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ORIGINAL ARTICLE

Treatment of combined traumatic brain injury and hemorrhagic shock with fractionated blood products versus fresh whole blood in a rat model

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Abstract

Introduction Treatment of combined traumatic brain injury and hemorrhagic shock, poses a particular challenge due to the possible conflicting consequences. While restoring diminished volume is the treatment goal for hypovolemia, maintaining adequate cerebral perfusion pressure and avoidance of secondary damage remains a treatment goal for the injured brain. Various treatment modalities have been proposed, but the optimal resuscitation fluid and goals have not yet been clearly defined. A growing body of evidence suggests that in hypovolemic shock, resuscitation with fresh whole blood (FWB) may be superior to component therapy without platelets (which are likely to be unavailable in the pre-hospital setting). Nevertheless, the effects of this approach have not been studied in the combined injury. Previously, in a rat model of combined injury we have found that mild resuscitation to MABP of 80 mmHg with FWB is superior to fluid resuscitation or aggressive resuscitation with FWB. In this study, we investigate the physiological and neurological outcomes in a rat model of combined traumatic brain injury (TBI) and hypovolemic shock, submitted to treatment with varying amounts of FWB, compared to similar resuscitation goals with fractionated blood products—red blood cells (RBCs) and plasma in a 1:1 ratio regimen.

Materials and methods 40 male Lewis rats were divided into control and treatment groups. TBI was inflicted by a free-falling rod on the exposed cranium. Hypovolemia was induced by controlled hemorrhage of 30% blood volume. Treatment groups were treated either with fresh whole blood or with RBC + plasma in a 1:1 ratio, achieving a resuscitation goal of a mean arterial blood pressure (MAP) of 80 mmHg at 15 min. MAP was assessed at 60 min, and neurological outcomes and mortality in the subsequent 24 h.

Results At 60 min, hemodynamic parameters were improved compared to controls, but not significantly different between treatment groups. Survival rates at 48 h were 100% for both of the mildly resuscitated groups (MABP 80 mmHg) with FWB and RBC + plasma. The best neurological outcomes were found in the group mildly resuscitated with FWB and were better when compared to resuscitation with RBC + plasma to the same MABP goal (FWB: Neurological Severity Score (NSS) 6 ± 2, RBC + plasma: NSS 10 ± 2, $p = 0.02$).

Conclusions In this study, we find that mild resuscitation with goals of restoring MAP to 80 mmHg (which is lower than baseline) with FWB, provided better hemodynamic stability and survival. However, the best neurological outcomes were found in the group resuscitated with FWB. Thus, we suggest that resuscitation with FWB is a feasible modality in the combined TBI + hypovolemic shock scenario, and may result in improved outcomes compared to platelet-free component blood products.

Keywords Traumatic brain injury · Hemorrhage · Neurological outcomes · Resuscitation

Introduction

Lately, there has been renewed interest in the role of different blood transfusion regimens in trauma. With the recognition of early coagulopathy [1, 2], a shift towards a more balanced RBC:plasma and RBC:platelet ratio is seen.

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Survival in patients transfused with a plasma:RBC ratio > 1 has been shown to have improved survival rates [3–7]. A recent meta-analysis of studies regarding RBC:platelet ratios, suggests a mortality benefit in adhering to a 1:1 ratio [8]. Nevertheless, other recent analysis suggest that data supporting such an approach may be prone to various biases and remain inconclusive [9, 10]. Some studies suggest that a high plasma:RBC ratio may be associated with other complications such as ARDS and multi-organ failure [7, 11], and therefore advise cautious use of high volumes of plasma and platelets once bleeding is controlled. The evidence supporting greater plasma and platelet to RBC ratios (approaching the consistency of fresh whole blood) [12] supplemented with literature evolving from battlefield experience has revived the interest in fresh and stored whole blood as a more balanced resuscitation medium [13]. A retrospective analysis of several years of military experience demonstrates a mortality benefit in administration of FWB compared with RBC and plasma for severe hemorrhage [14]. Multi-trauma is often associated with traumatic brain injury (TBI) [15]. While mortality in isolated TBI is low, despite neurological impairment (which may improve over time) [16, 17], the combination of hemorrhagic shock and TBI is a leading cause of severe morbidity and mortality worldwide, resulting in significantly worse outcomes compared to each of these insults alone [15, 16, 18–20]. Cerebral blood flow which is compromised by TBI and subsequent edema, is further impaired by hypovolemia as a result of bleeding, leading to an increase in the contusion volume [21] and uncoupling of cerebral autoregulation [22, 23].

Current literature supports recommendations for treatment of TBI [24, 25] and treatment of hemorrhagic shock, but studies investigating the combined injury are scarce, as are the treatment guidelines [26, 27]. The treatment goal in both TBI and hypovolemic shock is elevation of blood pressure, pursuing sufficient perfusion to vital organs. In the brain—the main goal is avoidance of ischemia, secondary injury, and prevention of apoptosis [28]. Preserving a cerebral blood flow (CPP) of 50–70 mmHg is achieved by several means—crystalloid and colloid infusions [29], administration of vasopressors [30], and synthetic blood products [19, 27, 31, 32].

Despite the existing data, the optimal treatment for combined TBI and hypovolemic shock has not been determined—neither regarding the medium nor regarding quantity. Studies using large animal models lack long-term follow-up regarding neurological recovery [22, 29, 33] and a rat model study has been inconclusive [34]. Furthermore, recent data suggest that massive fluid transfusions may be deleterious in the treatment of hypovolemic shock as well [35–39]. Previously, we evaluated treatment strategies for the combined injury, comparing the physiological response and neurological outcome to varying volumes crystalloid and FWB resuscitation in a rat model of combined TBI and hypovolemic shock [40, 41]. We found that mild resuscitation with goals of restoring MAP to 80 mmHg (which is lower than baseline) provided best results when considering hemodynamic stability, survival and neurological outcomes.

In the current study we investigate the physiological response and neurological outcome to FWB versus plateletless, fractionated blood (plasma:RBC 1:1 ratio) resuscitation in a rat model of combined TBI and hemorrhagic shock. We study three main outcomes—mortality at 48 h, physiological parameters in the initial hour post-injury, and neurological outcomes 24 h after injury, trying to assess the optimal resuscitation medium.

Materials and methods

The experiments were conducted according to the recommendations of the Declarations of Helsinki and Tokyo and in adherence with the Guidelines for the Use of Experimental Animals of the European Community. The experiments were approved by the Animal Care Committee of Ben-Gurion University of the Negev (Joint Animal Care Committee for Ben-Gurion University and Soroka Medical Center, Beer-Sheva, Israel).

Rat model

Spontaneously breathing, male Lewis rats weighing 200–300 g were anesthetized with a mixture of isoflurane (initial inspired concentration 2%) in 100% oxygen (1 l/min). The rectal temperature was maintained at 37 °C using a heating pad and anesthesia was considered as sufficient for surgery when the tail reflex was abolished. All rats were primarily divided into two cohorts—treatment and control, and further divided into treatment groups consisting of 8 rats each.

1. Control: TBI
2. Control: controlled bleeding
3. Control: TBI + controlled bleeding
4. Treatment: whole blood resuscitation to mean arterial blood pressure (MABP) 80 mmHg
5. Treatment: RBC + plasma resuscitation to mean arterial blood pressure (MABP) 80 mmHg.

Eight rats per group would allow to prove a difference of 1.5 standard deviations (*t* test; $p = 0.05$; power = 0.80) in case of a continuous measurement, or 3 versus 8 events in case of a dichotomous endpoint (Chi-squared test, $p = 0.05$; power 0.80).

Vascular access

Tail vein was percutaneously cannulated with a 22G neoflon catheter (Becton, Dickinson and Company, Franklin Lakes, NJ) for injection of resuscitation fluid. Tail artery was percutaneously cannulated with a 24G neoflon catheter for blood sampling and invasive blood pressure monitoring.

Blood sampling

150 µl of arterial blood was sampled in heparinized syringes. Blood was analyzed (GEM Premier 3000; Instrumentation Laboratory) for: hematocrit, hemoglobin, pH, pO_2, pCO_2, lactate and BE at the following time points: baseline, 0 (immediately after insult), 30, 60 and 120 min.

Physiologic parameters

Systolic, diastolic and mean arterial blood pressures were monitored invasively at the following time points: baseline, 0 (immediately after insult), 30, 60 and 120 min.

Traumatic brain injury

Under general anesthesia, the scalp was infiltrated with 0.5% bupivacaine. The scalp was incised and reflected laterally, and a cranial impact of 0.5 J was delivered by a silicone-coated rod, protruding from the center of a free-falling plate as previously described [17, 42, 43]. The impact point was 1–2 mm lateral to the midline of the skull's convexity. Following TBI, the incision was sutured and the rats were laid on their left side for recovery from anesthesia which took place within 60 min post TBI.

Controlled hemorrhage

Following anesthesia, arterial and vein catheter insertion and infliction of TBI, blood was aspirated from the tail artery catheter at a rate of 1 ml/min into a syringe washed with 8 units of heparin and 1 ml normal saline. Total blood loss was 30% of calculated blood volume. Resuscitation was begun 15 min after completion of the hemorrhage until achievement of MAP of 80 mmHg according to treatment group.

Blood transfusion

Male Lewis rats, apart from the experiment groups were assigned to be blood donor rats. Lewis rats do not require blood grouping. Rats were anesthetized, cannulated and blood was aspirated into CPDA-1 whole blood tubes (Teva Medical, Ashdod, Israel), at a final concentration of 7 ml blood/1 ml CDPA-1. Blood for the RBC + plasma groups was centrifuged for fractionation of blood products—RBC and plasma. Blood was transfused until achieving the goal MAP. The average volumes transfused were: 1.5 ± 0.2 ml for the FWB group and 1.62 ± 0.2 ml for the RBC: plasma group, $p > 0.1$.

Neurological evaluation

Neurological severity score

NSS was determined by a blinded observer [42]. Points are assigned for alterations of motor functions and behavior, such that the maximal score of 25 represents greatest neurological dysfunction while a score of 0 indicates an intact neurological condition. Specifically, the following were assessed: ability to exit from a circle (3-point scale), gait on a wide surface (3-point scale), gait on a narrow surface (4-point scale), effort to remain on a narrow surface (2-point scale), reflexes (5-point scale), seeking behavior (2-point scale), beam walking (3-point scale), and beam balance (3-point scale). Assessment of NSS was done at three selected time points 1 h post-injury, 24 h post-injury and 48 h post-injury, allowing evaluation of neurologic improvement over time.

Statistical analysis

Data were analyzed using SPSS 18 (SPSS Inc, Chicago, IL). Data are presented as mean ± SD or median ± IQ. Comparison of parametric data was done using multivariate ANOVA and repeated measures ANOVA and post hoc Bonferroni test. Non-parametric data were analyzed using the Wilcoxon signed ranks test, and Kruskal–Wallis test. Alpha error correction, due to multiple comparisons was not applied. Mortality rates were analyzed using the Kaplan–Meier survival curve model. Statistical significance was considered when $p < 0.05$.

Results

Bleeding and resuscitation volumes

Bleeding volumes (30% of calculated blood volume) did not differ significantly between the groups (6.3 ± 0.3 ml, 6.3 ± 0.1 ml, $p > 0.05$). Resuscitation volumes to reach MAP of 80 mmHg were not significantly different between the groups (1.5 ± 0.2 ml for the FWB group and 1.62 ± 0.2 ml for the RBC:plasma group, $p > 0.1$).

Hemodynamic parameters

MAP was measured at baseline, 0, 15, 30, and 60 min. 0–15 min was the timeframe to reach the resuscitation goal. All groups had a similar baseline of 95 mmHg. All groups subjected to hemorrhage shared a common pattern of: MAP decline to 45 mmHg following 30% blood volume loss, with a subsequent gradual rise toward baseline levels. Treatment groups differed significantly regarding the incline rate and the final MAP at 60 min. The TBI only group had a distinct pattern of a rise from 94 to 107 mmHg after insult. Figure 1 demonstrates the hemodynamic pattern of the experimental groups versus the control group which did not receive resuscitation. Within the untreated control groups, the TBI group does not suffer a significant decline in MAP. At 60 min, the TBI group has a significantly greater MAP compared to the bleeding groups (107 ± 13 versus 93 ± 7 mmHg and 84 ± 19 mmHg $p = 0.0038$). At 15 min, the TBI + bleeding had a significantly lower BP compared to the other control groups. Within the treatment groups, the insult causes a similar decline in MAP in all groups (42 ± 3, 43 ± 4, 43 ± 7 mmHg, $p > 0.05$). The recovery rate toward baseline was greater in all treatment groups, compared to untreated TBI + bleeding (Fig. 1). At 60 min post-injury, treatment groups achieve a higher MAP compared to control. Within the treatment groups, resuscitation to 80 mmHg in the FWB group resulted in a higher MAP albeit statistically indifferent (97 ± 8 versus 86 ± 4 mmHg, $p = 0.17$). That is, the hemodynamic response was similar in both resuscitation groups—RBC + plasma and whole blood.

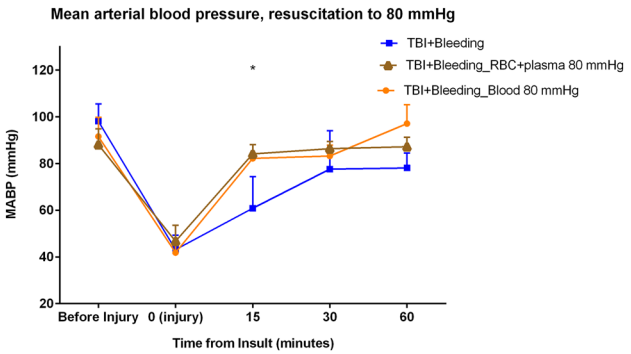

Fig. 1 MAP in the first hour after injury. All bleeding groups share a common pattern of rapid decline in MAP to 40 mmHg. The TBI + bleeding group recovers slowest and by 60 min reaches a significantly lower MAP compared to baseline, to bleeding alone and to treatment groups. Resuscitation to 80 mmHg achieves a higher MAP compared control, and there is no significant difference in hemodynamic response to resuscitation with fresh whole blood (FWB) or component therapy (RBC + plasma)

Neurologic recovery

Neurologic recovery was assessed by NSS at 1 h and 24 h post-insult (Fig. 2). The untreated combined TBI + bleeding group fairs significantly worse at 1 h, compared to all other groups, with subsequent death of all rats in the group. The bleeding only group has a very mild initial impairment with subsequent improvement to nearly normal. TBI and treated TBI + bleeding groups improved over time, with a significantly better neurologic recovery at 24 h, both compared to baseline and to the untreated groups. Neurological recovery was improved in the FWB compared to the RBC + plasma group (FWB NSS 6 ± 1, RBC + plasma 10 ± 2, $p = 0.02$).

Mortality

Survival of the different groups is presented in Fig. 3. At 24 h no individuals from the untreated TBI + bleeding group survive, while the TBI group has a 75% survival. Treatment with both FWB and RBC + plasma achieves a 100% survival rate at 24 h.

Arterial blood gas analysis

Values from arterial blood sampling at $t = 0$, 15 min and 60 min are presented below in text. Clinically significant

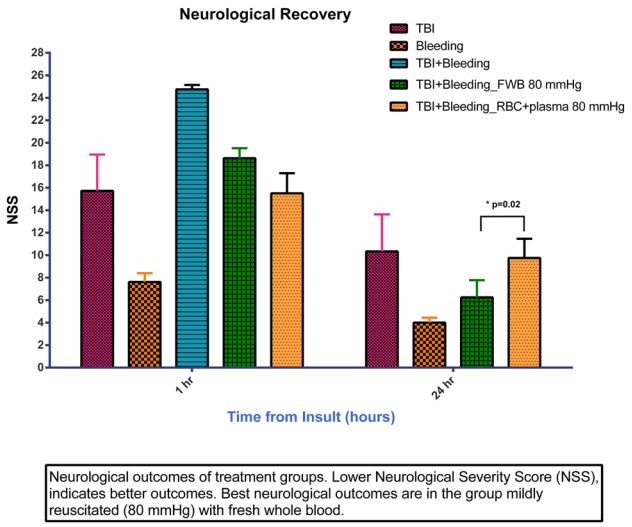

Fig. 2 Neurological recovery represented as NSS scores. At 1 h, the least favorable outcome is of the untreated TBI + bleeding group (NSS 25 ± 1, $p = 0.0158$). All other groups show some level of recovery over time. At 24 h, both treatment groups have improved NSS when compared to surviving controls. Neurological outcomes in the group resuscitated with fresh whole blood (FWB) are better, compared to resuscitation with platelet free components (RBC + plasma) (NSS 6 ± 2 versus 10 ± 2, $p = 0.02$). The bleeding only group fairs best at all time points (not shown). Data presented as median ± IQ range. *NSS* neurological severity score

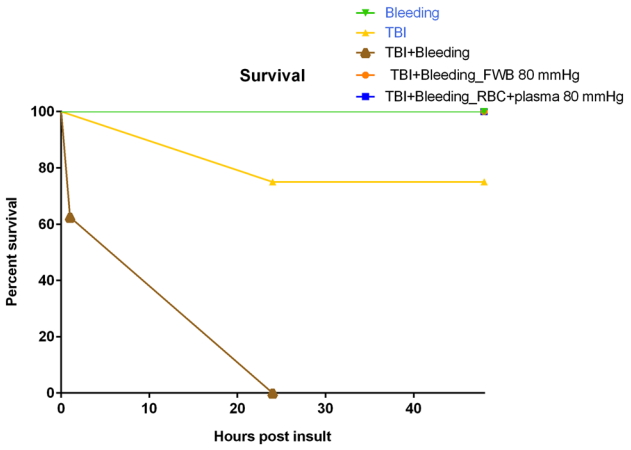

Fig. 3 Survival curves. Treatment groups have similar improved survival when compared to controls—100%

findings are hemoglobin and lactate levels. Hemoglobin concentration declines significantly in all bleeding groups immediately after injury, compared to baseline (8.5, 7.4, 8.2, 8.1 g/dl) and remains below baseline at all time points. Treatment groups demonstrate a similar mild increase in hemoglobin concentrations at 60 min post-injury (8.1, 8.2 g/dl). Lactate concentrations increase in all bleeding groups, with a decrease towards baseline in all treatment groups at 60 min. Resuscitation to 80 mmHg achieves significantly lower lactate levels at 60 min (1.3 ± 0.2 and 1.4 ± 0.4 mmol/l). PaO_2 does not differ significantly between groups and time points. $PaCO_2$ at 60 min in the untreated TBI + bleeding group remains significantly elevated compared to baseline and treatment groups (57 versus 42 mmHg).

Discussion

This study compared outcomes of rats suffering TBI combined with hemorrhagic shock, resuscitated with FWB or RBC + plasma. Based on findings from previous studies in animal models [40, 41] and accumulating data from recent literature, we adopted a mild resuscitation goal of 80 mmHg which has been demonstrated to achieve the most favorable outcomes. We found that resuscitation with FWB and with RBC + plasma achieves similar hemodynamic goals at 60 min post-injury, and are associated with 100% survival at 24 h. Furthermore, at 24 h, neurological impairment was reduced in the groups resuscitated with FWB. All groups, aside from the TBI only control group which did not suffer bleeding, demonstrated a similar pattern of rapid decrease of MAP to 40 mmHg, followed by a subsequent rise toward baseline levels. While it is known that outcomes of the combined injury (TBI and hemorrhagic shock) are far worse than any of these insults alone [15, 34, 41, 44–47], little evidence exists on the best resuscitation medium and goals. Absence of sufficient hemodynamic compensation at this particular time point, the "golden hour", may impair cerebral perfusion pressure, exacerbating the secondary damage [44, 48–50], thus requiring restoration of volume and hemodynamics. Excessive resuscitation measures may induce collateral processes such as coagulation disorders, TRALI, and multi-organ failure [1, 2, 51–54]. Thus, the ideal resuscitation strategy merits particular attention. While increasing evidence supports mild resuscitation with blood products, particularly with a high plasma: RBC ratio or using FWB in hemorrhagic shock [4, 5, 12, 21, 32, 40, 55, 56], it is not clear what are the overall effects in the combined injury. In this study, we find that resuscitation with FWB and RBC + plasma in a 1:1 ratio yields similar effects as far as hemodynamics and survival. At 60 min both groups achieve higher MAP compared to control, with no significant difference between the treatment groups. Nevertheless, the neurological outcome and survival are significantly affected by the concurrent incidence of these two insults. Non-treated rats have significantly worse outcomes at 1 h, and, suffer a 100% mortality rate at 24 h without any further interventional treatment, while both treatment groups have a 100% survival at this time frame. When comparing the neurological outcome using the NSS score, the groups resuscitated with FWB fare better compared to resuscitation with fractionated platelet free products. While neurological recovery assessment was extended to the 24 h post-insult period, several other studies have demonstrated that this effect may last 48 h post-insult [40, 41] and up to 3 weeks later [57]. This is in line with several clinical observations suggesting improved outcomes following the use of FWB for treatment of hemorrhagic shock [13, 14, 58, 59]. While the overall volume of replenished intravascular volume remains similar in both groups thus achieving similar hemodynamic goals, the neurological outcomes, which reflect additional processes going on—are affected by the resuscitation medium. Such processes include inflammatory response [60], coagulation disorders [1, 2, 52, 61] and brain edema [59], which both affect and are affected by TBI, hypotension and hemorrhagic shock.

Several strategies have been implied in order to maintain adequate tissue perfusion and a cerebral perfusion pressure of 50–70 mmHg, amongst them: crystalloids, colloids, vasopressors and synthetic hemoglobin substitutes [19, 28–30]. Using blood products for resuscitation allows use of smaller volumes (achieving similar hemodynamic goals), thus avoiding complications of large volumes of fluids [20, 31, 35, 36, 41, 62]. In this study, we find that it is not only the amount of fluid administered which makes the difference, but also the consistency of the medium.

The use of blood component therapy evolved in the 1960s and 1970s when a switch was made from use of whole

blood. Since then, there were no rigorous studies comparing the effects of these therapies. Several studies were conducted in particular situations—pediatric burns, cardiac surgery, and liver disease [63–69]. Few, mostly observational studies compared the effects of component therapy versus fresh whole blood in trauma and hemorrhagic shock, with a great body of evidence coming in from the recent conflicts in Afghanistan and Iraq [3, 55, 58, 70]. Few studies look into the effect of massive transfusion and the combined TBI and hemorrhagic shock [56] recommending the use of a high FFP:RBC ratio. To our knowledge, there is no study comparing the effects of FWB and component therapy in this situation. While this study remains a small-scale animal model, it may provide an insight into the possible utility of this medium in TBI and multiple trauma. The indications for use of FWB are narrow [71, 72], and most situations could be reasonably managed by adequately tailoring component therapy. One exception is in the setting of massive transfusion—most frequent in austere military settings and massive casualty situations where component therapy may not be adequate—either due to provider-related issues, i.e. logistical obstacles in obtaining, maintaining and storage component therapy, or patient-related issues i.e. the need to overcome the lethal triad of trauma—hypothermia, acidosis and coagulopathy. The combined injury (TBI and hemorrhage) is encountered frequently in the setting of multiple trauma and the requirement of massive transfusion, thus the possible utility of FWB. This may be particularly useful in situations where separated components are not available, or in limited resource settings [73]. FWB collection can be achieved with limited equipment and infrastructure [74–79].

While the current study was not designed to elucidate particular mechanisms, we have several hypotheses regarding the improved neurological outcomes in group treated with FWB. Despite the fact that similar volumes were used for resuscitation in both groups, the high 1:1 ratio of RBC:plasma may have had an effect on brain edema. One study looking into the systemic effects of high plasma:RBC ratio resuscitation, finds an increased incidence of TRALI and signs of pulmonary edema [11, 54]. This edema may very well occur in the brain as well as in the lungs, thus deteriorating neurological outcomes [27]. Hemorrhage of 30% blood volume inflicts coagulopathy particularly in brain injured patients [52, 61], which is may be exacerbated when large volumes of blood are administered. This coagulopathy is thought to be a result of increased thromboplastin, reduced platelets and consumption of fibrinogen [80], although the precise mechanism is not clear. In a study of TBI and hemorrhage, lower mortality was found in the group resuscitated with a high FFP:RBC ratio compare to low FFP:RBC ratio thus emphasizing the need for restoration of coagulation function in addition to volume [56]. Administration of FWB restores platelets and coagulation factors lacking in the RBC:plasma solution. Allogeneic blood infusion may be exacerbated by hormonal and immune responses associated with transfusion [81, 82]. Nevertheless, one study found that resuscitation with whole blood ameliorates the immune response after hemorrhagic shock [60], thus providing additional protection.

A major limitation of this study is the relatively short-term follow-up. Evaluation of neurological function and survival later on may have revealed more subtle differences between the groups. Furthermore, it remains unclear whether rats treated with blood components just recover more slowly than those with FWB. Another limitation is absence of parameters marking inflammation (such as CRP, interleukins, cytokines), and signs of immune reactions to blood transfusion. Coagulation and morphological histological studies would elucidate systemic processes and the effects on brain morphology, following the different resuscitation strategies. Furthermore, we did not provide a control group of bleeding only (without TBI), resuscitated with FWB or RBC + plasma. Such a group may have given an insight as to whether the beneficial effects seen in the FWB resuscitation group are unique to the combined injury.

Conclusions

Rapid treatment of combined hemorrhagic shock and TBI is necessary for survival, and maintenance of cerebral perfusion. While control of the bleeding source is fundamental, replenishing diminished volume and blood products is required as well. In this study we find that mild resuscitation with goals of restoring MAP to 80 mmHg (which is lower than baseline) with FWB or RBC + plasma, yield similar hemodynamic outcomes, with 100% survival at 48 h. The neurological outcomes at 24 h are better in the group resuscitated with FWB. These findings in a rat model, demonstrate that resuscitation with FWB may be feasible, with a possible benefit in the combined TBI + hemorrhagic shock injury, which is prevalent in situations where component therapy may be limited. Further studies should include larger sample sizes, longer term follow-up and brain histological studies and try to elucidate the physiological mechanisms underlying these observations.

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