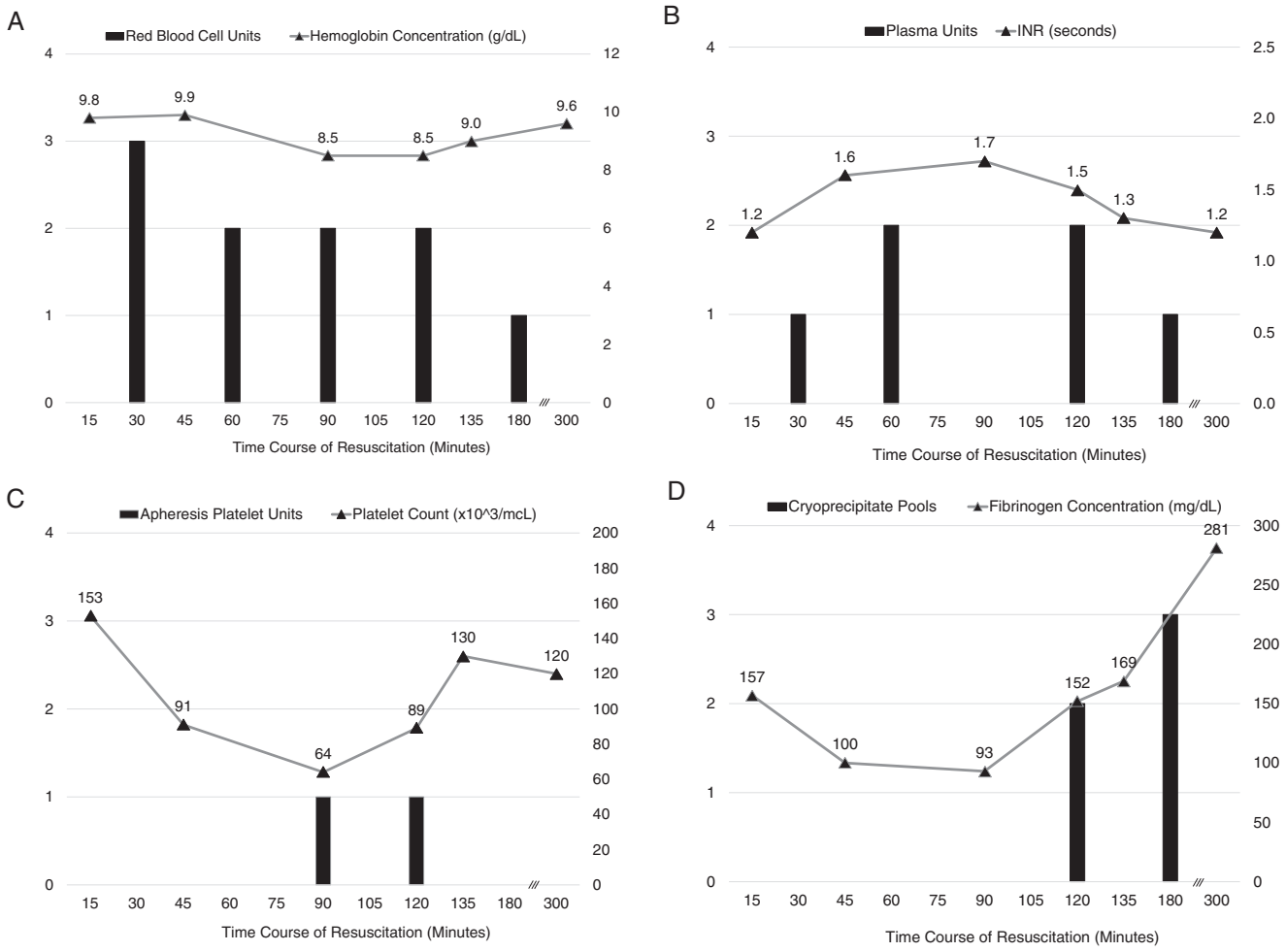

Fig. 3. Graphic representation of laboratory study results at the time of specimen draw compared to blood components transfused at the time of transfusion. (A) Over the course of the resuscitation, 10 units of RBCs were transfused maintaining the hemoglobin concentration ≥8.5 g/dL. (B) Over the course of the resuscitation, 6 units of plasma were transfused, maintaining the INR <1.8. The drop in INR from 1.7 to 1.5 between 90 minutes and 120 minutes in the absence of plasma transfusion is attributed to the plasma from the platelet unit transfused at 90 minutes. (C) Over the course of the resuscitation, 2 units of apheresis platelets were transfused, maintaining the platelet count ≥60 × 10^3/μL. (D) Over the course of the resuscitation, 5 pools of cryoprecipitate were transfused, maintaining the fibrinogen concentration >90 mg/dL. The rise in fibrinogen concentration from 93 to 150 between 90 minutes and 120 minutes in the absence of cryoprecipitate transfusion is attributed to the plasma from the platelet unit transfused at 90 minutes.

achieved plasma:RBC ratios balanced to 1:2 or greater by Hour 4).[15] Similarly, the results of a large retrospective study suggest that for patients within a certain range of trauma injury severity scores, the magnitude of their plasma deficit at 3 hours into the resuscitation, that is, how many fewer plasma units compared to RBC units had been administered, might also be an important predictor of mortality,[16] once again emphasizing the importance of the early intervention with plasma. This is consistent with what is known about the development and progression of the trauma-induced coagulopathy[17] and perhaps plasma's beneficial effects on traumatically damaged endothelium.[18]

Further support for early blood component transfusion comes from the Prehospital Air Medical Plasma (PAMPER) trial, which demonstrated a reduction in 30-day mortality among trauma patients who received 2 units of plasma during their helicopter evacuation compared to patients who received the standard of care.[11] In a secondary analysis, receipt of any blood product during the prehospital phase of resuscitation produced a significantly improved 30-day survival rate compared to patients who received crystalloids alone.[12] Additionally, among those who received any prehospital blood components, each liter of crystalloid that was administered was associated with a 65% increase in 30-day mortality. In fact, the lowest mortality in this analysis was found in patients who received both RBCs and plasma compared to those who received RBCs or plasma alone. However, in the Control of Major Bleeding After Trauma

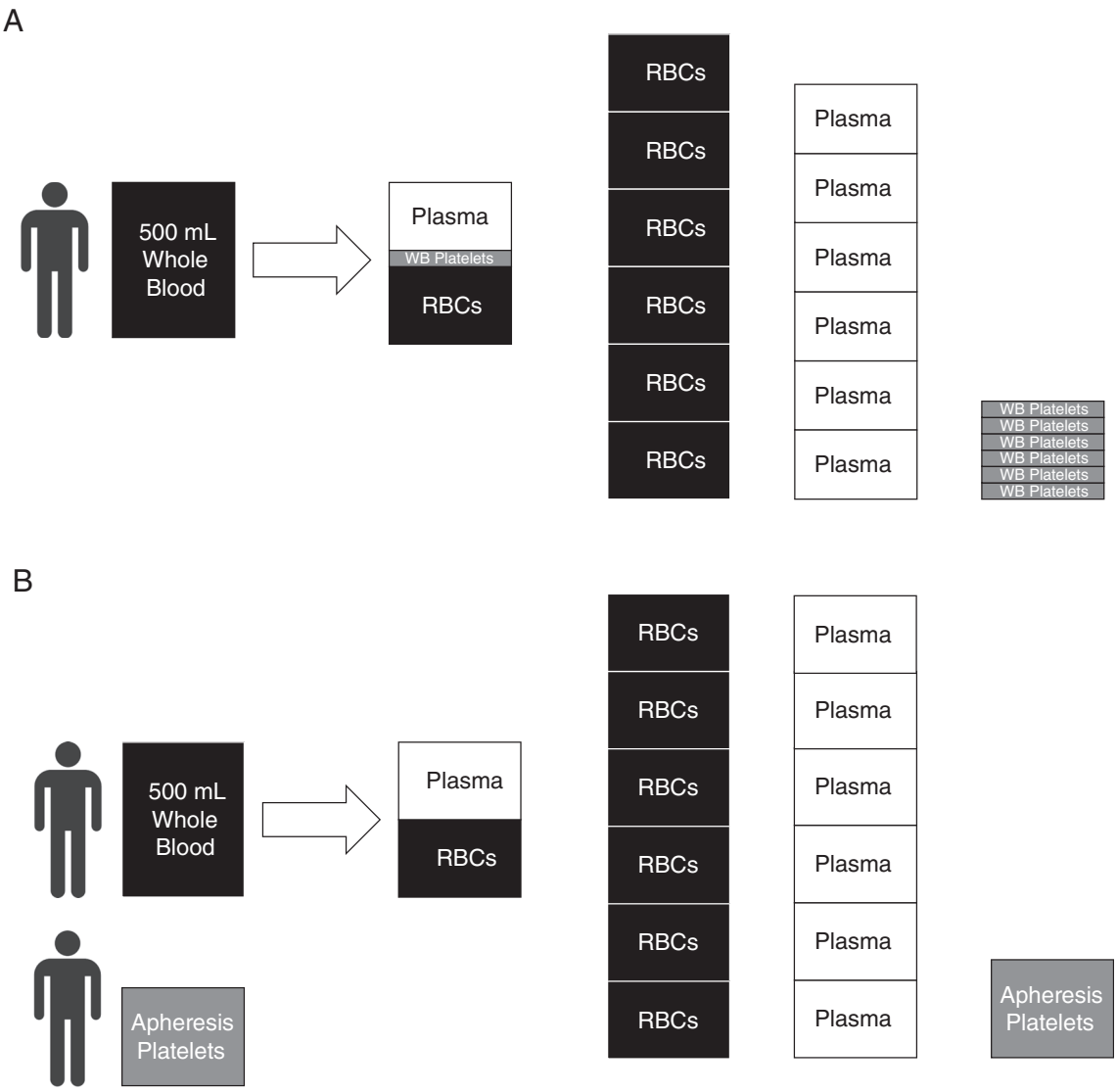

Fig. 4. Graphic representation of two methods of achieving a 1:1:1 (plasma:platelet:RBC) ratio-based blood product resuscitation strategy. (A) One unit of RBCs, 1 unit of plasma, and 1 unit of platelets derived from WB constitute a 1:1:1 ratio-based resuscitation strategy. Most blood banks do not issue individual WB-derived platelets; they are usually issued in pools of 4 to 6 units. (B) One unit of RBCs, 1 unit of plasma, and 1 unit of apheresis platelets also constitute a 1:1:1 ratio-based resuscitation strategy.

(COMBAT) trial of plasma transfusion to traumatically injured patients transported to the hospital by ambulance, no benefit of prehospital transfusion with plasma was observed.[19] However, there were patient demographic and transportation time differences between these two studies including the fact that only 32% of the patients in the COMBAT trial received the full two doses of plasma in their median 16- to 19- minute ambulance transportation time compared to 89% of the patients in the PAMPER trial, who received the full two doses of plasma during their median 40- to 42-minute helicopter transportation time.

Recognizing the potential importance of providing plasma early in the resuscitation has led to several innovations in the blood bank including the use of thawed or liquid plasma[20,21] and the use of group A plasma instead of group AB plasma for recipients of unknown ABO group.[22–24]

Platelets are also an important aspect of fixed ratio resuscitation. In ratio-based parlance, the platelet contribution is equivalent to the number of platelets derived from a unit of WB. WB-derived platelets are administered in pools of 4 to 6 individual units to produce a dose of platelets sufficient for an adult (Fig. 4A). However, in the United States, the vast majority of platelets transfused are prepared by apheresis from a single donor and suspended in plasma (Fig. 4B).[25] One single donor apheresis unit or 1 pool of 4 to 6 WB-derived platelets provide an equivalent quantity of platelets, and one dose of either a pool of WB platelets or an apheresis single-donor unit should be administered for

every 4 to 6 RBCs transfused to achieve a 1:1 ratio of platelet:RBC. All platelets, be they apheresis units or WB-derived pools, are considered equivalent in terms of hemostatic efficacy and are used interchangeably in civilian trauma centers.[26]

Each apheresis unit or WB-derived platelet pool is suspended in roughly the equivalent of 1 unit of plasma. In the case of the WB-derived platelet pool, the plasma comes from the original WB units (Fig. 4A) while in the apheresis platelet unit, the plasma is collected concurrently from the donor during the apheresis donation (Fig. 4B). Although stored for 5 to 7 days, the activity of most coagulation factors in the plasma that accompanies either a WB-derived pool of 4 to 6 units or an apheresis platelet is adequate for hemostasis.[27–29] Thus, each dose of platelets could also be considered as an additional plasma unit when calculating the total plasma:RBC ratio. For example, Fig. 2B demonstrates the total plasma:RBC ratio for this patient at the end of his resuscitation, including the plasma contained in the apheresis platelet units along with the plasma units. Within 2.5 hours after admission, the ratio was nearly 1:1. This approach is not applicable, however, if the apheresis platelet is suspended in platelet additive solution as this replaces approximately two-thirds of the plasma.[30] Currently, only a small minority of platelets in the United States are suspended in platelet additive solution.

The concept that platelets suspended in plasma contribute essentially an additional unit of plasma has not been described in studies in civilian trauma patients resuscitated using conventional components. In the Pragmatic, Randomized, Optimal Platelet and Plasma Ratios (PROPPR) trial, transfused apheresis platelets were counted only toward the platelet contribution and were not included when determining the total number of plasma units transfused.[14] In the PROMMTT study, only plasma:RBC and platelet:RBC ratios were assessed.[15] However, this study also did not include the platelet contribution when assessing total plasma units transfused.

As this case illustrates, even though platelets have not previously been considered when calculating the total quantity of plasma transfused, platelets do contribute clotting factors in the form of plasma and this contribution can be appreciated when monitoring patient laboratory values. As shown in Fig. 3B, the INR decreased between minutes 90 and 120 even though no plasma units were transfused; the improvement in the INR was likely due to the plasma contained in the apheresis platelet transfused during that interval. As shown in Fig. 3D, the fibrinogen concentration also increased between minutes 90 and 120, even though no cryoprecipitate pools were transfused; this improvement was also likely due to the administration of fibrinogen in the plasma fraction of the apheresis platelet transfused during that interval.

Cryoprecipitate is not specifically referenced in the 1:1:1 ratio-based approach and is not typically included in the first pack of most MTPs.[4] Cryoprecipitate is a concentrated form of fibrinogen derived from plasma. It is administered in pools of 4 to 6 units, with the total amount of fibrinogen per pool typically approaching 2000 mg in approximately 100 mL of plasma.[31] There is approximately 700 mg of fibrinogen in a unit of plasma, assuming there is approximately 3 mg/mL of fibrinogen in a 230-mL plasma unit, so the number of doses of cryoprecipitate can be adjusted based on the number of plasma units transfused.[20] Cryoprecipitate should be transfused when a trauma patient's fibrinogen concentration is <150 to 200 mg/dL and fibrinogen supplementation is required beyond what is provided in plasma.[32]

As this case illustrates, how the patient is resuscitated with conventional components in a "goal-directed" manner may be more important than the final ratio of components transfused. Early in the resuscitation, before the results of laboratory testing can be obtained, use of LTOWB or conventional components with a ratio-based approach is the best way to replicate the contents of WB. As the resuscitation proceeds, laboratory testing, with either expedited traditional laboratory tests (complete blood count, INR, fibrinogen) or viscoelastic hemostatic assays (thromboelastography/rotational thromboelastometry) can complement the ratio-based approach by monitoring the patient's coagulation status and identify opportunities for the transfusion of additional products.[6,33] Current recommendations are to begin the resuscitation with a balanced ratio of components (plasma:platelet:RBC ratio of 1:1:1-2) and then transition to laboratory-guided resuscitation when laboratory studies become available and are returned in a relevant period in relation to the rate of bleeding.[32]

CONCLUSION

When LTOWB is not available, providing a balanced resuscitation with conventional components in plasma:RBC ratios of 1:1-1:2 is the ideal approach early in the resuscitation of massively bleeding trauma patients. There is no need to transfuse additional plasma-containing components to achieve a desired ratio when the patient is no longer bleeding.

Apheresis platelets or pools of WB-derived platelets should be administered for every 4 to 6 RBC units transfused to maintain a 1:1 ratio of platelet:RBC. Recognize that each dose of platelets is suspended in roughly the equivalent of 1 unit of plasma that could also be considered in the cumulative dose of plasma administered. Transfuse cryoprecipitate when patients are hypofibrinogenemic and need a concentrated source of fibrinogen. Laboratory testing performed throughout the resuscitation can detect an evolving coagulopathy and identify situations in which patients may benefit from transfusion of additional components beyond what is administered with the ratio-based protocol.

Centers providing MTPs for trauma patients should clarify with stakeholders when patients should be transitioned from ratio-based to laboratory-guided resuscitation and specify how the plasma that is provided when platelets are transfused is counted in the ratio-based approach.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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