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

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

Krisztián Sisák, MD

PhD Thesis

Supervisor:
Prof. Zsolt J. Balogh, MD, PhD, FRACS (Ortho)
Director of Trauma Services, Hunter New England Area Health Service
Discipline Head of Traumatology, University of Newcastle

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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.**

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II. **Sisak K**, Soeyland K, McLeod , Jansen M, Enninghorst N, Martin A, Balogh ZJ. Massive transfusion in trauma – blood product ratios should be measured at 6 hours. **ANZ J of Surgery. 2012;82:161-7.**

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III. **Sisak K**, Manolis M, Hardy BM, Enninghorst N, Bendinelli C, Balogh ZJ. Acute transfusion practice during trauma resuscitation: Who, when, where and why? **Injury. 2012 Aug 30. [Epub ahead of print].**

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IV. **Sisak K**, Hardy BM, Manolis M Enninghorst N, Balogh ZJ. Epidemiology of acute transfusions in major orthopaedic trauma. **J Orthop Trauma. Accepted 2012 Nov 9.**

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List of abbreviations

APTT	Activated Partial Thromboplastin Time
ATLS	Advanced Trauma Life Support
BE	Base Excess
CI	Confidence Interval
CRYO	Cryoprecipitate
ED	Emergency Department
ET	Early Transfusion (within 24hrs)
FFP	Fresh Frozen Plasma
GCS	Glasgow Coma Score
HB	Haemoglobin Concentration
HR	Heart Rate
ICU	Intensive Care Unit
IQR	Inter-quartile Range
ISS	Injury Severity Score
LISS	Less Invasive Stabilization System
LOS	Length of Stay
MOF	Multiple Organ Failure
MTP	Massive Transfusion Protocol
OT	Operating Theatre
ORIF	Open Reduction Internal Fixation
PLT	Platelets (Pooled)
PT	Prothrombin Time
PRBC	Packed Red Blood Cells
SD	Standard Deviation
SI	Sacroiliac (screw)
SIRS	Systemic Inflammatory Response Syndrome
SBP	Systolic Blood Pressure

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Introduction

Traumatic shock is the result of severe tissue injury and reduced tissue perfusion due to haemorrhage. Exsanguination after trauma remains the leading cause of potentially preventable mortality[1,2]. Blunt injury dominates civilian trauma, often with multiple concomitant bleeding sites being responsible for overall blood loss. Some of these bleeding sources are due to musculoskeletal injuries, as these are present in the majority of the injured. In addition orthopaedic trauma surgery is required in more than 70% of trauma patients potentially adding to prehospital blood loss[3].

Whilst achieving timely bleeding control remains the key to the successful treatment of traumatic shock, without adequate trauma resuscitation, traumatic coagulopathy might quickly ensue. Preventing the harmful inflammatory response is also a key aspect of resuscitative efforts. The way that lost volume is replaced has significantly evolved during the last decade. The application of the damage control concept to resuscitation[4,5] has changed the way volume is replenished, by shifting the emphasis from uncontrolled volume replacement, to preventing the escalation of shock and coagulopathy and achieving definitive haemostasis. This concept of haemostatic resuscitation uses less crystalloid, thus reducing the dilution of clotting factors.

Haemorrhage and resuscitation both induce cellular changes potentially resulting in dysregulated immune responses and harmful systemic effects. Both the initial proinflammatory burst and the following recovery period have effects on the microcirculatory level. Although, patients' response to trauma and their potential for restoring the homeostasis are varied, during treatment minimising secondary injury is the key.

Recent practices focus on early administration of blood components and the permission of some hypotension, whilst bleeding control is achieved. Although there is extensive research ongoing, currently there is no haemoglobin-based oxygen carrier (HBOC) that has been approved and licensed for use in humans. The backbone of more restrictive resuscitative efforts remain the transfusion of packed red blood cells (PRBC), with approximately 8% of trauma patients receiving at least one unit of PRBC in the first 24 hrs[6]. Blood is an expensive and finite resource and PRBC transfusion is an independent risk factor for systemic inflammatory response syndrome (SIRS)[7], ICU admission, increased ICU length of stay, infectious complications[8,9], multiple organ failure (MOF)[10] and death. PRBC transfusion has predictable and reproducible immunomodulatory effects. Stored, older PRBC

units have increased proinflammatory affects because of a higher level of mediators due to lysis. Currently, some trauma centres use only PRBC units of less than 14 days for polytrauma patients. A liberal transfusion policy can introduce further risk to the already compromised patient.

Fresh whole blood has been successfully used in the military setting[11]. It contains all required blood components including, active red cells, platelets, stable and labile coagulation factors and plasma proteins. 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 provide a ratio resembling that of whole blood[12] 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[13]. Although the exact content of massive transfusion packs is debated, and varies in different institutions, their benefit in reducing bleeding related mortality has been demonstrated[14]. 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 24hr cumulative ratios, by patients surviving eventually receiving higher component ratios contrary to lower ratios in non-survivors. Recent evidence suggest that 6 hr ratios of blood components might be more predictive of outcomes than ratios at 24 hrs[15].

The exact circumstances of why, where and how PRBC transfusion is first initiated is difficult to extrapolate from registry based retrospective studies[5,16]. Widely accepted guidelines control transfusion triggers in critical care[17], 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 various injuries contribute to overall blood loss in blunt trauma. Orthopaedic injuries are the most frequent injuries, however their contribution to overall blood loss is largely unknown and 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. Whilst transfusion triggers are well established in intensive care and elective transfusion practice, only empirical guidelines exist in acute transfusions in trauma.
- Whilst, MTP driven resuscitation allows early delivery of blood components other than PRBCs to the bleeding patient, the available retrospective studies use 24 hr cumulative ratios of the various components to describe achieved ratios. The changes that occur in the delivery 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, verified by the Royal Australasian College of Surgeons in Australia. Based on the severely injured trauma admissions (injury severity score (ISS) 15 or above), it is the busiest (yearly more than 400 patients with ISS 15 or more) trauma service in the state of New South Wales, Australia.

1. Orthopaedic trauma related acute transfusions and transfusion triggers

Background:

Musculoskeletal injuries are the most common following blunt trauma. Up to three quarters of blunt trauma patients will require at least one orthopaedic intervention[3]. These often high-energy injuries and the subsequent procedures that are performed to treat them, all contribute to overall blood loss. 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 estimate potential blood loss are unreferenced and are not validated[18].

The circumstances of the initiation of early blood component replacement in trauma are unique to the patient and the injury. Haemorrhage in trauma largely differs from bleeding in the elective setting, as it occurs before fluid replacement. Blunt trauma can produce multiple bleeding sites, some of which are not immediately obvious. Extrapolating the indication for transfusion from elective patients to trauma scenarios is rather speculative and potentially misleading. Studies reviewing blood component usage in trauma are retrospective and registry based and fail to identify transfusion triggers[5,15].

Transfusion guidelines for trauma patients relate to haemodynamically stable patients in intensive care after initial resuscitation and haemorrhage control[19]. The ATLS (Advanced Trauma Life Support) system classifies hypovolaemic shock[20] and offers a widely used and often quoted guide for stratifying the bleeding patient into one of four groups. 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 unsuccesful[21,22]. Only empirical guidelines exist for ET in trauma.

We hypothesised that patients with predominantly orthopaedic injuries do regularly require acute transfusion and these injuries are a major contributors to overall blood product usage.

Our second hypothesis was that ET is indicated consistently on objective laboratory parameters.

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 24hrs 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.

To determine the influence of orthopaedic injuries on overall blood requirement, patients receiving ET were subdivided into three groups, patients with primarily orthopaedic injuries (where 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.

Secondly transfusion patterns and transfusion triggers were also examined for the same patient group. Five triggers were established prior to initiating the investigations. The actual trigger was identified real-time by the trauma fellow (using the established triggers if possible) by requesting and recording the reason for ordering first unit of transfusion from the initiating clinician. 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 to the need for time consuming and/or multiple procedures)
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).

ii. Other triggers identified during the study which could not be classified into the five groups above included low Hb with head injury (Hb below 100 g/l and severe traumatic brain injury), low BE, coagulopathy and hypovolaemia.

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. In addition, the activation of the MTP was recorded. 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 (haemostatic procedures and all other operations).

To examine for possible overtransfusion, Hb on admission to the ICU and at 24 hrs was also collected. Different Hb concentrations have been advocated in various patient populations[23], in our trauma population overtransfusion was defined as an Hb of ≥110g/l at 24hrs after admission. Coagulation parameters were checked for evidence of acute traumatic coagulopathy (defined as prothrombin time (PT)>13seconds - indicating the worst value within 24hrs).

For the orthopaedic injury related transfusion study, data are presented as mean ± Standard Deviation (SD) or percentages. Statistical analysis was performed using one way ANOVA with Tukey's post-hoc test for parametric continuous variables and Chi-squared test for categorical variables. For the transfusion trigger study, data are presented as median (range and interquartile range (IQR)) or percentages. Statistical analysis was performed using the Student's t-test for parametric continuous variables and Chi-squared test for categorical variables. Statistically significant difference was determined at $p<0.05$.

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 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. Causes of death included three patients with severe traumatic brain injury, three with a combination of head injury and pelvic ring injury with or without other concomitant orthopaedic injuries, one patient exsanguinated due to orthopaedic and pelvic injuries and one patient died due to sepsis. ICU LOS was significantly higher in the group with no orthopaedic injuries vs. patients with only orthopaedic injuries contributing to blood loss (p=0.008). Hospital LOS was significantly higher in the orthopaedic injury group (p=0.023). Detailed data is shown in Table 1.

Table 1. Basic demographics and outcome measures in early transfusion patients 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
Age (years)	40±21	48±20	46±23	0.355
ISS	28±15	28±18	23±13	0.342
Mortality	13% (7/54)	10% (1/10)	19% (5/27)	0.824
ICU LOS (days)	5±4*	7±7	10±10*	0.008*
LOS (days)	26±19*	17±13	16±12*	0.027*

ISS: injury severity score
ICU: intensive care unit
ICU LOS: intensive care unit length of stay (for ICU admitted patients)
LOS: length of stay
*: significant difference ($p<0.05$)

The percentage of orthopaedic related blood loss was calculated by, comparing all blood component usage due to orthopaedic injuries and all acute transfusions. Patients with musculo-skeletal injuries consumed the majority of acute transfusions with 80% (462/575) of

PRBC, 76% (277/357) of FFP, 76% (399/527) CRYO and 78% (174/222) of PLTs. Forty-eight per cent (31/64) of patients required activation of the MTP. Two thirds of patients had at least 4 units of PRBC within 24 hrs of arrival (42/64).

The detailed blood product consumption and transfusion timing in the three separate groups is detailed in Table 2. The ten patients with both orthopaedic and torso injuries required the most acute transfusions. These ten patients required significantly more PRBC than patients without any orthopaedic injuries (p=0.001).

Table 2. 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 activation	50% (27/54)	40% (4/10)	30% (8/27)	0.2201
ONegative 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
Time to first unit (hrs)	3.3±4.6	1.8±1.6	5±6	0.155
1st unit in ED	39% (21/54)	60% (6/10)	41% (11/27)	0.493
1st unit in OT	57% (31/54)	40% (4/10)	33% (9/27)	0.107
1st unit in ICU	4% (2/54)	0%	26% (7/27)	0.007*

MTP: Massive transfusion protocol
PRBC: Packed red blood cell
FFP: Fresh frozen plasma
CRYO: Cryoprecipitate
PLT: Platelet
ED: Emergency Department
OT: Operation Theatre
ICU: Intensive Care Unit
*: significant difference ($p<0.05$)

Emergency orthopaedic operations:

Eighty-four per cent (54/64) of patients required emergent (within 24hrs) orthopaedic intervention, with 41% (22/54) having multiple early procedures, 90 acute procedures in all. The procedures are detailed in Table 3.

Orthopaedic injuries and injury combinations:

Pelvis and acetabulum:

Twenty-five of the patients had a pelvic or acetabular fracture or ligamentous pelvic ring injury injury (39% (25/64)). Twenty-two had pelvic ring injuries. 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 (50%), 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 and 7.8±8.6 units of CRYO. MTP activation was required in 56% (14/25) and 36% (9/25) of patients had more than 10 units of PRBCs.

Table 3. Acute orthopaedic procedures requiring early transfusion

Region of injury	Procedure	
Pelvic ring injury	- pubic plate ± SI screw	4
	- external fixateur	2
	- spinopelvic dissociation	1
	- iliac wing fracture	2
Femoral shaft fracture	- intramedullary nailing	14
	- external fixateur	6
	- LISS plate	3
Tibial shaft fracture	- external fixateur	3
	- intramedullary nailing	6
	- ORIF	1
ORIF long bones	- (humerus, forearm, ankle)	21
External fixateur (not tibia or femur)	- (spanning, wrist)	5
Amputation		5
Wound management in theatre		14
	Total	90

SI: sacroiliac screw
LISS: Less Invasive Stabilization System
ORIF: Open Reduction Internal Fixation

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. 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 and 6.3±7.7 units of CRYO. MTP activation was required in 58% (14/24).

Tibia fracture:

Twenty patients had a total of 23 tibia fractures, 17 tibial shaft fractures, 5 tibial plateau fractures and one pilon fracture. Nine of the 20 patients suffered open tibia fractures, with three Gustillo-Andersen 3A, two 3B and four 3C fractures. Two of the patients died before orthopaedic intervention. Only 3 patients had isolated tibia shaft fractures, two with open fractures with vascular injuries and one resulting in an amputation.

Additional orthopaedic injuries:

Additional orthopaedic long bone fractures included 14 humerus fractures (nine of which required operative intervention), nine forearm fractures (eight treated operatively) and five ankle fractures. Thirty-five patients had large open wounds requiring surgery, usually as part of their initial orthopaedic management. In fourteen patients wound management was the only orthopaedic intervention in the first 24 hrs. Two patients with pelvic ring injuries developed a large degloving injury, which necessitated surgical management.

Results:

B. Transfusion triggers and patterns

Ninety one patients received at least one unit of PRBC within the first 24 hrs of admission. Forty-three per cent (39/91) of these patients had an activated MTP. Emergent surgery 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). The pre-transfusion Hb concentration was higher in ED.

***Transfusion triggers*:**

Frequent transfusion triggers according to the place of first unit of transfusion are shown in Table 4. 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 an acute transfusion was indicated because of ongoing or expected bleeding (40%) or a drop in Hb (40%). In the ICU 66% had a dropping Hb which triggered the acute transfusion. Detailed data, with haemodynamic parameters is presented in Table 4.

***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), 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 or more units of PRBC within 24 hrs, with a 14% (7/50) mortality in this group.

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. 15% (4/27) of coagulopathic patients received rVIIa during their resuscitation. MTP activation allowed early balanced component therapy with an FFP: PRBC ratio of 1:1.4.

Table 4. 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 1st 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)
Transfusion volume (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)

ED: Emergency department
OT: Operating theatre
ICU: Intensive care unit
PRBC: Packed red blood cells
SBP: Systolic blood pressure
HR: Heart rate (beats/min)
Hb: haemoglobin concentration (g/l) from relevant blood gas analysis
BE: base excess (mmol/l) from relevant blood gas analysis
h.schock: haemorrhagic shock
exp. or ong. bleeding: expected or ongoing bleeding

Data is presented as median, range and IQR

***Overtransfusion*:**

Patients were assessed for potential overtransfusion by recording their Hb concentrarion at ICU admission and at 24 hrs. Fifteen per cent (14/91) had a 24 hr Hb concentrarion of >110 g/l indicating potential unnecessary transfusion. There was no significant difference in pre-transfusion Hb concentration between patients receiving MTP activations and transfusions without MTP. However patients with MTP activation had a significantly lower ICU admission Hb (p=0.005). The 24hr overtransfusion rate was 8% (3/39) in the MTP and 21% (11/52) in the noMTP group. Thre 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. Other triggers had a lower but detectable rate of overtransfusion with tachycardia 14% (1/7), haemorrhagic shock 14% (3/22) and decreasing Hb 13% (3/23) having very similar rates. The differences between overtransfusion rates did not however reach significance.

Discussion:

Quality of life after major trauma is often determined by the functional outcome of orthopaedic injures[24,25]. The systemic inflammatory response to trauma and subsequent secondary factors such as timing and nature of intervention as well as resuscitation strategies all influence secondary organ injury and thus outcome.

Optimising resuscitative efforts in orthopaedic trauma requires accurate estimation of blood loss. The understanding of the circumstances of blood loss and blood volume replacement in orthopaedics has much improved regarding elective procedures[26] and fragility fractures[27]. Continuous fine tuning is taking place to decrease the substantial variability in transfusion practice, thus reducing costs and potential risks[28]. In trauma, current literature regarding acute transfusion is concentrated on abdominal and thoracic trauma. Data regarding early transfusion in extremity trauma focuses on the military experience, with a large number of severely injured soldiers who undergo lifesaving surgery after predominantly blast injuries[29] or on the other hand patients with isolated orthopaedic injuries, such as an isolated femur fractures[30].

Our prospective observational study found that musculoskeletal injuries are the main indications for blood product transfusion in the first 24 hrs with 70% of ET patients having

orthopaedic injuries. These patients consumed more than three quarters of all acute trauma related transfusions. Most patients had orthopaedic injury combinations, fractures and/or soft tissue injuries. Acutely transfused orthopaedic trauma patients almost always require orthopaedic intervention (92% overall). More than 80% of patients had emergent (within 24hrs) orthopaedic surgery, 40% having multiple early operations. Half of the patients required MTP activation, and one quarter require 10 or more units of PRBC. Patients with orthopaedic injuries spent less time in the ICU than patients with no orthopaedic injuries, but had a significantly longer overall length of stay. In early transfusion, from orthopaedic trauma, on average 7.2±6.6 units of PRBC and 4.3±5.2 units of FFP were needed.

Accurate prediction of the impact of multiple orthopaedic injuries (fractures, soft tissue injuries (Morel-Lavallee lesions), crush injuries, open wounds, major vessel injuries) on total pre-hospital blood loss requires senior orthopaedic input at the early stage of resuscitation. Considering the injury patterns and the extent, sequence and complexity of procedures required to treat them can help anticipate further blood loss in the operating theatre[31-33].

Isolated orthopaedic injuries other than femur fractures and pelvic ring injuries are unlikely to require an acute transfusion. Orthopaedic injury combinations can frequently require blood volume replacement. Sabboubeh et al.[34] describe the outcome after multiple intramedullary nailings in 27 patients, describing a transfusion requirement of 100% with 93% transfused in theatre. Although they mention that almost two thirds had non-orthopaedic injuries, the nature and impact of these injuries on the transfusion requirement of 5.3 units of PRBC is unknown. In our study musculoskeletal injuries were rarely isolated, and the most frequent pelvic fractures were often combined with femoral shaft fractures or other long bone injuries.

According to Como et al.[5] patients requiring massive transfusion (>10 units of PRBC within 24 hrs), have multiple injuries, with 70% having pelvic and/or extremity injuries but they do not analyse these injuries further. In our study 89% (16/18) of massively transfused (>10 units of PRBC within 24 hrs) patients had an orthopaedic injury, and from those who survived 24 hrs, only one did not require an orthopaedic intervention.

For pelvic ring injuries we found a 38% (25/65) acute blood transfusion rate, similar to that of the literature[35]. Starr et al.[36] found an average early transfusion requirement of 3 units of PRBC. In our study pelvic ring injury patients were amongst the highest consumers of blood products with more than 8 units, perhaps because of the high ratio of associated injuries.

Interpreting individual injury combinations and predicting transfusion requirement is challenging. 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. Our prospective study described the transfusion triggers, place and timing of blood component therapy in acute transfusion patients. A specific pattern of ET was observed, with 90% initiated within 6 hrs of admission and 90% commencing either in ED or in OT. Patients who received blood already in ED represent a more seriously injured group, with low SBP, elevated HR and a low BE, but a close to normal Hb concentration. 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), using multiple measurements and dynamic Hb changes over time. The real-time identified trigger was different amongst the various specialists as they were present at different stages of injury care.

There is limited literature available on civilian transfusion practice in trauma, investigating early blood product use in the care of the injured. Como et al.[5] set out to find categorical associations between demographic and transfusion data in a retrospective registry based study. They describe transfusion volume and injury severity. In contrast our study investigated a prospective cohort, with real-time identification of the reason, place, and timing of transfusion.

There is some data available regarding timing of transfusion. Kashuk et al.[37] have found that amongst massively transfused patients, more than 80% of PRBC is delivered within 6 hours of injury. Our study prospectively examined transfusion timing at half hourly intervals, showing that 80% of all ET are actually initiated within 4 hrs.

The place where the first unit was indicated separated patients requiring acute transfusion into distinct groups, with individual decision making patterns for the various patients. 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. To guide transfusion, numerous guidelines have been published, reviewing current evidence regarding PRBC transfusion[16,19]. In spite of the recommendations of considering all aspects of the patient’s physiology, no objective trigger is identified other than Hb concentration, generally 70g/l 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 extacellular space and haemodilution (due to crystalloid resuscitation). Despite being the universal trigger in the literature, 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. Even patients in haemorrhagic shock or permanent hypotension were found to have a Hb concentration >100g/l.

Available guidelines are derived almost exclusively from evidence obtained during elective surgery and the ICU setting, describing non-bleeding or already resuscitated patients. Hypothetical scenarios[38] and retrospective questionnaires[39] have been used to identify triggers for PRBC, FFP, PLT and albumin, finding great variance between the decision making of clinicians of different training levels, and also between surgeons and non-surgeons. Several parameters have been identified, that might be useful in predicting the necessity for transfusion, although the different thresholds studied, makes comparison impossible[40,41]. Few clinical studies with modest patient numbers undergoing elective procedures investigate real time identification of triggers[42]. 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[43], HR[44], BE[45] 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. Estimating previous or ongoing blood loss is difficult in the trauma setting, although it has been found to be a good predictor of transfusion requirement in elective orthopaedic surgery[46].

The clinical decision making of the different specialists and trainees varied. This is partially due to different team members being present at the various stages of treatment, with perhaps the various surgeons (general /orthopaedic /neurosurgical /vascular /cardiothoracic) and trauma surgeons/fellows being the only ones present at all stages of treatment. 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. Individual parameters (SBP, HR, Hb) as used in the elective and critical care setting, are insufficient in indicating for a transfusion as standalone triggers.

Arguably the used transfusion triggers can seem arbitrary, as they are not usually based on one specific number, however the decision to transfuse rarely can be made on the basis of a single physiologic parameter or laboratory result; clinical judgement continues to

play a vital role in decision making[47]. Ball et al.[48] examined the appropriateness of uncrossmatched blood transfusion in the ED setting, and deemed a transfusion appropriate if the patient was a non-responder to 2 litres of crystalloid, required emergency surgery, had solid organ or vascular injury associated with blood loss or further blood product transfusion was anticipated. They, in their retrospective study found the above triggers useful and only had head and spinal injuries prompting uncrossmatched blood transfusion outside these parameters. However, they only examined one type of blood component, a sole location and did not use physiological parameters as criteria.

Care of the bleeding patient is a dynamic process. The individual decision to transfuse is mostly precluded by multidisciplinary discussion, taking multiple factors into account (mechanism of injury, injury combinations, haemodynamic status, the need for early surgery, estimated potential blood loss (both prehospital and intraoperative)). Clinical experience, communication between team members and anticipation are crucial. Although a specific trigger can be designated in most cases, the overall clinical picture is just as important in indicating the need for blood components.

Our MTP was an integral part of the resuscitative efforts of the first 24 hrs. Activating it allowed for early balanced component therapy. Forty eight per cent (31/64) of the patients with orthopaedic injuries and 43% (39/91) of all acute transfusion patients had the MTP activated.

Haemorrhagic shock and resuscitation is a dynamic, time-critical process. The assessment of the effectiveness of resuscitation requires knowledge of the dynamics of blood component delivery.

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

Background:

Haemorrhagic shock accounts for 30 to 40% of all trauma deaths[49]. Timely haemorrhage control and judicious resuscitation are the key principles of haemorrhagic shock management.

Recently, numerous studies attempted to show the superiority of liberal component therapy with component ratios that approximate whole blood[50-53]. 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. This is due to the retrospective nature of the studies, which define massive transfusion as equal or more than 10 units of PRBC within 24hrs. By 24 hrs, especially among survivors, balanced cumulative values are achieved in most cases, regardless of the initial resuscitation strategy. The amount of blood components other than PRBC, eventually catch up to the amount of red blood cell transfusions. Current published results are also affected by survival bias, given that the majority of trauma deaths due to haemorrhage occur early following injury and most potentially preventable haemorrhagic deaths happen within the first 6 hours[14].

The aim of this study was to examine the effect of implementing a MTP on the timeliness of the delivery of balanced blood component therapy. We hypothesised that implementation of an MTP will significantly accelerate the process of providing an improved volume of fresh frozen plasma (FFP), cryoprecipitate (CRYO) and platelets (PLT) to complement PRBC transfusion, especially within the first 6 hrs of resuscitation.

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 5.) 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 equals to or exceeds 4 units of PRBC. 4 units of 0 Negative PRBCs and 4 units of AB positive FFP (thawed) are readily available at all times. The massive transfusion packs 1 and 2 (Table 5.) are released in an alternating sequence. Pooled platelets are equivalent to 6 units of platelets. 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 to be coherent with most of the published literature[54].

Table 5. Sequence of blood products included in consecutive MTP packs.

Massive Transfusion Pack 1	4 units of Packed Red Blood Cells 4 units of Fresh Frozen Plasma 10 units of Cryoprecipitate
Massive Transfusion Pack 2	4 units of Packed Red Blood Cells 4 units of Fresh Frozen Plasma 1 unit of Pooled Platelets

MTP: Massive transfusion protocol

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, where MTP patients were prospectively flagged. 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 prothrombin time (PT) of more than 13s or activated partial thromboplastin time (APTT) of more than 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 the administration were collected. The overall number of each blood component (PRBC, FFP, CRYO, PLT) was recorded. PRBC transfusions were further subdivided into 0 Negative, 0 Positive or cross-matched PRBCs.

The primary outcome measures were ratios of products given at each half hour during the first 24 hours and the time between administrations of components. The various blood product ratios (FFP:PRBC, CRYO:PRBC and PLT:PRBC) were calculated for every half hour in both groups and were graphically demonstrated, to illustrate blood product delivery dynamics. The 6 hr timeframe was used to highlight the role of MTP on early haemostatic resuscitation[13,14].

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[55]. Statistical analysis was performed by Student t-test or exact test for continuous variables and Chi-

squared test for dichotomous variables. For the cumulative blood product ratios, the AUC was compared using the Mann-Whitney test. A univariate regression analysis was performed for mortality as an outcome; adjusted to demographics, ISS, AIS, shock parameters, presence of coagulopathy and GCS. Data are presented as mean ± Standard Deviation (SD) or percentages. For blood and blood product ratios, median and range are presented.

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. Of these, 30 had massive transfusion before the introduction of the MTP during the 48-month period between January 2001 to December 2004 and 28 had massive transfusion during the 44-month period from January 2006 to April 2009.

The univariate comparisons of demographics, mechanism of injury, injury severity and pattern and physiological parameters are depicted in Table 6. 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)]. The mechanism of injury was predominantly blunt in both groups.

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 6).

Table 6. 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 type (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 within 24 hrs	27/30 (90%)	28/28 (100%)	0.238

ISS: Injury Severity Score
AIS: Abbreviated Injury Scale
Pre-MTP: before the implementation of the massive transfusion protocol
MTP: after the implementation of the massive transfusion protocol.

GCS: Glasgow Coma Score
*: 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) (Fig.2) and median PLT/PRBC (p=0.0002) ratios (Fig. 3).

Although the number of transfused unites of PRBC during the first 24 hours was almost identical in the two groups (Table 7.) [Pre-MTP: 19.6±9.7 vs. MTP: 19.8±8.5 (p=0.927.)], there was significantly higher use of 0 Negative [Pre-MTP: 1.6±2.2 vs. MTP: 3.4±3.2 (p=0.016)] and 0 Positive blood [Pre-MTP:0.8±2.6 vs. MTP: 3.8±4.5 (p=0.003)] after the implementation of the MTP. Although the use of FFP has not changed [Pre-MTP:8.1±6.2 vs. MTP:9.4 ±5.8 (p=0.416)], the delivery of CRYO [Pre-MTP:5.4 ±8.4 vs. MTP:11.6 ±9.1 (p=0.009)] and PLTs improved [Pre-MTP:5.8±6.8 vs. MTP: 10.1±6.5 (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).

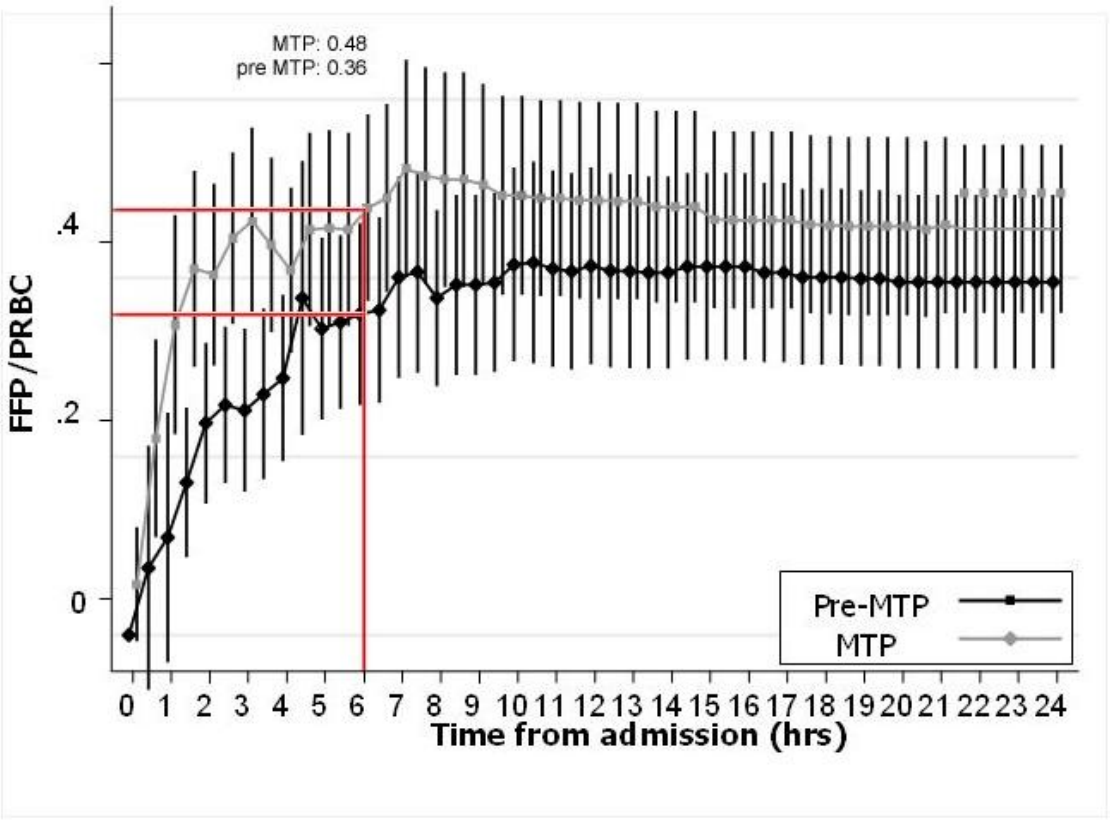
Table 7. Volume and ratio of blood products in the Pre-MTP and MTP groups.

	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±26	0.45±24	0.372
% with FFP: PRBC ratio of ≥1:2	37% (11/30)	50% (14/28)	0.427

MTP: Massive transfusion protocol
PRBC: Packed red blood cells
FFP: Fresh frozen plasma
PLT: Platelets
*: significant difference ($p<0.05$)

Figure 1.

Median FFP / PRBC pre-MTP and MTP in the first 6 and first 24 hours (95% Confidence Interval)



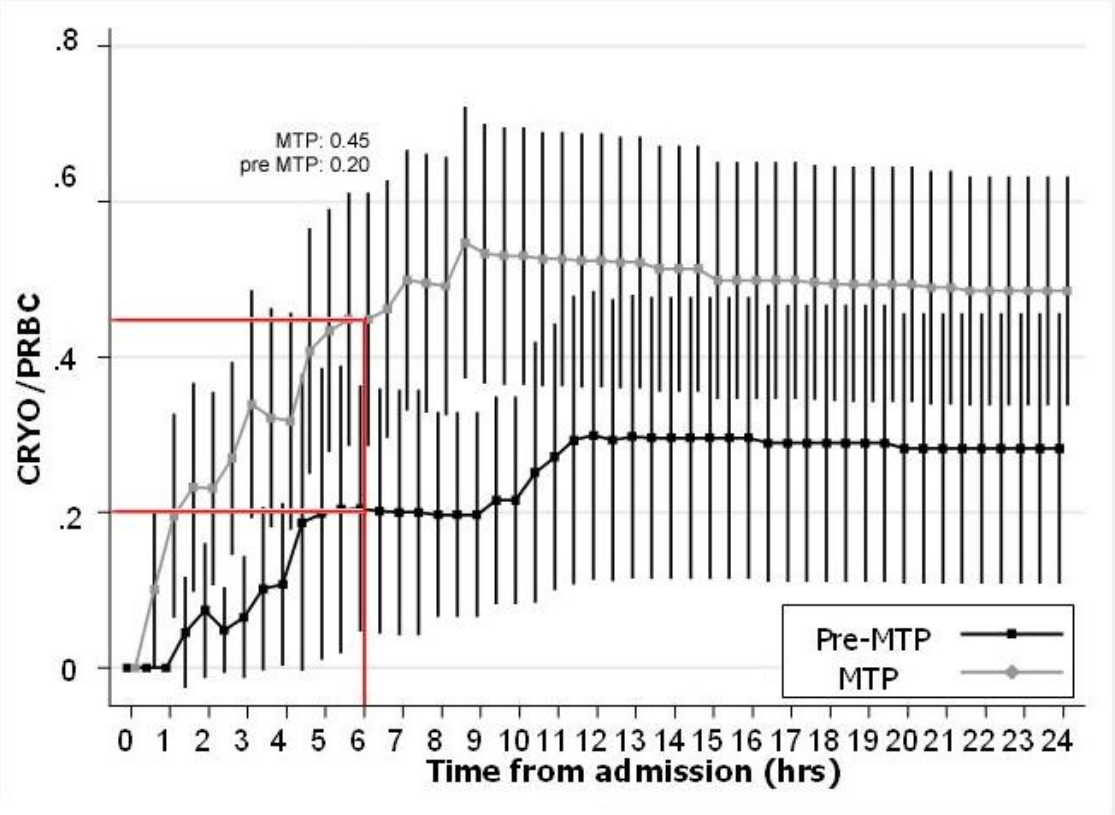
FFP/PRBC AUC at 6 and 24 hours

Time		Pre-MTP (n=30)	MTP (n=28)	P
6hrs	Median (range)	1.39 (0.00, 4.83)	2.14 (0.00, 4.19)	**0.004**
24hrs	Median (range)	8.88 (0.00, 20.45)	10.09 (0.00, 24.72)	0.26

FFP: Fresh frozen plasma
PRBC: Packed red blood cells
MTP: Massive transfusion protocol

Figure 2.

Median CRYO / PRBC pre-MTP and MTP in the first 6 and first 24 hours (95% Confidence Interval)



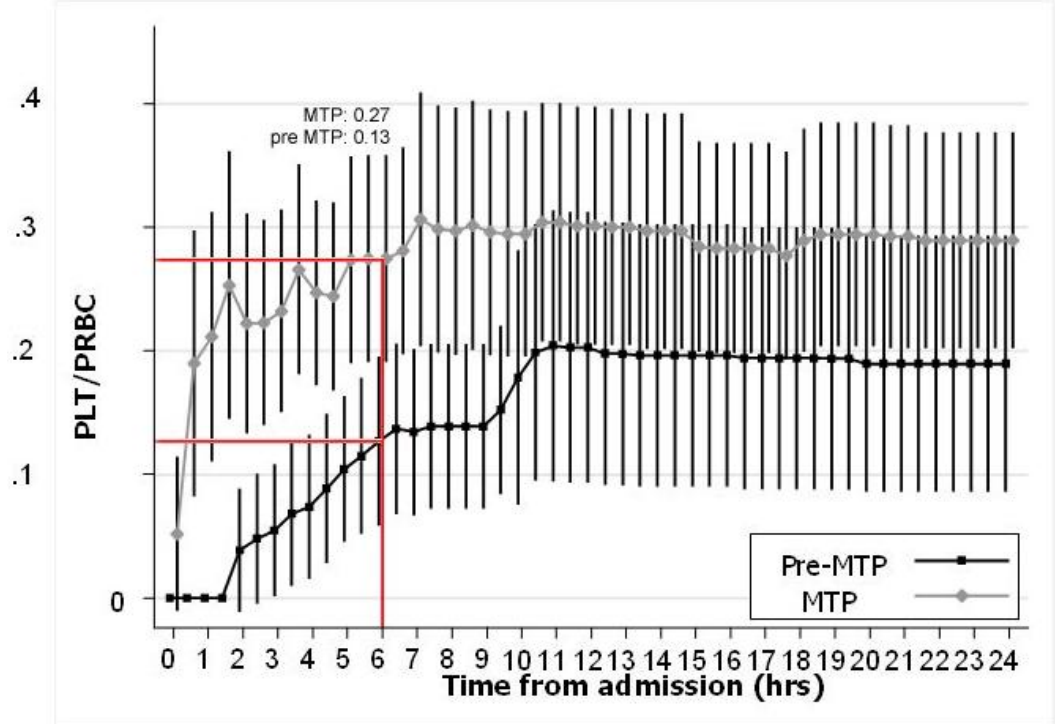
CRYO/PRBC AUC at 6 and 24 hours

Time		Pre-MTP (n=30)	MTP (n=28)	P
6hrs	Median (range)	0.00 (0.00, 3.14)	1.42 (0.00, 3.93)	**0.003**
24hrs	Median (range)	0.00 (0.00, 35.71)	12.64 (0.00, 23.34)	**0.01**

CRYO: Cryoprecipitate
PRBC: Packed red blood cells
MTP: Massive transfusion protocol

Figure 3.

Median PLT / PRBC pre-MTP and MTP in the first 6 and first 24 hours (95% Confidence Interval)



PLT/PRBC AUC at 6 and 24 hours

Time		Pre-MTP (n=30)	MTP (n=28)	P
6hrs	Median (range)	0.00 (0.00, 2.50)	1.31 (0.00, 3.20)	**0.0002**
24hrs	Median (range)	2.81 (0.00, 24.29)	6.51 (0.00, 18.68)	**0.0075**

PLT: Platelets
PRBC: Packed red blood cells
MTP: Massive transfusion protocol

Secondary outcomes are presented in Table 8. Pre-MTP and MTP patients had similar mortality, mortality within 24hrs and need for emergent surgery. ICU length of stay was not statistically different. . None of the outcome measures showed significant differences. The univariate regression analysis for the MTP group revealed that each 1 unit 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) (Table 8.).

Table 8. Secondary outcomes.

	Pre-MTP (n=30)	MTP (n=28)	p-value
Mortality	12/30 (40%)	13/28 (46%)	0.791
Mortality within 24 hrs	9/12 (75%)	10/13 (77%)	1.000
Time of early deaths (hrs)	5.4 ± 4.7	5.3 ± 2.9	0.937
Time of late deaths (days)	25.0 ± 33.3	12.3 ± 8.9	0.558
ICU LOS	5.8 ± 7.8	9.6 ± 14.4	0.243

Pre-MTP: before the implementation of the massive transfusion protocol.
MTP: after the implementation of the massive transfusion protocol.
Time of early deaths (hrs): time from admission to death for patients dying within 24 hrs.
Time of late deaths (days):): time from admission to death for patients dying after the first 24 hrs.
ICU LOS: Intensive car unit length of stay

Discussion

The aims of predefined ratios in using a massive transfusion protocol are optimisation of the ratios of blood products used[12], decreasing the time to receiving appropriate products[13], improvement in overall logistics, and decrease in errors of blood product administration[56], leading to a potential improvement in outcome in the bleeding patient[13]. MTPs have also been associated with decreased overall blood product use[57,58], potentially reducing the risk of the secondary hit of resuscitation.

Although, the evidence has been convincing regarding improved survival[13,52,53,59], the implementation of MTPs across trauma centres globally has been inconsistent[60]. Most of the MTPs are relatively new, 65% being less than 5 years old in the United States[57]. Despite a substantial drop in mortality found after implementation of an MTP, the ratio of FFP to PRBCs given in the first 24 hours was the same pre and post-MTP[13].

While the importance of timing in multi-component transfusion is clear, there are some uncertainties and institutional variance regarding massive transfusion pack contents, their sequence and the optimum ratios of components that are to be achieved. Higher FFP: PRBC ratio was an independent predictor of survival[52,53]. A registry based study from Kashuk et al.[37] found an FFP:PRBC ratio of 1:2 in survivors versus 1:4 in non-survivors and in a large multi-centre retrospective study by Zink [14] of 466 trauma patients' high ratios were associated with reduced mortality. Snyder[61] found that after risk adjustment the apparent benefits of ratios >1:2 were lost. In computer modelling studies[62,63] of massively bleeding patients the maximal reported survival benefit was with ratios ranging from 1:3.3 to 1:1.4. The ideal ratio in providing balanced component therapy remains unknown, as demonstrated in a recent review[64] examining the current available evidence supporting the often recommended FFP:PRBC ratio of 1:1. In all, only 11 studies were found that compared the effects of different component ratios, and only five of these actually used the 1:1 ratio in one of the compared groups. Surprisingly, only 3 of these studies described using a predefined MTP. Moreover, although there seems to be a survival benefit with higher ratios, there are potential caveats such as increasing the incidence of MOF and ARDS. 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).

The overall similarity in mortality after MTP implementation despite more severe patients has to be interpreted with caution, as the difference that has occurred in the management of the bleeding patient is not limited to the availability of a MTP, thus leading to bias. Other potential explanatory factors include the availability of a trauma team, better neurosurgical and neuro-critical care, the use of fresher blood products (less than 14days old), increased attention to early haemorrhage control, judicious use of crystalloids and availability of rFVIIa and tranexamic acid. Nonetheless, despite MTP patients having had a higher ISS, AIS head score and lower admission GCS, mortality did not increase. MTP patients spent almost 4 more days in ICU, although the difference was not significant (p=0.243).

Our study also raises questions about using 24 hour cumulative ratios to describe blood component therapy outcomes. By the end of the first 24 hrs patients either exsanguinate if haemorrhage control is unsuccessful or if surviving, blood component therapy catches up with PRBC transfusion, thus complicating the already complex equation with survival bias.

Recent evidence suggests that improved outcomes are more closely linked to decreasing the time between components, with improved ratios at 6 hours being more predictive of improved outcomes than ratios at 24 hours[14,65]. However, both of these studies have limitations. In the study by Gonzalez at al.[65] earlier delivery of FFP is suggested, but the basis of the study is the review of their transfusion protocol originating from the 1990s and its effect on coagulopathy. The 6 hr timeframe is not used in their study. In the multicentre retrospective study by Zink et al.[14] transfusion practices admittedly showed great variance between the 16 centres, and there is no mention whether any of the involved centres had an MTP in place or not. Furthermore, the difference in the overall number of transfused units per patient is unknown amongst the 3 groups, thus raising the issue that some of the bleeding patients might have expired before blood components other than PRBC became available.

In our study, examining the changes in a single, level 1 trauma centre over time, significant differences were seen in the delivery of FFP:PRBC, CRYO:PRBC and PLT:PRBC ratios (using area under the curve) at 6 hours and CRYO and PLT at 24 hours following implementation of the MTP. Thus, our study showed a significant change in practice.

Arguably our sample size is relatively small. However, the number of patients is not significantly different from other studies examining massively transfused patients[13], the relatively small study population resulted in some parameters being non-equivalent, such as admission GCS, AIS head and ISS. For the same reason our ability to detect statistically significant differences in mortality was limited. This limitation was anticipated (the effect of MTP on mortality was not the primary aim of our study). One could speculate that a similar mortality in a group with a higher ISS and AIS head could be the result of a more balanced early blood component therapy; however the evidence is insufficient to draw definite conclusions.

The applicability of our findings are more relevant to trauma centres experiencing lower volumes of patients requiring massive transfusion, than seen in the large civilian and military units that provide the majority of evidence for MTPs and trauma resuscitation. Our results showed that with focused consultant led management even in low volume centres, optimal early balanced component therapy can be achieved in the most critically shocked trauma patients.

The retrospective design used is common to observational studies of this type and future prospective studies are warranted to confirm the results presented.

Conclusions

Musculo-skeletal injuries have been proven to be the leading cause for early transfusion among blunt trauma patients, with more than 70% of acute transfusions initiated for patients with orthopaedic injuries. The awareness of the MTP could help provide optimal component therapy to this group frequently undergoing emergency orthopaedic intervention.

Blood transfusion in the first 24 hrs is more liberally indicated based on vital signs, blood gas results, injury patterns and anticipated major bleeding. Haemogblobin concentration is rarely a relevant transfusion trigger. A focused, consultant led trauma care with a mature MTP can provide early balanced component therapy.

The implementation of a massive transfusion protocol resulted in a significant change in practice, allowing early balanced transfusion by 6 hours of admission in the haemorrhaging trauma patient. This time frame is more relevant and should be used when evaluating the efficacy of MTP and haemostatic resuscitation with different plasma to red blood cell ratios.

Clinical implications and future directions

Patients' susceptibility to secondary organ injury after trauma depends on the pattern and the severity of injury, genetic predisposition and modifiable factors such as nature and type of intervention and the resuscitation strategy.

The optimal resuscitation strategy balances the restoration of the haemostasis and volume replacement. Before haemorrhage control, as long as the vital organs are perfused, the haemostasis is favoured over volume replacement. Although blood component replacement is essential in haemostatic resuscitation, the volume of products needs to be tailored to the individual requirement of the injured.

1. We have identified that orthopaedic injury patients 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. This highlights the importance of understanding the impact of combined orthopaedic injuries on resuscitation strategies both during management in the emergency department and during surgery. The awareness and anticipation of such major blood loss from musculo-skeletal injuries should prompt to utilise the MTP more frequently and focus on procedures, which aim haemorrhage control and limit further surgery related blood loss. Overall 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. 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.

Transzfúziós Triggerek és a Masszív Transzfúziós Protokoll hatása az első 24 óra traumás reszuszcitációjában

Dr. Sisák Krisztián
PhD dolgozat összefoglalója

Szegedi Tudományegyetem, Szent-Györgyi Albert Klinikai Központ, Ortopédiai Klinika és John Hunter Kórház, Newcastle Egyetem, Traumatológia, Új-Dél Wales, Ausztrália
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BEVEZETÉS

Traumát követő megelőzhető halálokok közül a leggyakoribb, a tompa sérülést következtében kialakuló vérzés. A vérzéscsillapítást kísérő hemosztatikus vagy ún. „damage control" reszuszcitáció fontos eszköze a vér és vérkomponens transzfúzió. A transzfúzió nemcsak drága, de ismert rizikófaktora többek között a szisztémás gyulladásos reakciónak,a szeptikus szövődményeknek, a többszervi elégtelenségnek és a sérülést követő mortalitásnak. A vérkomponensek együtt, teljes vérhez hasonló arányokban, előre definiált csomagokban történő rendelkezésre bocsátása (Masszív Transzfúziós Protokoll (MTP)) csökkenti a poszttraumás mortalitást és a felhasznált vérkomponensek mennyiségét.

A tompa erőbehatást követően előforduló leggyakoribb sérülések a végtagokat érintő lágyrész- és csontsérülések, melyek akut transzfúziós igénye nagyrészt ismeretlen. Elfogadott protokollok irányítják az intenzív ellátás során, haemodinamikailag stabil betegeknél történő transzfúziót. Ezzel ellentétben, az első 24 órában, akutan történő vérátömlesztést főleg empirikus gyakorlat vezérli. Ebben a korai időszakban a transzfúziós triggerek nem egyértelműen definiáltak. Az MTP hatása az első 6 órában elérhető vérkomponens arányokra nem ismert. E dolgozat célja a fenti tényezők pontos feltérképezése volt.

BETEGANYAG ÉS MÓDSZER

A dolgozat beteganyagát a John Hunter Kórház (Newcastle Egyetemi Kórház, Ausztrália, 1-es szintű Trauma Centrum) adta. Két egymástől független klinikai vizsgálatot végeztünk.

1. Egy 12 hónapos prospektív tanulmányt végeztünk a végtagsérülések akut transzfúziós igényének, illetve az első 24 óra transzfúziós triggereinek megállapítására.
    a. Betegbevonási kritérium: minden traumás beteg, akinél a felvételt követő elsö 24 órában legalább 1 egység vörösvértest massza transzfúziója történt.
    b. A vizsgált változók: életkor, nem, injury severity score (ISS), sérülés típusa, transzfúziót megelőző vérgáz eredmények (Haemoglobin (Hb), base excess (BE)), vérnyomás és pulzus értékek. Az első egység transzfúziójának helye, ideje és az indikáló orvosa (szakterület és tapasztalat), valamint az alkalmazott transzfúziós trigger szintén jegyzésre került. Vérkomponensek mennyisége és az MTP használata is rögzítésre került.
    c. Kimenetel: mortalitás, intenzív osztályos (ITO) felvétel ill. ITO-s tartózkodás hossza, sürgős műtéti beavatkozás szükségessége.
2. A MTP bevezetésének hatását elemzésére, egy 8 évet átölelő retrospektív tanulmányt végeztünk. A vizsgálat célja az volt, hogy megállapítsuk, hogy a kezelés első 6 órájában hogyan változik az egyes vérkomponensek kiadása. Az MTP alkalmazását megelőző 4 évet (pre-MTP) hasonlítottuk össze egy 40 hónapos MTP bevezetését követő periódussal. Az átmeneti 2005-ös évet figyelmen kívül hagytuk.
    a. Betegbevonási kritérium: az első 24 órában legalább 10 egység vvt masszát kapó traumás betegeket vettük figyelembe, a traumás adatbázist illetve a transzfúziós intézet adatbázisát használva.

b. A vizsgált változók: életkor, nem, abbreviated injury scale (AIS), injury severity score (ISS), felvételkori Glasgow Coma Score (GCS), sérülés típusa, felvételkori vérgáz eredmények (pH, base excess (BE)), vérnyomás és koagulációs paraméterek.
c. A vérkomponensek arányainak meghatározásához mind a vérkomponens (vvt massza (PRBC), FFP, cryoprecipitátum (CRYO), vérlemezke (PLT)) kiadásának, mind pedig felhasználásának időpontját rögzítettük. A beadott vérkomponensek összessége szintén dokumentálásra került.
d. Kimenetel (elsődleges): a vérkomponense arányát (FFP:PRBC, CRYO:PRBC és PLT:PRBC) az első 24 óra minden fél órájában meghatároztuk és grafikusan ábrázoltuk. Az első 6 órát külön vizsgáltuk az MTP hatásának hangsúlyozására.
    i. A vér komponens arányokat a görbe alatti terület (AUC – area under the curve) segítségével kalkuláltuk.
e. Kimenetel (másodlagos): mortalitás (korai (24 órán belül) és késői (24 órán túl)), sürgős sebészeti beavatkozás szükségessége, ITO-s felvétel ill. ITO-s tartózkodás hossza.

EREDMÉNYEK:

Eredmények:

1A. Az összes traumás beteg 9%-a (91/965) kapott legalább 1 egység vvt masszát az első 24 órában, ebből 70%-nak (64/91) volt 1 vagy több végtagsérülése. A betegeket három csoportra osztottuk: csak végtagsérülés (54 beteg), végtag és egyéb sérülés (10 beteg) és végtagsérülés nélkül (27 beteg). A három csoport között nem voltak demográfia eltérések. A végtagsérültek (részben vagy kizárólagosan) mortalitása 13% (8/64) volt. ITO-s tartózkodás hossza a végtagsérülés nélküli betegeknél magasabb volt, mint a kizárólag végtagsérülteknél (10±10 vs. 5±4, p=0.008). Fordított eltérés volt ugyanezen csoportok között az összes kórházban töltött időben (26±19 vs. 16±12, p=0.027). A végtagsérülések miatti vérvesztés tette szükségessé az összes akut transzfúzió 80%-át (462/575). A végtagsérült betegek (részben vagy kizárólagosan) 48%-nál (31/64) a MTP is aktiválásra került. E betegek két harmada (42/64) több mint 4 egység vvt masszát kapott. A végtagsérült betegek 84%-a (54/64) ortopéd trauma miatti műtéten esett át az első 24 órában. A csak végtagsérültek átlagos vérkomponens felhasználása 6.6±5.4 egység PRBC és 4.0±4.5 egység FFP volt. A végtag és törzssérültek 10.8 ±11.1 egység PRBC és 6.3 ±8.1 egység FFP volt.

Leggyakoribb sérülések:

A. 25 betegnél észleltünk medencesérülést illetve acetabulum törést (39% (25/64)), ebből csak 3 esetben volt izolált a sérülés.
B. 24 betegnél észleltünk legalább egy femurtörést (37% (24/64)), ebből csak 2 esetben volt izolált a sérülés.
C. 20 betegnél észleltünk legalább egy tibiatörést (31% (20/64)), 9 nyílt törés, ebből csak 3 esetben volt izolált a sérülés.

Eredmények:

1B. A akut transzfúziós betegek 43%-ánál (39/91) MTP aktiváció vált szükségessé. Sürgős műtéti beavatkozás (24 órán belül) 86%-ban (78/91) került sor, melynek 47%-nál (37/78) a beavatkozás célja elsősorban a vérzéscsillapítás volt. Összes mortalitás 14% (13/91) volt, ebből 5/13 24 órán belül történt. Az akut transzfúziók 59%-a (54/91) 2 órán belül történt, és az MTP-k 92%-a (36/39) szintén ilyen korán kerül indikálásra. Transzfúziós triggerek a transzfúzió helyének függvényében: 1 Táblázat.

1. Táblázat.

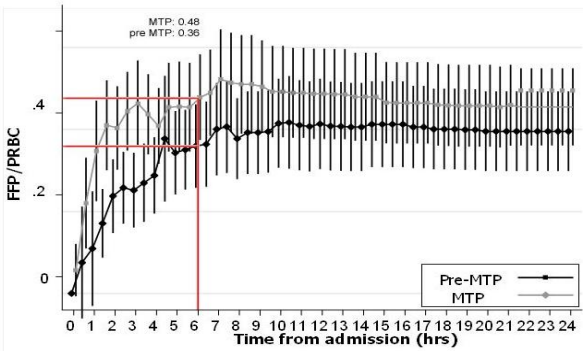
Transzfúzió helye	SBO	Műtő	ITO	Összesen
Betegek száma	47	35	9	91
ISS	32 (4-66, IQR:20-43)	18 (4-59, IQR:13-29)	25(9-45, IQR:20-34	25 (4-66, IQR:16-34)
Vvt massza mennyisége	8 (1-34, IQR:2-10)	3 (1-14, IQR:2-6)	3(1-27, IQR: 2-3)	4(1-34, IQR:2-8)
Transzfúziós trigger				
Vérzéses sokk	37% (17/47)	14% (5/35)	0%	24% (22/91)
Várható vagy zajló vérzés	23% (11/47)	40% (14/35)	11% (1/9)	29% (26/91)
Csökkenő Hemoglobin	9% (4/47)	40% (14/35)	66% (6/9)	26% (24/91)
Hipotenzió	15% (7/47)	6% (2/35)	0%	10% (9/91)
Tachycardia	15% (7/47)	0%	0%	8% (7/91)

Traumatológus indikálta a transzfúziók 34%-át (31/91), és az MTP-k 62%-át (24/39). 31%-ot (28/91) aneszteziológus, 19%-ot (17/91) sürgősségi orvos, 12%-ot (11/91) intenzív szakorvos és 3%-ot (3/91) általános sebész indított. A triggerek szakterülettől függően változtak: leggyakoribb trigger: traumatológus – vérzéses sokk 45% (14/31), aneszteziológus és intenzív szakorvos – csökkenő hemoglobin koncentráció 46% (13/28) illetve 55% (6/11). Sürgősségi orvosok és általános sebészeknél több triggert is használtak szinte egyenletes eloszlással.
Az MTP aktiválása kiegyensúlyozott komponens terápiát tett lehetővé: FFP: PRBC arány: 1:1.4.

Eredmények: 2.

A MTP bevezetése előtti időszakban (48 hónap) 30 betegnél történt masszív transzfúzió, míg a MTP bevezetése után (40 hónap) 28 betegnél. Nem voltak demográfiai eltérések a két csoport között. Az ISS magasabb volt a későbbi csoportban [Pre-MTP: 36±12 vs. MTP: 42±12 (p=0.045)], hasonlóan a fejsérülésre vonatkozó AIS érték magasabb volt a második csoportban [Pre-MTP: 1.6±2.0 vs. MTP: 2.6±1.8 (p=0.043)]. A vérgáz értékekben nem volt eltérés a két csoport között. A kórházba érkezéskori GCS alacsonyabb volt az MTP csoportban (p=0.023).

A görbe alatti területet vizsgálva az első 6 órábara vonatkoztatva magasabb medián FFP/PRBC arányokat észleltünk az MTP csoportban (p=0.004)(1.ábra). Hasonló eltérések észleltünk a medián CRYO/PRBC arányokban (p=0.003) és a medián PLT/PRBC (p=0.0002) arányokban.



1.Ábra. FFP/PRBC arányok a MTP bevezetése előtt és után

A 0 negatív és 0 pozitív vérfelhasználás a MTP bevezetése után növekedett [0 neg: Pre-MTP: 1.6±2.2 vs. MTP: 3.4±3.2 (p=0.016)] illetve [0 poz: Pre-MTP:0.8±2.6 vs. MTP: 3.8±4.5 (p=0.003)]. Bár a FFP mennyiség nem változott [Pre-MTP:8.1±6.2 vs. MTP:9.4 ±5.8 (p=0.416)], a CRYO [Pre-MTP:5.4 ±8.4 vs. MTP:11.6 ±9.1 (p=0.009)] és PLT mennyiség növekedett [Pre-MTP:5.8±6.8 vs. MTP: 10.1±6.5 (p=0.018)].
A mortalitás nem változott [Pre-MTP: 40%(12/30) vs. 46%(13/28)].

DISZKUSSZIÓ:

A traumás sokk során a reszuszcitáció célja az elveszett volumen pótlása, miközben a vérzéscsillapítás folyik. A reszuszcitáció úgy optimális, hogy a lehető legkisebb másodlagos kárt okozva, csökkenti a többszervi szövődmények valószínűségét. Ehhez nem csak az elvesztett vértérfogat pontos becslése, de a különböző vérkomponensek gyors ütemű, a sérültre szabott pótlása szükséges.

Prospektív tanulmányunk 91 akut transzfúzión átesett beteget vizsgált, 1 év alatt. Tapasztalatunk szerint az akut transzfúziók 70%-a ortopéd sérülés miatt történik. A sérülések gyakran kombináltak és a végtagsérült betegek 80%-a sürgős műtéti beavatkozáson esik át. A felhasznált átlagos vérkomponens mennyiség 7.2±6.6 egység PRBC és 4.3±5.2 egység FFP volt.

Tanulmányunk ugyancsak leírta az első 24 órában alkalmazott transzfúziós triggereket, öt releváns triggert észleltünk (1. Táblázat). . Hemoglobin koncentráció csak az esetek 25%-ban (23/91) volt a transzfúziós trigger. A különböző szakemberek transzfúziós szokásai eltérőek voltak. Az akut transzfúziók 90%-a az első 6 órában történik. A sérültek 43%-ánál (39/91) MTP aktiváció történt.

Bár az utóbbi 5 év fontos vívmánya a MTP-k bevezetése, a MTP által okozott vérkomponens elérhetőség dinamikája nagyrészt ismeretlen. Retrospektív tanulmányunk bizonyította hogy a MTP fő előnye, a teljes vérhez hasonló vérkomponens arányok hozzáférhetőkké válnak, a klinikailag legrelevánsabb kórházba érkezést követő 6 órában. Az átlag FFP: PRBC arány 6 óránál 1:2.8 volt a pre-MTP csoportban és 1:2.1 a MTP csoportban (p=0.010).

Összefoglalásképpen a következő állítások tehetők:

- ortopéd trauma felelős az akutan felhasznált vérkomponensek 75%-áért. Az első 24 órában transzfundált végtagsérültek átlagos vérkomponens felhasználása 7.2±6.6 egység PRBC és 4.3±5.2 egység FFP. Az első 24 órában transzfundált végtagsérültek esetében majdnem 50%-ban MTP aktiváció válik szükségessé, és a felhasznált vér mennyiségét figyelembe véve, kombinált végtagsérülés esetén az MTP aktiválása tovább javíthatja a vérkomponens arányt
- akut transzfúzió esetén a statikusan mért hemogblobin koncentráció nem alkalmazható transzfúziós triggerként. Az első 24 óra transzfúziós triggerei csak részben (50%-ban) objektívek (vérzéses sokk (SBP≤90Hgmm és BE≤-6mmol/l illetve csökkenő hemoglobin koncentráció (≤80g/l vagy ≤100g/l és 30g/l csökkenés ≤2 órán belül).
- A MTP aktiválása javítja a korai vérkomponens hozzáférhetőséget, elsősorban az első 6 órában.

A fenti megállapítások a dolgozat szerzője szerint kiemelt jelentőséggel bírnak; rámutatnak arra, hogy a végtag- és medencetrauma felelős az akut transzfúziós szükséglet túlnyomó részéért, nem pedig a hasi vagy mellkasi sérülések; az akut transzfúzió triggerei jelentősen eltérnek a nem az első 24 órában adott transzfúziójától; a MTP alkalmazása az első 6 órában jelentősen javítja a FFP, CRYO és PLT hozzáférhetőségét.

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Appendix