Resuscitation with pre-hospital blood products in adults with trauma-related haemorrhagic shock: the RePHILL RCT

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Scientific summary

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Scientific summary

Background

For many years, trauma care focused upon providing basic treatments on scene to facilitate safe transfer to hospital for further and definitive care. In the last two decades however, the emphasis in civilian practice has started to change in the direction of delivering more advanced interventions to patients while still in the pre-hospital phase. This shift, intended to provide earlier physiological stability and prevent so-called secondary damage occurring, has been driven in part by lessons learned in conflict by military medical systems, and include advanced haemorrhage control and blood product-based resuscitation.

The introduction of blood component resuscitation during military casualty retrieval initially produced encouraging results with reports of reduced mortality amongst recipients receiving red blood cells (RBCs) and pre-thawed plasma. Extrapolating results from military trauma-based studies into civilian practice is not straightforward. The mechanisms and severity of injury sustained in conflict are rarely replicated in civilian practice, the patient demographic of active combatants is comparatively narrow and the medical infrastructure in dedicated field hospitals is different to many civilian emergency departments (EDs).

The provision of blood products as early treatment of major haemorrhage may seem logical, but it is also not without complication. Stored RBCs carry a significant metabolic burden when administered rapidly and have the potential to cause further disruption to coagulation and myocardial function. There are also considerations around the provision of blood products including the demand for 'universal' blood products, regulatory compliance and secure cold-chain governance to avoid unnecessary wastage of products.

The lack of robust evidence surrounding the administration of pre-hospital RBCs or plasma in civilian practice, coupled with the challenges this poses to the transfusion community, made a prospective randomised controlled trial (RCT) important if further developments in this area of practice are to be justifiable.

Objectives

The primary objective of the RePHILL trial was to investigate the clinical effectiveness of pre-hospital blood products (PHBP) resuscitation compared to the current standard care of restricted crystalloid-based resuscitation in participants developing haemorrhagic shock following major trauma. This was assessed through the primary outcome, a composite of episode mortality and a failure to clear lactate.

The secondary objectives included examining the effect of PHBP on systolic blood pressure (SBP), heart rate, capillary oxygen saturation, on scene times, fluid and transfusion requirements, coagulopathy and platelet function, transfusion-related complications, blood product wastage and haemoglobin concentration on ED arrival.

Methods

Ethics and regulatory approvals

The study was sponsored by University Hospitals Birmingham NHS Foundation Trust and approved by the South Central Research Ethics Committee (15/SC/0691) and the Medicines and Healthcare products

Regulatory Agency. The EudraCT number is 2015-001401-13 and International Standard Randomised Controlled Trial number is ISRCTN62326938. The trial was co-ordinated by Birmingham Clinical Trials Unit.

Design

The study was a multi-centre, allocation concealed, open-label, parallel group, RCT.

Inclusion and exclusion criteria

Participants were eligible for inclusion if the following criteria were met:

- traumatic injury;
- pre-hospital emergency medical (PHEM) team attend;
- hypotension SBP <90 mmHg (or absence of palpable radial pulse) believed to be due to traumatic haemorrhage.

The trial exclusion criteria were:

- children (known or apparently aged <16 years);
- blood administered on scene, prior to randomisation;
- traumatic cardiac arrest where (1) the arrest occurred prior to arrival of the PHEM team and/or (2) the primary cause is not hypovolaemia;
- refusal of blood product administration (e.g. known Jehovah's Witness);
- pregnancy (known or apparent);
- isolated head injury without evidence of external haemorrhage;
- known prisoners in the custody of HM Prison and Probation Services.

Setting

The trial was conducted in four civilian pre-hospital critical care services who operated within the NHS England major trauma networks.

- East Anglian Air Ambulance, Norwich, UK (www.eaaa.org.uk, accessed 7 February 2022).
- Magpas Air Ambulance, Huntingdon, UK (www.magpas.org.uk, accessed 7 February 2022).
- Midlands Air Ambulance and MERIT, West Midlands Ambulance Service NHS Trust, West Midlands, UK (www.midlandsairambulance.com and https://wmas.nhs.uk, accessed 7 February 2022).
- The Air Ambulance Service, Warwickshire (https://theairambulanceservice.org.uk, accessed 7 February 2022).

Major trauma network treatment protocols were informed by the National Institute for Health and Care Excellence Clinical Guidelines 39 Major trauma: assessment and initial management (www.nice.org.uk/guidance/ng39, accessed 7 February 2022).

Consent

Major traumatic haemorrhage is a life-threatening condition that requires urgent treatment. The time-critical nature meant that it was impractical to obtain informed consent from the patient, a personal or professional legal representative without the potential for causing harm through delaying treatment. In accordance with the Medicines for Human Use (Clinical Trials; Amendment No. 2) Regulations 2006, approval was obtained from the Research Ethics Committee to enrol patients prior to obtaining informed consent. For patients who survived to be admitted to hospital, the local research teams sought written, informed consent from the patient or a legal representative to continue in the trial.

Randomisation and masking

Randomisation (variable block size, stratified by site 1 : 1 ratio) was implemented through a central and secure trial database at the Birmingham Clinical Trials Unit. Blood bank staff prepared sealed treatment

boxes with either red blood cell/lyophilised plasma (LyoPlas) or 0.9% saline according to the randomisation schedule.

Allocation concealment was implemented by using opaque boxes that were externally identical in appearance and weight. This ensured pre-hospital teams were unaware of the treatment allocation prior to enrolling a participant.

When a participant met the trial eligibility criteria, randomisation was achieved by opening the sealed boxes. Once opened, those administering the trial intervention were aware of group assignment. Those assessing outcomes in hospital were not informed of group assignment but may have been able to access it through hospital records.

Trial treatments

- Intervention: Up to two units of RBC and up to two units of LyoPlas.
- Control: Up to four (250 ml) bags of 0.9% saline.

Trial treatments were administered until either hospital arrival or until hypotension resolved (i.e. SBP ≥90 mmHg or a radial pulse was palpable). If all four units of trial treatments were given, non-trial 0.9% saline was then given. Following arrival in hospital, further resuscitation and transfusion was at the discretion of the treating clinician.

The primary outcome was a composite measure consisting of episode mortality and lactate clearance defined as a failure to achieve lactate clearance ≥20% per hour in the first 2 hours from randomisation.

The secondary outcomes comprised:

- individual components of the primary outcome;
- all-cause mortality within 3 hours of randomisation;
- pre-hospital time and type and volume of fluid;
- vital signs (SBP, heart rate, capillary oxygen saturation);
- (venous) lactate concentration;
- haemoglobin concentration on ED arrival;
- trauma-induced coagulopathy [defined as International Normalised Ratio (INR) >1.5];
- coagulation measured viscoelastically by rotational thromboelastometry (ROTEM);
- platelet function using multiple electrode impedance aggregometry (MultiPlate);
- total blood product receipt;
- acute respiratory distress syndrome;
- transfusion-related complications;
- organ failure-free day.

Sample size and statistical analysis

The trial set out to detect a 10% absolute difference between groups in the proportion of participants experiencing the primary outcome assuming an event rate of 20% in the control group and 10% in the intervention. For 80% power and type 1 error rate of 0.05, 438 participants (219 per group) were required. Allowing for 10% attrition, the sample size was set at 490 participants.

During May 2018, the Data Monitoring Committee (DMC) reported a much higher than anticipated pooled event rate for the primary outcome (65%) to the Trial Steering Committee (TSC). The TSC advised to continue the trial with the original sample size unchanged, noting that the trial retained 80% power to detect a relative risk of 0.82 (71.7% control, 58.3% intervention).

All primary analyses of the primary and secondary outcomes followed the intention-to-treat principle. The analyses used a model-based approach with pre-hospital critical care service included as a fixed effect covariate in the model. Treatment effects are presented with two-sided 95% confidence intervals (CIs). No adjustment for multiple comparisons was made. Binary outcomes were analysed using log-binomial regression models to obtain adjusted relative risks along with 95% CIs. A relative risk <1 favoured the RBC/LyoPlas group. Adjusted risk differences along with 95% CIs were estimated using a binomial regression model with identity link. A risk difference <0 favoured the RBC/LyoPlas group. Continuous data were analysed using linear regression models to obtain adjusted mean differences between groups along with 95% CIs. We planned a priori a Bayesian analysis of the primary outcome and its individual components using non-informative, sceptical and informative priors.

Patient and public involvement

Patient and public involvement (PPI) was intrinsic to the development, management and oversight of RePHILL.

During the initial stages of the trial's development the sponsor engaged a major trauma-specific focus group, the purpose being for PPI representatives to provide their perspective on the study, ask questions and discuss challenges. Valuable feedback was provided from this session that helped drive how key issues (e.g. patient consent) were addressed in the trial protocol. Furthermore, given the nature of the trial interventions, the Jehovah's Witness Hospital Liaison Committee were also consulted and provided guidance on the management of patients within the Witness community.

Throughout the life of the trial, dedicated representatives who sat on both the Trial Management Group (TMG) and TSC provided PPI input.

Results

Recruitment

The trial opened to recruitment on 29 November 2016, with the first patient being recruited on 6 December 2016. The last patient was recruited on 1 January 2021. The trial was closed on 2 January 2021 prior to achieving the intended sample size due to the ongoing impact of the COVID-19 pandemic. The decision to close the trial was made by the TSC and sponsor, without any knowledge of the data or results of interim analyses.

Five hundred and eighty potential participants were assessed for eligibility from which 432 participants were randomised [RBC/LyoPlas (n = 209) or control (n = 223)].

Baseline characteristics

The baseline characteristics were well-balanced between the two groups. Participants were predominantly white (62%), males (82%). The median age was 38 [interquartile range (IQR) 26 to 58]. Road traffic collision (62%), stabbing (16%) and falls (14%) were the commonest mechanisms of injury. Injury patterns were blunt trauma (79%) and penetrating trauma (22%). Brain injury was also present in 48%. Participants received on average 430 ml crystalloid fluids and tranexamic acid (90%) prior to randomisation.

Participants were severely injured. The median injury severity score was 36 (IQR 25 to 50); median new injury severity score was 43 (IQR 34 to 57) and average blood pressure was 73/46 mmHg. Transfer to hospital was facilitated by road ambulance in 62% of participants. The median transfer time was 83 (IQR 65 to 100.5) minutes after the emergency call.

Intervention delivery and follow-up

199/209 randomised to the intervention group (RBC/LyoPlas) received the allocated intervention. The average (mean) volume of fluid administered was 1.57 [standard deviation (SD) 443 ml] units of RBC and 1.25 units LyoPlas (SD 709 ml). Five participants were withdrawn from follow-up.

215/233 randomised to the control group (0.9% saline) received the allocated intervention. The average volume infused was 2.55 units of 0.9% saline (638 ml).

Primary outcome

Amongst the participants randomised to RBC/LyoPlas, 128/199 (64.3%) experienced the primary outcome compared to 136/210 (64.8%) of those randomised to 0.9% saline. The adjusted risk ratio was 1.01 (95% CI 0.88 to 1.17) and adjusted difference −0.025% (95% CI −9.0% to 9.0%), $p = 0.996$.

The breakdown for the composite primary outcome for the RBC/LyoPlas group was:

- Failure to clear lactate alone [$n = 40$ (20%)].
- Failure to clear lactate and mortality [$n = 58$ (29%)].
- Mortality alone [$n = 30$ (15%)].

The breakdown for the composite primary outcome for the 0.9% saline group was:

- Failure to clear lactate alone [$n = 37$ (18%)].
- Failure to clear lactate and mortality [$n = 76$ (36%)].
- Mortality alone [$n = 23$ (11%)].

The Bayesian analysis revealed that the probability that the risk difference for the primary outcome was >0% or >10% was 48.2% and 1.3% (non-informative priors), 44.1% and 0.3% (sceptical priors) and 53.4% and 1.6% (informative priors) respectively.

Secondary outcomes

The event rates for the individual components of the primary outcome comprised of:

- Episode mortality 88/203 (43%) in the RBC/LyoPlas group compared to 99/218 (45%) in the 0.9% saline group [adjusted average differences −3% (−12% to 7%), $p = 0.57$].
- Failure to clear lactate 98/196 (50%) compared to 113/206 (55%) [adjusted average difference −5% (−14% to 5%), $p = 0.33$].

Vital signs on arrival at hospital and through to 24 hours were similar between groups.

The haemoglobin concentration on arrival to hospital was 133 (19) g/L in the RBC/LyoPlas group compared to 118 (23) g/L in the 0.9% saline group, an adjusted average difference of 15 g/L (95% CI 10 to 19), $P < 0.0001$. There were no between group differences in tests of coagulation, and platelet function was similar.

Blood product use was similar following hospital admission through to 24 hours. A post-hoc analysis found that total (pre-hospital and hospital) blood and plasma use was higher in the RBC/LyoPlas group [mean difference 1.80 units (95% CI 0.58 to 3.01) and 1.54 units (95% CI 0.57 to 2.50)] respectively.

Death within 3 hours occurred in 32/197 (16%) compared to 46/208 (22%), adjusted average difference −7% (−15% to 1%); $P = 0.08$, and within 30 days it occurred in 86/204 (42%) compared to 99/219 (45%), adjusted average difference −4% (−13% to 6%); $P = 0.44$.

Adverse events

Rates of complications and adverse events were similar across groups, and only two serious adverse events were recorded.

Complications relating to transfusion in the first 24 hours were similar for the RBC/LyoPlas group 11/148 (7%); compared to 0.9% saline 9/137 (7%).

Acute respiratory distress syndrome developed amongst 9/142 (6%) in the RBC/LyoPlas group and 3/129 (2%) in the 0.9% saline group [adjusted relative risk 2.71 (0.75 to 9.81)].

The number of organ failure-free days were also similar across groups [12.9 (SD 13.0) RBC/LyoPlas vs. 12.1 (13.1) 0.9% saline].

No patients required dose reductions or had treatment discontinued for drug-related toxicity. There were no treatment-related deaths.

Conclusion

In adults with severe injuries and haemorrhagic shock secondary to major trauma in a civilian setting, the RePHILL trial did not demonstrate that pre-hospital RBC/LyoPlas resuscitation was superior to 0.9% sodium chloride.

Future research should seek to identify if specific groups of patients may benefit and explore the effects of alternative transfusion strategies.

Trial registration

This trial is registered as ISRCTN62326938.

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