The Initial Trauma Center Fluid Management of Penetrating Injury: A Systematic Review

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Abstract

Background Damage-control resuscitation is the prevailing trauma resuscitation technique that emphasizes early and aggressive transfusion with balanced ratios of red blood cells (RBCs), plasma (FFP), and platelets (Plt) while minimizing crystalloid resuscitation, which is a departure from Advanced Trauma Life Support (ATLS) guidelines. It is unclear whether the newer approach is superior to the approach recommended by ATLS.

Questions/purposes With these recent changes pervading resuscitation protocols, we performed a systematic review to determine if the shift in trauma resuscitation from ATLS guidelines to damage control resuscitation has improved mortality in patients with penetrating injuries.

Methods A systematic search of PubMed, the Cochrane Library, and the Current Controlled Trials Register was performed for studies comparing mortality in massively transfused penetrating trauma patients receiving either balanced ratios of blood transfusion per damage control resuscitation tenets or undergoing an alternate blood volume resuscitation strategy. Studies were deemed appropriate for inclusion if they had a Newcastle-Ottawa Scale score of 6 or greater as well as at least 30% penetrating trauma. Twenty

studies that reported on a total of 12,154 patients were included.

Results Transfusion ratios varied widely, with 1:1 and 1:2 ratios of FFP:RBC most often defined as high ratios for purposes of comparison with other low ratio groups. Fourteen of 20 studies found significantly lower 30-day mortality when higher transfusion ratios of FFP, RBC, and/or Plt were used; six of 20 studies found mortality to be similar between higher and lower transfusion ratios.

Conclusions Patients with penetrating injuries who require massive transfusion should be transfused early using balanced ratios of RBC, FFP, and Plt. Randomized, controlled trials are needed to determine optimal ratios for transfusion.

Introduction

Examination of the most recent available data shows that in 2009, gunshot wound (GSW)-related injuries accounted for 76,100 emergency department visits. Of those visits, the most frequent diagnosis was open wounds of extremities, accounting for 32% (24,260) of the injuries followed by head, neck, and trunk wounds [8]. Gunshot wounds have the potential to be a substantial portion of orthopedic admissions, and many require additional nonorthopaedic procedures [4], necessitating a multidisciplinary approach to their care. Although patients who require a trauma surgeon for life-threatening injuries will often undergo nonorthopaedic procedures first, the entire team should be well versed in the newest resuscitation strategies with initial management requiring the surgical specialties to work in concert.

Although Advanced Trauma Life Support (ATLS) guidelines state that doctors should resuscitate with 2 L of crystalloid solution before moving on to type-specific blood

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[22], studies in the trauma arena are beginning to refute this practice. Crystalloid fluid resuscitation transiently improves volume status but can exacerbate coagulopathy of trauma through dilution and hypothermia [37], lacks oxygen-carrying capacity [13], and contributes to greater proinflammatory gene transcription in trauma patients [39]. Furthermore, the transient increase in blood pressure from boluses of crystalloid fluid in an uncontrolled hemorrhage situation has the potential to dislodge clot formation that patients have already established [1], worsening hemorrhage.

In the event of hypotension in a hemorrhagic penetrating injury trauma patient, delaying fluid resuscitation and allowing the patient to remain hypotensive with a systolic blood pressure of approximately 90 mmHg [17] is a relatively new tenet of trauma surgery. Coined by the military during their trauma studies, damage control resuscitation [16] is an approach that uses permissive hypotension in trauma patients to reduce both surgical and nonsurgical bleeding. Analogous to the elective orthopaedic surgical practice of allowing hypotension to decrease blood loss [25, 31, 32, 35, 41] and supported by animal models that showed reduced risk of death in trials investigating hypotensive resuscitation [23], using permissive hypotension before surgical control of bleeding has led to improved survival in the military population [17] and has been adopted in civilian trauma [7]. Although damage control resuscitation encourages limited crystalloid resuscitation for reasons previously described, it also advocates initial resuscitation with blood (red blood cells [RBCs]), plasma (fresh-frozen plasma [FFP]), and platelets (Plt) early and in a 1:1:1 ratio rather than using the initial ATLS-defined 2 L of crystalloid resuscitation, particularly in patients who are expected to require massive transfusions (generally defined as greater than or equal to 10 units RBCs in the first 24 hours of care). Massive transfusion protocols (MTP) have been advocated in the literature and established in many trauma centers [29] to facilitate the transfusion needs of severely injured trauma patients such that resuscitation is done in balanced ratios.

With these recent changes pervading resuscitation protocols, it is unclear whether the newer approach is superior to the approach recommended by ATLS. We have reviewed the literature to determine if the shift from ATLS resuscitation guidelines to damage control resuscitation has improved mortality.

Search Strategy and Criteria

A systematic search of PubMed, the Cochrane Library, and the Current Controlled Trials Register was performed for studies comparing mortality in massively transfused penetrating trauma patients receiving either balanced ratios

of blood transfusion according to damage control resuscitation principles or undergoing an alternate blood volume resuscitation strategy. The search was performed using the following search string: (trauma) AND (massive transfusion protocol OR transfusion protocol OR MTP or transfusion ratio OR thromboelastogram OR TEG OR ROTEM OR thromboelastography) AND (mortality OR death OR died) with the search further limited to English language in the last 10 years. PubMed's "related articles" function was additionally used to broaden the search and each citation was reviewed for relevance.

Studies were included if they met the following criteria: (1) design included a randomized controlled trial, prospective observational study, retrospective cohort study, or level IV epidemiologic study; (2) included patients with at least 30% penetrating injury; (3) examined transfusion strategies involving ratios of RBCs with FFP and/or Plts; and (4) mortality was a reported outcome. Studies were excluded if they were case reports, letters, comments, or reviews.

The Newcastle-Ottawa Scale (NOS) [40] was applied by two raters to each of the observational studies to assess their quality. Disagreements were resolved by consensus. A score of 6 or greater was defined a priori as adequate quality to be included in this review.

Included Studies

A total of 396 titles were identified through database searching and additional sources, resulting in a total of 395 titles after a duplicate was removed. After assessing appropriateness based on title, 69 abstracts were closely reviewed and 37 were excluded based on study criteria (Fig. 1). A total of 32 full-text articles were assessed for eligibility, and one was excluded based on a NOS < 6 with an additional 11 excluded because their study populations included less than 30% penetrating trauma. The final review included 20 studies reporting outcomes on 12,154 patients (Fig. 1).

Comparability of Groups

Military and civilian studies from North America, Europe, and Australia were included, and all studies evaluated mortality rates with respect to transfusion ratios involving RBC with FFP, Plts, or both. There were three different definitions of massive transfusion (MT) with the predominant definition included in 17 studies describing MT as ≥ 10 units RBCs in 24 hours [2, 3, 5, 6, 9–12, 15, 19, 21, 26–28, 33, 34, 42]. Other definitions included patients receiving ≥ 10 units RBCs by completion of the operation before intensive care unit admission [30] and receiving ≥ 10 units RBCs in the first

Fig. 1 Flow diagram is shown of article search and selection process in a systematic review of penetrating trauma and initial resuscitation published through December 10, 2013.

12 hours of arrival [20]. Only one study [18] did not use a MT definition when evaluating their patient outcomes.

Prevalence of penetrating trauma among the study groups widely varied from as low as 30% in civilian studies to as high as 94% in combat studies. Injury Severity Score (ISS) means and medians also ranged from 17 to 45 with higher ISSs seen in studies specifically geared toward examining MT. Admission international normalized ratio (INR) was quantified in 10 of the studies [2, 5, 12, 18, 19, 26–28, 34, 42] with medians and means ranging from 1.1 to 1.9 with the intent to illustrate the acute coagulopathy of trauma (Table 1).

Comparisons of ratios of blood products given varied widely in the representative studies. “High” ratios were defined as the ratio of FFP:RBC or Plt:RBC of either $\geq 1:2$ [3, 5, 10, 19, 26, 27, 30, 33] and $\geq 1:1$ [11, 18, 28, 42] as the most common “high” ratio definitions with additional “high” ratio definitions of 1:1.4 [2], “better than 2:3” [9, 15], and $\geq 1:6$ with respect to platelets only [21]. Four studies did not specifically define “high” ratios as previously described, but either compared two time periods where resuscitation strategies differed [6, 12, 34] such that ratios were intentionally higher than conventional resuscitation or only examined outcomes of those patients who received FFP in the first 12 hours of admission versus those who did not [20] (Fig. 2).

Results

Comparisons of Resuscitation

The majority (15 of 20) of studies were retrospective comparative studies of trauma patients comparing ratios of FFP:RBC and/or Plt:RBC and examining outcomes

including early (< 6 hours or < 24 hours) and late (24 hours to 30 days) mortality, intensive care unit and hospital length of stay, ventilation days, etc, to determine if varied transfusion ratios had differing outcomes (Table 2). The specific ratio combinations examined and the grouping of patients were diverse and largely dependent on whether the study was examining the effect of a single blood component (FFP or Plt) or combination of blood components (FFP and Plt). One study was an epidemiologic study [26], examining improved military survival with increased Plt and plasma use over a 10-year period. Three studies examined historical controls before use of a MTP with patients after MTP initiation [10, 15, 33] to determine if outcomes differed after a change in resuscitation methodology. Two prospective studies were undertaken: (1) a small, single-institution study by Sharpe et al. [30] evaluated patients who received MT (≥ 10 units RBC) by the completion of their operation and evaluated mortality based on ratios; and (2) a larger, multicenter study involving 10 Level I trauma centers with Holcomb et al. [18] stratified patients into various ratios and evaluated mortality.

Thirty-day Mortality

Of 20 studies, 14 showed that higher ratios of FFP:RBC and/or Plt:RBC were associated with improved mortality in all trauma patients (Table 2). The remaining six studies showed no significant difference in 30-day mortality after implementation of MTP with higher ratios or comparing ratios retrospectively in all trauma patients, strongly suggesting that damage control resuscitation with higher ratios

Table 1. Patient demographics and admission laboratory values

Study	Number	Penetrating	Age (years)	ISS	INR	Hgb	Plt	pH	BD	SBP (mmHg)
Pidcoke et al., 2012 [26]	3632	49% OIF 84% OEF	26 ± 6	OIF 19 (13–27) OEF 22 (14–29)*	1.5 ± 0.8	12 ± 3	252 ± 106	NR	4 (2–8)	117 ± 29
Holcomb et al., 2012 [18]	905	35.6%	37 (24–53)	27 (17–36)	1.3 (1.1–1.5)	11.5 (9.9–13.1)	NR	7.3 (7.2–7.3)	7 (4–11)	102 (82–124)
Cap et al., 2012 [5] (platelets)	414	93% low ratio 89% high ratio	26 (21–31)	23 24	1.6 1.9*	11.3 11.4	275 254	NR	8 10*	103 100
Sharpe et al., 2012 [30]	135	49%	36	32	NR	NR	NR	NR	NR for cohort	NR for cohort
Brown et al., 2011 [3]	437	INR ≤ 1.5: 33% INR 1.16–1.35: 33% INR: 1.36–1.66: 38% INR ≥ 1.67: 31%	45 ± 18* 42 ± 18 37 ± 18 38 ± 17	30 ± 17 31 ± 15 33 ± 16 36 ± 16	NR B: 1.6 ± 0.7 P: 1.6 ± 0.7	12 ± 2 11 ± 2 11 ± 2 9 ± 3*	289 ± 81 231 ± 92 200 ± 79 149 ± 72*	NR	8 ± 6 10 ± 6 10 ± 6 13 ± 7*	110 ± 30 108 ± 31 97 ± 27 94 ± 31*
Rowell et al., 2011 [27]	703	35%	B: 44 ± 18 P: 31 ± 12*	B: 37 ± 15 P: 26 ± 15*	NR B: 1.6 ± 0.7 P: 1.6 ± 0.7	NR	NR	NR	B: 11 ± 6.7 P: 11.2 ± 7.3	B: 103 ± 31 P: 102 ± 32
Sambasivan et al., 2011 [28]	1788	35.5% low ratio 28.7% high ratio	38 (26–53) 30.5 (21–49)*	20 (10–29)* 29 (19.5–41)	1.1 (1–1.3) 1.3 (1.2–1.6)*	12 (11–14) 12 (10–14)	245 219*	7.3 (7.2–7.4) 7. (7.2–7.4)	6.6 (9–7.4) 6 (10–3)	115 (93–138) 120 (100–140)*
Simmons et al., 2011 [34]	96	39%	30 ± 16	29 ± 16	1.8 ± 1.0	10.4 ± 2.6	216 ± 120	7.2 ± 0.2	2.5 ± 12.2	96 ± 36
deBiasi et al., 2011 [9]	515	37%	39.5 ± 19	32 ± 16	NR	NR	NR	NR	NR	NR
Inaba et al., 2010 [21] (platelets)	657	55%	12.6% ≥ 55	28.7 ± 14.5	NR	NR	NR	NR	NR	NR
Duchesne et al., 2010 [12]	196	CRE: 67% DCR: 77%	CRE: 28 ± 12 DCR: 30 ± 14	CRE: 23 ± 11 DCR: 25 ± 12	CRE: 1.4 ± 0.5 DCR: 1.5 ± 0.7	9.2 ± 2.1 8.8 ± 1.8	NR	NR	CRE: 8.7 ± 1.9 DCR: 7.3 ± 1.7	NR
Inaba et al., 2010 [20] (plasma)	284 Matched pairs	Plasma: 40% No plasma: 37%	Plasma: 37 ± 21 None: 36 ± 18	Plasma: 24 ± 13 None: 23 ± 12	NR	NR	NR	NR	NR	SBP < 90 Plasma: 9.3% None: 9.9%
Shaz et al., 2010 [33]	216	MTP: 49% Pre-MTP: 41%	MTP: 35 ± 15 Pre: 38 ± 16	MTP: 27 ± 12 Pre: 29 ± 15	NR	NR	NR	NR	MTP: 13.6 ± 6.3 Pre: 12.9 ± 6.3	NR
Dente et al., 2009 [10]	157	40%	36 ± 1.6	29 ± 1.4	NR	NR	NR	NR	13.5 ± 0.87	NR
Zink et al., 2009 [42]	452	33% low ratio 36% med ratio 37% high ratio	36 36 28	29 32 33.5	1.3 1.3 1.5*	11 10.8 10.9	220 196 200	NR	NR	101.5 100 102
Holcomb et al., 2008 [19]	466	35%	39 ± 18	32 ± 16	1.6 ± 0.9	NR	NR	7.2 ± 0.2	11 ± 7.7	107 ± 33
Gunter et al., 2008 [15]	259	Pre-TEP: 61% TEP: 48%*	Pre: 36 (24–50) TEP: 30 (24–43)	Pre: 25 (16–34) TEP: 25 (24–41)*	NR	NR	NR	NR	NR	NR

Table 1. continued

Study	Number	Penetrating	Age (years)	ISS	INR	Hgb	Plt	pH	BD	SBP (mmHg)
Duchesne et al., 2008 [11]	385	≤ 10 units RBC: 58% > 10 units RBC: 71.8%*	≤ 10: 31 ± 13 > 10: 33 ± 11	≤ 10: 21 > 10: 27*	NR	NR	NR	NR	NR	≤ 10: 116 ± 15 > 10: 92 ± 27*
Cotton et al., 2008 [6]	211	Pre-TEP: 30% TEP: 50%*	Pre: 39 ± 18 TEP: 36 ± 15	Pre: 30 ± 16 TEP: 32 ± 17	NR	NR	NR	NR	NR	NR
Borgman et al., 2007 [2]	246	Low ratio: 94% Med ratio: 92% High ratio: 95%	24 (21–30)	18 (16–25) 17 (13–25) 18 (16–25)	1.8 (1–2.9) 1.6 (1.3–2.1) 1.5 (1.3–2.2)	9 (7–11) 11 (9–13) 11 (9–13)*	225 (120–281) 177 (128–241) 218 (154–278)	NR	13 (4–14) 9 (3–14) 8 (4–13)	90 (80–106) 98 (74–116) 97 (80–122)

* $p < 0.05$, reported as mean, mean $\pm$ SD, or median (range); ISS = Injury Severity Score; INR = international normalized ratio; Hg = hemoglobin; Plt = platelets; BD = base deficit; SBP = systolic blood pressure; OIF = Operation Iraqi Freedom; OEF = Operation Enduring Freedom; CRE = conventional resuscitation efforts; DCR = damage control resuscitation; MTP = massive transfusion protocol; TEP = trauma exsanguination protocol; RBC = red blood cells; B = blunt injury patients; P = penetrating injury patients; NR = not reported.

of FFP:RBC or Plt:RBC is either superior or equivalent to the older ATLS protocols.

Of those studies who found equivalent mortality, Holcomb et al. [18] showed a decreased mortality risk observed during the first 6 hours (adjusted hazard ratio = 0.31, $p < 0.001$) as well as noting that patients in moderate and high ratio groups had lower mortality rates than the low ratio group ($p < 0.001$) but that benefit was lost at 30 days. The study accounted for survival bias, not including patients who died within the first 30 minutes, but evaluated all patients who received 3 or more units of blood products and not just MT patients. Brown et al. [3] and Inaba et al. [21] did not evaluate 30-day mortality; however, early mortality at 24 hours improved with ratios of FFP:RBC of 1:2 or higher, regardless of arrival INR in Brown et al.'s study and Inaba et al. showed improvements in mortality with increasing ratios of Plt:RBC at 12 and 24 hours. Rowell et al. [27] only saw 30-day mortality improvement in patients with penetrating injuries with high FFP:RBC ratios, whereas Dente et al. [10] only saw 30-day mortality improvement in patients with blunt injuries after MTP. Both studies showed improved 24-hour mortality overall but not at 30 days in all patients. Another study by Inaba et al. [20] evaluating 284 matched patients as well as a study by Sambasivan et al. [28] using propensity scores showed no significant difference in mortality between cohorts but evaluated only non-MT patients.

Discussion

Damage control resuscitation advocates early and aggressive resuscitation with RBC, FFP, and Plt in a 1:1:1 ratio. Although the practice started in the military, trauma centers around the world have been quick to evaluate more aggressive resuscitation with their own patient groups after multiple retrospective reviews have shown that improved ratios of blood components appear to result in improved mortality outcomes. Civilian trauma studies have followed suit, changing initial resuscitation practices with the intent of improving mortality. These initial resuscitation changes are in disagreement with current ATLS protocols to fluid challenge a hypotensive trauma patient with 2 L of crystalloid and thus deserve closer inspection. Although resuscitation modes varied, 14 of 20 studies found high transfusion ratios improved mortality and the remainder found equivalent mortality with none demonstrating worse outcomes using aggressive blood product resuscitation.

This study had a number of limitations. First, the majority (12 of 20; Table 1) of studies had more blunt than penetrating injury. Although we limited studies to those with at least 30% penetrating injury, the differing physiology of each injury pattern has potential to affect mortality outcomes and patient response to resuscitation. Using ISSs and base

Fig. 2 Example of high and low blood product ratios is shown.

deficit as a surrogate marker of analogous presentation severity, the groups appear to be similar, but definitive comparison is impossible without a true meta-analysis. Two studies specifically did a subgroup analysis on blunt versus penetrating injury with opposite findings: (1) Dente et al. showed only blunt trauma had improved 30-day mortality after implementation of a MTP [10], whereas (2) Rowell et al. showed penetrating injury patients had improved mortality while blunt did not [27]. Another limitation of this study was the inclusion of combat studies, which, although they include significantly higher percentages of penetrating trauma, will also inherently contain a presumed higher percentage of blast injury within the penetrating injury cohort. We recognize that combat injuries are different than civilian injuries; however, the physiology of the injured patients is similar and their ISS and base deficits were fairly similar, so we chose not to exclude them. Of note, only one military study [34] specifically separated blast (50% pre-MTP and 58% MTP) and GSW (47% pre-MTP and 36% MTP) populations in the demographic description, but outcomes were evaluated as a group during the comparative two time periods. Nonetheless, all five of the military studies [2, 5, 12, 26, 34] found improved survival with higher transfusion ratios. An additional limitation of this study was the differing definitions of “high” and “low” ratios of blood products being compared as well as differing definitions of MT. The predominant MT definition of ≥ 10 units of RBC in the first 24 hours is used by the authors’ institution, but arguments have been made to use different definitions [24, 42]. Our institution also practices a transfusion goal of 1:1:1 (FFP:Plt:RBC) until laboratory information is available through thromboelastography and then performs goal-directed transfusion to restore a normal coagulation profile on thromboelastogram, acknowledging that we come closer to 1:1:2 based on thawing practices and product availability. The lack of consensus makes direct comparisons difficult and reaching an accord should be a goal of the trauma community at large. Finally, we would be remiss if we did not mention that this analysis does not include evaluation of other resuscitation tools such as thromboelastography or other products such as colloids, cryoprecipitate, and other coagulation factors, but as a result of the large preponderance of clinical studies of each of these, to include them is beyond the scope of this review.

There has been a general trend away from ATLS initial crystalloid resuscitation practices in favor of giving blood products instead if the patient is determined to need immediate resuscitation. Although not examined or searched for specifically in the study design (we chose to concentrate on transfusion ratios and mortality), we found that two of the studies specifically addressed crystalloid use with implementation of MTP: (1) Pidcock et al. [26] noted that although crystalloid use decreased over the 10-year study period, it did not have a significant effect on survival in regression models; and (2) Dente et al. [10] found that after initiation of MTP, crystalloid use decreased significantly in the first 6 hours (6.9 L versus 9.2 L, $p = 0.006$). Although these studies do not explicitly implicate decreased crystalloid use as a potential contributor to improved mortality, limitation of crystalloid resuscitation is inherent to the tenets of damage control resuscitation with the intent to avoid well-described dilution of coagulation factors, induction of inflammation, and hypothermia. This may explain the trend at trauma centers away from traditional ATLS guidelines in favor of using blood products for first-line resuscitation.

Massive transfusion protocols have been advocated in the literature and adopted by many trauma centers [29] to facilitate the transfusion needs of severely injured trauma patients such that resuscitation is done in balanced ratios. However, studies disagree about the preferred ratio of RBC:FFP. Studies have recommended ratios ranging from 1:1 and 1:3 to decrease mortality while avoiding potential complications of multiple organ failure and adult respiratory distress syndrome that can occur with increased transfusion of FFP and Plts [38]. However, there are no published randomized controlled trials specifically investigating transfusion ratios. These are needed and currently in process.

The results of this review suggest that close monitoring of blood loss and replacement with blood products in balanced ratios is prudent in patients who require massive transfusion. We also suspect the next set of clinical questions will involve comparisons of empiric transfusion of patients using MTP with goal-directed therapy using a thromboelastogram (TEG) or rotational thromboelastometry (ROTEM), which better reflects the hemostatic process as compared with classic coagulation measures such as

Table 2. Ratio comparisons and mortality

Study	Number	MT definition	Account for survival bias	Ratio comparisons	Early mortality (death within 24 hours of admission)	30-day or in-hospital mortality
Pidcock et al., 2012 [26]	3632	≥ 10 units RBC + FWB in first 24 hours	Not able to exclude subjects with death within 1 hour admission, however mitigated by longer transport times averaging 54 minutes	Low FFP/low Plt High FFP/low Plt Low FFP/high Plt High FFP/high Plt Low and high defined as ratios ≤ 0.5 or ≥ 0.5	NR	Low FFP/low Plt 17% High FFP/low Plt 17% Low FFP/high Plt 16% High FFP/high Plt 12%* Mortality decreased over time (OIF to OEF) despite increased ISS as ratios improved; high platelet ratio more strongly correlated with survival than FFP ratio, although possible colinearity (platelets contain plasma)
Holcomb et al., 2012 [18]	905	Did not use; included all with 3 units products	Excluded patients who died within 30 minutes of arrival	Low (< 1:2), moderate (≥ 1:2 to < 1:1), and high (≥ 1:1) ratios and the times in which those ratios were met	10.5% (30 minutes to 6 hours) 4.6% (6–24 hours) Total 24-hour mortality 15.1% Decreased mortality in high ratio group at 6-hour mark but became nonsignificant at 30-day mark	25% overall mortality Protective association of transfusion ratios highest at 6 hours, diminished with time as causes of death shifted from hemorrhage to other complications
Cap et al., 2012 [5]	414	≥ 10 units RBC within 24 hours	Excluded patients who died within 1 hour of presentation	6-hour platelet (aPLT) transfusion ratios Low 1:10 aPLT:RBC High more than 1:10 (similar to ratio 1:2 or higher)	Low 22%* High 10% Increased mortality at 24 hours independently associated with ISS and being in low group	Low 22% High 19% Increased mortality at 30 days independently associated with ISS, being in low platelet group; decreased mortality was associated with high plasma ratio and revised trauma score
Sharpe et al., 2012 [30]	135	≥ 10 units RBC by completion of operation	Excluded patients who died intraoperatively	High: > 0.5 Medium: 0.33–0.5 Low: < 0.3 Ratios at end of operation	23% overall	High 29%* Medium 40% Low 57.7%
Brown et al., 2011 [3]	437	≥ 10 units RBC in 24 hours	None	Ratio of FFP:RBC of at least 1:2 in patient groups stratified by INR INR ≤ 1.5 INR 1.16–1.35 INR 1.36–1.66 INR ≥ 1.67	Early mortality increased with increasing INR INR ≤ 1.5: 18% INR 1.16–1.35: 24% INR 1.36–1.66: 28% INR ≥ 1.67: 35% Decrease in mortality with transfusion 1:2 regardless of INR on arrival ≥ 1:2–29% < 1:2–48%*	NR

Table 2. continued

Study	Number	MT definition	Account for survival bias	Ratio comparisons	Early mortality (death within 24 hours of admission)	30-day or in-hospital mortality
Rowell et al., 2011 [27]	703	≥ 10 units RBC in 24 hours	Excluded patients who died within 30 minutes of arrival	Low (< 1:2) and high (≥ 1:2) ratios of Plt:RBC and FFP:RBC in first 6 hours of admission	24-hour mortality blunt injury: FFP high: 22%, low: 33%* Platelets high: 20%, low: 30%* 24-hour mortality penetrating injury: FFP high: 21%, low: 37%* Platelets high: nonsignificant difference	30-day mortality blunt injury: FFP high: 40%, low: 44% Platelets: nonsignificant differences 30-day mortality penetrating injury: FFP high: 29%, low: 45%* Platelets nonsignificant difference
Sambasivan et al., 2011 [28]	1788	≥ 10 units RBC in 24 hours	Excluded patients who died within 2 hours of arrival	FFP:RBC ratio and Plt:RBC ratio Low is < 1:1 High is ≥ 1:1 Also considered ratios using 1:2 as a cut point	NR	FFP:RBC Low: 12.9%, high: 23.3% Plt:RBC Low: 14.3%, high: 21.1% Multivariate propensity-adjusted hazards model of time to death in terms of FFP:RBC ratio, ISS, GCS, PTT, and propensity score used to determine significance; differences not significant
Simmons et al., 2011 [34]	96	≥ 10 units RBC in 24 hours	None	Cumulative ratios calculated at ED, OR, and end of first 24 hours; comparing mortality between 2 time periods: T1 → 12/2003 to 6/2004 T2 → 9/2007 to 5/2008	NR	T1: 47%, T2: 20% T2 total ratio after OR and at 24 hours was significantly higher than T1 (p < 0.001)
deBiasi et al., 2011 [9]	515	≥ 10 units RBC in 24 hours	Excluded patients who died within 15 minutes arrival and those defined as “likely to die” with a TRISS < 0.010	3 subgroups of interest: 10+ units (MT), 5–9 units, and 1–4 units RBC looking at ratios and plasma deficit (RBC - FFP) hourly Ratio cut points: “better than” 2:3, “better than” 1:3 and less or equal to 1:3 Low plasma deficit 0–2 units behind RBC Moderate plasma deficit 3–6 units High plasma deficit > 6 units	NR	1–4 units RBC: 30.9% 5–9 units RBC: 25.9% 10 + units RBC: 48.2%* Low FFP deficit: 35.1% Moderate FFP deficit: 39% High FFP deficit: 63.6%* No significant difference in ratio cut points on mortality

Table 2. continued

Study	Number	MT definition	Account for survival bias	Ratio comparisons	Early mortality (death within 24 hours of admission)	30-day or in-hospital mortality
Inaba et al., 2010 [20] (platelets)	657	≥ 10 units RBC in 24 hours	Excluded patients who died in the emergency department	Plt:RBC comparison Low < 1:18 Medium ≥ 1:18 and < 1:12 High ≥ 1:12 and < 1:6 Highest ≥ 1:6	12-hour mortality Low: 48.2% Medium: 38.7% High: 27.4% Highest: 14.5%* 24-hour mortality Low: 65.5% Medium: 37.7% High: 29.3% Highest: 16.9%*	NR
Duchesne et al., 2010 [12]	196	≥ 10 units RBC in 24 hours	None	Ratios of conventional resuscitation efforts (CRE) not defined; CRE involved aggressive crystalloid resuscitation and no predefined transfusion protocol Damage control resuscitation (DCR) attempts transfusion at 1:1 FFP:RBC and 1:2 Plt:RBC	NR CRE: 45.2% DCR: 26.4%* Adjusting for age, gender, ISS, injury type, DCR had survival benefit (OR 0.19, CI 0.05–0.33)*	
Inaba et al., 2010 [20] (plasma)	284 Matched pairs	≥ 10 units RBC in first 12 hours	Patients who died within the first 24 hours after hospital admission were excluded	Nonmassively transfused patients divided into 2 cohorts: (1) received plasma in first 12 hours, and (2) no plasma in first 12 hours	NR Plasma: 17.3% None: 14.1%	
Shaz et al., 2010 [33]	216	≥ 10 units RBC in 24 hours	None	PreMTP versus MTP ratios at 6 hours, 24 hours, and entire hospital stay ≥ 1:2 high < 1:2 low	MTP 29% Pre-MTP 32% High: 21% low: 54%*	MTP: 48% Pre-MTP: 50% High: 41% low: 56%*

Table 2. continued

Study	Number	MT definition	Account for survival bias	Ratio comparisons	Early mortality (death within 24 hours of admission)	30-day or in-hospital mortality
Dente et al., 2009 [10]	157	≥ 10 units RBC in 24 hours	Patients who died before 10 units RBC could be transfused were excluded	RBC:FFP in MTP group 1:1–2:1 2:1–3:1 > 3:1 RBC:Plt in MTP group 1:1–2:1 2:1–3:1 > 3:1	MTP: 17.6% Pre-MTP: 36% RBC:FFP in MTP group 1:1–2:1 14%* 2:1–3:1 19% > 3:1 57% RBC:Plt in MTP group 1:1–2:1 10%* 2:1–3:1 18% > 3:1 50%	MTP: 38.4% Pre-MTP: 50% Blunt trauma had 66% mortality pre-MTP versus 50% with MTP, a significant improvement* RBC:FFP in MTP group 1:1–2:1 31% 2:1–3:1 36% > 3:1 57% RBC:Plt in MTP group 1:1–2:1 36% 2:1–3:1 27% > 3:1 50%
Zink et al., 2009 [42]	452	≥ 10 units RBC in 24 hours	Excluded patients who died within 30 minutes of arrival	Low < 1:4 Medium ≥ 1:4 to 1:1 High ≥ 1:1	6-hour mortality of FFP:RBC Low 37.3% Medium 15.2% High 2%* 6-hour mortality of Plt:RBC Low 22.8% Medium 19% High 3.2%* Most mortality differences occurred in first 6 hours and persisted through hospital discharge	FFP:RBC Low 54.9% Medium 41.1% High 25.5%* Plt:RBC Low 43.7% Medium 46.8% High 27.4%*
Holcomb et al., 2008 [19]	466	≥ 10 units RBC in 24 hours	Patients who died within 30 minutes of admission	Units totaled at 6 hours and 24 hours for comparison Low < 1:2 High ≥ 1:2 FFP:RBC and Plt:RBC categorized into 4 groups: high-high, high-low, low-high, low-low	6-hour survival: high-high 98%* high-low 86% low-high 83% low-low 58% 24-hour survival: high-high 87%* high-low 75% low-high 77% low-low 50%	30-day survival high-high 73%* high-low 54% low-high 68% low-low 43% FFP:RBC ratio ≥ 1:2 was associated with improved 30-day survival (40.4% versus 59.9%, p < 0.001) plt:RBC ratio ≥ 1:2 was associated with improved 30-day survival (40.1% versus 59.9%, p < 0.01)

Table 2. continued

Study	Number	MT definition	Account for survival bias	Ratio comparisons	Early mortality (death within 24 hours of admission)	30-day or in-hospital mortality
Gunter et al., 2008 [15]	259	≥ 10 units RBC in 24 hours	None	Pre-TEP versus TEP looking at intraoperative and 24-hour ratios of FFP:RBC and Plt:RBC Also evaluated expected and unexpected survivors versus probability of survival calculated by TRISS score	Pre-TEP: 39% TEP: 35%	Pre-TEP: 63% TEP: 48%* Unexpected survivors Pre-TEP: 4% TEP: 18%* Unexpected death Pre-TEP: 19% TEP: 7% Patients who achieved intraoperative and first 24-hour ratios of > 2:3 were more likely to survive ≤ 10 units: 1:1 11.8% 1:4 21.2%* > 10 units 1:1 26% 1:4 87.5%* Using multiple logistic regression in > 10 units RBC, difference in ratio was only variable consistent with increased risk mortality (RR 18.88, CI 6.32–56.36, p = 0.001)
Duchesne et al., 2008 [11]	385	> 10 units RBC in 24 hours	Patients who did not arrive alive to the ICU were excluded	FFP:RBC ratios of 1:1 and 1:4 in patients who received ≤ 10 units RBC and > 10 units RBC	NR	Pre-TEP: 65.8% TEP: 51.1%* Unexpected survivors Pre-TEP: 5.1% TEP: 22.3%* Unexpected deaths Pre-TEP: 22.2% TEP: 8.5%* 28% overall mortality Low 65% Medium 34% High 19%*
Cotton et al., 2008 [6]	211	≥ 10 units RBC in 24 hours	None	Pre-TEP versus TEP patients; TEP patients had delivery and transfusion of blood products in prescribed ratios	NR	Pre-TEP: 65.8% TEP: 51.1%* Unexpected survivors Pre-TEP: 5.1% TEP: 22.3%* Unexpected deaths Pre-TEP: 22.2% TEP: 8.5%* 28% overall mortality Low 65% Medium 34% High 19%*
Borgman et al., 2007 [2]	246	≥ 10 units RBC in 24 hours	None	Low 1:8 Medium 1:2.5 High 1:1.4	Early death from hemorrhage Low 92.5% Medium: 78% High: 37%*	Pre-TEP: 65.8% TEP: 51.1%* Unexpected survivors Pre-TEP: 5.1% TEP: 22.3%* Unexpected deaths Pre-TEP: 22.2% TEP: 8.5%* 28% overall mortality Low 65% Medium 34% High 19%*

* p < 0.05; MT = massive transfusion; RBC = red blood cells; FWB = fresh whole blood; TRISS = Trauma Injury Severity Score; ICU = intensive care unit; FFP = fresh-frozen plasma; Plt = platelets; aPLT = apheresis platelets; INR = international normalized ratio; ED = emergency department; OR = operating room; MTP = massive transfusion protocol; TEP = trauma exsanguination protocol; NR = not reported; ISS = Injury Severity Score; OIF = Operation Iraqi Freedom; OEF = Operating Enduring Freedom; GCS = Glasgow Coma Score; PTT = partial thromboplastin time; OR = odds ratio; CI = confidence interval; RR, relative rate.

prothrombin time, partial thromboplastin time, and INR [14]. A study recently published by our institution [36] retrospectively reviewed MTP versus TEG and found that TEG had improved mortality over MTP in patients with penetrating injury. Further studies are certainly warranted, but the decrease in mortality with higher transfusion ratios is promising.

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