

**Acute Transfusion in Major Trauma: Triggers and the
Benefit of a Massive Transfusion Protocol**

Krisztián Sisák, MD
Summary of PhD Thesis

Department of Orthopaedics, Albert Szent-Györgyi Medical and
Pharmaceutical Center, University of Szeged, Hungary
and
Department of Traumatology, John Hunter Hospital and University of
Newcastle, New
South Wales, Australia

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INTRODUCTION

Exsanguinating bleeding after trauma remains the leading cause of potentially preventable mortality. Several potential bleeding sites in blunt trauma are due to musculoskeletal injuries, as these are present in the majority of the injured. Orthopaedic trauma surgery is required in more than 70% of trauma patients potentially adding to the pre-hospital blood loss.

In the last decade the emphasis has shifted from uncontrolled fluid resuscitation, to preventing the escalation of shock and coagulopathy whilst achieving definitive haemostasis. Haemorrhage and resuscitation both induce cellular changes that can result in dysregulated immune responses and harmful systemic effects. The backbone of more restrictive resuscitative efforts remains the transfusion of packed red blood cells (PRBC). Blood is an expensive and finite resource and transfusion is an independent risk factor for systemic inflammatory response syndrome (SIRS), ICU admission, increased ICU length of stay, infectious complications, multiple organ failure (MOF) and death. PRBC transfusion has predictable and reproducible immunomodulatory effects. A liberal transfusion policy can introduce further risk to the already compromised patient.

Fresh whole blood has been successfully used in the military setting. It contains all required blood components, however due to issues regarding, availability, screening, storage and especially safety, the use of whole blood in the civilian setting is unlikely. Providing other blood components in predefined packs to achieve a ratio resembling that of whole blood is the main benefit of haemostatic resuscitation. The implementation of a massive transfusion protocol (MTP) allows the release and administration of blood components, in an immediate and sustained manner, reducing bleeding related mortality. To characterize the effect of blood component therapy invariably 24 hr cumulative blood component ratios (PRBC to either fresh frozen plasma (FFP), cryoprecipitate (CRYO) or platelets (PLT)) and overall volumes of the various blood components are used to describe outcomes. As the majority of haemorrhagic deaths happen within the first 6 hours, survival bias could affect 24 hr cumulative ratios, by patients surviving eventually receiving higher component ratios contrary to lower ratios in non-survivors.

Widely accepted guidelines control transfusion triggers in critical care, with only empirical practice influencing decision making in early trauma related transfusions. A clear understanding of decision making in the early use of PRBC in trauma resuscitation would help achieve an effective use of available resources, whilst simultaneously reducing the associated risk of transfusions.

AIMS

Despite numerous advancements in the understanding of early resuscitative efforts in major trauma, many questions are still unanswered. In particular:

- We only have a limited understanding of how orthopaedic injuries contribute to overall blood loss in blunt trauma. This is often underestimated.
- We do not possess reproducible guidelines of why and how blood component transfusion is initiated in the first 24 hrs in major trauma.
- The changes that occur in the availability of blood components by implementing a MTP, in the clinically most relevant first 6 hrs after injury, is largely unknown.

Thus, our clinical investigations were undertaken with three main aims in mind:

1. To establish the contribution of orthopaedic injuries to overall blood component consumption in the first 24 hrs after injury. We hypothesised that orthopaedic injuries are major contributors to acute blood product usage.
2. To describe the pattern and triggers of acute transfusions. We hypothesised that acute transfusions after trauma are indicated on objective parameters.
3. To examine the effect of a MTP on balanced component delivery in the first 6 hrs in massively transfused patients. We hypothesised that the implementation of a MTP accelerates the delivery of blood components, especially in the first 6 hrs after injury.

CLINICAL STUDIES:

Two separate clinical studies were performed. All cases involved in the clinical investigations were patients of the John Hunter Hospital. The John Hunter Hospital is a University affiliated, Level 1 Trauma Centre. Based on the severely injured trauma admissions (injury severity score (ISS) > 15), it is the busiest trauma service in the state of New South Wales, Australia.

1. Orthopaedic trauma related acute transfusions and transfusion triggers

Background:

Up to three quarters of blunt trauma patients will require at least one orthopaedic intervention. In the absence of significant torso injuries orthopaedic trauma can potentially be the sole contributor to lost blood

volume. The available empirical guidelines that help to estimate potential blood loss are unreferenced and are not validated. Studies reviewing blood component usage in trauma are retrospective and registry-based and fail to identify transfusion triggers.

Transfusion guidelines for trauma patients relate to haemodynamically stable patients after initial resuscitation and haemorrhage control. In the ATLS (Advanced Trauma Life Support) protocol, the recommendation regarding early transfusion (ET) is not exact and is unreferenced. Attempts to verify the validity of physiological parameter thresholds used for classifying the bleeding patient have been unsuccessful.

Material and Methods:

A 12 month prospective observational clinical study was undertaken to identify consecutive trauma admissions, requiring at least one unit of PRBC within 24 hrs of arrival to hospital. The patients were identified prospectively on a daily basis by the trauma fellows and trauma surgeons during the daily ward round.

Patients receiving ET were subdivided into three groups, patients with primarily orthopaedic injuries (musculoskeletal injuries exclusively or mainly explain the blood loss and transfusion requirement), patients where orthopaedic injuries partially contributed to blood product requirement along with torso injuries and patients with no orthopaedic injuries.

Transfusion patterns and triggers were also examined for the same patient group. Five triggers were established prior to the study, and using these triggers the trauma fellow requested and recorded the reason for the first unit of transfusion from the initiating clinician, in real time. The corresponding recorded physiological parameters were collected.

The established triggers were:

1. institutional definition of haemorrhagic shock (systolic blood pressure (SBP) ≤ 90 mmHg and base excess (BE) ≤ -6 mmol/l)
2. expected and ongoing bleeding (prehospital blood loss and/or expected further blood loss intraoperatively due surgery)
3. dropping haemoglobin (Hb) (Hb drop to below 80 g/l or below 100 g/l and 30 g/l drop within 2hrs)
4. low SBP (persistent hypotension on serial measurements < 90 mmHg for at least 30 mins despite fluid replacement)
5. tachycardia (persistent elevated heart rate (HR) on serial measurements > 110 beats/min for at least 30 mins despite fluid replacement)

Collected variables in the first study included:

Age, gender, ISS, mechanism of injury, pre-transfusion haemodynamic parameters (SBP, HR, BE, Hb (prior to the first unit of PRBC transfusion) were collected. Timing of transfusion (from admission to the first unit of PRBC) and place of transfusion (emergency department (ED), operating theatre (OT) or intensive care unit (ICU)) was recorded. The transfusion initiating clinician's specialty and grade was also studied. The volume of the various blood components was recorded, determining the number of units of PRBC, fresh frozen plasma (FFP), cryoprecipitate (CRYO) and platelets (PLT).

Main outcome measures were mortality (within 24hrs and overall), ICU admission, hospital and ICU length of stay (LOS). Emergent (within 24 hrs) surgical procedures were noted.

Results:

A. Orthopaedic injury related transfusions

Nine per cent (91/965) of all major trauma admissions received early transfusion. Seventy per cent (64/91) of these transfused patients had one or more orthopaedic injuries. Ten of these patients had additional bleeding sources identified. The injury mechanism was predominantly blunt (94% (60/64)). The three early transfusion groups (only orthopaedic injuries, orthopaedic and torso injuries and only torso injuries) showed no differences in basic demographics and mortality. The overall mortality amongst patients with orthopaedic injuries was 13% (8/64). Five of the deaths happened within 24 hrs. ICU LOS was significantly higher in the group with no orthopaedic injuries (10±10) vs. patients with only orthopaedic injuries (5±4) contributing to blood loss (p=0.008). Hospital LOS was significantly higher in the orthopaedic injury group (26±19 vs. 16±12) (p=0.023).

Orthopaedic related injuries consumed the majority of acute transfusions with 80% (462/575) of PRBC, 76% (277/357) of FFP, 76% (399/527) of CRYO and 78% (174/222) of PLT. Forty-eight per cent (31/64) of patients required activation of the MTP. Two thirds of the patients had at least 4 units of PRBC within 24 hrs of arrival (42/64). Eighty-four per cent (54/64) of patients required emergent (within 24hrs) orthopaedic intervention, 90 acute procedures in all.

The detailed blood product consumption and transfusion timing in the three separate groups is detailed in Table 1.

Table 1. MTP activation, transfusion timing and acute blood product usage in the three groups (only orthopaedic injuries, orthopaedic and other injuries, no orthopaedic injuries)

Groups	Orthopaedic injuries only (n=54)	Orthopaedic and other injuries (n=10)	No orthopaedic injuries (n=27)	p-value
MTP	50% (27/54)	40% (4/10)	30% (8/27)	0.2201
ONeg PRBC	1.7±2.8	2.8 ±3.0	0.9±1.4	0.093
Overall PRBC	6.6±5.4	10.8 ±11.1*	4.3±5.0*	0.001*
FFP	4.0±4.5	6.3 ±8.1	2.9±4.1	0.174
CRYO	5.5±6.9	10.3 ±14.7	4.7±7.8	0.180
PLT	2.5±4.2	4.2±8.0	1.8±4.3	0.402
1 st unit (hrs)	3.3±4.6	1.8±1.6	5±6	0.155
1 st unit in ED	39% (21/54)	60% (6/10)	41% (11/27)	0.493
1 st unit in OT	57% (31/54)	40% (4/10)	33% (9/27)	0.107
1 st unit in ICU	4% (2/54)*	0%	26% (7/27)*	0.007*

*: significant difference (p<0.05)

Orthopaedic injuries and injury combinations:

Pelvis and acetabulum:

Twenty-five of the patients had a pelvic or acetabular fracture or ligamentous pelvic ring injury (39% (25/64)). Twenty-two had pelvic ring injuries. Nine patients required surgery in the first 24 hrs. Only three of the patients had orthopaedic injuries isolated to the pelvic girdle. The most frequent additional injury combinations were femur fracture (6 patients) or femur and tibia fracture (6 patients). Four of the 25 patients also had a laparotomy. In four of the eight deaths, bleeding due to pelvic ring injury was a contributor. These patients had the highest ISS with a value of 39±22. Seventy-two per cent (18/25) were admitted to the ICU, spending an average of 4±4 days there. These patients used on average 8.1±6.8 units of PRBCs, 5.4±5.3 units of FFP. MTP activation was required in 56% (14/25) and 36% (9/25) of patients had more than 10 units of PRBCs.

Femur fracture:

Twenty-four (37% (24/64)) of the patients had at least one femoral shaft fracture and received early transfusion, two patients having bilateral femur fractures. Twenty-three were treated operatively within 24 hrs. Only 2

of the patients had orthopaedic injuries isolated to the femoral shaft. Five of the femur fractures were open. Patients with a femoral shaft fracture used on average 7.1 ± 6.1 units of PRBCs, 4.4 ± 5.1 units of FFP. MTP activation was required in 58% (14/24).

Tibia fracture:

Twenty patients had a total of 23 tibia fractures, 17 were tibial shaft fractures and 6 periarticular fractures. Nine patients suffered open tibia fractures, with three Gustillo-Andersen 3A, two 3B and four 3C fractures. Only 3 patients had isolated tibia shaft fractures. Ten patients had operative intervention within the first 24hrs.

Additional orthopaedic injuries:

Additional long bone fractures included 14 humerus fractures (nine treated operatively), nine forearm fractures (eight treated operatively) and five ankle fractures. Thirty-five patients had large open wounds requiring surgery. Two patients with pelvic ring injuries developed a large degloving injury, which necessitated surgical management.

Results:

B. Transfusion triggers and patterns

Forty-three per cent (39/91) of ET patients had an activated MTP. Emergent surgery (<24 hrs) was necessary in 86 % (78/91) of patients. Forty seven per cent (37/78) of the patients had surgery primarily for bleeding control, 41 haemostatic procedures in all. Overall mortality was 14% (13/91) with 54% (7/13) having had a MTP activation. Thirty-eight per cent (5/13) of deaths happened within 24hrs, with one exsanguination related death.

Timing and place of transfusion:

ETs start within 2 hrs of arrival in 59% (54/91), with the 92% (36/39) of the MTP activations happening in this timeframe. The timing of the first transfused unit of blood differed in the various locations (ED, OT, ICU). Patients receiving transfusion in ED had a higher ISS, received blood quicker and in larger volumes, having worse physiological parameters (lower SBP, higher HR and lower BE). Detailed data is presented in Table 2.

Table 2. Place timing of first unit of transfusion. Transfusion volume, physiological parameters and transfusion triggers according to place of transfusion.

Place of transfusion	ED	OT	ICU	Total
Number of patients	47	35	9	91
ISS	32 (4-66, IQR:20-43)	18 (4-59, IQR:13-29)	25(9-45, IQR:20-34)	25 (4-66, IQR:16-34)
Time to 1 st unit	0.5 (0.5-4, IQR:0.5-1.5)	3 (1-23, IQR:2-6)	11(0.5-20, IQR:6-17)	2(0.5-23, IQR:0.5-4)
MTP activation	64% (30/47)	23% (8/35)	11% (1/9)	43% (39/91)
PRBC	8 (1-34, IQR:2-10)	3 (1-14, IQR:2-6)	3(1-27, IQR: 2-3)	4(1-34, IQR:2-8)
SBP	85 (45-120, IQR:79-96)	100(74-120, IQR:86-103)	100(71-125, IQR:100-110)	90(45-125, IQR:80-100)
HR	118 (60-163, IQR:87-130)	90(53-130, IQR:80-100)	90(60-145, IQR:70-115)	100(53-163,IQR:80-120)
HB	105 (56-166, IQR: 92-129)	91(50-137, IQR:78-111)	88(76-108, IQR:82-93)	96(50-166, IQR:85-114)
BE	-4.7 (-22.1-2.7, IQR:-8.9--2.2)	-3.7 (-9.1-0.5, IQR:-5.9—2.5)	-2.6(-5.7-2.7, IQR:-4.5—1.5)	-4.2(-22.1-2.7, IQR:-7.2—2.4)
Transfusion triggers				
h. schock	37% (17/47)	14% (5/35)	0%	24% (22/91)
exp. or ong. bleeding	23% (11/47)	40% (14/35)	11% (1/9)	29% (26/91)
dropping Hb	9% (4/47)	40% (14/35)	66% (6/9)	26% (24/91)
low SBP	15% (7/47)	6% (2/35)	0%	10% (9/91)
tachycardia	15% (7/47)	0%	0%	8% (7/91)

Data is presented as median, range and IQR

Transfusion triggers:

The transfusion triggers used to initiate an acute transfusion varied in the different environments. In the ED patients were either in haemorrhagic shock (37%) or had ongoing or expected bleeding (23%). In the OT ongoing or expected bleeding (40%) or a drop in Hb (40%) was the most frequent triggers. In ICU 66% had a dropping Hb triggering the acute transfusion.

Indicating clinician:

Various members of the trauma team were responsible for initiating the first unit of transfusion with varying frequency. The trauma surgeon initiated the first blood transfusion in 34% (31/91), out of those 77% (24/31) had MTP. 31% (28/91) were triggered by the anaesthetist, with 21% (6/28) being MTPs. 19% (17/91) were started by the ED doctor 41% (7/17) being MTPs. The remaining transfusions were ordered by the ICU doctor 12% (11/91) and the surgical team (3/91) with one MTP activation in each group.

Clinicians of different specialties indicated a transfusion using different trigger patterns. Most frequent trigger by specialty: trauma – haemorrhagic shock 45% (14/31), whilst anaesthesia and ICU – dropping Hb 46% (13/28) and 55% (6/11) respectively. ED doctors and general surgeons had an even distribution of triggers.

Blood product usage:

Eighteen patients 20%(18/91) received ≥ 10 units of PRBC; the mortality of this group was 28% (5/18). Fifty patients 55%(50/91) received ≥ 4 units of PRBC within 24 hrs, with 14% (7/50) mortality. The patients attracting MTP activation consumed the majority of blood products used by the trauma service, 83% (118/142) of the ONegative, 72% (413/575) of all PRBC, 83% (295/357) of FFP, 94% (493/527) of CRYO and 95% (210/222) of PLTs. MTP activation allowed early balanced component therapy with an FFP: PRBC ratio of 1:1.4.

Overtransfusion:

Patients were assessed for potential overtransfusion by recording their Hb concentration at ICU admission and at 24 hrs. Fifteen per cent (14/91) had a 24 hr Hb concentration of >110 g/l indicating potential unnecessary transfusion. The 24hr overtransfusion rate was 8% (3/39) in the MTP and 21% (11/52) in the non-MTP group. There were 32 patients 35% (32/91) who only received 1 or 2 units of PRBC. The overtransfusion rate was higher in this low volume transfusion group at 25% (8/32).

In terms of transfusion trigger, overtransfusion rate was highest with low SBP 22% (2/9) or expected and ongoing haemorrhage 19% (5/26) as the trigger.

Discussion:

Our prospective observational study found that musculoskeletal injuries are the main indications for blood product transfusion in the first 24

hrs consuming more than three quarters of all acute trauma related transfusions. Eighty-nine per cent (16/18) of massively transfused (>10 units of PRBC \leq 24 hrs) patients had an orthopaedic injury. Our study provides prospectively collected baseline numbers of early transfusion requirements in orthopaedic trauma.

Understanding why, where and by whom is transfusion initiated in the acute setting might help reduce the amount overall blood component usage. A specific pattern of ET was observed, with 90% initiated within 6 hrs of admission and 90% commencing either in ED or in OT. A single objective trigger cannot be utilised in the ET setting, and Hb concentration was only used as a trigger in one quarter of the cases (23/91). The real-time identified trigger was different amongst the various specialists as they were present at different stages of injury care.

Due to the acute and dynamic nature of traumatic shock, it is difficult to identify 'hard' triggers and standardise transfusion guidelines. The tissue injury and the physiological derangement coupled by pathophysiological inflammatory responses and therapeutic confounders further complicate decision making for acute transfusion. Current guidelines recommend an intensive care and trauma transfusion trigger of 70g/l Hb concentration for patients without comorbidities. As demonstrated by our study, admission Hb concentration is unreliable in trauma, because of the variations in injury patterns, the duration of prehospital time, the delay in intrinsic compensatory fluid transfer from the extracellular space and haemodilution (due to crystalloid resuscitation). Hb concentration in our study averaged >100 g/l, and only if used as a dynamic marker, showing a significant drop was it used as a transfusion indicating parameter.

Our study used five important triggers, all of which relevant to the acute transfusion settings. The triggers were based on relevant parameters or their combinations, and included SBP, HR, BE and the more conventional Hb concentration. Just as important, although not easily quantifiable, is the insight into the severity of injuries, and what procedure combinations are required for their treatment.

The clinical decision making of the different specialists and trainees varied. The trauma surgeon was most likely indicate a transfusion because of haemorrhagic shock, whilst the ED doctors, anaesthetists and ICU doctors initiated blood transfusion mostly on the basis of a single physiological parameter or blood test result.

Our MTP was an integral part of the resuscitative efforts of the first 24 hrs. Activating it allowed for early balanced component therapy.

2. The effect of a massive transfusion protocol on blood component delivery in the first 6 hrs

Background:

In the civilian setting the development of Massive Transfusion Protocols (MTPs) has been central in achieving improved component ratios and frequently improved outcomes compared to historic cohorts. Evidence on MTPs compares outcomes based on the cumulative ratios of blood products administered during the first 24 hours following injury. By 24 hrs, especially among survivors, balanced cumulative values are achieved in most cases, regardless of the initial resuscitation strategy.

Material and Methods:

A retrospective study was undertaken to compare the dynamics of blood component delivery in patients requiring massive transfusion before (pre-MTP) and after the implementation of the MTP. The pre-MTP period was 48 months before January 2005 and the MTP period was 40 months from January 2006. In 2005 an institutional Massive Transfusion Protocol (MTP) (Table 3) was developed and implemented. The ratios PRBC, FFP, PLT and CRYO in each pack were determined in consultation with the trauma service, blood bank and the haematology service. An MTP is triggered by a member of the trauma team when massive transfusion is needed or the anticipated need is ≥ 4 units of PRBC. 4 units of O Negative PRBCs and 4 units of AB positive FFP (thawed) are readily available at all times. The massive transfusion packs 1 and 2 are released in an alternating sequence. After the delivery of the first two massive transfusion packs, continuation and adjuncts (rVIIa) to the massive transfusion are discussed with the on-call haematologists. The 12-month transitional period (development and implementation of MTP) between January 2005 and January 2006 was not considered for this study. Massive transfusion was defined as 10 or more units of PRBCs during the first 24 hours after admission.

Table 3. Sequence of blood products included in consecutive MTP packs.

MTP 1	4 units of PRBC, 4 units of FFP, 10 units of CRYO
MTP 2	4 units of PRBC, 4 units of FFP, 1 unit of Pooled PLT

All trauma patients over the age of 16 years who required greater than or equal to 10 units of PRBCs within 24 hours were included. Patients were identified by blood bank receipts, and cross referenced with the trauma registry. General information collected on each case included demographics, abbreviated injury scale (AIS), injury severity score (ISS), Glasgow Coma Score (GCS) on admission, shock parameters on admission including systolic blood pressure (SBP), pH and base excess, as well as coagulation profile at admission (coagulopathy at admission was defined as PT >13s / APTT >35s). To determine ratios of blood products and the timing of their administration, data on what blood products were released from the blood bank and the time of administration were collected. The overall number of each blood component (PRBC, FFP, CRYO, PLT) was recorded. PRBC transfusions were subdivided into O Negative, O positive or cross-matched PRBCs.

The primary outcome measures were ratios of products (FFP:PRBC, CRYO:PRBC and PLT:PRBC) given at each half hour during the first 24. Secondary outcomes included mortality (within 24 hrs and overall), time of death after admission (for mortality within 24 hrs and overall), the need for surgery within 24 hrs and ICU length of stay.

The blood component ratios (FFP/PRBC, CRYO/PRBC and PLT/PRBC) for each patient were calculated on the cumulative values of their blood components every half hour with the total area under the curve (AUC) estimated using the trapezoidal rule.

Results

The effect of implementing a MTP on early component delivery

During the 88-month study period, 58 patients required 10 or more units of PRBCs during the first 24 hours after admission. Thirty had massive transfusion before the introduction of the MTP during a 48-month period and 28 had massive transfusion during a 44-month period after. The univariate comparisons of demographics, mechanism of injury, injury severity and pattern and physiological parameters are depicted in Table 4. The demographics were not different in regard to age ($p=0.46$) and gender ($p=0.77$). The two groups differed significantly in their respective ISS [Pre-MTP: 36 ± 12 vs. MTP: 42 ± 12 ($p=0.045$)], and AIS head [Pre-MTP: 1.6 ± 2.0 vs. MTP: 2.6 ± 1.8 ($p=0.043$)]. There was no difference in haematology and blood gas results and systolic blood pressure values preceding transfusion. Admission GCS was lower in the MTP group ($p=0.023$).

Table 4. Patient demographics, injury type and severity.

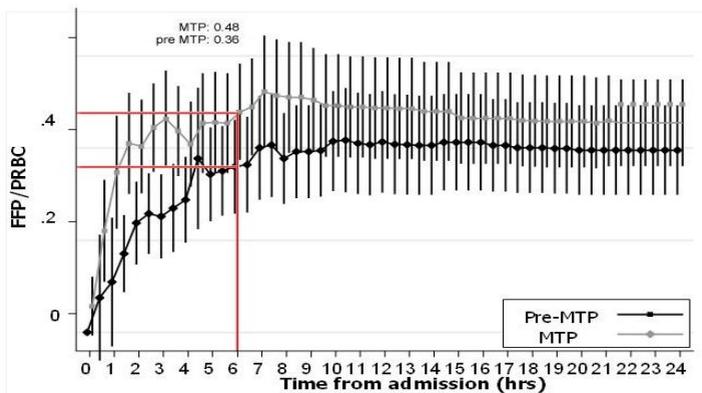
	Pre-MTP (n=30)	MTP (n=28)	p-value
Age (years)	46.0 ± 17.7	42.6 ± 18.8	0.477
Gender (males)	23/30 (77%)	20/28 (71%)	0.659
Injury (%blunt)	28/30 (93%)	25/28 (89%)	0.665
ISS	36 ± 12*	42 ± 12*	0.045*
AIS Head	1.6 ± 1.8*	2.6 ± 2.0*	0.043*
GCS	11 ± 5*	8 ± 5*	0.023*
Surgery ≤ 24 hrs	27/30 (90%)	28/28 (100%)	0.238

*: significant difference (p<0.05)

The area under the curve (AUC) showed that significantly earlier delivery of higher median ratios of FFP/PRBC (p=0.004) occurred in the initial 6 hours, post implementation of the MTP (Fig. 1). Median ratios of FFP/PRBC elevate close to maximum levels within 3 hrs. Similar findings were demonstrated for median CRYO/PRBC ratios (p=0.003) and PLT/PRBC ratios.

Figure 1.

Hourly median FFP / PRBC ratios pre-MTP and after the implementation of the MTP



The number of transfused units of PRBC during the first 24 hours was almost identical in the two groups (Table 5.) There was significantly higher use of 0 Negative (p=0.016) and 0 Positive blood (p=0.003) after the

implementation of the MTP. The use of FFP has not changed ($p=0.416$), but the delivery of CRYO ($p=0.009$) and PLTs improved ($p=0.018$). There was no significant change in the percentage of patients achieving FFP:PRBC ratio of 1:2 or above 37% vs 50% ($p=0.427$).

Table 5. Volume and ratio of blood products in the Pre-MTP and MTP groups.

	Pre-MTP (n=30)	MTP (n=28)	p-value
Overall PRBC	19.6 ± 9.7	19.8 ± 8.5	0.927
0 Negative PRBC	1.6 ± 2.2*	3.4 ± 3.2*	0.016*
0 Positive PRBC	0.8 ± 2.6*	3.8 ± 4.5	0.003*
Cross-matched PRBC	17.2 ± 10.0	12.7 ± 7.0	0.053
FFP	8.1 ± 6.2	9.4 ± 5.8	0.416
Cryoprecipitate	5.4 ± 8.4*	11.6 ± 9.1*	0.009*
PLT	5.8 ± 6.8*	10.1 ± 6.5*	0.018*
FFP:PRBC ratio at 6 hrs	0.36 ± 0.27	0.48 ± 0.27	0.101
FFP:PRBC ratio at 24 hrs	0.40 ± 0.26	0.45 ± 0.24	0.372
% FFP: PRBC ratio of ≥1:2	37% (11/30)	50% (14/28)	0.427

*: significant difference ($p < 0.05$)

Secondary outcomes showed no significant differences. Patients had similar mortality, mortality within 24hrs, need for emergent surgery and ICU length of stay. The univariate regression analysis for the MTP group revealed that each 1 point drop in GCS has an odds ratio of 1.3 for mortality ($p=0.016$), and each 0.1 drop in pH has an odds ratio of 2.7 for mortality ($p=0.020$).

Discussion

The aims of predefined ratios in using a massive transfusion protocol are optimisation of the ratios of blood products used. MTPs have also been associated with decreased overall blood product use, reducing the risk of a secondary hit of resuscitation. There are institutional variances regarding massive transfusion pack contents, their sequence and the optimum ratios of components that are to be achieved. Higher FFP: PRBC ratio is an independent predictor of survival.

The ideal ratio in providing balanced component therapy remains unknown, as demonstrated in a recent review examining the current available evidence supporting the often recommended FFP:PRBC ratio of 1:1. Although the evidence is not compelling, and survival bias still needs to be

addressed, it seems a reasonable strategy to strive for a ratio of FFP:PRBC of at least 1:2. In our study both pre-MTP and MTP 24 hour FFP: PRBC ratios were in this range, with figures of 1:2.5 and 1:2.2 respectively ($p=0.370$). Mean FFP: PRBC ratios at 6 hours were 1:2.8 in the pre-MTP group and 1:2.1 in the MTP group ($p=0.010$).

Our study raises questions about using 24 hour cumulative ratios to describe blood component therapy outcomes. By 24 hrs patients either exsanguinate if haemorrhage control is unsuccessful or if surviving, blood component therapy catches up with PRBC transfusion. We demonstrated significant differences in the delivery of FFP:PRBC, CRYO:PRBC and PLT:PRBC ratios at 6 hours following implementation of the MTP.

CONCLUSIONS

To summarize our hypotheses can be answered as follows:

1. Musculo-skeletal injuries are the leading cause for early transfusion after blunt trauma, and consume more than 75% of all blood components used in the first 24 hrs. These injuries required an average of 7.2 ± 6.6 units of PRBCs and 4.3 ± 5.2 units FFP, with 48% (31/64) requiring MTP activation. The awareness and anticipation of such major blood loss should prompt to utilise the MTP and focus on procedures, which aim haemorrhage control and limit further surgery related blood loss. It is an important message for trauma centres primarily dealing with blunt multi-system trauma that most of the blood transfusions are related to extremity and pelvic injuries rather than thoracic and abdominal trauma.
2. We also clarified the 5 most relevant transfusion triggers in major trauma patients that were used during the first 24 hours. A statically measured haemoglobin concentration is insufficient as a trigger in the trauma setting. Although all 91 ET patients had a definable trigger, arguably only 50% (46/91) (haemorrhagic shock and dropping Hb) could be called objective. Liberal transfusions (expected and/or ongoing bleeding, low SBP and tachycardia) based on vital signs, blood gas results, and experience based anticipated bleeding requires a larger scale investigation to better define their clinical role. The overtransfusion rate is higher with these more liberal transfusions. These triggers might not be evidence based or backed up by latest laboratory science, but they demonstrate how human decision making actually works in these challenging clinical scenarios. These results could serve base for standardising

transfusions during acute resuscitation, similar to how transfusions are regulated in the elective setting or in critical care medicine.

3. The evaluation of our massive transfusion practice revealed that the implementation of MTP results in earlier balanced transfusion. The difference between the FFP/PRBC ratios of the traditional resuscitations methods and an MTP assisted strategy is no longer relevant by 24 hours. Based on our research the efficacy of component therapy delivery is best described by blood component ratios achieved in the first 6 hours. This more relevant time frame should be used in future studies, when evaluating the efficacy of MTP and haemostatic resuscitation with different plasma to red blood cell ratios, which is the current priority focus for many leading trauma institutions and their collaborative efforts.

Peer-reviewed scientific publications related to the thesis:

- I. **Sisak K**, Dewar D, Butcher N, King K, Evans J, Miller M, Yoshino O, Harrigan P, Bendinelli C, Balogh ZJ. The treatment of traumatic shock: recent advances and unresolved questions. **European Journal of Trauma and Emergency Surgery. 2011;37:567-575.**
IF:0.328
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