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Pre-hospital blood product resuscitation for trauma: a systematic review

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Abstract

Introduction: Administration of high ratios of plasma to packed red blood cells is routine practice for in-hospital trauma resuscitation. Military and civilian emergency teams are increasingly carrying pre-hospital blood products (PHBP) for trauma resuscitation. This study systematically reviewed the clinical literature in order to determine the extent to which the available evidence supports this practice.

Methods: Bibliographic databases and other sources were searched to July 2015 using keywords and index terms related to the intervention, setting and condition. Standard systematic review methodology aimed at minimising bias was used for study selection, data extraction and quality assessment (protocol registration PROSPERO: CRD42014013794). Synthesis was mainly narrative with random effects model meta-analysis limited to mortality outcomes.

Results: No prospective comparative or randomised studies were identified. Sixteen case series and eleven comparative studies were included in the review. Seven studies included mixed populations of trauma and non-trauma patients. 25/27 studies provided only very low quality evidence. No association between PHBP and survival was found (OR for mortality: 1.29, 95% CI: 0.84–1. 96, P=0.24). A single study showed improved survival in the first 24 hours. No consistent physiological or biochemical benefit was identified, nor was there evidence of reduced in-hospital transfusion requirements. Transfusion reactions were rare, suggesting the short-term safety of PHBP administration.

Conclusions: While PHBP resuscitation appears logical, the clinical literature is limited, provides only poor quality evidence and does not demonstrate improved outcomes. No conclusions as to efficacy can be drawn. The results of randomised controlled trials are awaited.

Keywords

Wounds and Injuries; Haemorrhage; Emergency Medical Services; Blood Component Transfusion; Erythrocyte Transfusion; Plasma; Meta-Analysis; Military Medicine

Introduction

Liberal blood product resuscitation has probably contributed to improved casualty survival in recent conflicts (1, 2). Early administration of plasma in high ratios to packed red blood cells (PRBC) is characteristic (3). The reintroduction of military pre-hospital blood product (PHBP) resuscitation was a logical evolution and is increasingly mirrored in civilian practice. However, the evidence supporting plasma rich resuscitation is limited to systematic reviews of predominantly retrospective, observational studies (4, 5). A Cochrane review of plasma in massive transfusion is yet to be published (6), while a review of plasma transfusion in the critically ill failed to identify any relevant randomised studies (7). A recent observational study (8) associated early plasma administration with improved 30 day survival (9). However, the PROPPR trial found that despite achieving earlier haemostasis, resuscitation with plasma, platelets and PRBC in 1:1:1 ratios did not improve overall survival compared to 1:1:2 (10).

PHBP were used during the Vietnam War (11). with civilian pre-hospital PRBC administration reported in 1985 (12). In 2008, plasma and PRBC were added to the capabilities of the British military's Medical Emergency Response Team (Enhanced) (MERT(E)) (13). Other nations have implemented similar strategies (14, 15). Retrieval by MERT(E) is associated with improved survival after major injury (16). However blood product administration is not unequivocally benign; in addition to transfusion reactions, increasing blood product receipt after trauma has been independently associated with ARDS (17), multi-organ failure (18) and mortality (19-21). This suggests a context-specific balance of risks and benefits. In addition, widespread implementation of PHBP resuscitation (especially plasma) in civilian practice is challenging. Only 4% of US and UK donor pools are universal (group AB) plasma donors and the shelf-life of thawed plasma is only 24

hours. Nonetheless, various PHBP combinations have been delivered with minimal wastage (22-28).

The aim of this systematic review was to determine the extent to which PHBP resuscitation for trauma is supported by clinical evidence.

Methods

The study was registered with PROSPERO (CRD42014013794), was conducted according to the published protocol (29) and is reported according to PRISMA guidelines (30) (Supplementary Digital Content 1, PRISMA Checklist). Relevant studies were sought from bibliographic databases (monthly searches to July 2015) and other relevant sources; see protocol (30) for full details and Medline search strategy (see also Text, Supplementary Digital Content 2, EMBASE search strategy). Standard systematic review methodology aimed at minimising bias was used for study selection and data extraction. Studies were eligible if they evaluated blood products (case-series) or compared these to other resuscitative fluids (controlled studies); were in patients aged ≥ 16 years with traumatic haemorrhage; and were conducted in a military or civilian setting. There was no restriction by outcome. Data not included in published manuscripts or abstracts were sought from the relevant authors.

Ten studies which met selection criteria were not taken forward for analysis (Table, Supplementary Digital Content 3, relevant studies excluded). Seven reported no patient outcomes. Three reported PHBP as an inconsistent component of a care bundle; no association between PHBP receipt and outcomes could be determined.

Risk of bias assessments were made using the Newcastle-Ottawa Scale (31) for comparative studies. Case series and uncontrolled before-and-after series were assessed with appropriate tools (32, 33). The quality of evidence provided by each study was reported using the GRADE method (34). GRADE allows ratings to be upgraded due to strengths or downgraded due to limitations. In this review studies were downgraded for important disparities between cohorts, lack of control for injury burden and significant loss-to-follow-up. Given the inherent limitations of observational studies, merely meeting most or all design quality criteria was insufficient to merit upgrading; no studies were upgraded.

Two cohort studies reported additional subgroup analyses (35-i, 36-i). One reported matched patients and primary retrievals (patients transported directly from the incident scene to the trauma centre) (35-ii, 36-iii). The second reported primary retrievals (36-ii). Data from either main or sub-studies were included as appropriate and are indicated accordingly.

Due to the disparate nature of populations, interventions and outcomes, only limited meta-analysis was possible. Consequently a narrative synthesis of the available evidence was constructed. Evidence for the following outcomes was considered: long term mortality (30 days or in-hospital), early mortality (pre-hospital or at 24 hours), in-hospital transfusion requirements, vital signs and biochemical/haematological indices up to and at Emergency Department arrival.

Pooled estimates of mortality were calculated using inverse weighting and mixed models to reflect heterogeneity between studies. Meta-analysis of 30 day/index admission survival was performed

using the Mantel-Haenszel method with a random effects model. The principal summary statistic was the Odds Ratio. Statistics were computed with *Review Manager 5.3* (Nordic Cochrane Centre, Copenhagen, Denmark) and *R* 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection is shown in Fig. 1. Sixteen case series and eleven comparative studies (1 case control, 10 retrospective cohort) were included. Nine studies considered military trauma patients. Eighteen considered civilian patients, of which seven pooled trauma and non-trauma patients. The aims of case series were varied; frequent themes were feasibility, process description or characterisation of PHBP-recipients. Comparative studies examined associations between PHBP receipt and physiological parameters or clinical outcomes.

Both arms of one cohort study (37) formed part of a case series (38) which formed one arm of a second cohort study (39). As each study reported different aspects of PHBP resuscitation, each was considered individually. Only the final study was included in summary measures. One military study (40) contained an intervention cohort drawn from a larger case series (41).

Tables 1 and 2 summarise the various study and population characteristics. For interventions and important differences between cohorts see (Table, Supplementary Digital Content 4, Study Interventions and Differences). In total, 1080/4714 (23%) patients in comparative studies received PHBP; 2668 PHBP-recipients were reported in case series, of whom 1463 (55%) had sustained trauma.

No blinded or randomised studies were identified - other than one prospective case series, all were retrospective observational studies. Only two studies provided more than “Very Low” quality evidence (see Table, Supplementary Digital Content 5, Risk of bias assessments). Most comparative studies were limited by differences between groups (injury burden, additional in-transit interventions or in-hospital treatment) without control by case matching or statistical methods. Common limitations of case series included lack of a clear research question, pooling of trauma and non-trauma patients, small numbers and lack of robust clinical outcome measures.

Long-term Mortality

Long-term mortality amongst PHBP-recipients varied from 8% to 52% (Fig. 2A). This analysis included unpublished absolute survival data for one cohort study (35-i) (J. Brown. 2015, pers. comm. 08 June). One study reported 67% mortality amongst six subjects, but was excluded from analysis due to 60% loss-to-follow-up (15). Early studies reported loss to follow-up of 18% (12) and 20% (14). Later studies either minimised such losses through design or improved record keeping or (particularly when published in abstract) had insufficient information to allow loss to follow-up to be assessed. In studies from military operations in Afghanistan survival of non-coalition casualties was reported up to point of transfer to host nation medical facilities (up to 47% of study population). Significant post-transfer mortality was considered unlikely as patients were only transferred once in established recovery (42, 43). The pooled mortality estimate of 32% (95% CI: 26% - 38%) exceeds the 23% mortality reported in profoundly hypotensive (SBP<90mmHg) trauma patients treated without PHBP (44, 45) and provides no obvious evidence of benefit. Meta-analysis of uncorrected mortality data was performed, using matched data where available. PHBP receipt

was not associated with reduced mortality (OR for mortality: 1.29, 95% CI: 0.84–1.96) (Fig. 3A). Heterogeneity was substantial (I^2 = 63%). Limiting the meta-analysis to matched studies provided no evidence of benefit (Fig. 3B). Only three studies reported mortality adjusted for confounders (Fig. 4A) (35, 36, 46). These were not combined statistically.

Matched cohort studies (35-ii, 40) reported markedly lower mortality amongst PHBP-recipients than the unmatched PHBP cohorts from which they were drawn (35-i, 41). This may indicate tasking of more capable assets to casualties with more severe injuries, resulting in fewer non-recipient matches as injury burden increases. If so, matched studies will underestimate mortality amongst PHBP-recipients but may also underestimate the potential effect size of PHBP due to the exclusion of patients at greater risk of death, amongst whom a survival benefit might be more evident.

Seven cohort studies reported mortality (Fig. 3A). Only one study found an association between PHBP receipt and absolute survival (40), while three reported increased absolute mortality (35-i (unpublished data), 37, 46). However, the mortality difference reported in the first of these (35-i) was lost when only matched patients were considered (35-ii).

An absolute mortality reduction of 11% was reported amongst battlefield casualties matched by injuries to historical controls from the same facility (40). Acknowledged confounders included limited in-hospital plasma and PRBC transfusions received by both cohorts - 75% of non-recipients received no blood products after hospital arrival. Transfusion practice at this facility became more liberal over time (47); reflected in larger in-hospital transfusion volumes received by the later

PHBP cohort. Other differences included shorter transport times, more frequent pre-hospital airway support, more tranexamic acid and higher in-hospital transfusion ratios (FFP:PRBC 1:1 vs. 0.46:1) amongst PHBP recipients. Recent data from this facility show a stepwise annual survival improvement at all levels of injury (2), suggesting that comparison with this historical cohort will have introduced significant confounding.

A contemporaneous cohort study of battlefield casualties with major trauma (New Injury Severity Score≥16) treated at the above facility (46) found an independent association between PHBP receipt and mortality in multivariate analysis. However, marked differences in injury mechanisms, wounding patterns and especially injury burden probably defied statistical correction. These military studies were limited by frequent non-availability of pre-hospital vital signs, hence pre-transfusion physiological status could not be assessed.

Significant baseline differences are found in two smaller civilian cohort studies (37, 48). The former compared 50 injured pre-hospital PRBC recipients with 9 patients who also received plasma. Indications for plasma transfusion included known pharmaceutical anticoagulation. Plasma recipients had a pre-transfusion INR of 2.6 (vs. 1.5 amongst non-recipients) and this remained higher at hospital arrival. In-hospital treatment also differed; plasma recipients received transfusion ratios closer to 1:1 and less crystalloid. Plasma recipients had a higher Trauma Injury Severity Score (TRISS)-predicted mortality and over 50% died, despite more aggressive blood product resuscitation. The latter study (in subjects well matched by injury burden) found no survival difference, though PHBP-recipients had longer pre-hospital times (mean: 30min) than

non-recipients (mean: 12min) (48). Neither study was adequately powered to detect a mortality difference.

The earliest matched cohort study identified that PHBP-recipients received almost four times more pre-hospital crystalloid, were intubated more frequently and received 50% more PRBC during in-hospital resuscitation than non-recipients (49). No survival benefit was found. The authors speculated that PHBP "may have compensated for…longer transport times and possibly more gravely injured patients".

The most robust studies to date are two contemporaneous cohort studies (35, 36). The first compared 50 blunt trauma patients who received a median of 1.3u pre-trauma centre (PTC) PRBC to 1365 non-recipients. Despite similar injury burdens, unadjusted mortality in PHBP-recipients was 28% vs. 16% in non-recipients (P=0.02) (J Brown 2015, pers. comm. 08 June). PHBP recipients were more often secondary transfers (48%) than non-recipients (4%)—introducing a high risk of selection bias due to the probability that more "unavoidable" early deaths were included amongst non-recipients. As in military studies, PHBP-recipients were managed more aggressively, receiving 2.5 times more PTC crystalloid, more in-hospital PRBC and more platelet transfusions. However, in regression analysis PHBP receipt was associated with reduced 30 days mortality. 35 PHBP-recipients were propensity matched with 78 non-recipients. PHBP-recipients were less frequently hypotensive at hospital arrival and the median PRBC transfusion was 69% greater than for non-recipients. Regression analysis again found an association between PHBP-receipt and improved 30 day survival. However, whether statistics can correctly adjust for very different transfusion strategies in a relatively small study is uncertain. In contrast, the same group's larger study

comparing 240 PHBP-recipients to 480 non-recipients, transported by a single service to one trauma centre, found no overall survival benefit from PTC PRBC (36-i).

Early mortality

Six case series reported pre-hospital mortality (23, 25, 50-53). Three cohort studies and one case series reported 24-hour mortality (Fig. 2B) (35-37, 54). Two of the latter reported adjusted odds ratios, including three subgroup analyses (Fig. 4B) (35, 36). These suggest an effect on early mortality, but are limited by the small proportion of PHBP-recipients. Of note, mortality amongst PHBP-recipients is almost 50% greater when only primary retrievals are considered (36) suggesting that these are a different population from secondary transfers. This may lead to marked selection bias when proportions of primary retrievals and secondary transfers differ between cohorts (35-i). However, early survival benefits remained when matched cohorts containing similar proportions of secondary transfers were considered (35-ii). Statistical significance was lost when primary retrievals alone were considered (35-iii).

In-hospital transfusion

Six studies reported in-hospital blood product resuscitation (Fig. 5) (35-37, 40, 46, 49). Four studies matched by injury burden (35, 36, 40, 49), two did not (37, 46). In military studies PHBP-recipients received more in-hospital transfusions (40, 46). The former reflects changes in transfusion practice over time, whilst the latter studies are confounded by differences in injury. No study provided evidence of reduced in-hospital transfusion requirements.

Vital Signs

Four case series report an increase in SBP (12, 53, 54) or decrease in HR or Shock Index (54, 55) associated with PHBP receipt. Amongst military casualties PHBP receipt was associated with a significantly greater correction in Shock Index (56). However, PHBP-recipients were significantly more haemodynamically compromised prior to transport, thus had greater scope for correction. Consequently, reporting absolute correction biases the study in favour of PHBP. Two-thirds of eligible patients were excluded due to non-availability of pre- and post-transfusion vital signs. This may indicate selection bias if vital signs were unrecordable or interventions prioritised in the sickest patients.

In a matched subgroup analysis pre-hospital hypotension was more common in PHBP-recipients but was less common at hospital arrival (35). However, in a larger study, although pre-hospital SBP were similar, PHBP-recipients were more frequently shocked on arrival (36). The final civilian cohort study identified no difference in haemodynamic changes between PHBP-recipients and non-recipients (48). In a case-control study, patients hypothermic at ED arrival were more likely to have received PHBP (57). However the significance of this is unclear, as crystalloids were warmed before administration whereas PRBC were not (F. M. von Recklinghausen (2015) pers. comm. June 23). Collectively, the published data provide no evidence that PHBP improves physiology compared to crystalloids.

Coagulopathy and Acid-Base

Two overlapping studies report correction of predominantly warfarin-related anticoagulation with pre-hospital plasma. In a case series of mixed trauma and non-trauma patients, INR reduced from

4 to 2 (38). In a cohort study—whose pooled subjects formed part of that series—greater absolute correction (INR 2.6 to 1.6) was seen in plasma recipients than non-recipients (INR 1.5 to 1.3) (37). However, pharmaceutical anticoagulation is not analogous to trauma-induced coagulopathy (TIC) thus these papers demonstrate only that plasma-mediated reversal of pharmaceutical anticoagulation can be delivered pre-hospital and should not be extrapolated to suggest a benefit in the treatment of trauma induced coagulopathy (TIC). In blunt trauma patients, PHBP were associated with reduced odds of TIC, however the PHBP group also received greater volumes of crystalloid (35). The association was not found in the same group's larger study in which both cohorts received comparable crystalloid volumes (36). It is possible that greater crystalloid loading reduced TIC-inducing hypoperfusion. In military data, PHBP receipt was independently associated with TIC (46) but this probably reflects vastly greater tissue disruption in PHBP-recipients.

PHBP receipt has been associated with greater acidosis at hospital arrival compared to non-recipients with comparable injury burdens (48). PHBP-recipients had mean flight times of 34min vs. 12min for non-recipients. This provided greater opportunity for PHBP administration, but potentially longer uncontrolled bleeding. In contrast, PHBP receipt was associated with a non-significant trend to lower serum lactate concentration when pre-hospital times were less than 150 minutes (58). However, no details of study size or blood products administered were available.

Adverse events

Amongst 759 PHBP-recipients in studies which specifically reported presence or absence of transfusion reactions (12, 14, 25, 36, 38, 55, 59), only three possible reactions were noted. One patient suffered transient shortness of breath after infusion of 5L crystalloid and 900ml PRBC (12),

although this was probably secondary to volume overload, one patient developed a “fine [truncal] rash” following one unit of PBRC (14) and one patient had a reaction during a subsequent in-hospital transfusion (36). These studies suggest that PHBP receipt is associated with a minimal risk of transfusion-related adverse events.

Discussion

PHBP resuscitation is increasingly employed to try to reduce the 23% mortality amongst hypotensive trauma patients (44, 45). However, provision of universal PHBP components to all trauma networks involves substantial clinical, logistical and fiscal costs. In this first systematic review of the topic, we evaluated the clinical evidence around PHBP for trauma. We identified 27 observational studies which reported relevant clinical outcomes. 26/27 were retrospective. 25/27 provided very poor quality evidence. Common limitations were the lack of a control group or a control group which differed significant from PHBP-recipients. Most comparative studies were too small to permit adjustment for confounders. Studies frequently pooled primary retrievals with secondary transfers, despite these being distinct populations. While PHBP resuscitation is achievable with minimal wastage of universal donor components, and with short-term safety, no more than low quality evidence supports this as a “standard of care”. This review did not identify an overall survival benefit. Evidence for improved survival at 24 hours is derived from only two observational studies and, even if a true effect, may not translate to improved long-term outcomes.

Differences between patients and/or treatment pathways further limited the studies considered in this review. Even when subjects were matched, PHBP-recipients received more in-hospital

transfusions. Consequently, even where associations between PHBP and improved survival are found after statistical correction, this improvement cannot be confidently attributed to PHBP receipt.

The available clinical data shows no evidence that PHBP reduces in-hospital transfusion. This is consistent with recent animal modelling of pre-hospital resuscitation (60). Although TIC was reduced by blood products in various ratios compared to saline, transfusion requirements over the subsequent 150 minutes of "hospital" resuscitation were similar in all groups. Similarly, a previous animal model of uncontrolled splenic haemorrhage showed that whilst Hextend increased blood loss compared to blood products—potentially reflecting the previously reported exacerbation of TIC produced by hetastarches (61)—there was no difference in post-resuscitation blood loss between blood product resuscitation and Hartmann's solution (62). The combination of lyophilised plasma and PRBC in a 1:1 ratio has been shown to reduce total blood loss in a swine polytrauma model compared to both plasma alone and to 1:1 FFP:PRBC resuscitation (63). Short-term survival was not improved by resuscitation with blood products compared to crystalloid. Long-term animal survival studies would be ethically challenging and have not been performed.

As with our findings from the clinical literature, a swine model of PHBP resuscitation did not improve acid-base status. A non-significant trend to less extreme maxima for serum lactate and pH amongst "haemostatically resuscitated" animals was found, however there were fewer than ten animals per group (60). In other animal studies, neither plasma lactate concentration (63) nor acid-base status (62) has been influenced by different blood product ratios. Any metabolic benefit from PHBP remains uncertain.

Strengths and Limitations

The searches for this review were not restricted by language nor by date and included all major citation databases, specialist resources and reference lists from included studies. It is unlikely that material which would significantly change the findings has been overlooked.

The most significant weakness of the study is the low quality of evidence on which the review could draw. Consequently, no conclusions about the efficacy of PHBP resuscitation can be drawn. The extent to which this review makes use of "grey literature" reflects the poor state of evidence in this area. This material has not been subjected to the same degree of peer review as that in published papers, but is nonetheless recognised as being an essential component of a systematic review (64).

These considerations limited the possible statistical syntheses to unadjusted mortality alone, with no indication identified of improved long term survival after PHBP receipt. However the marked differences between the populations in included studies render this finding tenuous. These difficulties are consistent with previous reviews of blood product resuscitation for trauma (65, 66). Meta-analysis produces not only an estimate of overall effect size, but a measure of heterogeneity from which the consistency of the literature can be assessed. In meta-analysis of both unmatched and matched studies, heterogeneity was present and significant, demonstrating the degree of uncertainty which exists about a measurable benefit of PHBP resuscitation.

This review considered both military and civilian studies. The validity of extrapolating from studies of predominantly younger, massively traumatised males to the civilian population is questionable.

However, the inclusion of military case series illustrates the marked change in resuscitation practice over the last decade and thus further factors which must be considered when interpreting the existing literature. Transfusion criteria used by the Israeli military initially required 2L crystalloid administration prior to administration of PRBC, with casualties receiving an average of 4.4L of pre-hospital crystalloid (14). Lyophilised plasma has now replaced crystalloid in Israeli retrieval missions (67), such that "crystalloid infusion was minimised" (15). Similar practices have been adopted by the UK military, with casualties retrieved by MERT(E) in Afghanistan receiving up to 4u PRBC and 4u plasma (41) with crystalloid minimised (3). This is borne out in data examined in this review (46). In contrast, civilian studies continue to include failure to respond to 2L intravenous crystalloid as an indication for PHBP. This is despite good quality evidence that aggressive clear fluid administration increases mortality and morbidity after penetrating trauma (68). Pre-hospital cannulation (as a surrogate for fluid administration) was associated with greater mortality in every patient subgroup examined in a registry study, other than those with Injury Severity Scores <9 (69), while more than 1L of pre-hospital fluid has been shown to be an independent risk factor for death in patients without severe traumatic brain injury (70). High ratios of crystalloid to PBRC given in-hospital increase morbidity (71). Whether PHBP are associated with similar volume effects is unknown. It is possible that the negative impact of crystalloid loading prior to PHBP administration has masked benefit from PHBP in many studies to date.

Safety

Very few PHBP-related adverse events were identified, implying transfusion safety. However, blood transfusions supress the immune system and are associated with a stepwise increase in infectious complications for each unit of PRBC transfused, starting with single unit transfusions (72). Similarly, a dose-response relationship exists between transfusion and development of multi-

organ failure (73). This is a concern given the frequency with which patients in this review received PHBP but little or no in-hospital transfusion, calling into question their need for PHBP transfusion. No study in this review associated PHBP with reduced in-hospital transfusion. However, if administered inappropriately liberally, PHBP may lead to excess morbidity.

In order to address these various questions, four randomised clinical trials and one cohort study comparing various combinations of blood products and crystalloid are underway (see Table, Supplementary Digital Content 6, ongoing studies). If PHBP trauma resuscitation is beneficial, universal provision should be advocated. However, robust evidence is required to justify the clinical, logistical and financial costs of making PHBP "standard care". This review demonstrates the lack of such evidence and makes ongoing support for these studies imperative.

Military and expedition settings require the consideration of factors specific to austere environments. Although evacuation times in recent operations have typically been short, future conflicts may require prolonged pre-evacuation field and en-route care. These timelines may necessitate PHBP support. Data collection on future operations will be essential to establish the place of PHBP in "Remote Damage Control Resuscitation"

Conclusions

The literature reporting PHBP for trauma resuscitation is contradictory and provides only poor quality evidence. Evidence-based conclusions to guide practice cannot be drawn. While PHBP resuscitation appears logical the potential harms of this practice must be recognised. More rigorous evidence of benefit is required to justify universal adoption. Whether PHBPs improve

survival despite these competing risks is unknown. The only satisfactory way to answer this outstanding question of benefit from PHBP-based resuscitation for major traumatic haemorrhage is by randomised controlled trials.

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Figure 1. PRISMA diagram for selection of included studies.

†including studies only available in abstract. ‡trial design or authors blinded to allocations.

Figure 2. Mortality amongst PHBP-recipients. A) Overall B) Within 24h

Grey bars: case series. Black bars: cohort studies. Solid bars: Trauma patients. Hashed bars: studies including both trauma and non-trauma patients. Unfilled bars: subgroup analyses or patients drawn from a larger series, published separately (not included in estimation of mortality). Pooled estimate of mortality shown with 95% confidence interval.

Figure 3. Meta-analysis of unadjusted risk of mortality.

A) All comparative studies B) Studies with matched cohorts

Figure 4. Forest plot of adjusted mortality. A) Overall B) at 24 hours

Data shown for adjusted Odds Ratios, other than Brown et al (2015) (35) which shows Hazard Ratio.

■: data from main study ◆: data from subgroup analysis

Figure 5. In-hospital transfusion requirements for A) PBRC and B) plasma. O'Reilly et al (2014) (40) and Smith et al (2014) (46) reported total transfusion data from primary receiving hospital. Brown et al (2015) (35, 36) and Kim et al (2012) (37) reported transfusion data within 24h of admission. Data shown as median (IQR) except for Kim et al (2012) (37) (median only). Δ: median transfusion for PHBP-recipients, X: median transfusion for non-recipients. Price et al (1999) (49) also reported statistically significantly greater in-hospital transfusion volumes for PHBP-recipients (mean 1414ml (SD: 1660ml)) vs. non-recipients (1007ml (SD: 935ml)).

Supplemental Digital Content

PHBP SR - Supplementary 1 - PRISMA Checklist.pdf

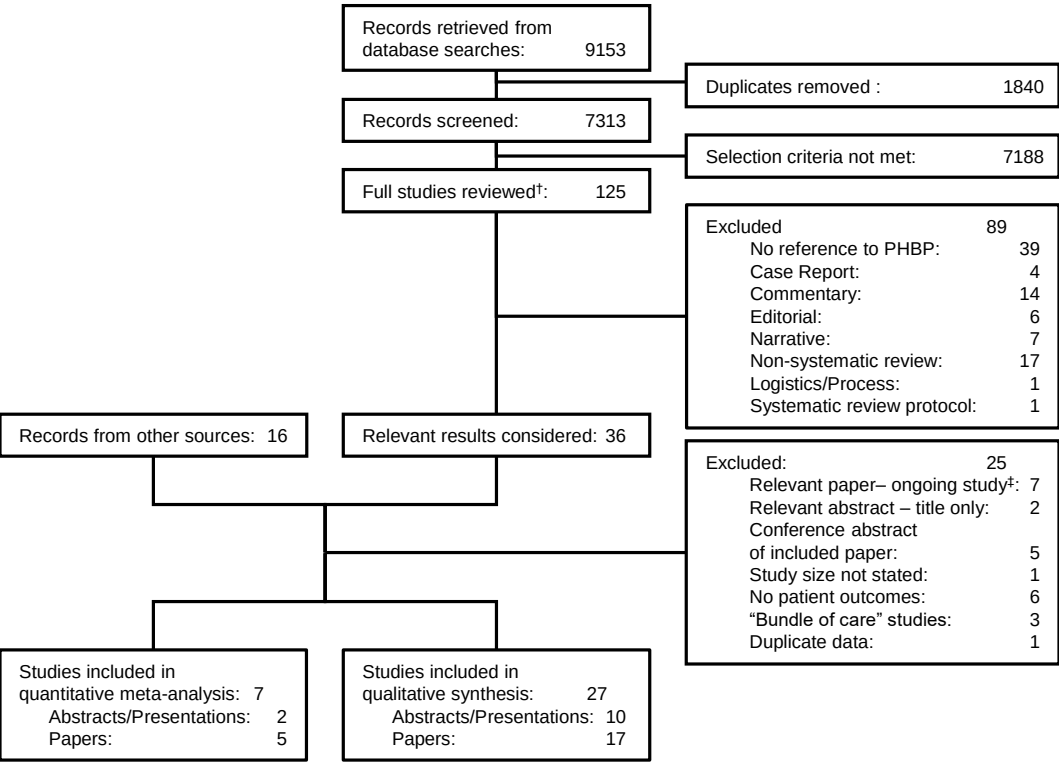
PHBP SR - Supplementary 2 – EMBASE Search Strategy.doc

PHBP SR - Supplementary 3 - Exclusions.docx

PHBP SR - Supplementary 4 - Interventions and Diff erences.docx

PHBP SR - Supplementary 5 - Risk of Bias.docx

PHBP SR - Supplementary 6 - Ongoing.docx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Duplicates removed : 1840
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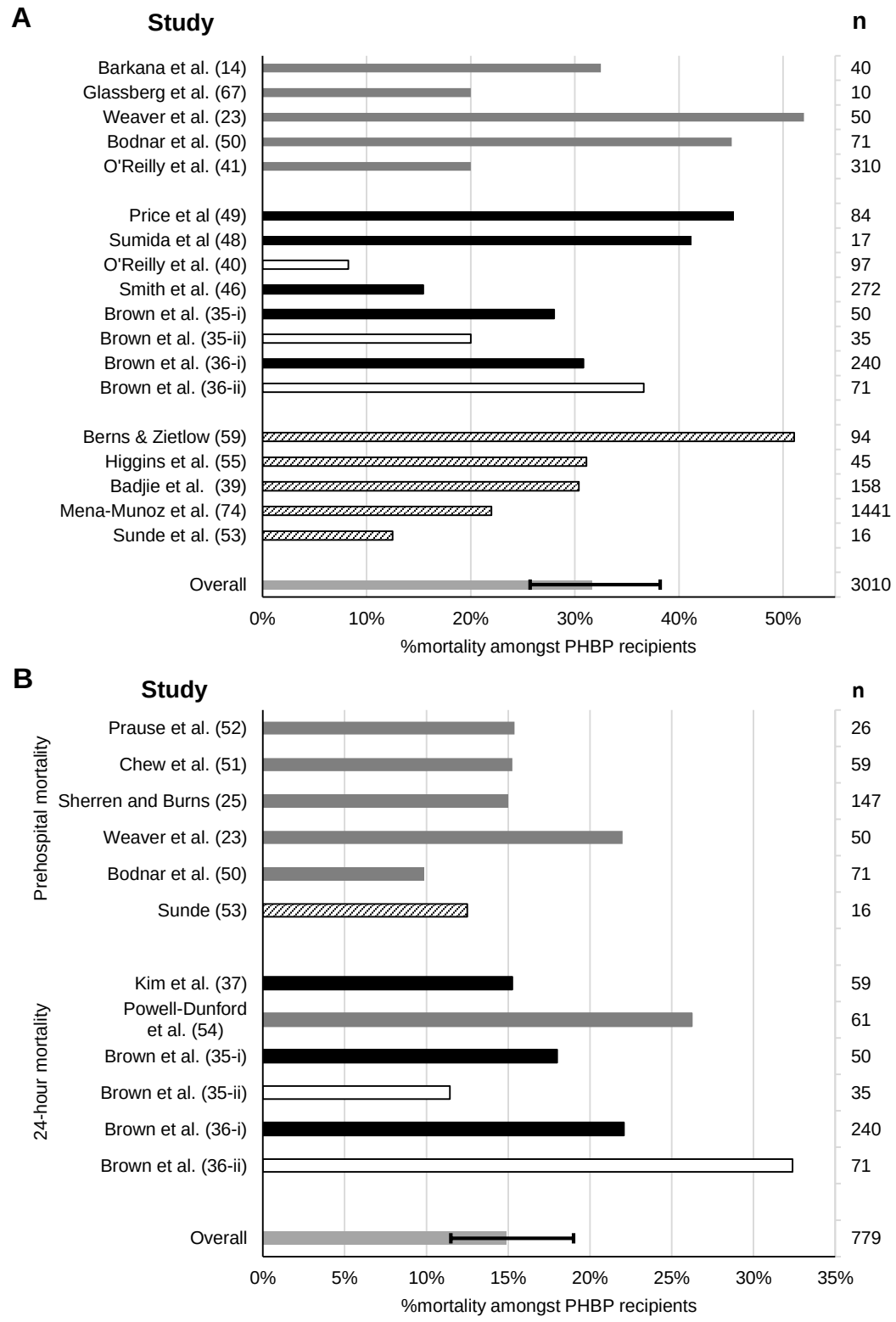
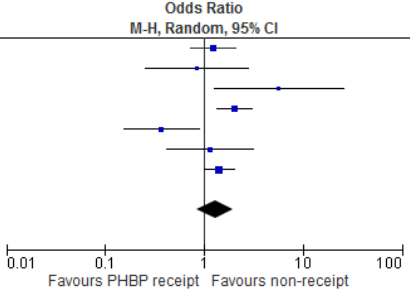
Full studies reviewed†: 125
Excluded 89
No reference to PHBP: 39
Case Report: 4
Commentary: 14
Editorial: 6
Narrative: 7
Non-systematic review: 17
Logistics/Process: 1
Systematic review protocol: 1
Records from other sources: 16
Relevant results considered: 36
Excluded: 25
Relevant paper– ongoing study‡: 7
Relevant abstract – title only: 2
Conference abstract of included paper: 5
Study size not stated: 1
No patient outcomes: 6
"Bundle of care" studies: 3
Duplicate data: 1
Studies included in quantitative meta-analysis: 7
Abstracts/Presentations: 2
Papers: 5
Studies included in qualitative synthesis: 27
Abstracts/Presentations: 10
Papers: 17


A
Study
n
Barkana et al. (14)
Glassberg et al. (67)
Weaver et al. (23)
Bodnar et al. (50)
O'Reilly et al. (41)
Price et al (49)
Sumida et al (48)
O'Reilly et al. (40)
Smith et al. (46)
Brown et al. (35-i)
Brown et al. (35-ii)
Brown et al. (36-i)
Brown et al. (36-ii)
Berns & Zietlow (59)
Higgins et al. (55)
Badjie et al. (39)
Mena-Munoz et al. (74)
Sunde et al. (53)
Overall
40
10
50
71
310
84
17
97
272
50
35
240
71
94
45
158
1441
16
3010
0%
10%
20%
30%
40%
50%
%mortality amongst PHBP recipients
B
Study
n
Prehospital mortality
24-hour mortality
Prause et al. (52)
Chew et al. (51)
Sherren and Burns (25)
Weaver et al. (23)
Bodnar et al. (50)
Sunde (53)
Kim et al. (37)
Powell-Dunford et al. (54)
Brown et al. (35-i)
Brown et al. (35-ii)
Brown et al. (36-i)
Brown et al. (36-ii)
Overall
26
59
147
50
71
16
59
61
50
35
240
71
779
0%
5%
10%
15%
20%
25%
30%
35%
%mortality amongst PHBP recipients

A

Study or Subgroup	PHBP recipients Events	PHBP recipients Total	Non-recipients Events	Non-recipients Total	Odds Ratio M-H, Random, 95% CI	Year
Price et al. (49)	38	84	65	162	1.23 [0.72, 2.10]	1999
Sumida et al. (48)	7	17	14	31	0.85 [0.26, 2.81]	2000
Kim et al. (37)	5	9	9	50	5.69 [1.27, 25.51]	2012
Smith et al. (46)	42	272	64	775	2.03 [1.34, 3.08]	2014
O'Reilly et al. (40)	8	97	19	97	0.37 [0.15, 0.89]	2014
Brown et al. (35-ii)	7	35	14	78	1.14 [0.42, 3.14]	2015
Brown et al. (36-i)	74	240	115	480	1.41 [1.00, 2.00]	2015
Total (95% CI)		**754**		**1673**	**1.29 [0.84, 1.96]**	
Total events	181		300			

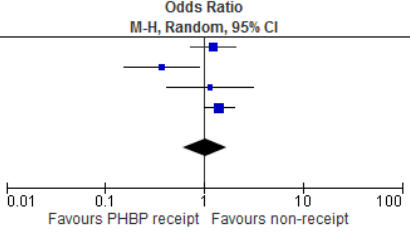
Heterogeneity: Tau² = 0.17; Chi² = 16.31, df = 6 (P = 0.01); I² = 63%
Test for overall effect: Z = 1.17 (P = 0.24)

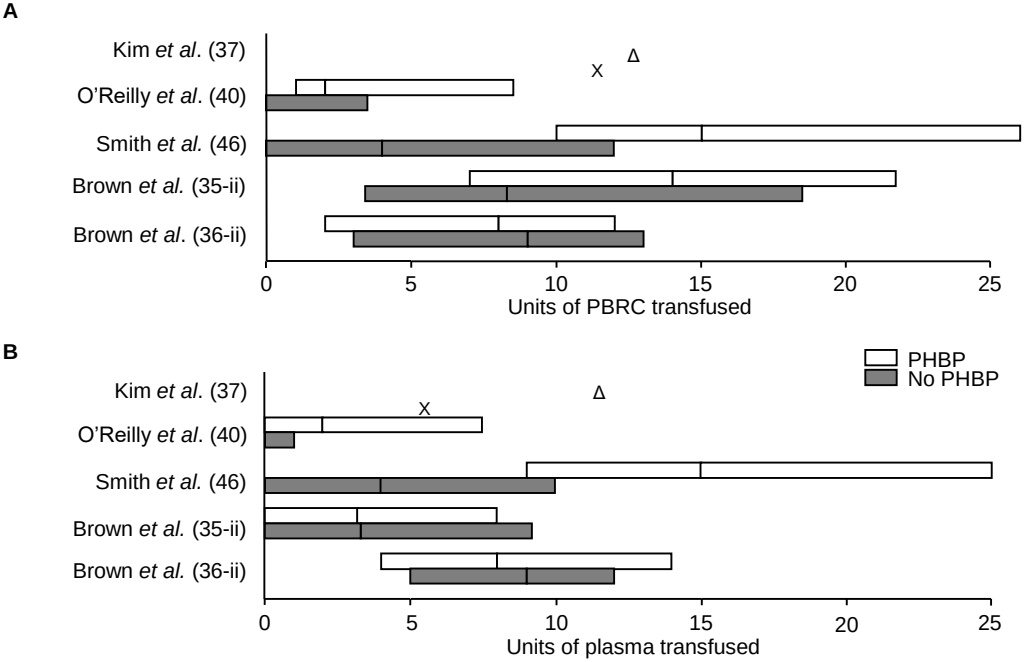


B

Study or Subgroup	PHBP recipients Events	PHBP recipients Total	Non-recipients Events	Non-recipients Total	Odds Ratio M-H, Random, 95% CI	Year
Price et al. (49)	38	84	65	162	1.23 [0.72, 2.10]	1999
O'Reilly et al. (40)	8	97	19	97	0.37 [0.15, 0.89]	2014
Brown et al. (35-ii)	7	35	14	78	1.14 [0.42, 3.14]	2015
Brown et al. (36-i)	74	240	115	480	1.41 [1.00, 2.00]	2015
Total (95% CI)		**456**		**817**	**1.02 [0.62, 1.69]**	
Total events	127		213			

Heterogeneity: Tau² = 0.15; Chi² = 7.80, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 0.08 (P = 0.93)




A
Kim et al. (37)
O'Reilly et al. (40)
Smith et al. (46)
Brown et al. (35-ii)
Brown et al. (36-ii)
X
Δ
0
5
10
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20
25
Units of PBRC transfused
B
PHBP
No PHBP
Kim et al. (37)
O'Reilly et al. (40)
Smith et al. (46)
Brown et al. (35-ii)
Brown et al. (36-ii)
X
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0
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25
Units of plasma transfused

Table 1: Case Series – Study and Patient characteristics

Authors	Paper/ Abstract Timing	Purpose of study	Context[1] Trauma / Mixed (Secondary Transfers)	Patients in study (%male)	Age	Mechanism of injury	Injury Burden	Intervention
Dalton (1993) (12) Portland, OR, USA	Full Text (Retrospective)	demonstrate safety	Civilian Trauma (unknown)	112 (unknown)		RTA: 81 (72%) Penetrating: 16 (14%) Other: 15 (13%)	mean ISS: 32	PBRC:416ml [R:100-1250]
Berns and Zietlow. (1998) (59) Rochester, MN, USA	Full Text (Retrospective)	describe protocols and experience	Civilian Mixed (Trauma: 48%) (Transfers: 91%)	94 (75%)	51-60 (21-30 to 71-80)	Unknown	Unknown	"average" 2u PRBC
Prause *et al*. (1999) (52) Graz, Austria	Full Text (Retrospective)	Description of process	Trauma (Transfers: 0%)	26 (unknown)	?	Unknown	Polytrauma: 12 Amputations: 4 Torso trauma: 6 Craniocerebral: 2 Unspecified: 2	Not specified
Badjie *et al*. (2012) (38) Rochester, MN, USA	Abstract (Retrospective)	evaluate the impact of using thawed plasma on board	Civilian Mixed (Trauma: 48%) (Transfers: 91%)	81 (48%)		Unknown	Unknown	PBRC: 3 units Plasma: 2 units
Higgins *et al*. (2012) (55) Portland, ME, USA	Full Text (Retrospective)	describe the PHBP experience, focussing on protocol compliance, provider safety, patient outcomes and transfusion complications.	Civilian Mixed (Trauma 71%) (Transfers: 68%)	45 (unknown)		Unknown	Unknown	PBRC: mean 1.4u (SD: 0.23u)
Chew *et al*. (2013) (51) Victoria, Australia	Abstract (Retrospective)	report PHBP supply procedures to audit supply procedures and use	Civilian Mixed (Trauma >78%) (Transfers: 12%)	59 (58%)	Median 37 Range: 16-81	RTC: 46 (78%) Other trauma or medical: 13 (22%)	Unknown	PBRC: 2u (IQR: 2-4u)
Mena-Munoz *et al*. (2013) (74) Pittsburgh, PA, USA	Abstract (Retrospective)	characterise PHBP-recipients	Civilian Mixed (Trauma 25%) (Transfers: 92%)	1441 (unknown)	?	Unknown	Unknown	Up to 2u PBRC
Sherren *et al*. (2013) (25) Sydney, Australia	Abstract (Retrospective)	Unclear	Civilian Trauma (Transfers: 0%)	147 (69%)	34.5 (22-52)	Blunt: 121 (82%) Penetrating: 9 (6%) Other: 17 (12%)	RTS: 5.967 (4.083-6.904)	PBRC: 3u (Range: 1-6u)
Weaver *et al* (2013) (23) London, UK	Abstract (Prospective)	examine the impact of on-scene blood transfusion for seriously injured patients	Civilian Trauma (Transfers: 0%)	50	Mean : 35	Unknown	Unknown	PRBC: mean 2.8u
Bodnar *et al*. (2014) (50) Queensland, Australia	Full Text (Retrospective)	describe the characteristics, clinical interventions and outcomes of PHBP-recipients	Civilian Trauma (Transfers: 0%)	71 (79%)	39.6 (SD=16.7)	Blunt: 52 (73%) Penetrating: 19 (27%)	ISS: 32.11 (18.19) RTS: 4.7 (2.73) TRISS: 0.573 (0.396)	PBRC: mean 1.8u (SD: 0.7u)
Sunde *et al*. (2015) (53) Bergen, Norway	Full Text (Retrospective)	evaluate feasibility of introducing FDP and PRBC	Civilian Mixed (Trauma 56%) (Transfers: 0%)	16 (88%)	Range 23-51	Blunt: 5 (31%) Penetrating: 4 (25%) Non-Trauma: 7 (44%)	Unknown	FDP: 200ml (Range: 100-200ml) PBRC "given to 4 patients"
Barkana *et al*. (1999) (14) Israel	Full Text (Retrospective)	"characterise aspects" of PHBP use "evaluate potential effects on morbidity & mortality"	Military Trauma (Transfers: 0%)	40 (unknown)	Range: 18-37	Blast: 19 (47.5%) Penetrating: 12 (30%) Blunt: 9 (22.5%)	ISS: 18 (11.5-25)	PRBC: 1u (IQR: 1-2) [R: 1-4]

Malsby *et al.* (2013) (15) Afghanistan	Full Text (Retrospective)	Process refinement	Military Trauma (Transfers: 0%)	15 (100%)		Explosive: 13 (87%) GSW: 2 (13%)	unknown	Median 1u blood products (IQR: 0.5-1.5u) [R: 0-2] (Various combinations of PHBP administered)
Glassberg *et al*. (2013) (67) Israel	Full Text (Retrospective)	Description of initial experience with pre-hospital lyophilised plasma	Military Trauma (Transfers: 0%)	10 (unknown)		Penetrating: 8 (80%) Other 2 (20%)	ISS: 19 (17.5-23.5)	FDP: 1.5u (IQR: 1-2) PRBC transfusion implied
O'Reilly *et al*. (2014) (41) Afghanistan	Full Text (Retrospective)	Description of initial experience with PHBP	Military Trauma (Transfers: 0%)	310 (97%)	24 (21-27)	Explosive: 226 (73%) GSW: 80 (26%) Blunt: 3 (1%) Burn: 1 (0.3%)	mISS 20 (16-29) mNISS 29 (18-48)	PBRC: 2u (IQR: 1-2) [Range: 0-4] Plasma: 2u (IQR: 1-2) [Range: 0-4]
Chen (2014) (75) Israel	Abstract (Retrospective)	Unclear	Military Trauma (Transfers: 22%)	90 (80%)	28 Range: 12-60	Explosive: 20 (22%) RTC: 26 (29%) GSW: 32 (36%) Stab: 5 (5%) Other: 7 (8%)	unknown	PRBC: mean 1.2u 392ml (SD: 322)
Powell-Dunford *et al.* (2014) (54) Afghanistan	Full Text (Retrospective)	Description of process risk mitigation	Military Trauma (Transfers: 0%)	61 (98%)	24 (20-28)	Explosive: 45 (74%) GSW: 16 (26%)	unknown	PBRC: 1u (IQR: 1-1) [Range: 1-2] Plasma: 0u (IQR: 0-0) [Range: 0-1]

FDP: Freeze Dried Plasma.

mISS and mNISS: ISS and NISS derived from the military edition of the Abbreviated Injury Scale (2005)

1"military": casualties of armed conflict.

Table 2. Comparative Studies: Study and Patient Characteristics (all trauma except for Badjie *et al*. (2013))

Authors	Study Type Paper/ Abstract (Timing Context)	Purpose of study	Group (Secondary transfers)	Patients in study arm (% male)	Age	Mechanism of injury	Injury Burden	Intervention
Price *et al*. (1999) (49) Portland, OR, USA	Matched Cohort Abstract (Retrospective Civilian)	compare efficacy of early blood transfusion	Non-recipients (unknown)	162	unknown	Unknown	unknown	
			PHBP-recipients (unknown)	84	unknown	Unknown	unknown	PBRC: 426ml
Sumida *et al*. (2000) (48) Chattanooga, TN, USA Hartford, CN, USA	Cohort Full Text (Retrospective Civilian)	analyse the effect of PHBP on physiologic parameters and outcomes	Non-recipients (unknown)	31 (unknown)	30.4	Unknown	ISS: 27.8 RTS: 7.0 TRISS: 0.669	
			PHBP-recipients (unknown)	17 (unknown)	31.2	Unknown	ISS: 28.0 RTS: 6.3 TRISS: 0.524	"blood": 711mL
Kim *et al*. (2012) (37) Rochester, MN, USA	Cohort Full Text (Retrospective Civilian)	will delivery of pre-hospital plasma improve coagulopathy	PBRC only (Transfers: 54%)	50 (60%)	41	Penetrating: 9 (18%)	ISS: 23 TRISS: 0.66	PRBC: 1u
			PBRC + Plasma (Transfers: 100%)	9 (100%)	54	Penetrating: 3 (33%)	ISS: 27 TRISS: 0.24*	PRBC: 2.5u Plasma: 2.1u
Badjie *et al* (2013) (39) Rochester, MN, USA	Cohort Abstract (Retrospective Civilian)	to evaluate mortality rates of patients who received a 1:1 FFP: RBC ratio en-route	PBRC:Plasma 2:1 (unknown)	79 (unknown)	Unknown but "comparable"	Reasons for transport not stated by "comparable"	unknown	Up to 2u PRBC+2u Plasma+2u PRBC OR 2u Plasma+4u PRBC
			PBRC:Plasma 1:1 (unknown)	79 (unknown)			unknown	Up to 3u plasma + 3u PRBC
			PHBP-recipients (Transfers: 0%)	66 (61%)	median 40	Unknown		Not specified
Brown *et al*. (2015) (35-i) Pittsburgh, PA, USA	Cohort Full Text (Retrospective Civilian)	Is pre-trauma centre RBC transfusion associated with reduced mortality and early TIC?	Non-recipients (Transfers: 4%)	1365 (67%)	41 (26-54)	unknown	ISS: 33 (22–41)	
			PHBP-recipients (Transfers: 48%)	50 (64%)	41 (28-52)	unknown	ISS: 37 (24–43)	PRBC: 1.3 (1.0–2.3)
Brown *et al.* (2015) (35-ii) Pittsburgh, PA, USA	Matched Cohort Full Text (Retrospective Civilian)	Is pre-trauma centre RBC transfusion associated with reduced mortality and TIC in a matched cohort?	Non-recipients (Transfers: 24%)	78 (72%)	37 (24–55)	unknown	ISS: 30 (23–43)	
			PHBP-recipients (Transfers: 29%)	35 (60%)	36 (28–52)	unknown	ISS: 34 (18–43)	PRBC: 1.2 (1.0–2.0)
Brown *et al.* (2015) (36-i) Pittsburgh, PA, USA	Cohort Full Text (Retrospective Civilian)	Is pre-trauma centre PBC transfusion associated with reduced 24h mortality, TIC, shock and Tx requirements in air medical transport	Non-recipients (Transfers: 75%)	480 (67%)	49 (31-68)	Blunt: 395 (82%) Penetrating: 85 (18%)	ISS: 17 (9-27)	
			PHBP-recipients (Transfers: 68%)	240 (69%)	49 (28-71.5)	Blunt: 191 (80%) Penetrating: 49 (20%)	ISS: 18 (10-29)	PRBC: 300ml (IQR: 200-500)
Brown *et al.* (2015) (36-ii) Pittsburgh, PA, USA	Cohort Full Text (Retrospective Civilian)	Is pre-trauma centre PBC transfusion associated with reduced 24h mortality, TIC, shock and Tx requirements in patients transported from scene	Non-recipients (Transfers: 0%)	142 (68%)	37 (25-65)	Blunt: 98 (69%) Penetrating: 44 (31%)	ISS: 22 (13-29)	
			PHBP-recipients (Transfers: 0%)	71 (83%)	42 (24-55)	Blunt: 98 (69%) Penetrating: 44 (31%)	ISS: 22 (10-34)	PRBC: 300ml (IQR: 200-500)
Wheeler *et al.* (2013) (57) Lebanon, NH, USA	Case-Control Full Text	identify factors associated with hypothermia	Non-hypothermic (Transfers: 0%)	647 (68%)	39 (SD: 19)	unknown	ISS: 16 (SD: 11) RTS: 7.34 (SD: 1.19) TRISS: 0.93 (SD: 0.16)	PRBC given to 3% of subjects

	(Retrospective Civilian)		Hypothermic (<35°C) (Transfers: 0%)	60 (68%)	41 (SD: 20)	unknown	ISS: 26 (SD: 12) RTS: 5.86 (SD: 1.85) TRISS: 0.75 (SD: 0.29)	Up to 3u PRBC given to 17% of subjects
O'Reilly *et al*. (2014) (40) Afghanistan	Matched Cohort Full Text (Retrospective Military)	"PHBP will be associated with reduction in mortality"	Non-recipients	97 (100%)	23 (21-28)	Explosive: 48 (49%) GSW: 46 (47%) Blunt: 3 (3%)	mISS: 16 (9-25) mNISS: 21 (14-34)	
			PHBP-recipients	97 (98%)	24 (20-28)	Explosive: 50 (52%) GSW: 46 (47%) Blunt: 1 (1%)	mISS: 16 (9-25) mNISS: 22 (15-33)	PRBC: 1u (IQR: 1-2) [R: 0-4] Plasma: 2u (IQR: 1-2) [R: 0-4]
Smith *et al*. (2014) (46) Afghanistan	Cohort Abstract (full data available) (Retrospective Military)	Is PHBP receipt associated with reduced mortality or coagulopathy?	Non-recipients	775 (96.6%)	median band: 17-24	Explosive: 423 (55%) GSW: 274 (35%) MVC: 46 (6%) Burn: 11 (1%) Other: 21 (3%)	ISS: 18 (14-26) NISS: 25 (18-34)	
			PHBP-recipients	272 (98.5%)	median band: 17-24	Explosive: 250 (92%) GSW: 19 (7%) MVC: 3 (1%)	ISS: 26 (18-30) NISS: 41 (29-54)	PBRC: 2u (IQR: 1-2) [R: 0-4] Plasma: 2u (IQR: 1-2) [R: 0-4]
Gross *et al*. (2014) (56) Afghanistan	Conference Poster (Retrospective Military)	Not stated	Non-recipients	54 (unknown)	25 (22-28)	unknown	unknown	
			PHBP-recipients	66 (unknown)	25 (24-29)	unknown	unknown	not specified

mISS and mNISS: ISS and NISS derived from the military edition of the Abbreviated Injury Scale (2005)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Protocol p3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Protocol p3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Protocol p3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Protocol (Suppl)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Protocol p3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Protocol p3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Protocol pp3-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1-2 & Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl File 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary File 2: EMBASE Search Strategy

1 (red blood cell$ or red cell$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (103973)

2 (RBC$ or pRBC$ or PRC$ or RCC$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (56232)

3 (blood product$ or blood component$ or whole blood).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (68383)

4 blood administrat$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (256)

5 (blood adj3 resuscitat$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2799)

6 (plasma adj3 resuscitat$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1069)

7 (freeze dried plasma or fresh frozen plasma or liquid plasma or thawed plasma or spray dried plasma or lyophili?ed plasma or FDP or FFP).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (16810)

8 (hemostatic resuscitat$ or haemostatic resuscitat$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (133)

9 damage control resuscitat$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (237)

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (214180)

11 (pre-hospital or prehospital or pre-trauma or pretrauma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (13713)

12 (point of injury or point of wound$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (271)

13 (on scene or en route or in transit or retrieval).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (69262)

14 out of hospital.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (9408)
15 (air or helicopter$ or aviation or rotary wing).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (319881)
16 paramedic$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (21340)
17 exp paramedical personnel/ (362883)
18 exp emergency physician/ (6248)
19 (emergency adj3 doctor$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1185)
20 first aid.mp. or exp first aid/ (11842)
21 exp emergency treatment/ (175524)
22 exp traffic accident/ (46473)
23 (evacuation$ or field or battlefield or wartime or military or casualt$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (642507)
24 exp army/ (10233)
25 (advanced trauma life support or ATLS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1106)
26 (basic trauma life support or BTLS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (28)
27 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (1581097)
28 trauma.mp. or exp injury/ (1616710)
29 injur$.mp. (1174622)
30 (haemorrhag$ or hemorrhag$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (362963)
31 exp bleeding/ or bleed$.mp. (653782)
32 shock.mp. or hypovolemic shock/ or traumatic shock/ or hemorrhagic shock/ (232638)
33 exp hypovolemia/ or hypovol$.mp. (14499)
34 (blood adj2 loss).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (51109)

35 low blood pressure.mp. or exp hypotension/ (105125)

36 hypotens$.mp. (133901)

37 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2675652)

38 10 and 27 and 37 (6184)

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Supplementary File 3: Relevant excluded studies

Authors	Year	Publication / Meeting / Source	Volume	Issue	Page(s)	Reason for exclusion
Hall *et al.*	1990	Annals of Emergency Medicine	19		49	Unavailable
Brown *et al.*	1995	Society for Academic Emergency Medicine	Conference Proceedings		16	Unavailable
Ciraulo *et al.*	1998	Critical Care Medicine	26	(Suppl 1)	51A	Abstract of included paper
Tilney *et al.*	2007	Annals of Emergency Medicine	50	3 (Suppl)	S92	Case series - no clinical outcomes
Calderbank *et al.*	2011	Emergency Medicine Journal	28	10	882-883	Case series - no clinical outcomes
Bates *et al.*	2012	Air Medical Journal	31	6	260	Study size and outcomes not quantified
Edgar *et al.*	2012	British Journal of Surgery	99	Suppl 6	12	Abstract of excluded paper
Chin *et al.*	2013	Journal of Surgical Research	179	2	337	Abstract of included paper
Holcomb *et al.*	2013	Circulation	128	22		Abstract of included paper
Lockey *et al.*	2013	Transfusion	53	Suppl 1	17S-22S	Case series - no clinical outcomes
Morrison *et al.*	2013	Annals of Surgery	257	2	330-334	Bundle of care study
O'Reilly *et al.*	2013	Royal Society of Medicine: Military Section	Colt Foundation Prize Meeting			Abstract of included paper
Edgar *et al.*	2014	Journal of the Royal Naval Medical Service	100	1	12-Jul	Bundle of care study
Jenkins *et al.*	2014	Shock	41	Suppl 1	84-89	Case series - no clinical outcomes
Spiess *et al.*	2014	ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT02303964			Ongoing study - PUPFTH
Wolf *et al*.	2014	Transfusion Medicine	24	s2	24	Case series – no clinical outcomes
Bebarta	2015	Critical Care Medicine	42	12 (Suppl)	e146	Case series - no clinical outcomes
Brown *et al.*	2015	Prehospital Emergency Care	19	3	343-350	RCT in progress - PAMPER
Chapman *et al.*	2015	Shock	44	(Suppl 1)	63-70	RCT in progress - COMBAT
Chin *et al.*	2015	Surgery	157	1	10-19	RCT in progress - COMBAT
Holcomb *et al.*	2015	Prehospital Emergency Care	19	1	1-9	Bundle of care study
Holcomb *et al.*	2015	ClinicalTrials.gov	https://clinicaltrials.gov/ct2/show/NCT02272465			Cohort study in progress - PROHS
Midwinter *et al.*	2015	National Institue for Health Research: Efficacy and Mechanistic Evaluation Programme	http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/139212/EME_funding_outcomes_table_Feb-15.pdf			RCT in setup - RePHILL
Moore *et al.*	2015	Shock	41	Suppl 1	35-38	RCT in progress - COMBAT
Stubbs *et al.*	2015	Transfusion	55	8	1830-37	Duplicate data from Kim *et al.* (2012)

Supplementary File 4 – Interventions and Differences

Table 1: Studies reporting 30-day or long-term mortality

Author	Year	PHBP recipients / total study size	Intervention	Differences between groups (PHBP-recipients vs. non-recipients)
Dalton	1993 (12)	112	PBRC:416ml [R:100-1250]	N/A
Berns	1998 (59)	94	"average" 2u PRBC[3]	N/A
Price	1999 (49)	84/246	PRBC: 626ml ±262ml	Pre-hospital crystalloid: 3.0L vs. 0.8L Tracheal intubation: 47% vs. 34% In-hospital blood products: 1.4L vs. 1L
Barkana	1999 (14)	40	PRBC: 1u (1-2u) [R:1-4u]	N/A
Sumida	2000 (48)	17/48	mean 710.7ml "blood"	Flight time 33min vs. 12 min
Higgins	2012 (55)	45	PBRC: 1.4u ± 0.23u	N/A
Badjie	2013 (39)	79/158	3u TP+3u PRBC vs. 2u PRBC+2u TP+2u PBRC	None reported
Glassberg	2013 (67)	10	1.5u LP (1-2u) (PRBC not reported)	N/A
Mena-Mundoz	2013 (74)	1441	Up to 2u PBRC	N/A
Weaver	2013 (23)	50	mean 2.8u PBRC	N/A
Bodnar	2014 (50)	71	1.8u PBRC ±0.74u	N/A
O'Reilly	2014 (41)	310	PBRC: 2u (1-2) [R:0-4] Plasma: 2u (1-2) [R:0-4]	N/A
O'Reilly	2014 (40)	97/194	PBRC: 1u (1-2) [R:0-4] Plasma: 2u (1-2) [R: 0-4]	Advanced Airway: 20% vs. 9% Tranexamic acid receipt: 23% vs. 0% Pre-hospital time: 68min vs. 110min In-hospital transfusion: 2u PBRC + 2u FFP vs. none
Powell-Dunford	2014 (54)	61	PBRC: 1u (1-1) [R:1-2] Plasma: 0u (0-0) [R :0-1]	N/A
Smith	2014 (46)	272/1047	PBRC: 2u (1-2) [R: 0-4] Plasma: 2u (1-2) [R: 0-4]	Explosive injuries: 92% vs. 55% GSW: 7% vs 35% median NISS: 41 vs 25. Tranexamic acid receipt: 21% v. 0.5%. In-hospital tx: 15 u PRBC+15 u plasma vs. 4u + 4u
Brown	2015 (35-i)	50/1365	PRBC: 1.3u (1–2)	Secondary transfer: 48% vs. 4% Pre-hospital crystalloid: 2.6L vs. 1.0L In-hospital tx: 15u PRBC + 3u plasma vs. 7u + 3u
Brown	2015 (35-ii)	35/113	PRBC: 1.2u (1–2)	In-hospital tx: 14u PRBC vs. 8u PRBC
Brown	2015 (36-i)	240/720	PRBC: 300ml (200-500ml)	Emergency surgery: 48% vs. 28%
Brown	2015 (36-ii)	71/213	PRBC: 300ml (200-500ml)	None
Sunde	2015 (53)	16	LP: 200ml (R: 100-200ml)	N/A

Supplementary Table 2: Studies reporting pre-hospital mortality

Author	Year	PHBP recipients / total study size	Intervention[1]	Differences between groups (PHBP-recipients vs. non-recipients)
Prause	1999 (52)	26	not specified	N/A
Chew	2013 (51)	59	PBRC: 2u (2-4u)	N/A
Sherren	2013 (25)	147	PBRC: 3u (1-6u)	N/A
Weaver	2013 (23)	50	PRBC: mean 2.8u	N/A
Bodnar	2014 (50)	71	PBRC: mean 1.8u (±0.7u)	N/A
Sunde	2015 (53)	16	LP: 200ml (R: 100-200ml)	N/A

Supplementary Table 3: Studies reporting 24h mortality

Author	Year	PHBP recipients / total study size	Intervention[1]	Differences between groups (PHBP-recipients vs. non-recipients)
Kim	2012 (37)	59	PRBC : 2.5u vs. 1u Plasma: 2.1u vs. 0u	Warfarin: 22% vs. 2% Prehospital crystalloid:2.4L vs. 1.6L Pre-transfusion INR: 2.6 vs. 1.5 In-hospital PRBC: 12.7u vs. 11.4u In-hospital plasma: 11.5u vs. 5.5u In-hospital crystalloid: 6.3L vs. 16.4L
Brown	2015 (35-i)	As 30-day mortality table		
Brown	2015 (35-ii)			
Brown	2015 (36-i)			

Supplementary File 5 – Risk of Bias Assessments

Risk of Bias in Case Series

	Design		Cases			Intervention		Outcome		Follow-up			
Study	Clear objective	Specified inclusion criteria	Representative	Consecutive	Adequate number	Consistent	Treatment ascertainment[1]	Robust measures	Blinded assessment	Duration	Completeness	Well described results	Quality of Evidence
Dalton (1993) (12)	-	+	+	?	+	-	+	?	-	+	+	+	Very Low
Berns and Zietlow (1998) (59)	+	+	?	+	-	-	+	-	-	+	+	-	Very Low
Barkana *et al* (1999) (14)	-	+	+	+	+	-	+	+	-	+	+	+	Very Low
Prause *et al* (1999) (52)	-	-	+	?	-	+	+	?	-	-	+	-	Very Low
Badjie *et al* (2012) (38)	-	+	-	+	-	-	+	-	-	-		-	Very Low
Higgins *et al* (2012) (55)	-	-	?	+	-	+	+	+	-	+	+	+	Very Low
Chew *et al* (2013) (51)	+	-	+	+	+	-	+	+	-	-	+	-	Very Low
Mena-Mundoz (2013) (74)	-	-	-	+	+	+	+	-	-	-	+	-	Very Low
Sherren & Burns (2013) (25)	-	-	+	+	+	+	+	-	-	-	+	-	Very Low
Malsby *et al* (2013) (15)	-	+	+	?	-	-	+	-	-	-	-	+	Very Low
Glassberg *et al* (2013) (67)	+	+	+	+	-	+	+	+	-	+	+	+	Very Low
Weaver *et al* (2013) (23)	-	+	+	+	+	+	+	+	-	+	+	+	Very Low
Bodnar *et al* (2014) (50)	+	+	+	+	+	+	+	+	-	+	+	+	Very Low
O'Reilly *et al* (2014) (41)	+	+	+	+	+	+	+	+	-	+	+	+	Very Low
Chen (2014) (74)	+	+	?	+	+	+	+	?	-	-	?	+	Very Low
Powell-Dunford (2014) (54)	-	+	+	?	+	-	+	-	-	-	-	-	Very Low
Sunde *et al* (2015) (53)	+	+	+	+	-	+	+	+	-	+	+	+	Very Low

[1]Treatment ascertainment assumed to be satisfactory due to haemovigilance requirements

Risk of Bias in Comparative Studies (Newcastle-Ottawa Scale)

	Cohorts				Controls for			Follow-up		
Study	PHBP-recipients representative	Non-recipients from same population	Treatment ascertainment[1]	Outcome absent before treatment	Injury Severity[2]	≥1 other factor	Outcome by record linkage	Duration	Completeness	Quality of Evidence
Price *et al* (1999) (49)	+	-	+	+	+	+	+	-	+	Very Low
Sumida *et al* (2000) (48)	+	+	+	-	-		+	-	+	Very Low
Kim *et al* (2012) (37)	-	-	+	+	-	-	+	+	+	Very Low
Badjie *et al* (2013) (39)	-	-	+	+	-	-	+	+	+	Very Low
Wheeler *et al* (2013) (57)	+	+	+	-	-	-	+	+	+	Very Low
Gross *et al* (2014) (56)	+	+	+	-	-	-	+	+	+	Very Low
O'Reilly *et al* (2014) (40)	-	-	+	+	+	-	+	+	+	Very Low
Smith *et al* (2014) (46)	+	-	+	+	+	+	+	+	+	Very Low
Brown *et al* (2015) (35)	+	+	+	+	+	+	+	+	+	Low
Brown *et al* (2015) (36)	+	+	+	+	+	+	+	+	+	Low

[1]Treatment ascertainment assumed to be satisfactory due to haemovigilance requirements

[2]Statistical correction or case matching

Supplementary Table 6: Ongoing Prospective Trials and Cohort Studies

Study	Design	Status	Authors	Year	Journal	Vol	Issue	Pages/Article
Control Of Major Bleeding After Trauma (COMBAT)	Pilot RCT	Recruiting	Moore *et al*.	2015	Shock	41	Suppl 1	35-38
Prehospital Air Medical Plasma trial (PAMPER)	RCT	Recruiting	Brown *et al*.	2015	Prehospital Emergency Care	19	3	343-50
Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH)	RCT	Recruiting	Reynolds *et al*.	2015	Trials	16	1	321
Resuscitation with Pre-HospItaL bLood products (RePHILL)	RCT	Funding and regulatory approvals obtained	Midwinter *et al*.	2015	http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/139212/EME_funding_outcomes_table_Feb-15.pdf			
Prehospital Resuscition On Helicopters Study (PROHS)	Prospective cohort	Recruiting	Holcomb *et al*.	2015	https://clinicaltrials.gov/ct2/show/NCT02272465			