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Effect of pre-hospital red blood cell transfusion on mortality and time of death in civilian trauma patients

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ABSTRACT

Background: Current management principles of haemorrhagic shock after trauma emphasize earlier transfusion therapy to prevent dilution of clotting factors and correct coagulopathy.

London's air ambulance (LAA) was the first UK civilian pre-hospital service to routinely offer pre-hospital red blood cell (RBC) transfusion (phRTx). We investigated the effect of phRTx on mortality.

Methods: Retrospective trauma database study comparing mortality before-implementation with after-implementation of phRTx in exsanguinating trauma patients. Univariate logistic regression was performed for the unadjusted association between phRTx and mortality was performed, and multiple logistic regression adjusting for potential confounders.

Results: We identified 623 subjects with suspected major haemorrhage. We excluded 84 (13.5%) patients due to missing data on survival status. Overall 187 (62.3%) patients died in the before phRTx period and 143 (59.8%) died in the after phRTx group. There was no significant improvement in overall survival after the introduction of phRTx ($p=0.554$). Examination of pre-hospital mortality demonstrated 126 deaths in the pre-phRTx group (42.2%) and 66 deaths in the RBC administered group (27.6%) There was a significant reduction in pre-hospital mortality in the group who received RBC ($p<0.001$).

Conclusions: phRTx was associated with increased survival to hospital, but not overall survival. The "delay death" effect of phRTx carries an impetus to further develop in-hospital strategies to improve survival in severely bleeding patients.

Key words: Emergency Medical Service; Injuries and Wounds; Erythrocyte Transfusions; Mortality

BACKGROUND:

Haemorrhagic shock is the major preventable cause of death after trauma and carries a considerable mortality even in specialist centres.¹ Major bleeding following injury remains a major public health problem with an incidence of 83 per million in the UK.² Current management principles include damage control resuscitation strategies that minimize the use of crystalloids and emphasize earlier transfusion therapy to correct acute traumatic coagulopathy and prevent further dilution and consumption coagulopathy.^{3,4} The move from crystalloid resuscitation to early blood transfusion resuscitation in recent years in the pre-hospital setting in civilian practice, has mirrored military experience in recent conflicts. However, the current body of evidence supporting such practice is limited, and mostly describe the practicality rather than the effectiveness of the intervention.^{5,6} Nevertheless, the concept is clinically logical where the risk of transfusion-related adverse events is minimal.⁵

A recent study described an association between phRTx and increased 24-hour survival.⁷ Powell et al. found that shorter times to RBC transfusion were associated with decreased risk of death in traumatically injured patients.⁸ The UK National Institute for Health and Care Excellence guidelines on the management of active bleeding in major trauma recommend using crystalloids only when blood products are not available on scene.⁹ In 2012 London's air ambulance (LAA) became the first UK civilian pre-hospital service to routinely offer pre-hospital red blood cell (RBC) transfusion (phRTx). The aim of this study was to investigate the effect of phRTx on mortality.

METHODS

Setting:

LAA is a pre-hospital service responding to major trauma victims within the Greater London area consisting of approximately of 5000 km² with a population of approximately 8.5 million people. A helicopter emergency medical service (HEMS) paramedic working in the London Ambulance Service emergency operating centre targets patients with major trauma and dispatches a doctor – paramedic team by helicopter during daytime and by rapid response cars at night.^{10,11} The doctor - paramedic team undertake approximately 2000 missions per year and operate 24-hours a day. The receiving hospitals are four designated major trauma centres in the London trauma network.

Practice:

LAA teams use basic pre-hospital criteria to identify patients with major trauma that require early administration of blood products. A standard operating procedure instructs that patients are declared a “Code Red” when there is: 1) Suspected or confirmed haemorrhage AND 2) Systolic blood pressure < 90mmHg (at any time). In cases without documented non-invasive blood pressure, patients with central pulse only were assumed to have a systolic blood pressure of 90 mmHg or less.^{12,13} Paediatric patients with central pulse only were considered to fulfil the “Code Red” criterion for hypotension.

Prior to 2012 the "Code Red" declaration involved permissive hypotensive resuscitation using only crystalloids in the pre-hospital phase. It also triggered a pre-defined in-hospital major haemorrhage protocol i.e. for blood products to be available on arrival in hospital.^{14,15} In 2012, blood was supplied for pre-hospital administration in “Code Red” patients.¹⁶ The LAA carry a

Golden Hour Box™ (Pelican BioThermal, MN, USA) that contains 4 units of O negative RBCs. The boxes can maintain a steady state temperature of 2-4C for 48-72 hours. LAA utilizes a Belmont Buddy lite™ (Belmont Instrument Corporation, MA, USA) warming system to pre-warm administered blood.

Study design:

A retrospective before and after trauma database cohort study was conducted to identify all patients declared "Code Red" by the pre-hospital team and transported to a major trauma centre for resuscitation or pronounced life extinct on-scene due to exsanguination. Patient records were examined by two pre-hospital clinicians to identify patients who were in pre-hospital cardiac arrest before the implementation of the phRTx procedure and met the "Code Red" criteria without other non-haemorrhagic lethal injury (e.g. massive head injury). Patients subject to inter-hospital transfer or with missing outcome data (i.e. survival status) were excluded. We included patients in the 38-month period from January 2009 through February 2012 before and the 35-month period from April 2012 to February 2015 after the introduction of the phRTx procedure. March 2012 was excluded due to possible implementation phase variability of practice.

Data was collected on demographics, incident characteristics and survival to hospital discharge. Injury Severity Score was not calculated as pre-hospital deaths are usually not transferred to hospital and will have little or no pre-hospital or in-hospital data.¹⁷ Strengthening the reporting of observational studies in epidemiology guidelines were applied.¹⁸

Statistical analysis:

Data is presented as numbers (percentages) for dichotomous data and median (quartiles) for continuous data. The unadjusted association between phRTx and mortality for both pre-hospital

and in-hospital deaths to investigate effect on time of death was assessed using univariate logistic regression. For further analyses adjusting for potential confounders multiple logistic regression models were fitted, including age, gender, time from emergency call to emergency services to arrival in emergency department (ED) and dominating mechanism of injury (penetrating versus blunt) as potential confounders. Missing data was 24 (4.5%) for age and 195 (36.2%) time to ED. The latter is considered high, and complete-case analysis is generally not recommended.^{19,20} We thus performed multiple imputation using the function `mice` in the R package `mice`.²¹ Regression models were fitted to each of 10 imputed datasets, and results pooled. Comparisons of covariates between pre-hospital deaths and patients brought to a major trauma centre were performed using chi-square tests and Mann-Whitney tests for binary and continuous data, respectively. Statistical significance was assumed at $P < 0.05$. Data were analysed using STATA/SE version 11.2 (©StataCorp LP, USA) and R 3.2.²²

RESULTS

During the study period, the pre-hospital service attended 11 915 patients of which 623 (5.2%) met the criteria for suspected major haemorrhage. We excluded 84 (13.5%) subjects due to missing data on survival status. Descriptors of patients included before and after the implementation of phRTx are recorded in Table 1. LAA transfused a median of 2 (quartiles 1 and 3) units of pre-hospital RBCs during the study period. LAA provided phRTx to 21 patients below the age of 18. First 24 hours, the MTCs transfused a median (quartiles) of 7 (4 – 12) and 0 (0 – 5) units of RBC before and after phRTx, respectively. Overall 187 (62.3%) patients died in the before phRTx period and 143 (59.8%) died in the after phRTx group. (Figure 1 Flow diagram).

In the unadjusted analysis there was no significant improvement in overall survival after the introduction of phRTx ($p=0.554$). Results were unchanged when adjusting for confounders (Table 2). Examination of pre-hospital mortality demonstrated 126 (42.2%) deaths in the pre-blood group and 66 (27.6%) deaths in the blood administered group. There was a significant reduction in pre-hospital mortality in the group who received blood ($p<0.001$). (Figure 1 Flow diagram). The result remained significant when adjusting for confounders in a multiple regression analysis (Table 3).

DISCUSSION

This study demonstrates that the introduction of pre-hospital red blood cells for transfusion in trauma patients was associated with decreased pre-hospital mortality in patients with suspected major haemorrhage. There was however no decrease in overall mortality. A recent systematic review on the use of pre-hospital blood product resuscitation in trauma, showed no overall survival benefit, but there was some evidence for improved survival at 24 hours.⁵ The quality of evidence in this review was poor, with only 27 observational studies identified, however, its findings are consistent with our results. It is plausible that early transfusion with RBC may mitigate early haemorrhage/coagulopathy in patients with haemorrhagic shock and avoid the haemodilution seen with aggressive crystalloid resuscitation,^{23,24,25} leading thus to improved short term survival. However, randomised control trials are needed to validate these findings, and one such trial, that is comparing blood transfusion with intravenous fluid in the pre-hospital setting, is currently recruiting in the UK (REPHILL).²⁶

The current study includes 21 patients under the age of 18 years subject to phRTx although only 4 were below the age of 10, emphasising the feasibility of this intervention also for paediatric

trauma patients.²⁷ Early fibrinogen substitution is associated with a clinically relevant reduction in volume of RTx in children, indicating a need for studies looking into more balanced transfusion protocols, also in the pre-hospital phase of care.²⁸

Further, the availability and administration of blood and blood products may improve survival where other haemostatic pre-hospital interventions are employed e.g. tourniquet application or aortic occlusion with a REBOA (resuscitative endovascular balloon occlusion of the aorta) technique.²⁹ In this study four units of blood were available for transfusion, but only a median of two units were administered. This may be related to the short transport times in our trauma system. It is unclear whether mortality might have been influenced more by administration of greater quantities of blood in those patients with high rates of bleeding. Conversely, concerns with potential harm associated with blood transfusion must not be ignored. In addition to transfusion reactions, some studies have shown that increased use of blood components for management of bleeding is independently associated with acute respiratory distress syndrome, multi-organ failure, and immunomodulation which could potentially increase the risk for infections.^{30,31,32,33} However, all these studies have been observational, and one systematic review and meta-analysis concluded that a restrictive RTx strategy compared with a liberal transfusion strategy was not associated with reduced risk for infection.³⁴

Comparison of future studies is likely to be further complicated by the administration of different types and quantities of blood products in combination with red blood cells (e.g. freeze-dried plasma, fresh-frozen plasma, fibrinogen).^{35,36} The use of pre-hospital transfusion has been developed to improve the mortality of bleeding trauma patients. A secondary benefit of improved survival to hospital which has been recently raised is the possibility of increased rates of organ

donation which might mitigate the financial burden of pre-hospital transfusion and improve outcomes in organ recipients.³⁷

Strengths and limitations

The retrospective observational "before" and "after" design of the current study carries several limitations. The study involved a review of trauma registry data restricted to variables already defined in the trauma registries. Pre-hospital deaths are usually not transferred to hospital and will have little or no pre-hospital or in-hospital data, thereby limiting matching of cohorts. The patients were managed in four major trauma centres in London, limiting our ability to capture data on injury patterns and hospital interventions. Management of major trauma has evolved in multiple areas over the last decade. Uncontrolled "before" and "after" study design fail to adjust for changes of practice occurring in the study period. Patients that died in the pre-hospital phase before implementation of phRTx were identified through manual investigation of cases with documented evidence of hypovolaemic aetiology without catastrophic head injuries and cardiac arrest, to prevent potentially introducing selection bias. The pre-hospital deaths that occurred after implementation of phRTx were identified through the administration of RBC. This means that any exsanguinating cases that died in the pre-hospital phase after the introduction of phRTx without transfusion are excluded.

We describe a mixed cohort of patients subject to penetrating and blunt mechanism of injuries. These mechanisms are historically managed differently, with more complex interventions instigated on-scene for patients subject to blunt trauma. Conversely, victims of penetrating injuries are generally more subject to short on-scene times with load-and-go approach which minimise the time available for phRTx. In a prospective observational study, Holcomb et al. was

limited in their propensity-matching by an imbalance in characteristics between the cohorts with and without blood products on helicopters. They argued that a large, multi-centre, randomized study will be required to detect survival differences after phBTx.³⁸ Prospective well-powered studies should also stratify analyses according to mechanism of injury to investigate effect of phRTx on these trauma sub-populations.

Conclusions:

LAA was the first UK civilian pre-hospital service to routinely carry RBCs for fluid resuscitation of exsanguinating trauma patients. We found that phRTx was associated with increased survival to hospital, but not overall survival. The “delay death” effect of phRTx carries an impetus to further develop in-hospital strategies to improve survival in severely bleeding patients. phRTx appears logical and randomized multi-centre studies investigating the causal relationship between phRTx and outcome are warranted.

List of abbreviations:

LAA: London's air ambulance

RBC: red blood cell

phRTx: Red blood cell transfusion

HEMS: Helicopter emergency medical service

PH: Pre-hospital

MTC: Major trauma centre;

ED: Emergency department

REBOA: Resuscitative endovascular balloon occlusion of the aorta

Ethics approval and consent to participate:

The project protocol was considered by the LAA research and development committee. It met local criteria for, and was registered as, a trust service evaluation project (ID 6191). No additional interventions were carried out and the study recorded only the frequency of events in

normal practice with a view to service improvement. Ethical approval was therefore not sought.

Consent for publication of individual person's data not applicable.

Authors contributions: All authors designed the study, collecting data and contributed in writing the manuscript; MR, SE and JR analysed the data. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

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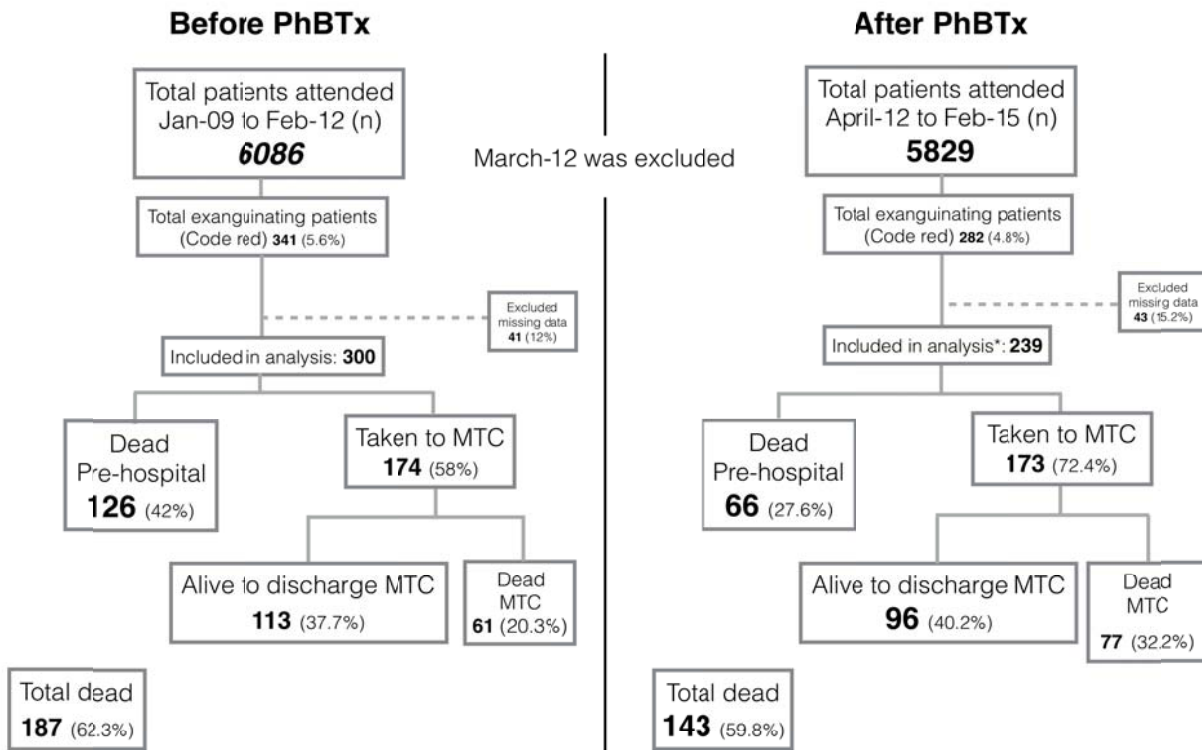
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Legends:

Figure 1: Flow chart of patients



Legend: Flow chart of patients before and after implementation of pre-hospital red blood cell transfusion

Table 1 Patients included before and after implementation of phRTx

	To MTC			PH-deaths		
	Before phRTx	After phRTx	P-value	Before phRTx	After phRTx	P-value
Included patients	174	173		126	66	
Age (years)†	30 (23 - 42)	32 (24 - 45)	0.117 [#]	32 (22 - 50)	33 (24 - 45)	0.240 [#]
Gender (Male)	133 (76.4%)	123 (71.1%)	0.258*	107 (84.9%)	60 (90.9%)	0.242*
Dominant injury (Blunt)	117 (67.2%)	113 (65.3%)	0.705*	72 (57.1%)	33 (50%)	0.345*
Origin call to arrive in ED (minutes)†	72 (58 - 86)	79 (65 - 93)	0.005 [#]	-	-	

Values are counts and percentages unless otherwise stated; †Median and quartiles; *Chi-square test; [#]Mann-Whitney test. phRTx: Pre-hospital red blood cell transfusion; PH: Pre-hospital; MTC: Major trauma centre; ED: Emergency department.

Table 2 Logistic regression models with overall death as dependent variable.

	Univariate logistic regression models		Multiple logistic regression model	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
phRTx (yes)	0.90 (0.64, 1.28)	0.554	0.92 (0.64, 1.32)	0.648
Age (years)	1.01 (1.00, 1.02)	0.289	1.01 (1.00, 1.02)	0.068
Gender (female)	0.76 (0.50, 1.16)	0.196	0.74 (0.48, 1.14)	0.172
Time to ED (minutes)	1.00 (0.99, 1.01)	0.363	1.00 (0.99, 1.01)	0.467
Dominant MOI (penetrating)	1.27 (0.89, 1.82)	0.196	1.30 (0.86, 1.96)	0.185

CI: Confidence intervals; phRTx: Pre-hospital red blood cell transfusion; MOI: Mechanism of injury

Table 3 Logistic regression models with pre-hospital death as dependent variable.

	Univariate logistic regression models		Multiple logistic regression model	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
phRTx (yes)	0.53 (0.36, 0.76)	<0.001	0.52 (0.35, 0.78)	0.001
Age (years)	1.00 (0.99, 1.01)	0.709	1.01 (1.00, 1.03)	0.033
Gender (female)	0.42 (0.26, 0.67)	<0.001	0.42 (0.26, 0.70)	<0.001
Time to AE (minutes)	0.99 (0.98, 1.01)	0.376	1.00 (0.98, 1.01)	0.771
Dominant MOI (penetrating)	1.63 (1.14, 2.34)	0.008	1.68 (1.07, 2.65)	0.024

CI: Confidence intervals; phRTx: Pre-hospital red blood cell transfusion; MOI: Mechanism of injury