Seguridad en la transfusión de plasma incompatible y hematíes en pacientes con hemorragia masiva

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RESUMEN

Existe un interés creciente en la importancia de emplear hemocomponentes de una forma precoz en la resucitación de los pacientes con hemorragia masiva (incluidos los pacientes con trauma). Sin embargo, hay varios factores que deben ser analizados: la hemólisis intravascular tras la administración de sangre completa, la hemólisis tras la transfusión de plasma incompatible en productos sanguíneos o la transfusión incompatible de plasma.

PALABRAS CLAVE: Trauma, Sangrado masivo, Transfusion, Plasma, Incompatibilidad, Sangre completa grupo O, Hemolisis.

Safety of transfusing incompatible plasma and emergency issued red blood cells to massively bleeding patients

SUMMARY

There is growing appreciation of the importance of using blood products early in the resuscitation of massively bleeding patients (including trauma patients). However, several factors must be considered: intravascular hemolysis after group O RBCs in LTOWB transfusion, hemolysis following the transfusion of incompatible plasma containing blood products or incompatible plasma transfusion.

KEYWORDS: Trauma, Massive bleeding, Transfusion, Plasma, Incompatible, Low titer group O whole blood, Hemolysis.

There is growing appreciation of the importance of using blood products early in the resuscitation of massively bleeding patients including trauma patients. Historically, the resuscitation of these patients involved the administration of large volumes of crystalloid fluid, which was designed to accomplish several goals including increasing the patient's blood pressure and providing a mechanism to transport the large natural reserve of red blood cells (RBC), clotting factors, and platelets to the tissues and the site of injury[1].

However, several factors were not considered in this approach. First, it is now becoming clear that there is not the need to maintain a near normal systolic blood pressure in most massively bleeding trauma patients. A prospective trial published in 1994 demonstrated that hypotensive patients with penetrating injuries who were aggressively treated with Ringer's acetate solution before they were taken to the operating room had significantly worse survival and longer lengths of stay in the hospital compared to similarly injured patients who were not aggressively treated with crystalloid fluids until they entered the operating room (62 % vs 70 % survival to discharge; p= 0.04, and fourteen vs eleven days in hospital; p=0.006, respectively)[2]. Other studies have found similar survival disadvantages following the liberal administration of crystalloid fluids in trauma resuscitation[3-7], while other publications have reported on the non-physiologic contents of different crystalloid fluids[8,9]. The latest US miliary resuscitation guidelines (Tactical Combat Casualty Care - TCCC) prohibit the use of crystalloids in favor of administering blood products in balanced ratios to avoid the pitfalls of overzealous crystalloid resuscitation[10]. Building on these data, a recent practice guideline from the Trauma, Hemostasis, and Oxygenation Research (THOR) network suggests that the target systolic blood pressure during the resuscitation should be 100 mmHg and blood products should be used as the primary resuscitation fluid[11].

Underpinning the recommendation to use blood products in trauma resuscitation are data from clinical studies. Both military and civilian observational studies have found survival benefits following the transfusion of blood products, primarily RBCs, to injured patients[12,14]. The Prehospital Air Medical Plasma (PAMPer) cluster randomized trial found that the supplementation of the standard of care (RBCs and/or saline) with up to two units of plasma for injured patients transferred to hospital by helicopter reduced 30-day mortality by nearly 10 % for patients treated with plasma compared to those who received the standard of care (23.3 % vs 33 %, respectively; p=0.03)[15]. In fact, a secondary analysis of this study found that patients who were resuscitated with any blood product had significantly higher survival than those who were resuscitated with saline alone, and that receipt of both RBCs and plasma was associated with the highest survival rates[16]. The Resuscitation with Pre-Hospital blood products (RePHILL) randomized trial compared the outcomes of injured patients who received either lyophilized plasma and RBCs, or saline while en route to the hospital[17]. There was not a significant difference in the primary composite outcome of this trial, which was either episode mortality (prehospital and in-hospital mortality combined) or the failure to reach lactate clearance <20 % per hour in the first two hours after randomization. However, the former outcome utilized a time point that

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was perhaps inappropriately long to measure the effect of prehospital transfusion. This is because the median length of follow up of patients in this study was eight days, long after patients would have been expected to die from traumatic bleeding[18,19]. However, when considering the reported rate of death at three hours, which was a secondary outcome in this study but is a time point that is germane to measuring the effectiveness of prehospital transfusions[20], there was a 25 % relative risk reduction in death amongst the patients who received prehospital blood products. Thus, the use of prehospital blood products is expected to increase in the future.

As blood collectors try to meet the increasing demands for blood products, innovative ways of supplying these products must be found. The desire to provide prehospital and early in-hospital balanced resuscitation has led to the modern renaissance of cold stored low titer group O whole blood (LTOWB). The advantages of this product have been reviewed elsewhere[21-25], but a theoretical problem exists: since LTOWB will likely be first administered very early in the resuscitation when the patient's ABO group is unknown, it is possible that this product will be administered to a recipient whose blood group is not group O (i.e., they might be A, B, or AB). The group O RBCs in LTOWB are compatible with patients of all ABO groups, but the naturally occurring anti-A and anti-B that are always found in the plasma of group O individuals might bind to the A and/or B antigens on a non-group O recipient's RBCs and cause their destruction (a process known as hemolysis) (table 1). If intravascular hemolysis occurs, the recipient might experience a severe reaction involving fever, chills, hypertension, renal failure, disseminated intravascular coagulation (DIC), and hemoglobinuria[26]. These reactions can be fatal. To mitigate the risk of intravascular hemolysis, group O donors with a low titer of both anti-A and anti-B must be selected. The question then becomes, what constitutes a low titer of these antibodies?

A recent scoping review of nearly ten databases since their inception was performed to elucidate the lowest anti-A and/or anti-B titer that was responsible for causing hemolysis following the transfusion of incompatible plasma containing blood products, such a platelets[27]. The authors found 49 eligible studies consisting of case reports and short cases series. The titer of the incompatible antibody was reported in 46 cases; in 31/46 (67 %) cases, the titer of the incompatible antibody was ≥256. This suggests that the risk of hemolysis when transfusing incompatible plasma could be largely mitigated if donors with anti-A and/or anti-B titers of ≥256 are excluded from donating LTOWB, a titer threshold that has been widely adopted worldwide[28].

Table 1. *ABO donor and recipient compatibilities*

Recipient blood group	ABO antigens on RBC	Antibodies in plasma	Compatible donor RBC groups	Compatible donor plasma groups
A	A	Anti-B	A, O	A, AB
B	B	Anti-A	B, O	B, AB
O	None	Anti-A and anti-B	O	Any ABO group
AB	A and B	None	Any ABO group	AB

Note that low titer group O whole blood (LTOWB) is considered a universal donor product that is compatible with recipients of any ABO group.

To this end, several studies have been published that specifically addressed the occurrence of hemolysis following the transfusion of LTOWB in trauma. To determine if hemolysis occurred following the transfusion of LTOWB, recipients should be stratified by their ABO group: group O recipients who would not hemolyze following receipt of LTOWB versus non-group O recipients who are at risk of hemolysis. The biochemical markers of intravascular hemolysis include lactate dehydrogenase (LDH) and bilirubin, which are both normally found inside the RBCs, and haptoglobin, which is a molecule that binds to free hemoglobin in the plasma. If hemolysis occurs, LDH and bilirubin should increase when they are liberated from the RBCs and haptoglobin should decrease as it becomes consumed binding plasma free hemoglobin. Potassium can also be a marker of hemolysis as it would be released from the RBCs when they are destroyed. Intravascular hemolysis was not detected amongst the non-group O trauma patients at a single healthcare system when they received a median of one unit of LTOWB at a titer threshold of <50[29], when they received a median of two LTOWB units at a titer threshold of <50[30], and when they received a median of four units at titers of <50[31], and <100[32]. In none of these studies was there any clinical suspicion of hemolysis amongst the non-group O LTOWB recipients. Similar results have been found in injured non-group O children who received LTOWB during their resuscitation[33,34]. Thus, moderate quantities of LTOWB appear to be serologically safe in trauma patients, i.e., intravascular hemolysis was not detected.

Recently, a study describing LTOWB use amongst primarily non trauma patients on whom emergency uncrossmatched blood had been ordered found that after receipt of a median of two LTOWB units with a titer <200 there were not any differences in several laboratory markers of hemolysis and coagulation, as well as hemoglobin and creatinine, at either 24 hours or seven days after transfusion between the non-group O and group O recipients[35]. In total, these data indicate that the transfusion of moderate quantities of LTOWB to bleeding patients does not result in clinically detectable hemolysis.

Another blood product that is being used to treat massively bleeding trauma patients early in the resuscitation when the recipient's ABO group might not be known is group A plasma[36], especially when group AB plasma is not available. Group AB plasma is highly desirable because it does not contain anti-A or anti-B, so it is compatible with recipients of all ABO groups (table 1). However, group AB individuals are very uncommon, comprising only approximately 3 % of the population[37], so their plasma is a very scarce resource. Thus, as plasma is an important part of balanced resuscitation, some centers in the US have started using group A plasma when group AB plasma is not available[38]. The rationale for using group A plasma is that the majority (>85%) of recipients will be either groups A or O[37], thus they will not hemolyze from receipt of group A plasma. Furthermore, approximately 80 % of group B and AB patients will have soluble B substance in their plasma that can adsorb the anti-B antibody in group A plasma, as well as having group B antigen on some body tissues that can also adsorb the antibody and prevent hemolysis from occurring[39]. In a recent survey of 103 American

adult Level 1 trauma centers[38], 91 % of respondents reported using group A plasma in emergencies when the recipient's ABO group is unknown, and 66 % reported not having a limit on the number of group A plasma units that can be transfused. In fact, 83 % of respondents did not titer the anti-B in the group A plasma units used in emergencies, and 47 % reported using group A plasma even if the recipient's ABO group is known to be B or AB while they are having a massive bleed. Given the widespread use of group A plasma in situations where it could be transfused in an incompatible manner with the potential for intravascular hemolysis to occur, what is the evidence for the safety of this practice?

The first study to address this question was the Safety of the use of group A plasma in Trauma (STAT) study[40]. This was a retrospective, multicenter study of 809 injured group A (control) patients and 354 injured group B/AB patients who received at least one unit of group A plasma during their initial resuscitation. In this study, the B/AB patients received a mean of four units of group A plasma (approximately 1 liter). However, there was not a significant difference in in-hospital mortality, early mortality, and hospital length of stay between the group A patients and the B/AB patients who could have hemolyzed from receipt of group A plasma. Furthermore, logistic regression models for in-hospital mortality and 24-hour mortality did not find receipt of group A plasma to be a significant predictor of those endpoints. In this study, 76 % of the participating institutions did not titer the anti-B in the group A plasma and yet there were not any reports of acute hemolytic transfusion reactions attributable to ABO incompatibility. In this study, laboratory derived biochemical markers of hemolysis were not analyzed, thus, it is not possible to determine if hemolysis occurred. However, even if hemolysis occurred, it did not lead to worse outcomes for the potentially affected group B/AB patients.

The STAT study provided evidence that administering group A plasma to injured B/AB recipients during their resuscitation was safe. However, the study only considered the volume of incompatible plasma that was administered in the form of the incompatible plasma units themselves. Other sources of incompatible plasma, such as LTOWB, platelets, cryoprecipitate, and even the small quantity of plasma in RBC units should be considered. To that end, a second study was performed (Seheult *et al*., 2020). This follow on study was also retrospective in design and multicenter in nature and featured a total of 2618 trauma patients who had received at least one RBC unit and one plasma unit (or one LTOWB unit) in their resuscitation. In this study there were 1282 patients who received a median of 342 ml of incompatible plasma from any source and 1336 patients who did not receive any incompatible plasma. In this study, the fixed marginal effects model did not reveal a significant difference in 6- or 24-hour mortality, or 30-day mortality between the two groups stratified by their survival probability. Once again, the laboratory markers of hemolysis were not evaluated so it was not possible to determine if hemolysis actually occurred amongst the patients who received incompatible plasma. While the volume of incompatible plasma that was transfused in this study was relatively small, it reflected the practice at nine trauma hospitals and further reinforced the safety of administering incompatible plasma to bleeding trauma patients.

A third study that evaluated the effect of incompatible plasma transfusion on mortality has been recently published (Donohue *et al*., 2023). This was a secondary analysis of the 347 patients that a single American trauma center contributed to three multicenter trials that evaluated different strategies for using blood products in trauma resuscitation. In this analysis, the total volume of incompatible plasma that was transfused in the patient's first two days in the hospital was determined, in addition to several outcome measures. In this cohort of trauma patients, there were 180 patients who received a median of 684 ml. of incompatible plasma and 167 patients who did not receive any incompatible plasma. As in the previous two studies, although it could not be determined if there was biochemical evidence of hemolysis, this analysis did not find a significant difference in 24-hour and 30-day survival between these two groups of patients, and receipt of incompatible plasma was not a significant predictor of either mortality outcome in the multivariate Cox proportional-hazards regression model. There was also not a statistically significant difference in the hospital or intensive care unit lengths of stay between these two groups.

More evidence that hemolysis does not typically occur when incompatible blood products are transfused in trauma comes from several studies of recipients with RBC-directed antibodies other than anti-A and anti-B. As reviewed in Donohue et al., (2023) there have been several case series describing patients who have had antibodies to RBC antigens other than A and B, such as anti-D, anti-K and anti-Fy^{a}; these are antibodies that are stimulated only after exposure to another person's RBCs, such as during pregnancy or after transfusion, and they tend to be IgG in nature. Thus, the hemolysis that they would cause tends to be extravascular (i.e., occurring in the macrophages in the liver and spleen but not inside the vessels) such that the patient's only signs and symptoms of an extravascular hemolytic reaction caused by an IgG antibody are often mild fever, slight jaundice, and a lower than expected increment in the recipient's hemoglobin concentration following transfusion. In one series of seventeen patients who received at least one unit of uncrossmatched RBCs[44], seven of those patients were found to have received fifteen incompatible RBC units (i.e., the RBC unit was positive for an antigen to which the recipient had an antibody); in 6/7 of these patients there was not any clinical evidence or suspicion for a hemolytic reaction while the remaining patient had evidence of hemolysis even before he was transfused with the uncross matched RBC for a gastrointestinal bleed. Thus, it would appear as if the transfusion of emergency issued RBCs, i.e., RBCs that have not been shown to be antigen negative and compatible with the recipient's RBC-directed antibodies (other than anti-A and anti-B), in a massively bleeding patient is safe even if they have unexpected RBC antibodies. Again, extravascular hemolysis occurs by a different mechanism than the intravascular hemolysis caused by anti-A and anti-B as described above. Still, the fact that extravascular hemolysis is not detected after incompatible transfusion is reassuring because there is often an IgG component to the anti-A and anti-B in LTOWB and group A plasma.

The emerging evidence suggests that the transfusion of potentially incompatible plasma-containing products during trauma resuscitation is safe from a hemolysis perspective and that even if hemolysis does happen, it does not negatively influence patient

survival or morbidity parameters. Thus, there is not clinical or laboratory evidence against implementing a prehospital transfusion program with LTOWB or group A plasma for massively bleeding patients.

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