Prehospital blood transfusion in the en route management of severe combat trauma: A matched cohort study

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BACKGROUND: The value of prehospital blood transfusion (PHBTx) in the management of severe trauma has not been established. This study aimed to evaluate the effect of PHBTx on mortality in combat casualties.

METHODS: This is a retrospective cohort study of casualties admitted to the field hospital at Camp Bastion, Afghanistan, by the Medical Emergency Response Team from May 2006 to March 2011. Participants were divided into two consecutive cohorts by the introduction of PHBTx. Paired groups of patients were chosen by combining propensity score methodology with detailed matching of injury profile. Thus recipients of PHBTx were matched with nonrecipients who would have received it had it been available.

RESULTS: A total of 1,592 patients were identified. Of the 1,153 patients to whom PHBTx was potentially available, 310 received it (26.9%). The rate of severe injury (Injury Severity Score [ISS] > 15) rose from 28% before PHBTx was available to 43% thereafter ($p < 0.001$). Mortality in the latter group was higher (14% vs. 10%, $p = 0.013$) but not in the severely injured patients (32% vs. 28%, $p = 0.343$). Ninety-seven patients were paired. The mortality of matched patients who received PHBTx, compared with those with similar injury patterns who did not, was less than half (8.2% vs. 19.6%, $p < 0.001$). However, matched recipients had more prehospital interventions, reached hospital more quickly, and had lower heart rate at admission (all $p < 0.05$). Matched recipients received more red blood cells within 24 hours (median, 4 U; interquartile range [IQR], 2–10 U) than nonrecipients (median 0 U; IQR, 0–3.5 U) and more fresh frozen plasma (median, 2 U; IQR, 2–9 U vs. median, 0 U; IQR, 0–1 U) (both $p < 0.001$).

CONCLUSION: An aggressive approach to damage control resuscitation including the use of PHBTx was associated with a large improvement in mortality. However, because of confounders resulting from changes in practice, the isolated contribution of PHBTx cannot be determined from this study. (*J Trauma Acute Care Surg*. 2014;77: S114–S120. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level IV.

KEY WORDS: Combat injury; shock; hemorrhage; blood products; military trauma.

Hemorrhage remains the leading potentially preventable cause of combat death.[1,2] Advances in tactical combat casualty care[3] and hospital treatment[4,5] have led to a sustained improvement in mortality during the last decade.[6] Four key innovations in the hospital phase of care have been adopted and developed by the UK and US Armed Forces during this period. These are damage control surgery; the use of abbreviated surgery to remedy hemorrhage and contamination with definitve surgery delayed until physiology has been restored;[7] limited use of synthetic intravenous fluids, which may worsen coagulopathy through dilution of clotting factors and have profound proinflammatory effects;[8,9] hypotensive resuscitation (beginning prehospital), whereby normalization of blood pressure is delayed until hemorrhage has been controlled;[10] and balanced blood product use, whereby packed red blood cells (PRBCs) and fresh frozen plasma (FFP) are transfused in ratios of, or near to, 1:1, which is associated with improved outcomes and may help to alleviate the acute coagulopathy of trauma.[4,11] Taken together, these are known as damage control resuscitation (DCR).[12–14] As DCR developed, it became clear that early, aggressive resuscitation could lead to early correction of acidosis, coagulopathy, and hypothermia.[15,16]

En route care, that is, during transport from point of injury to admission to a field hospital, has also been enhanced with the development of physician-led clinical teams delivering treatment during helicopter transportation from point of wounding to hospital.[17] The UK military therefore sought to extend the DCR concept into the prehospital setting,[12,18] through the introduction of prehospital blood transfusion (PHBTx) using PRBCs and FFP.

The rationale, indications, and practicalities of this practice are explored more fully in a special report that accompanies this article in the current edition of *J Trauma*.[19] This study

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is intended to test the hypothesis that the introduction of PHBTx was associated with a reduction in mortality in combat casualties.

PATIENTS AND METHODS

This is a retrospective study of casualties admitted to the field hospital at Camp Bastion, Afghanistan, by the UK Medical Emergency Response Team–Enhanced (MERT-E) from May 2006 to March 2011, before and after the introduction of a prehospital blood product capability. The study was approved by the Royal Centre for Defence Medicine Academic Unit and the US Army Medical Research and Material Command. The setting[17] and the use of PHBTx[19] have been detailed elsewhere. Briefly, the MERT-E is an advanced medical retrieval platform, as described in detail previously.[17] In addition to standard en route care, the physician-led team can administer resuscitation fluids using the intraosseous and central or peripheral intravenous routes as well as perform chest decompression (thoracotomy, tube or open or needle decompression) and advanced airway managements including rapid sequence induction of anesthesia and endotracheal intubation. Through a process that began in July 2008, the capability was further enhanced by carrying 4 U of PRBC and thawed FFP, for prehospital transfusion.

Prehospital transfusion is considered for patients without a palpable radial pulse or who have a noninvasive systolic blood pressure of less than 80 mm Hg. The aim was to restore these parameters, rather than to resuscitate to normotension, unless a traumatic brain injury is suspected or time to definitive care is anticipated to exceed 1 hour.[20] If more than 1 U of PBRC is required, plasma is coadministered, to achieve a ratio of 1:1.

Sources of Data and Initial Analysis

This was a retrospective, registry-based study. Three prospectively collected data sets were used: the UK prehospital MERT registry, the UK Joint Theatre Trauma Registry (JTTR), and the US Department of Defense Trauma Registry (DoDTR). Patients were included if they were adults injured in combat and retrieved from the field by helicopter, under the care of the MERT-E. Patients with injury patterns that are incompatible with life were excluded (e.g., decapitation, head region Abbreviated Injury Scale [AIS] score of 6, hemicorporectomy). Patients in cardiac arrest on arrival at the hospital were not excluded, since the intervention (PHBTx) is potentially capable of preventing cardiac arrest in the prehospital phase. Participants were divided into two consecutive cohorts by the introduction of PHBTx in 2008 (pre-PHB and post-PHB). Discrete variables were analyzed using Fisher's exact test, while continuous variables were analyzed using the standard Student's *t* tests and Mann-Whitney U-test, as appropriate.

Cohort Matching and Analysis

Ideally, an examination of a resuscitative adjunct such as PHBTx would use prehospital physiology data (e.g., observations). Sufficient and reliable data of this kind were not available in the severely injured groups of recipients and suitable potential controls because of the exigencies of operational military prehospital practice where initial clinical and physiologic assessments are commonly made in close contact with the enemy. To compensate, we developed a matching process designed to achieve close matching of the patients' injury complexes.

Patients who were administered prehospital blood products (recipients) were paired with patients transported before July 1, 2008, who would have been expected to receive prehospital transfusion if it had been available. A logistic regression was conducted in the post-PHB cohort with receipt of PHBTx as the dependant variable using the variables sex, age, patient category (i.e., national status), mechanism of injury, and detailed injury data. The three most severe AIS codes for each patient, irrespective of body region, were included as variables in the

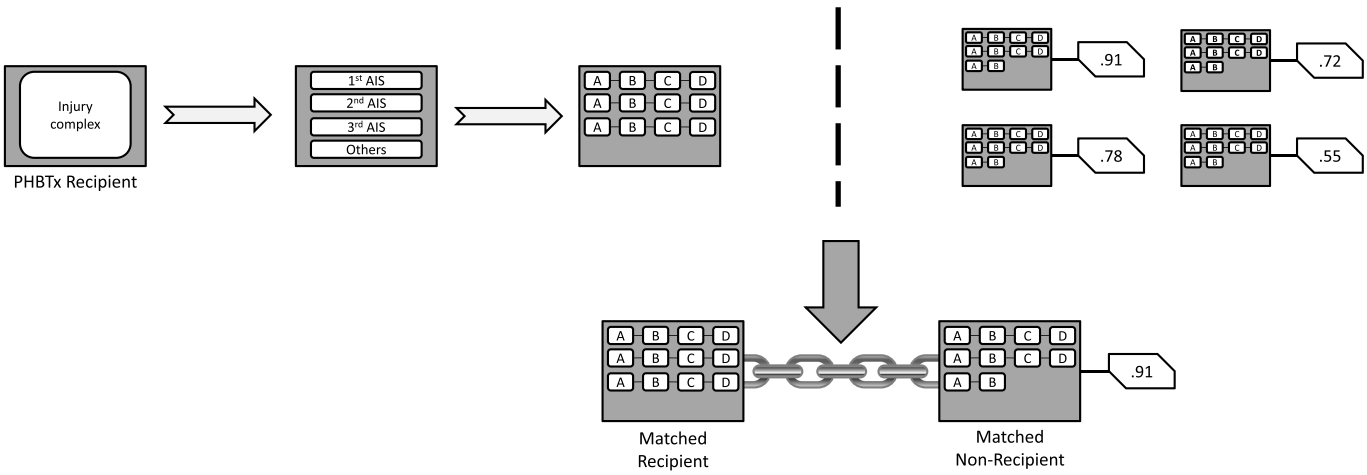

Figure 1. Matching process. Each cartouche represents a patient. On the left, a PHBTx patient's injury complex is broken down and the first, second, and third most severe AIS codes are used for matching. Each AIS code is broken down into its four principle components A to D: A, severity; B, body region; C, organ; D, form of injury. On the right, four patients from the period before PHBTx became available are selected as possible matches. In this case, the potential matches have two exactly matching injuries, but the third injury is only matched for severity and body region. Each potential match has been labeled with its propensity score, that is, the probability that the patient would have been administered PHBTx had it been available. The potential match with the most closely matched propensity score is chosen to become the matched nonrecipient.

regression model. An algorithm was then created to parse the first three digits of the AIS code for each injury to determine the fundamental injury descriptors: (1) body region of injury (head, face, neck, thorax, abdomen, spine, upper extremity, lower extremity, and other), (2) anatomic region (whole area, vessels, nerves, organs/muscles, skeletal/joints, and loss of consciousness), and (3) specific forms of injury (abrasions, lacerations, contusions, amputations, burns, etc.).

Matching proceeded in two stages. First, recipients patients were matched with one or more pre-PHB patients with similar detailed injury data. Preference was given to exact injury code matches for all three injuries, second-order matches were based on severity and Descriptors 1 and 2 mentioned earlier, third-order matches were based on severity and Descriptor 1 mentioned earlier, and so on. Greedy matching[21] was then used to order the potential matches according to their propensity score (as calculated based on the described logistic regression) and select the best control currently available. Once a match was made, it was not reconsidered; in the event that more than one unmatched control fitted to a case, the control chosen for pairing was selected at random by the algorithm. This process is illustrated in Figure 1. A validation was conducted with reference to a separate database of patients not involved in this study.

This process produced groups of patients, matched recipients, and matched nonrecipients, consisting of matched pairs.[22] Consequently, categorical data were analyzed using McNemar test, nonparametric data using Wilcoxon signed-rank test, and parametric data using Student's paired *t* test. The primary outcome was mortality. Admission observations and total PRBC and FFP use were secondary outcomes.

Mortality for UK and US personnel was defined as death within 30 days of wounding. For other patients, follow-up was limited to the in-hospital stay in Afghanistan. This approach is pragmatic and has been used previously[17] because it is very difficult to track the progress of casualties from other countries through their respective evacuation chains. Transfusion volumes pertain to the first 24 hours.

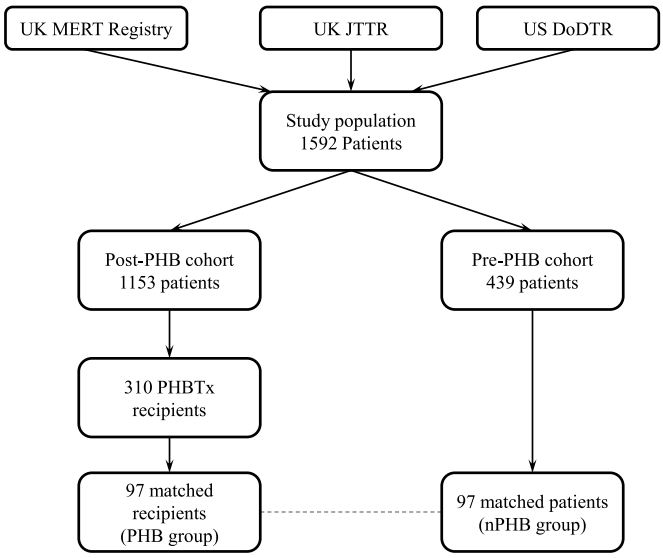

Figure 2. Study population flow chart. Pre-PHB/post-PHB, study cohorts after and before, respectively, the introduction of PHBTx. Matched recipients, PHBTx recipients successfully paired with patients from the pre-PHB cohort with similar injury profiles and high propensity scores for receiving PHBTx, had it been available to them.

TABLE 1. Comparison of Patients Admitted Before the Introduction of PHBTx (Pre-PHB) and Those Admitted Afterward (Post-PHB)

		Pre-PHB	Post-PHB	*p*
n		439	1,592	
Age		23 (21–28)	23 (20–27)	0.277**
Patient category	UK military	214 (48.7)	642 (55.7)	**<0.001***
	Coalition military	129 (29.4)	288 (25.0)	
	Afghan	96 (21.9)	223 (19.3)	
Sex	Male	425 (96.8)	1116 (96.8)	1*
Mechanism of injury	Blunt	25 (5.7)	43 (3.7)	**<0.001***
	Burn	4 (0.9)	8 (0.7)	
	Explosive	246 (56.0)	809 (70.2)	
	Gunshot wound	163 (37.1)	286 (24.8)	
	Other	1 (0.2)	7 (0.6)	
Military ISS		5 (2–16) [1–75]	9 (4–25) [1–75]	**<0.001****
Military NISS		8 (3–20) [1–75]	14 (5–34) [1–75]	**<0.001****
AIS score ≥ 3	Head and neck	43 (9.8)	119 (10.3)	0.853*
	Face	1 (0.2)	10 (0.9)	0.308*
	Chest	50 (11.4)	151 (13.1)	0.399*
	Abdomen	29 (6.6)	141 (12.2)	**0.001***
	Extremity	95 (21.6)	421 (36.5)	**<0.001***
	External	7 (1.6)	15 (1.3)	0.636*

*Categorical data are shown as n (%) and compared using Fisher's exact test.
**Ordinal and scale data are shown as median (IQR) with [range] added where relevant and compared using the Mann-Whitney U-test.
p values are shown for results in the comparison of pre-PHB and post-PHB. Significant results shown in bold.

RESULTS

A total of 1,592 patients were included: 439 before July 1, 2008 (pre-PHB), and 1,153 thereafter (post-PHB). Of the latter group, 310 (26.9%) received PHBTx during transfer (Fig. 2). Table 1 compares the two cohorts. Prehospital transfusions totaled 576 U of PRBC and 527 U of FFP. The rate of severe injury (Injury Severity Score [ISS] ≥ 16) rose from 28% to 42.5% ($p < 0.001$, χ^2) between the two cohorts. Mortality was higher in the post-PHB group. However, mortality among severely injured post-PHB patients was 134 (27.6%) of 485, whereas it was 39 (32.0%) of 122 in the pre-PHB cohort ($p = 0.343$, χ^2).

Of the 310 patients who received PHBTx, 97 were paired with patients from the pre-PHB cohort (Fig. 2). Table 2 shows the matched characteristics. The groups had excellent matching

TABLE 2. Matched Characteristics of Paired Groups of Patients Who Did and Did Not Receive PHBTx

		Recipients	Nonrecipients	*p*
n		97	97	
Age		24 (20–28)	23 (21–28)	0.975*
Patient category	UK military	45 (46.4)	38 (39.2)	0.248*
	Coalition military	31 (32)	45 (46.4)	
	Afghan civilian	21 (21.6)	14 (14.4)	
Sex	Male	95 (97.9)	97 (100)	U/T
Mechanism of injury	Blunt	1 (1)	3 (3.1)	U/T
	Burn	0 (0)	0 (0)	
	Explosive	50 (51.5)	48 (49.5)	
	Gunshot wound	46 (47.4)	46 (47.4)	
	Other	0 (0)	0 (0)	
Military ISS		16 (9–25)	16 (9–24.5)	0.686**
Military NISS		22 (15–33)	21 (14–34)	1**
AIS score ≥ 3	Head/neck	0	1 (1)	1*
	Face	0	1 (1)	1*
	Chest	24 (24.7)	25 (25.8)	1*
	Abdomen	18 (18.6)	18 (18.6)	1*
	Extremity	67 (69.1)	65 (67)	0.727*
	External	2 (2)	3 (2)	1*

*Categorical data are shown as n (%) and compared using McNemar test.

**Ordinal and scale data are shown as median (IQR) and compared using the Wilcoxon signed-rank test.

U/T, untestable because of the limitations of McNemar test (because of zero value or multiple categories; patient category was dichotomized to coalition or Afghan to allow testing).

of injury profiles, with 89 in each group being severely injured. Table 3 shows the treatments received and outcomes for both groups. The mortality rate in the prehospital transfusion recipients was half that of the nonrecipients (8.2% vs. 19.6%, $p = 0.013$, McNemar). There was also a small improvement in admission heart rate although not in other observations. However, matched recipients received more prehospital airway interventions and reached hospital more quickly than nonrecipients. Matched recipients patients received more blood products overall (Fig. 3*A*) and in higher FFP/PRBC ratios.

DISCUSSION

While PHBTx has a long history,[23,24] the current study is the first reported comparative analysis of prehospital blood use in contemporary conflict. The group that received PHBTx had a reduced mortality compared with the controls. However, several potentially confounding differences are identified. In particular, recipients received more blood products in total and higher FFP/PRBC ratios.

The treatment of hemorrhage requires the control of macroscopic bleeding, microcirculatory hemostasis, and the restoration of circulating blood volume. In the absence of definitive hemorrhage control, as is may occur in the prehospital setting, these goals may conflict. The administration of synthetic intravenous fluids not only increases cardiac output[25] and perfusion but also may precipitate further hemorrhage, by physically disrupting immature thrombus and by exacerbating hypoperfusion-induced coagulopathy.[26,27] Other detrimental effects include hyperchloremic metabolic acidosis and tissue edema. The administration of blood, whole or as components, is inherently more physiologic and thus conceptually attractive.

MERT-E practice, in line with current operational policy for casualties who are expected to receive a massive transfusion, is to coadminister units of red blood cell concentrate and plasma in equal quantities. This practice is based on retrospective military and civilian studies, which have shown that high FFP/PRBC ratios are associated with improved outcome,[4,11,28] although the methodological limitations of these studies—particularly with regard to survivorship bias[29,30]—are acknowledged. However, given the success of this strategy, in terms of survival and restoring normal physiology,[15] the paradigm has been extended to prehospital transfusion.

Prehospital transfusion could be associated with unnecessary use. Transfusion may also raise concerns about the effect of procoagulant factors, the transmission of blood borne viruses, and immunologic consequences.[31] Thus, while PHBTx is a conceptually appealing intervention, the benefits are unquantified and it is not without potential drawback and logistic cost.

A matched cohort design was used. Standard propensity scoring based on the available demographic data, mechanism, and ISS or New Injury Severity Score (NISS) was considered. ISS/NISS dominated these models. ISS and NISS have been criticized on many grounds.[32] In particular, they conflate injury patterns, which both loses information about particular injuries and makes very different injuries (e.g., severe head injury and proximal limb amputation) essentially interchangeable.[33] We therefore sought to match patients much more closely, making fuller use of the information contained in the AIS coding of the patient's injuries by using the approach described. This is a novel application of established techniques, which we believe may have wider applicability in the analysis of injury data, particularly if combined with physiologic data. The group of potential historical controls was considerably smaller than the equivalent group after the introduction of PHBTx (439 vs. 1,153). As such, it was inevitable that only a minority of PHBTX recipients would be matched to suitable controls. It is possible that this could introduce some element of selection bias, although there is no reasons to expect that recipients for whom a match was found should be systematically more or less physiologically disturbed than those which were not. However, it is inevitable that matching recipients to patients from a cohort with less severe injuries selects for less severely injured recipients. It is conceivable that the recorded effect would have been larger if more severely injured recipients and nonrecipients had been included in the comparison.

There was a large increase in total blood product use between the two matched groups with median PRBC use increasing from 0 to 4 ($p < 0.001$, Wilcoxon) and from 2 to 7 among those with ISS of 16 or greater ($p < 0.001$). This was despite the fact there was no increase in the proportion requiring massive transfusion (>90% of pairs were concordant as to whether they received ≥10 U of PRBC). It is known that there has been a steady increase in blood product use in recent years.[34] There was a significant difference in the use between the pre-PHB and post-PHB periods (Table 1). Severely injured

TABLE 3. Treatment and Outcomes of Matched Groups of Patients Who Did and Did Not Receive PHBTx

		Recipients	Nonrecipients	*p*
n		97	97	
Prehospital interventions	Intraosseous access	14 (14.4)	16 (16.5)	0.824*
	Advanced airway	19 (19.6)	9 (9.3)	**0.041***
	Chest decompression	19 (19.6)	22 (22.6)	0.629*
Prehospital time, min		68 (50–100)	109.5 (70–171)	**0.008****
Admission observations	Cardiac arrest	7 (7.2)	9 (9.3)	1*
	Systolic blood pressure	132 (111–145)	131 (114–150)	0.145**
	Respiratory rate	19 (15–24)	20 (16–26)	0.173**
	Heart rate	92 (74–115)	105 (82–128)	**0.041****
Tranexamic acid		22 (22.6)	0 (0)	U/T
Recombinant activated factor VII		2 (2)	10 (10.3)	**0.033***
Prehospital transfusion	PRBC	1 (1–2) [0–4]	N/A	
	FFP	2 (1–2) [0–4]	N/A	
In-hospital transfusion	PRBC	2 (1–8.5) [0–49]	0 (0–3.5) [0–26]	<**0.001****
	FFP	2 (0–7.5) [0–44]	0 (0–1) [0–20]	<**0.001****
	Cryoprecipitate	0 (0–0) [0–4]	0 (0–0) [0–3]	0.068**
	Platelets	0 (0–0) [0–7]	0 (0–0) [0–6]	<**0.007****
Total PRBC		4 (2–10) [0–53]	0 (0–3.5) [0–26]	<**0.001****
Total FFP		2 (2–9) [1–44]	0 (0–1) [0–20]	<**0.001****
Any in-hospital PRBC transfusion		75 (77)	38 (39)	<**0.001****
Massive transfusion		12 (12)	8 (8)	0.388*
FFP/PRBC ratio		1 (0.83–1.23)	0.46 (0–0.72)	<**0.001****
Mortality		8 (8.2)	19 (19.6)	**0.013****

*Categorical data are shown as n (%) and compared using McNemar test.
**Ordinal and scale data are shown as median (IQR) with [range] added where relevant and compared using the Wilcoxon signed-rank test.
Significant results shown in **bold**.
U/T, untestable because of the limitations of McNemar test (because of zero value). N/A, not applicable; U/,T untestable due to zero value.

pre-PHB patients who were transfused received a median (interquartile range [IQR]) of 6 U (3–12 U) of PRBC. Equivalent post-PHB patients who did not receive PHBTx received 10.5 U (4.5–22 U), a significant increase ($p = 0.003$, Mann-Whitney) (Fig. 3B). The PRBC use in severely injured post-PHB patients who did receive PHBTx was 12 U (4–19 U), which is not significantly higher than the latter group ($p = 0.9$, ISS and NISS were also similar). In addition, the FFP/PRBC ratio differed markedly between the matched groups. The 11 excess survivors in the intervention group are inadequate for survivorship bias to fully explain the increased total volumes and ratios. We conclude that there was a large secular trend in resuscitation practice between the two groups beyond the provision of a prehospital transfusion capability.

Other factors that may confound the analysis of mortality were identified. The fall in prehospital times probably reflects changes in the deployment of forces in Helmand Province during the study period, with the arrival of US Marine Corps units accompanied by US aeromedical assets. "Intelligent tasking" of aeromedical assets was implemented, as detailed previously.[17] The increased rate of prehospital procedures could represent increased need but, anecdotally, there seems to have been a lowered threshold for intervention in combination with the evolution and routine implementation of standard operating procedures. For example, rapid sequence induction is now used more often as a definitve form of analgesia or where the requirement for general anesthesia to facilitate surgery ("expected clinical course") is anticipated. The routine use of tranexamic acid and decreased recombinant activated factor VII use represent the effects of opposing trends in the evidence base for the two drugs.[5,35,36]

No clear assessment of the isolated benefit of PHBTx can therefore be made. However, our data provide strong evidence that the combination of intensive prehospital treatment, including prehospital transfusion, in the context of DCR can lead to substantial improvements in mortality. Hemostatic resuscitation was introduced in the post-PHB period, in that blood products were used frequently, early and in high FFP/PRBC ratios.[34] Rotational thromboelastrometry was deployed to guide coagulopathy management.[37] Counterintuitively, this "hemostatic" regimen involved much larger total transfusion volumes. This practice has been demonstrated to be able to correct physiologic derangement in very severely injured combat casualties.[15] These patients often need extensive debridement, which, in the context of normotension with euvolemia, may require considerable transfusion support. It contrasts with DCR practice as described by others where conservation of blood products has been reported as one of the advantages of hemostatic resuscitation.[38]

CONCLUSION

Transfusion of PRBC and FFP within a DCR treatment paradigm has been successfully projected into the prehospital phase of combat casualty care. Extensive changes in resuscitation practice make an isolated assessment of the contribution

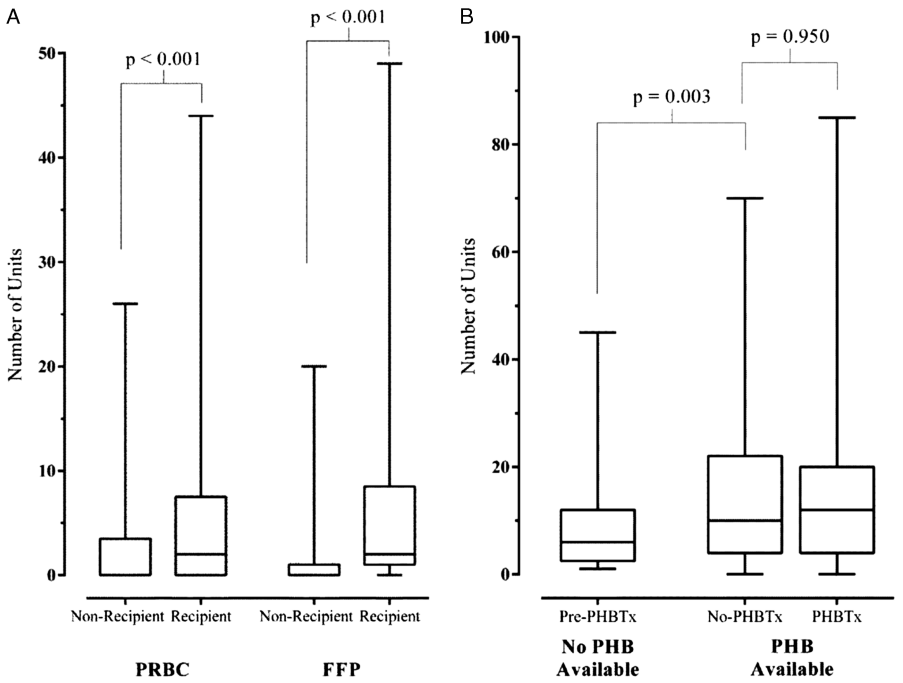

Figure 3. *A*, Units of PRBC and FFP transfused in the first 24 hours in the hospital to matched recipients and nonrecipients of prehospital transfusion. Groups compared with Wilcoxon signed-rank test. *B*, Total units of PRBC transfused in the first 24 hours to severely injured (ISS > 15) patients who received any PRBC or FFP and (1) were admitted before PHBTx was available, (2) were admitted after PHBTx was available but did not receive PHBTx, (3) received PHBTx. Groups were compared using Mann-Whitney U-test. *Boxes* show interquartile range with median. *Whiskers* show range.

of PHBTx impossible. However, adoption of an aggressive approach to DCR, with early use of blood product transfusion, including in the prehospital setting, was associated with a halving of mortality.

AUTHORSHIP

D.J.O. initiated and designed the project. J.J.M. obtained permissions, collated the data, and advised on the analysis and interpretation. A.A.M. conducted the matching process and advised on other aspects of the analysis. D.J.O. completed the statistical analysis and interpreted the results. J.O.J. provided clinical context and contributed to the data interpretation. T.E.R. and M.J.M. oversaw the project and contributed to the design and data interpretation. D.J.O. drafted the manuscript, to which all authors have contributed. All authors reviewed the manuscript.

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DISCLOSURE

The authors declare no conflicts of interest.

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