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Clinical paper

Pre-hospital blood products and calcium replacement protocols in UK critical care services: A survey of current practice

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Abstract

Introduction: In the United Kingdom, prehospital blood products are increasingly carried for the early resuscitation of hypovolaemia in patients who are shocked or in cardiac arrest. There is an association between hypocalcaemia and mortality in trauma patients, but no current national guidelines on the timing or dose of calcium replacement exist. The objective of this study was to establish the availability of prehospital blood products, and the current calcium replacement protocols used by UK prehospital services.

Methods: A cross sectional survey of all UK air ambulances and additional prehospital critical care organisations was conducted in April-May 2022 via an on-line questionnaire. The survey asked 11 questions about availability of prehospital blood products, calcium replacement for patients requiring prehospital blood products, and the use of point of care testing.

Results: There was a 100% response rate with 20/22 UK air ambulances carrying blood products and five additional prehospital services identified. There were 15 different combinations of prehospital blood products. 23/25 services had a standard operating procedure for the replacement of calcium. This was recommended before any blood product administration in 5 services (22%), during or after the 1st unit in 5 services (22%), during or after the 2nd unit in 6 services (26%) and during or after the 4th unit in 7 services (30%). Only six services carried point of care testing and no services routinely used this to measure calcium levels in patients requiring prehospital blood products.

Conclusion: In 2022, 91% of UK air ambulances carry prehospital blood products and there is significant variation between services in the combination of blood products provided. There is no consensus on the timing or dose of calcium replacement. Further prospective research should examine the association between traumatic bleeding and ionized calcium levels before and during blood product transfusion in order to produce more robust guidelines for routine calcium replacement.

Keywords: Calcium, Trauma, Hemorrhage, Transfusion, Prehospital, Emergency medical services

Introduction

Hypovolaemia is recognized as one of the four reversible causes of traumatic cardiac arrest.¹ In the UK, pre hospital blood products (PHBP) are increasingly carried by air ambulance and critical care services for the early resuscitation of trauma patients with signs of hypovolaemic shock, a low flow state or recent loss of vital signs suspected to be caused by haemorrhage. In 2016, the RESCUER study identified that 10 out of the 22 UK air ambulances carried prehospital blood products, and that within the 11 air ambulances studied, 1 in 40 air ambulance taskings was to a patient with hypotensive trauma who required fluid resuscitation.² Anecdotally

there has been increased utilisation of PHBP in the UK since this publication.

Packed red blood cells, plasma and platelets contain citrate as an anticoagulant, which can bind with calcium lowering the ionized calcium concentration. Calcium is important for platelet function, intrinsic and extrinsic coagulation pathways and cardiac contractility.³ An association has been reported between hypocalcaemia and an increase in mortality, coagulopathy and blood transfusion requirements in trauma patients.⁴⁻⁷ It remains unclear whether hypocalcaemia in trauma patients with hypovolaemic shock is primarily contributing to mortality or whether it is simply an indicator of a deranged pre-morbid physiology but calcium replacement is considered important during emergency blood transfusion.

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There is currently no national guideline advising when prehospital calcium replacement should occur for the bleeding trauma patient in relation to the number of blood products infused. In-hospital, clinicians have access to blood gas ionized calcium levels to guide replacement but this is not available in the prehospital setting. Point of care testing is feasible, however it is unclear to what extent this is currently available within UK prehospital critical care services. Due to the limited evidence in the literature, it is hypothesized that there is significant variability in calcium replacement protocols during PHBP resuscitation.

The objective of this study was to establish the availability of PHBPs in the UK and to identify the current calcium replacement protocols used by the prehospital services who carry blood products.

Methods

This was a cross-sectional survey with purposive sampling conducted in April-May 2022. The on-line questionnaire comprised 11 questions asking for detail on the blood products carried by the service, the type/dose of calcium replacement carried, whether there was a Standard Operating Procedure (SOP) for calcium replacement and whether the service used a point of care testing (POCT) device. The questionnaire was delivered using the Smart Survey app (Supplementary Appendix 1). The questionnaire was sent to two separate air ambulance contacts to pre-test before being sent out to all participants with no changes required. The results from the first two air ambulances were included in the survey.

Within the UK there are 22 air ambulance charities. Prehospital critical care is also provided by a number of BASICS schemes and independent organisations. A representative (medical director, blood lead, or research lead) from each air ambulance was contacted by email on 4th April 2022 and invited to complete an online questionnaire. Non-respondents were emailed again after two weeks. To ensure other organisations were included the British Association for Immediate Care (BASICS) was contacted, and a Twitter post invited respondents from other services who carry PHBP to get in contact with the lead author. The survey closed on 11th May 2022.

The survey results were collated anonymously, confidentially, and no patient details were included. Therefore this study did not require ethical approval. Only the authors had access to the survey app. No statistical analysis of the results was necessary and the results are presented in descriptive format. Reporting of the results used the CROSS (Consensus-based checklist for reporting of survey studies) checklist. There was no patient or public involvement in the design, conduct or reporting of this study.

Results

Survey responses

22 air ambulances were contacted and the response rate was 100 %. 5 additional organisations providing PHBP resuscitation in the UK were identified: this included two Emergency Department based pre-hospital teams; one ambulance service critical care team not affiliated with an air ambulance; and two BASICS schemes. One participant from the Republic of Ireland also expressed an interest in being included and submitted a response: this was excluded as other services in this country did not participate. Duplicate survey entries occurred for two services but the responses matched so were

amalgamated. There was no missing data. This provided a total of 27 complete survey responses from separate services in the UK.

Provision of PHBP

Of the 22 air ambulances, 20 are now carrying PHBP (91 %). In total there were 25 services identified as carrying PHBP in the UK, and within these there were 15 different combinations of products used. The type of PHBP carried is listed in [Table 1](#). Packed Red Blood Cells (PRBC) O negative are carried by 23 services (92 %), PRBC O positive by 4 services (16 %), Fresh Frozen Plasma (FFP) by 15 services (60 %), lyophilised plasma (LyoPlas) by 9 services (39 %), Fibrinogen by 2 services (8 %) and Prothrombin Complex Concentrate by 1 service (4 %).

Calcium replacement

Of the 25 services carrying PHBP, only one service does not carry calcium replacement therapy. One service reported that they carry 10 % calcium gluconate, one uses either calcium gluconate or calcium chloride, and 22 services carry 10 % calcium chloride.

Two of the 25 services with PHBP do not have a SOP to define the timing of calcium replacement during prehospital blood transfusion. Of the 23 services with a SOP, there were 11 different variations of when calcium should be routinely administered during PHBP resuscitation. The different combinations can be viewed in [Table 2](#). 22 services administer 10 ml boluses of calcium replacement and two services administer 5 ml boluses of 10 % Calcium chloride.

From the responses to the survey questions viewed together it was possible to ascertain when the earliest recommended calcium replacement was advised in the SOP. This was before any PHBP were given in 5 services (22 %), during or after the 1st unit of PHBP in 5 services (22 %), during or after the 2nd unit of PHBP in 6 services (26 %) and during or after the 4th unit of PHBP in 7 services (30 %).

It was not specifically asked whether there was a separate SOP for paediatric practice but 9 services documented in the survey that they have a specified regime for calcium replacement in children. These were 0.1 mg/kg every 20 ml/kg PHBP (1); 0.1 mg/kg after the 1st and 5th bolus (1); 0.2 mg/kg after 20 ml/kg PHBP (1); and 0.2 mg/kg 'as per adult bolus timings' (6).

Point of care testing

Six services carry point of care testing: 3 services carry the epoc[®] Blood Analysis System (Siemens Healthineers); 2 services have the Abbott i-STAT 1 and one service carries the Abbott i-STAT Alinity product. None of these have a specific SOP for when to check calcium levels for trauma patients who are being considered for PHBP resuscitation or when a certain calcium level would trigger replacement.

Future research

All but one of the 25 services would be interested in participating in further research to assess prehospital calcium levels in trauma patients.

Discussion

PHBP are now carried by 91 % of air ambulances in the UK as well as by several other organisations providing prehospital critical care.

Table 1 – Type of blood products carried by UK prehospital critical care services.

Type of blood product	Number (n = 25)
2 PRBC O neg, 2 FFP	5
2 PRBC O neg	3
4 PRBC O neg, 4 FFP	3
4 LyoPlas	2
2 PRBC O neg, 2 PRBC O pos, 4 FFP	2
3 PRBC O neg	1
4 PRBC O neg	1
4 PRBC O neg, 2 FFP	1
2 PRBC O neg, 2 LyoPlas	1
2 PRBC O neg, 3 LyoPlas	1
2 PRBC O neg, 2 FFP, 2 LyoPlas	1
2 PRBC O neg, 1 FFP, 4 LyoPlas	1
4 PRBC O neg, 2 FFP, 4 LyoPlas	1
2 PRBC O neg, 2 PRBC O pos, 4 LyoPlas, 6 g fibrinogen, 3000iu Beriplex	1
2 PRBC O neg, 2 PRBC O pos, 4 FFP, 4 LyoPlas, 4 g fibrinogen	1

PRBC = packed red cells, O neg = O negative, O pos = O positive, FFP = fresh frozen plasma.

Table 2 – Guidelines for calcium replacement during PHBP administration.

Timing of calcium replacement	Number of organisations (n = 25)
Before any PHBP	5
After 2 PRBC + 2 FFP	5
After 1 PRBC	3
No SOP	2
After 1 PRBC + 1 FFP	2
After 1 PRBC + 1 LyoPlas	2
During 1st PRBC	1
After 1 FFP	1
After 2 PRBC	1
After 2 FFP	1
After 2 LyoPlas	1
After 2 PRBC + 2 LyoPlas	1

SOP = Standard Operating Procedure, PRBC = packed red cells, O neg = O negative, O pos = O positive, FFP = fresh frozen plasma.

This has increased from six years ago when only 10 air ambulances carried PHBP. The PHBP provision varies significantly by individual service and includes PRBC (O negative and O positive), FFP, lyophilised plasma, fibrinogen concentrate, and prothrombin complex concentrate. In 2016–2017 a survey of European practice in prehospital blood transfusion within 14 countries found that 48 % of respondents had prehospital access to PRBC, 22 % to FFP and 14 % used lyophilised plasma.⁸ There were only 10 responses from the UK in this survey. It is relevant to note that three UK air ambulances are now carrying Group O RhD positive PRBC in line with other countries. This allows the more scarce Group O RhD negative type to be preserved for females of childbearing age (aged < 50 years) and may become a supply strategy used more commonly in the future.⁹

There is limited evidence in the literature for the benefit of PHBP.¹⁰ Despite this, many prehospital clinicians lack equipoise for PHBP use and believe that the treatments delivered in the resuscitation room of the trauma centre should be equitably delivered to the same patient at the incident scene to maximize chances of survival. Recently the RePHILL trial did not show that prehospital PRBC-LyoPlas resuscitation was superior to 0.9 % sodium chloride for adult patients with trauma related haemorrhagic shock, although there appeared to be a trend for increased survival at 3 hours in the

PHBP group.¹¹ Two earlier randomised control trials assessed the effect of pre-hospital FFP transfusion: the COMBAT trial¹² found no difference in mortality between crystalloid and FFP, and the PAM-PeR trial¹³ reported that 2 units of FFP use before standard care (crystalloid and PRBC) resulted in a 30 day mortality that was 10 % lower than the standard care group. A post-hoc analysis found that the conflicting results may be due to different transport times, with increased mortality in the standard care group when transport times exceeded 20 minutes.¹⁴

With the exception of one of the services carrying blood, all others carry calcium replacement therapy but not all have a SOP. There are significant variations in the timings and dose of routine calcium replacement in relation to the number of PHBP administered: this highlights the lack of robust evidence to inform practice. A number of retrospective observational studies have assessed the ionized calcium levels on arrival to the Emergency Department (ED) in shocked trauma patients. A 2019 study reviewed ionized calcium level in patients recruited to the PAMPer and COMBAT trials before any calcium replacement.¹⁵ 35.7 % of patients receiving crystalloid and 52.6 % of those receiving prehospital plasma had hypocalcaemia (≤ 1.0 mmol/L) on arrival to hospital. The authors recommended giving 10mls calcium gluconate for every 1–2 U of PHBP.

A UK study found that 30/55 trauma patients had a pretransfusion ionized calcium < 1.1 mmol/L, which increased to 35/37 patients after receiving transfusion in the ED.¹⁶ The majority of patients only received a two-unit blood product transfusion and this produced a statistically significant difference in ionized calcium level (it was unclear if the first units were PRBC or FFP). A retrospective review of military patients transported by the UK Medical Emergency Response Team had a median PHBP administration of 4 units (PRBC and FFP) and found a 70.0 % incidence of hypocalcaemia (<1.12 mmol/L).¹⁷ The authors recommended the consideration of intravenous calcium replacement in all patients transfused with PHBP, as after only one unit the median calcium level dropped below the lower limit of normal.

The majority of UK prehospital services use 10 % calcium chloride (6.8 mmol calcium) for replacement in trauma patients requiring blood transfusion. Two services carry 10 % calcium gluconate (2.25 mmol calcium) or 10 % calcium chloride, depending on the stock available. European guidelines published in 2019 recommend the use of 10 % calcium chloride as it contains a higher dose of elemental calcium: this is thought to be preferable in patients with severe hypovolaemia and hepatic hypoperfusion who are less able to clear citrate in a rapid transfusion of blood products.¹⁸

However, whilst hypocalcaemia is associated with worse outcome in bleeding trauma patients, there are also risks from hypercalcaemia. MacKay and colleagues retrospectively assessed 41 patients with massive transfusion protocol activation: 35 patients had hypocalcaemia and 9 patients had hypercalcaemia at some point during the first 24 hours of injury.¹⁹ The Youden index (a summary measure of the Receiver Operating Characteristic curve measuring the effectiveness of a diagnostic marker and enabling the selection of an optimal threshold value) identified that mortality was only greater in patients with extreme hypocalcaemia (<0.84 mmol/L) rather than any hypocalcaemia (<1.0 mmol/L). However any hypercalcaemia above the reference range (>1.25 mmol/L) was associated with increased mortality.

The COCA trial of calcium in out of hospital medical cardiac arrest found no benefit and, although not reaching statistical significance, there was a trend for worse outcomes in patients who received calcium.²⁰ Studies have suggested that high levels of calcium immediately after administration may cause cytosolic and mitochondrial calcium overload during cardiac arrest leading to cardiac hypercontraction,^{21,22} oxidative stress, and activation of enzymes which cause cell death.^{23,24} Similar pathology could potentially occur in hypovolaemic patients with a low flow state and myocardial ischaemia.

This suggests that a protocol of early routine calcium replacement for all bleeding trauma patients may be harmful if overcorrection occurs. Two services provide 5 ml boluses of 10 % calcium chloride rather than 10 ml boluses. This may reduce the risk of overcorrection and allow less of a 'peak and trough' effect if given more frequently at lower doses. Further research should include an analysis of both hypo- and hypercalcaemia in trauma patients.

The six services which carry POCT do not routinely measure calcium levels in order to guide replacement therapy during PHBP administration. It was not investigated whether the cartridges currently used by the services would allow for serum calcium measurement or whether this would require alternative products. There is a lack of evidence in the literature specifically around the use of POCT for calcium replacement. Published prehospital studies in HEMS services or ED response vehicles using POCT in critically ill patients

have found a number of limitations including a narrow operational temperature range, sensitivity to vibration, difficulty filling cartridges, faulty cartridges and the requirement to use blood obtained by invasive means.^{25–27} Further research is required to establish whether POCT for calcium levels is feasible or accurate before implementation can be considered.

There are a number of limitations of this study. The survey may not have been accessed by every UK prehospital organisation who administer PHBP, although all air ambulance charities were represented. The survey results are cross-sectional and other services may be developing resources for using PHBP or changing the type of PHBP carried in the near future. The wording of the response to the question of when calcium replacement should be initiated according to the SOP was copied exactly to ensure that this was represented accurately. However the individual completing the survey may have misworded whether the replacement should occur before, during or after each specified unit which changes the meaning of the direction. Importantly, the survey did not specifically ask the order of administration of blood products although most respondents gave this detail. The order of transfusion could influence the decision to administer calcium replacement: FFP has a higher citrate concentration than PRBC or LyoPlas and therefore any SOP may be inclined to deliver calcium chloride sooner if FFP is given earlier in the regime. Finally, the results may not be generalizable to other international prehospital services who carry blood products, although it is likely that variability also exists in their practice.

Conclusion

In 2022, PHBP are administered by the majority of UK air ambulances (91 %) and by a number of other prehospital critical care services. There is significant variation in both the blood products carried and the protocol for calcium replacement between services. This highlights a need for more evidence regarding the optimal PHBP resuscitation strategy, and the impact of bleeding and PHBP administration on blood calcium levels to safely guide routine prehospital calcium replacement.

CRedit authorship contribution statement

Caroline Leech: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Eleri Clarke:** Formal analysis, Writing – review & editing, Visualization.

Declaration of Competing Interest

Caroline Leech is a prehospital doctor working with The Air Ambulance Service. Eleri Clarke has no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2022.100282>.

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