Towards a more complete understanding of who will benefit from prehospital transfusion

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For with much wisdom comes much sorrow,

and as knowledge grows, grief increases.

Ecclesiastes 1:18

Introduction

The optimal transfusion strategy for patients with severe bleeding has changed over time and by national resuscitation philosophy - from whole blood to plasma to individual components, then to crystalloids and colloids and now once again whole blood is being reconsidered. The in-hospital transfusion strategy can be guided by hemodynamic monitoring and laboratory evaluation especially after the initial resuscitation effort when the patient is more stable. However, in the prehospital phase of the resuscitation, it is more difficult to determine when and how patients with bleeding should be transfused, and the ability to predict which patients will go on to require a massive transfusion is severely limited in this setting. In reality, during the initial resuscitative phase of care, whether in- or out-of-hospital, transfusion decisions are mostly guided by pragmatic clinical data and constrained by logistical and technical considerations.

In this commentary it will be demonstrated that the results of the recently published randomized controlled trials (RCT) that investigated the effects of prehospital transfusion are not necessarily conflicting, but rather they help to establish the nature of the patients who might benefit from prehospital transfusion.

Background

There have been three civilian observational trials that investigated the effect of prehospital RBC transfusion on mortality in injured patients. In a logistic regression analysis of a retrospective, propensity matched, single-center study, Brown et al.[1] found an approximately 5-fold increase in 24-hour survival (adjusted odds ratio=4.92; 95% CI, 1.51-16.04; p=0.01), lower incidence of shock upon arrival at the emergency department (adjusted odds ratio=0.28; 95% CI, 0.09-0.85; p=0.03), and lower 24-hour total RBC transfusion requirement (Coefficient -3.6 RBC units; 95% CI, -7.0 to -0.2; p=0.04) amongst 240 patients who received a median of approximately one prehospital RBC unit compared to 480 patients who were not transfused in the prehospital phase of their resuscitation. A multivariate regression analysis of retrospective data from a historical case control study by the London Air Ambulance service in the United Kingdom found a significant reduction in prehospital mortality for patients with major trauma who received a median [interquartile range (IQR]) of 2 (1-3) RBC units during their helicopter transport to hospital (n=239) versus patients who were not resuscitated with RBCs on the helicopters (n=300; odds ratio 0.52; 95% CI 0.35-0.78; p=0.001); the absolute risk reduction in prehospital death was approximately 14% (42.2% versus 27.6%, respectively).[2] This study did not find an improvement in overall survival following receipt of prehospital RBC transfusion versus not receiving prehospital RBC transfusion, although overall survival is not the ideal timepoint to evaluate the efficacy of one of the first interventions administered during the resuscitation (see below). A third observational study that evaluated mortality outcomes amongst injured patients who received prehospital transfusions during their helicopter evacuation to the hospital (n=142) compared to those who did not (n=916) found higher unadjusted mortality at several time points amongst the blood product recipients.[3] However,

these outcomes were confounded because the prehospital blood product recipients were more severely injured than the non-recipients.

There is also observational evidence that prehospital transfusion improves survival in military casualties.[4-7] In a retrospective study, Shackelford et al. reported that injured soldiers who received prehospital transfusions (plasma, RBC, or both; n=62) had significantly lower mortality than matched non-recipients (n=324) at 24 hours and 30 days.[8] This analysis found that only the transfusions that were administered within 15 minutes of MEDEVAC rescue (median 36 min from injury) were associated with reduced 24-hour mortality [hazard ratio, 0.17 (95% CI: 0.04-0.73; p=0.02)]; there was an approximately 17% absolute risk reduction in 24-hour mortality amongst the patients who received transfusions within 15 minutes compared to those whose transfusions were administered after that time (3.2% vs 21.0%, respectively). This absolute risk reduction value is quite similar to the 14% risk reduction in prehospital death observed in the London-based study.[2]

Data from the RCTs on prehospital transfusion

Whilst observational studies provide valuable insights into the use and effects of pre-hospital transfusion, by their design their interpretation is limited by the potential influence of unmeasured confounders on study outcomes – something that is mitigated by the use of a randomized design.

Over the past four years, three RCTs have evaluated the efficacy of administering prehospital transfusions to injured patients. The Prehospital Air Medical Plasma (PAMPer)[9] and Control of Major Bleeding After Trauma Trial (COMBAT)[10] trials were developed with harmonized inclusion criteria and were published in 2018. In the cluster-randomized multicenter PAMPer trial, two units of thawed plasma supplemented each helicopter base's standard care for resuscitating trauma patients, which could have included saline only or RBCs (13/27 of PAMPer participating air medical bases routinely carried RBCs). In the single-center COMBAT trial, the patients were transported by ground ambulance to the hospital and they were randomized to receive either two units of frozen plasma that were thawed on demand in the ambulance using specially designed bags or a volume of 0.9% normal saline guided by the patient's hemodynamic need; prehospital RBCs were not available in this study. The results of these trials were different. In PAMPer, there was a significant reduction in 30-day mortality between the prehospital plasma recipients (n=230) and non-recipients (n=271; 23.2% vs 33.0%, respectively, p=0.03), while in COMBAT, there was no difference in 28-day mortality between the prehospital transfusion recipients (n=65) vs. controls (n=60; 15% vs 10%, respectively, p=0.37). However, there were some important differences in patient demographics and study execution between these studies that could explain the discrepant results (**Table 1**), including the fact that considerably more patients in PAMPer received the full 2-unit dose of plasma in the prehospital period compared to those in COMBAT (89.1% vs. 32%, respectively) likely due to the longer median transport time in the former study. Note that the patients in COMBAT who did not receive the full dose of plasma in the prehospital period received the remainder of their dose in the ED. While the original sub-group analysis based on clinical evidence of severe traumatic brain (score

for injury to the head of >2 on the Abbreviated Injury Scale injury) did not find evidence of an interaction, a subsequent *post hoc* subgroup analysis of the PAMPer trial showed that the benefit of early prehospital plasma transfusion is predominantly amongst the patients with computed tomography-positive traumatic brain injury (TBI),[11] and those with blunt injury.[12] An analysis of injured patients in hemorrhagic shock at the center where the COMBAT study was performed found that 44.6% and 49.5% of the variance in the PT/INR and aPTT, respectively, was not due solely to decreased clotting factor activity suggesting that plasma's beneficial role in trauma resuscitation as shown in the PAMPer trial is not simply the replacement of these factors.[13]

The Resuscitation with Pre-Hospital Blood Products (RePHILL) study,[14] published in 2022, was a UK-based multicenter randomized trial of injured patients transported to hospital either by air or by ground. The patients were randomized to receive up to two units of RBCs and up to two units of lyophilized plasma (Lyoplas; n=199), or to receive up to a liter of 0.9% normal saline in 250 ml boluses (n=210). The primary outcome was a composite of either episode mortality (mortality occurring between the time of injury to the time of discharge from the primary hospital) or a failure to reach lactate clearance (<20% per hour in the first 2 hours after randomization), or both outcomes. The study enrolled 432 subjects of the intended 490 due to early termination because of COVID 19. As is apparent from **Table 1**, the patients enrolled in this study were quite different than those enrolled in either PAMPer or COMBAT insofar as the patients had a higher median injury severity score (ISS), and a larger percentage had traumatic brain injury. Compared to the patients in the COMBAT trial, the patients in RePHILL had a

longer time from injury until the administration of their first blood product and lower Glasgow coma scale (GCS) values. The time from randomization until arrival at the hospital was an average of 37 minutes for the patients in the prehospital transfusion group.

Although few of the measured mortality parameters were identical between these three studies, the values that were reported were higher amongst patients in the RePHILL study compared to the closest comparable value in the other two studies. In particular, there was a 43% episode mortality amongst the patients in the prehospital transfusion group in RePHILL, i.e., nearly half of the patients in this arm of the study died. In fact, the one mortality parameter in RePHILL that overlapped with one of the other studies, 30-day mortality, was nearly double that in PAMPer (42% vs. 23.3%, respectively). It is interesting to note that the patients in the prehospital transfusion group in RePHILL received a median of 5.04 RBC units in the 24-hours following admission, i.e., not including prehospital products, while those in PAMPer and COMBAT received a median of 3 and 2 RBC units, respectively (Table 1); a higher number of RBCs administered to trauma patients in this time period has been shown to be a predictor of mortality, which is consistent with the higher observed mortality in RePHILL than in the other two trials.[15] Not surprisingly, with seriously injured patients who had high mortality and at least a 50% failure to clear lactate at the specified rate in both groups, the occurrence of the composite outcome was not significantly different between these two groups of patients (64% vs. 65%, respectively; p=1.00).

Selecting the optimal outcome for prehospital transfusion trials amongst patients with hemorrhagic shock is challenging.[16] The 28-day, 30-day, or episode mortality primary endpoints in these three studies are standard outcome measures in many clinical trials of critically ill populations. However, this standard has been questioned and, while still controversial because long-term outcomes are relevant to hospital systems with limited budgets for implementing new interventions, expert opinion indicates that the primary outcome for efficacy trials examining hemostatic agents in bleeding patients should focus on more proximate times that reflect the period in which the intervention can directly affect the outcomes. To wit, the American National Heart, Lung, and Blood Institute (NHLBI) and Department of Defense (DoD) recently supported the development of recommendations for primary outcomes of pivotal trials in bleeding patients.[17] The recommendation for adult trauma patients was a primary outcome at 3- to 6-hours from injury or admission. This recommendation was based on a secondary analysis of three RCTs that evaluated blood product use in hemorrhaging trauma patients [COMBAT, PAMPer, and the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) studies] that showed that approximately 75% of the deaths from hemorrhage occurred within 6 hours of injury or admission.[18] Other data that support this recommendation include the finding that as early as 12-24 hours post injury, traumatic brain injury begins to predominate as the main cause of death, and by two weeks post injury, single and multiorgan failure with sepsis as well as traumatic brain injury are all equally or more common than hemorrhage as the cause of death.[19] Consistent with the consensus recommendation, several large multicenter trauma transfusion studies are undergoing regulatory review and have indeed proposed a 6 hour mortality primary endpoint.

It is not likely that a death that occurred 28- or 30-days following the injury could have been solely prevented by blood products that were administered within an hour of the injury. In fact, although the RePHILL study did not show a statistically significant difference in 3-hour mortality (transfusion group 16% mortality, control group 22% mortality; p=0.08), the adjusted relative risk ratio was 0·75 (0·50 to 1·13) amongst the patients who received prehospital transfusion; this translates into a 25% relative risk reduction in mortality at this time point. It should be noted that 3-hour mortality was not a primary endpoint of this study and therefore it might have been underpowered to detect an actual difference in mortality. Similarly, the PROPPR study found a 25% relative risk reduction in 24-hour mortality between injured patients resuscitated with a 1:1:1 blood product ratio strategy compared to a 1:1:2 strategy.[20] Given the large global disease burden posed by the severity of injuries that can occur in trauma, these relative risk reductions suggest that prehospital transfusions have the potential to promote long-term survival by increasing the chance that the patient will survive the initial resuscitation. The potential to produce a 25% relative risk reduction of death at 3-hours, even in a relatively small trial such as RePHILL that, like PROPPR, did not show a statistically significant mortality benefit from the intervention, should be generating considerable enthusiasm for prehospital transfusion in the trauma community. It would have been very interesting to have seen the outcome of the REPHILL study had it been powered for 3- or 6-hour mortality instead of the all-encompassing, and certainly less relevant from a bleeding perspective, episode mortality.

Patients and hospital systems want to know which interventions produce the best long-term outcomes. However, it should be noted that long term outcomes in bleeding patients, such as in-hospital mortality, relate to the administration of prehospital transfusions in the same way that the prehospital transfusion of RhD-positive RBCs or LTOWB to an injured RhD-negative female of childbearing potential relates to the occurrence of hemolytic disease of the fetus and newborn (HDFN) in a future pregnancy[21] – one has to survive the initial resuscitation to be able to develop long-term adverse events. While it is possible to power a study of prehospital transfusion with an overall mortality primary endpoint that overcomes the confounding caused by the "noise" created by the myriad non-hemorrhage related causes of death in trauma, such a study would necessarily be very large (e.g., the 20,000 patient CRASH-2 trial)[22] and costly to perform. Before proceeding with trials on this scale, it is first necessary to demonstrate the efficacy of the experimental intervention – improvements in 3- to 6-hour mortality would provide such a signal.

Where to from here?

It is too simplistic to conclude that prehospital transfusions either work or don't work based on the results of these studies. Differences in study design and setting, study blood products administered, mechanism of injury, nature of the control groups, and EMS practice patterns make a direct comparison of these studies difficult. However, these studies highlight many of

248 the aspects of prehospital transfusion that need further research. Some of these questions
249 include:

250 1. What is the optimum quantity of blood products to transfuse in the prehospital setting
251 given different transport times in different environments to patients who each might have
252 different physiologies?

253 In the PAMPeR trial, 89% of patients received the allocated intervention of 2 units of thawed
254 plasma. A quarter (26%) also received concurrent packed red cell transfusion as part of the
255 helicopter's standard care. In COMBAT, 32% received the allocated intervention of 2 units
256 thawed plasma in the prehospital phase whereas in RePHILL, 60% of the patients received 2
257 units of packed red cells and 40% received 2 units of Lyoplas (unpublished data) in the
258 prehospital phase resulting in an average administration of 1.57 RBC units and 1.25 Lyoplas
259 units per patient (the average number of prehospital transfusions were not reported in PAMPer
260 and COMBAT). These are all lower than the quantities of blood products described in a recent
261 retrospective cohort study of the patients who received prehospital transfusions in Finland,
262 where a median of two RBC and two lyophilized plasma units were transfused in a median of
263 only ~34 minutes of prehospital transport time.[23] The frequency of patients with an admission
264 INR >1.5 in RePHILL was not significantly different between those in the prehospital transfusion
265 group and those in the control group who did not receive any plasma (14% vs. 16%,
266 respectively; p=0.80). As mentioned above, while plasma has beneficial effects in bleeding
267 patients beyond clotting factor replacement that would be measured by the INR, the mean
268 volume of Lyoplas transfused was 266 ml, or only 3.8 ml/kg in a 70 kg patient. This is below the
269 recommended 10-15 ml/kg for reversal of a coagulopathy, and this likely explains why the INR

was not lower amongst the transfused patients. Similarly, the median INR on arrival of the patients in COMBAT's plasma group was 1.27 while the corresponding value was 1.15 (p=0.10) amongst the patients did not receive plasma; in fact, there was a significantly higher percentage of patients with admission INR >1.3 amongst the patients in the plasma group (44%) compared to those in the control group (24%; p=0.02). While these INR differences themselves are perhaps not clinically meaningful in trauma, they do reflect the small quantity of prehospital plasma that was transfused. This is not surprising because COMBAT featured a short 19-minute transport time to the hospital. Surely a larger dose of plasma would be required to produce a beneficial effect on survival, which could be administered to patients with longer transport times. In PAMPer, the 42-minute transport time permitted the full dose of plasma to be administered to most patients and mortality was reduced compared to those who did not receive plasma. In a subanalysis that combined COMBAT and PAMPer patients,[24] plasma was shown to be beneficial if the transport time exceeded 20 minutes, which might not always be the case in an urban environment where patients can be injured close to a hospital. These studies also highlighted the fundamental importance of getting the patient to hospital as quickly as possible following their injury; in COMBAT the patients arrived at the hospital 28 minutes after their injury while in RePHILL it took more than three times longer (**Table 1**) – in neither study did the patients benefit from prehospital transfusion but likely for very different reasons.

To potentially avoid transfusing small doses of individual blood components and to avoid the delay in transfusion caused by reconstituting lyophilized plasma or thawing regular plasma if other blood products are not available for transfusion during the preparation period, perhaps prehospital LTOWB should be preferentially transfused over components. It would have been interesting to see if administering 3-4 units of LTOWB in the prehospital setting would have benefitted the severely injured RePHILL patients, and RCTs involving prehospital LTOWB transfusion are underway in the USA [Type O Whole blood and assessment of AGE during prehospital Resuscitation (TOWAR) Trial; ClinicalTrials.gov identifier: NCT04684719] and also in the UK [Study of Whole blood In Frontline Trauma (SWiFT) trial].

2. When should prehospital transfusions cease?

It is interesting to note that the patients in the RePHILL prehospital transfusion group received significantly more RBC and plasma units in the 24 hours after arrival at the hospital compared to the patients in the control group. This occurred despite the fact that the patients in the prehospital transfusion group had a higher admission mean hemoglobin (Hb) concentration than the patients in the control arm (133 g/L vs. 118 g/L, respectively; $p<0.001$), a small and nearly identical fraction of patients in both groups had an admission INR >1.5 (described above), and the patients in both groups had identical mean admission systolic blood pressures (114 mmHg; $p=0.74$). So why did the prehospital transfusion group patients receive significantly more RBC and plasma units early in the admission than those in the control group? Perhaps these patients were under-resuscitated on their way to the hospital. In the RePHILL study, transfusions were administered until the systolic blood pressure increased above 90 mm Hg or a radial pulse became palpable. Although permissive hypotension has become widely

practiced,[25] perhaps using these blood pressure and pulse criteria are not sensitive enough to determine when transfusion therapy should cease because these criteria did not accurately predict the patient's blood product needs in their immediate future, at least in the RePHILL study. Similarly, it would appear that the admission Hb concentration is also a poor predictor of future transfusion requirements. Other explanations surely exist for why the patients in the prehospital transfusion group required significantly more RBCs and plasma in their first 24-hours in the hospital despite having either more favorable or identical laboratory and clinical parameters on admission. However, it is clear that future research should focus on developing criteria for initiating and stopping prehospital transfusions to optimize the transfusion support of these patients while being mindful of the potential harms from higher blood pressures caused by overzealous resuscitation.

3. Which patients benefit from prehospital transfusion?

A priori, it seems reasonable to think that severely injured and bleeding patients would benefit from prehospital transfusions. In the hospital, every minute that elapses between the time that the massive transfusion protocol is activated and its arrival at the bedside leads to increased mortality,[26] so why shouldn't the same apply before the patient arrives at the hospital? Not all trauma patients are the same and these three RCTs have covered the spectrum of injured patients. **Table 1** reveals that the patients in the COMBAT trial were overall the least severely injured, had short transport times, and they did not experience a survival benefit from receiving plasma. The patients in RePHILL were the most severely injured and had a high episode mortality rate despite receiving prehospital transfusions, albeit starting about an hour after injury. The patients in PAMPer might have had the optimal combination of injury severity and

the nature of the injury (i.e, CT evidence of TBI), transport time, time to treatment, and quantity of blood product received and thus demonstrated a survival benefit. Trauma care providers should be taught that the results of the COMBAT and RePHILL trials should not be generalized to condemn prehospital transfusions for all patients, but rather these studies help to identify groups of patients who might not benefit from prehospital transfusion due to the extent of their injury or the length of the delay in providing treatment for patients with very high injury severity. The challenge is to develop better/more implementable assessment tools to identify the phenotype of a trauma patient who will benefit from prehospital transfusions using data that is available at the beginning of the resuscitation when the decision to provide prehospital transfusions is being made.[27] As a specific example, a multi-omic characterization of PAMPer patients was recently performed and identified the specific subset of patients who benefited from plasma (hyperinflammatory endotype, traumatic brain injury) and unique biomarker signatures that characterize this group.[28] Given that the effect of transfusing two units of plasma would be to increase the concentration of clotting factors by approximately 7%,[29] it is likely that the benefit of plasma is something other than arresting bleeding, at least in this particular population. The development of near patient tests to enable this type of analysis at the time of injury may lead to future strategies of prehospital personalized resuscitation strategies. It might well be that some patients are not injured enough while others are too badly injured to benefit from transfusion. Similarly, recognizing patients with unsurvivable injuries (i.e., injuries leading to nonpreventable death) and excluding them from future studies will also help to better establish those patients who might benefit from prehospital

transfusions.[30-32] These should be major areas of future research to optimize patient care and to help steward the inventory of precious blood products.

The results of trials are neither positive nor negative per se, but rather they help us to better understand the disease process that is being studied. It is clear from these three trials that some trauma patients derive lifesaving benefit from prehospital transfusions, and the design of future studies and sub-analyses should be further refined to more clearly elucidate those patients who might benefit. Future efficacy studies should focus on short term outcomes such as 3- to 6-hour mortality, and, if possible, based on the number of patients needed to enroll to overcome the confounding, long-term outcomes.

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Table 1. Study design and patient demographics of the three RCTs on prehospital blood products use in trauma. BP = blood pressure.

Note that the demographics presented in this table are for the patients in each study who were randomized to receive prehospital blood products.

	PAMPer	COMBAT	RePHILL
Study characteristics			
Population	Age 18-90 years, systolic BP <90 mm Hg and HR >108 beats per min or systolic BP <70 mm Hg	Age >18 years, systolic BP 71–90 mm Hg and heart rate >108 beats per min or systolic BP ≤70 mm Hg	Age ≥16 years, systolic BP <90 mm Hg or absence of radial pulse
Intervention	Up to 2 units of thawed plasma	Up to 2 units of plasma thawed on demand	Up to 2 units of packed red blood cells and 2 units Lyophilized plasma
Comparator	0.9% saline and/or RBC	0.9% saline	0.9% saline
Number of patients randomized to receive prehospital blood products	230	65	199
Primary outcome	Mortality at 30-days	Mortality at 28-days	Composite of episode mortality or failure to reach specified lactate clearance
Statistically significant reduction in primary outcome amongst blood product recipients?	Yes	No	No
Patient characteristics			
On scene Glasgow Coma Scale. Median (IQR)	44.8%*	14 (7-15)**	8 (3-14)
Traumatic brain injury, %	33.3	20	48***

Included patients with traumatic cardiac arrest?	Yes if ≤5 minutes duration	Yes^	Yes if it occurred in presence of pre-hospital team and thought to be due to hypovolaeamia
Receipt of full study dose of blood products in prehospital period (% enrolled in treatment arm)	89.1	32	40
Injury severity score. Median (IQR)	22 (14-33)	Not reported	36 (25-49)
+New injury severity score. Median (IQR)	Not reported	27 (10-41)	43 (34-57)
Median initial INR (IQR)	1.2 (1.1-1.4)++	1.27 (1.11-1.40)+++	Not reported
Intervention characteristics			
Receipt of tranexamic acid, %	Not reported	9	87
Time from injury to arrival at hospital, minutes. Median (IQR) or Mean (SD)	Not reported	28 (IQR 22-34)	90 (SD 35)^^
Scene to hospital transport time, minutes. Median (IQR) or Mean (SD)	42 (IQR 34-53)	19 (IQR 16-23)	37 (SD 22)^^^
Time from injury to first transfusion, minutes. Median (IQR)	Not reported	24 (20-31)#	56##
Outcomes			
3-hour mortality, %	Not reported	Not reported	16
24-hour mortality, %	13.9	12	Not reported
28-day mortality, %	Not reported	15	Not reported
30-day mortality, %	23.2	Not reported	42
In-hospital mortality, %	22.2	Not reported	Not reported
Episode mortality, % (See text for definition)	Not reported	Not reported	43

Patients with INR >1.3 or >1.5 on admission, %	Not reported	>1.3, 44%###	>1.5, 14%~
24-hour RBC unit transfusion requirement, median (IQR)	3 (0-7)	2 (0-9)	6.34 (7.09)~~
24-hour plasma unit transfusion requirement, median (IQR)	0 (0-3)	0 (0-4)	5.04 (5.56)~~

+The new injury severity score (ISS) differs from the traditional ISS in that the new ISS is calculated based on the patients most severe injuries regardless of their anatomical region whereas the traditional ISS assigns one score per body region, regardless of the presence of multiple severe injuries in the same anatomical region (as might be caused by a penetrating wound that damages several vital organs in the same region)[33]

++Timing of INR not stated

+++INR on arrival at hospital

*% of patients with initial GCS score <8

**Lowest GCS

***Reported as "61 (48%) of 128 had concurrent brain injury" but unclear if this is the overall cohort. 48% of prehospital blood product recipients had "concomitant head injury"

^Not listed as an exclusion criterion

^^Reported as time from 999 call until arrival at ED

^^^Reported as time from randomization until arrival at ED

#Time to transfusion of first plasma unit

##This was calculated by adding the time from initial call to EMS arrival on scene plus the time from EMS arrival on scene to administration of first intervention

###Significantly higher than proportion in control group

~ Not significantly higher than proportion in control group

~~Mean (SD); significantly higher than the patients in the control group. Values do not include prehospital transfusions for any of the three studies.