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Achieving balanced transfusion early in critically bleeding trauma patients: an observational study exploring the effect of attending trauma surgical presence during resuscitation

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ABSTRACT

Background After 15 years of damage control resuscitation (DCR), studies still report high mortality rates for critically bleeding trauma patients. Adherence to massive hemorrhage protocols (MHPs) based on a 1:1:1 ratio of plasma, platelets, and red blood cells (RBCs) as part of DCR has been shown to improve outcomes. We wanted to assess MHP use in the early (6 hours from admission), critical phase of DCR and its impact on mortality. We hypothesized that the presence of an attending trauma surgeon during all MHP activations from 2013 would contribute to improving institutional resuscitation strategies and patient outcomes.

Methods We conducted a retrospective analysis of all trauma patients receiving ≥10 RBCs within 6 hours of admission and included in the institutional trauma registry between 2009 and 2019. The cohort was divided in period 1 (P1): January 2009–August 2013, and period 2 (P2): September 2013–December 2019 for comparison of outcomes.

Results A total of 141 patients were included, 81 in P1 and 60 in P2. Baseline characteristics were similar between the groups for Injury Severity Score, lactate, Glasgow Coma Scale, and base deficit. Patients in P2 received more plasma (16 units vs. 12 units; p<0.01), resulting in a more balanced plasma:RBC ratio (1.00 vs. 0.74; p<0.01), and platelets:RBC ratio (1.11 vs. 0.92; p<0.01). All-cause mortality rates decreased from P1 to P2, at 6 hours (22% to 8%; p=0.03), at 24 hours (36% vs 13%; p<0.01), and at 30 days (48% vs 30%, p=0.03), respectively. A stepwise logistic regression model predicted an OR of 0.27 (95% CI 0.08 to 0.93) for dying when admitted in P2.

Conclusions Achieving balanced transfusion rates at 6 hours, facilitated by the presence of an attending trauma surgeon at all MHP activations, coincided with a reduction in all-cause mortality and hemorrhage-related deaths in massively transfused trauma patients at 6 hours, 24 hours, and 30 days.

Level of evidence IV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ After 15 years of damage control resuscitation, studies still report that up to two-thirds of the massively transfused trauma patients receive unbalanced transfusion with concomitant high mortality rates.

WHAT THIS STUDY ADDS

⇒ Achieving balanced transfusion rates at 6 hours facilitated by the presence of an attending trauma surgeon during all massive hemorrhage protocol activations coincided with a reduction in all-cause mortality and hemorrhage-related deaths in massively transfused trauma patients at 6 hours, 24 hours and 30 days.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The presence of a dedicated attending trauma surgeon in the acute phase to facilitate resuscitation should be of highest priority for the critically bleeding trauma patients.

BACKGROUND

Hemorrhage remains the leading cause of early and potentially preventable trauma deaths.[1 2] Over 90% of hemorrhagic deaths occur within 24 hours, and the majority of these patients die within 6 hours.[3]

Despite concerns about survival bias,[4 5] rigorous evidence has demonstrated reduced mortality and improved outcomes for the trauma population since the introduction of damage control resuscitation (DCR),[6–13] and balanced transfusions are recommended in the latest clinical practice guidelines (CPGs) on major bleeding.[14 15]

However, it is well-known that adherence to CPGs is variable and inconsistent.[16–18] Despite the convincing evidence described above, up to two-thirds of trauma patients still receive insufficient coagulation factors, even 24 hours after admission, with increased mortality.[19–23] Adherence to massive hemorrhage protocol (MHP) can be used as a quality indicator measuring institutional performance during resuscitation. However, it is unknown whether balanced transfusions can be achieved outside clinical trials in critically injured trauma patients.

Since 2007, the institutional MHP at a high-volume trauma center has mandated resuscitation with plasma, platelets, and red blood cells (RBCs) in a 1:1:1 fashion in physiologically compromised bleeding trauma patients. We wanted to study the adherence to the MHP in the early (6 hours), critical

phase of DCR and assess the effect on mortality. The only major organizational change facilitating adherence to the MHP was the implementation of a 24/7 on-call attending trauma surgeon from September 2013. We hypothesized that the experienced trauma surgical presence during all MHP activations would contribute to improving institutional resuscitation strategies and outcomes. Additionally, we aimed to describe the need for emergency surgery and angiographic interventions, as well as complications with organ dysfunction.

METHODS

Data were extracted from the institutional trauma registry at Oslo University Hospital (OUH) and electronic health record system, for the years 2009–2019. Data linkage was not performed.

This was a retrospective study of massively transfused (≥10 units of RBC within 6 hours) adult (18 years and older) trauma patients at a Northern European Trauma Center. Patients with primary burns (n=1) and registered as dead on arrival (DOA) (n=10) were excluded. We wanted to study the period after the MHP had been well implemented in the institution, to avoid start-up problems and protocol implementation bias, hence start year 2009. The early period of DCR was defined as January 2009–August 2013 (period 1, P1), and the late period between September 2013 and December 2019 (period 2, P2).

Prospectively collected demographic characteristics, admission vital signs and injury characteristics were acquired from the institutional trauma registry. These included age, gender, mechanism of injury, time of injury, arrival time at the emergency department (ED), admission systolic blood pressure (SBP), heart rate, base deficit (BD), Glasgow Coma Scale (GCS) score, anatomic injury classified according to the Abbreviated Injury Scale (AIS) 1998 version,[24] Injury Severity Score (ISS), transfusions prior to intensive care unit (ICU) admission, Trauma and Injury Severity Score probability of survival with the National Trauma Data Bank 2005 coefficients, and 30-day survival. The main cause of death registered is the most likely condition that directly led to death after reviewing all available sources—patient electronic records, radiological imaging, and autopsy reports. Survival status, including 6 hours, 24 hours, and 30 days after injury, was retrieved from patient electronic records and the Norwegian Population Registry. Data on surgical procedures and angiographic interventions were extracted from the patient electronic records.

Transfusions and crystalloids administrated during the first 24 hours were extracted from the institutional trauma registry and patient electronic records. To mitigate the impact of survival bias, massive transfusion (MT) and ultramassive transfusion (UMT) were defined as ≥10 RBCs and ≥20 RBCs within 6 hours of admission, respectively.[19 20 24–27] Data on administration of tranexamic acid (TXA) and fibrinogen within the first 24 hours were collected from patient electronic records as was the number of 28-day ventilator-free, vasopressor-free, dialysis-free, and ICU-free days and venous thromboembolic events.

An MHP was formalized and gradually implemented at our institution in 2007. The MHP included plasma, platelets, and RBC in a 1:1:1 ratio, TXA and fibrinogen concentrate guided by arterial blood gases, physiologic response to resuscitation, and change in coagulation parameters (figure 1). Five units of 0 negative RBCs have been available in the trauma bay during the whole study period with about 15-minute delivery time for thawed plasma (Octaplasma) from the blood bank. In 2016, two units thawed AB plasma were added to the RBCs available in the trauma bay. Throughout the study period, all patients with

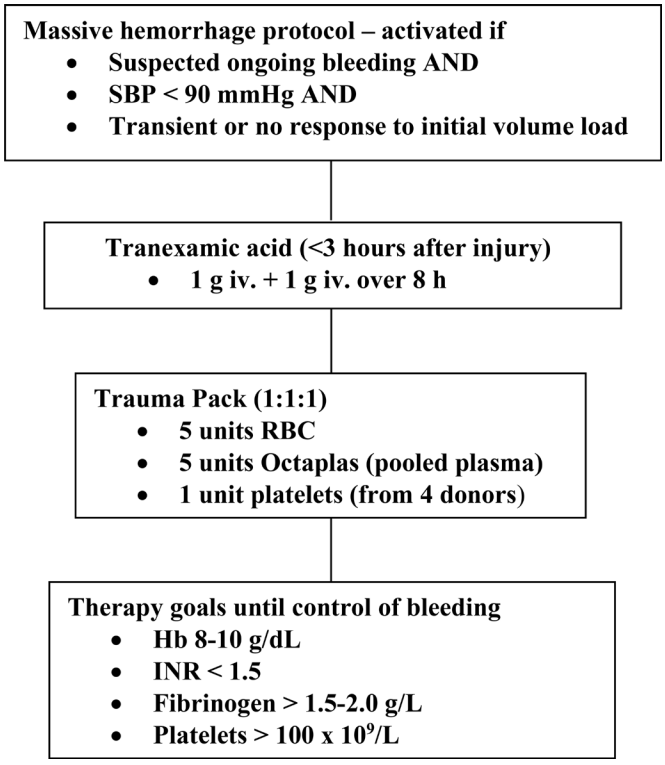

Figure 1 Basic massive hemorrhage protocol. Hb, hemoglobin; INR, international normalized ratio; iv, intravenously; RBC, red blood cell; SBP, systolic blood pressure.

suspected ongoing bleeding, SBP <90 mm Hg, and inadequate response to resuscitation were managed with the updated MHP and early hemostatic interventions applying DCR principles (figure 1). Key elements in DCR are early hemorrhage control, balanced transfusion of plasma, platelets, and RBCs, restricted volume of crystalloid, permissive hypotension, reversal of hypothermia and trauma-induced coagulopathy (TIC). Our treatment algorithm, including all indications for emergency interventions like thoracotomy, laparotomy and angiographic interventions, has been described earlier.[10 28]

Patients admitted in extremis or with cardiac arrest within the last 15 minutes undergo thoracotomy before laparotomy, to either treat cardiac tamponade or to digitally compress the aorta to prioritize central perfusion. Angiographic procedures were performed by a dedicated interventional team, who were available 24/7 with a response time of 30 minutes.

During the study period, the MHP has been continuously updated following the growing body of evidence in this field. TXA was added to the MHP in August 2010, based on the Crash 2 trial.[29] Hypocalcemia and hypofibrinogenemia have been increasingly monitored and correction initiated with target levels set at cCa^{2+} >1.2 mmol/L and fibrinogen >1.5–2.0 g/L, respectively.[30] The protocol for reversal of anticoagulants in bleeding trauma patients has gone through several adjustments. Viscoelastic hemostatic assays (VHAs) and other coagulation tests are integral parts of monitoring coagulation according to larger trials.[31] In February 2014, the trauma service got access to a dedicated trauma hybrid operating room. However, a dedicated operating room and access to interventional radiology were both readily available throughout the study period, minimizing any indications for resuscitative endovascular balloon occlusion of the aorta (REBOA). The trauma service structure has been consistent throughout the study period, monitored by a continuous

quality improvement program. Since the formalization of a dedicated trauma service in 2005, there has been attending trauma surgical presence coordinating all surgical involvement and securing multidisciplinary involvement throughout the hospital stay. However, instituting a formal on-call attending trauma surgical presence was only possible from 2013. Prior to 2013, the trauma team leader was a surgical fellow and had the same overall responsibility during on call. The only major change was the introduction in September 2013 of a formal 24/7 attending trauma surgeon present at all MHP activations.

Baseline characteristics are expressed as numbers and percentages or median and IQRs. Continuous data were compared with the use of Mann-Whitney U test. Categorical data were compared with the use of two-tailed Pearson χ^2 test or with the use of Fisher's exact test as appropriate. A p value of less than 0.05 derived from a two-tailed test was considered to indicate statistically significance.

Unadjusted survival curves were estimated with Kaplan-Meier method and tested with the log-rank test for differences. The exclusion of patients DOA represented 7% of the total cohort; therefore, a sensitivity analysis including these patients was performed. For the main outcome of all-cause 6-hour mortality after injury, we constructed a logistic regression model using a purposeful selection[32] of significant covariates, including potential confounders. Clinical variables were prespecified and considered clinically important. Regardless of periods, a multivariable analysis for the whole population was also performed to study the overall impact of the different transfusion ratios on 6-hour mortality. For this purpose, balanced transfusion with component administration was strictly defined as both plasma:RBC and platelets:RBC ≥1. The inter-related plasma:RBC and platelet:RBC ratios were included as a single variable with four categories: fresh frozen plasma (FFP):RBC ≥1 and platelet:RBC ≥1 (reference group), FFP:RBC ≥1, platelet:RBC ≥1 or FFP:RBC <1 and platelet:RBC <1. In addition to transfusion ratios, the covariates in this model included GCS, ISS, lactate and thoracotomy. The Hosmer-Lemeshow goodness-of-fit test was used to verify the adequacy of the model. Calculation of the accuracy of the test was measured by the area under the receiver operating characteristic curve for the prediction of 6-hour mortality.

All statistical analyses were performed using the IBM SPSS Statistics for Windows, V.28.0 (IBM Corp). The Strengthening the Reporting of Observational Studies in Epidemiology statement and Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement were adhered to.[33 34] Codes for extraction of the study population and defining variables will be available on request. The proportion of missing data was assessed for all variables and compared between cohorts.

RESULTS

A total of 19 618 patients were accessible in the OUH trauma registry for the period between 2009 and 2019. For the adult (18 years and older) trauma population with team activation at OUH in the study period, the proportion of MHP within 24 hours was 1.2%. After applying the inclusion and exclusion criteria, 141 patients were included in the survival analysis (figure 2), which represented 0.7% of all patients in the registry. The population consisted of 78% men, median age was 42 years, 82% had blunt injuries, and the median ISS was 42. P1 and P2 included 81 and 60 patients, respectively. Demographic and clinical characteristics at admission were comparable for the two groups except for a higher age (52 vs. 36), a higher median SBP (95 mm Hg vs. 70 mm Hg), and a higher median fibrinogen (2.0 vs. 1.3) and a lower international normalized ratio (INR) (1.2 vs. 1.3) in P2. Neither time from injury to admission nor AIS by body region differed between periods. Demographic and clinical characteristics at admission are displayed in table 1.

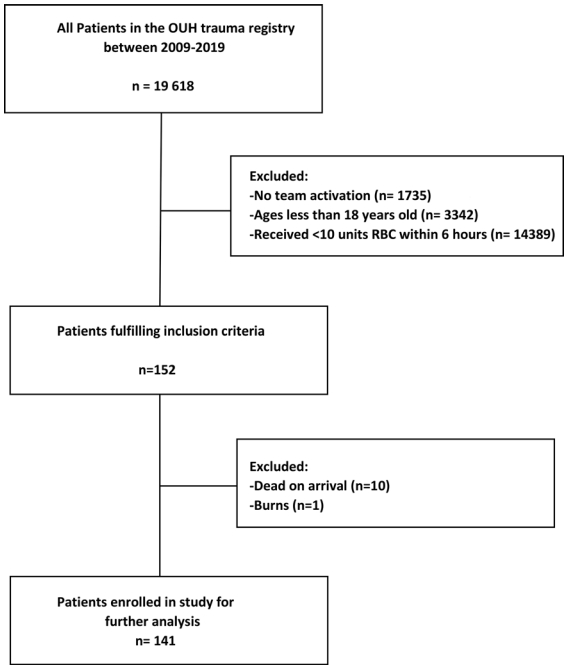

Figure 2 Outline of patient selection. RBC, red blood cell.

In the acute phase of resuscitation, that is, within 6 hours of admission, there were no differences in units of RBCs or platelets transfused between the periods (table 2). However, patients in P2 received more plasma (median, 16 units vs. 12 units; p<0.01) in the early phase of resuscitation. Thus, patients in P2 received a more balanced plasma:RBC ratio (1.00 vs. 0.74; p<0.01) and platelets:RBC ratio (1.13 vs. 0.92; p<0.01). The use of crystalloids in the acute phase decreased from 2.2 L in P1 to 0.5 L in P2 (p<0.01). Total transfusions within the first 24 hours after injury showed a similar pattern of differences between the periods. In P2, more fibrinogen was administered within 6 hours (median 1 g vs. 0 g; p<0.01), and a higher proportion of patients arriving at the hospital within 3 hours received tranexamic acid (94% vs. 45%; p<0.01).

Annual median plasma:RBC ratios in the acute resuscitation phase are shown in figure 3, visualizing an abrupt change between 2013 and 2014. The annual plasma:RBC ratios in P1 never exceeded 0.82, whereas in P2, the ratios were 1.00 or higher. In P2 within 6 hours of admission, more patients received plasma:RBC in a ratio ≥1 (68% vs. 21%; p<0.01), platelets:RBC ≥1 (75% vs. 47%, p<0.01), and both ratios ≥1 (55% vs. 16%, p<0.01) compared with P1.

The overall mortality at 6 hours decreased from 22% in P1 to 8% in P2 (p=0.03) (table 3). The difference in mortality remained significant at 24 hours (36% vs. 13%, p<0.01) and at 30 days (48% vs. 30%, p=0.03). The sensitivity analysis of the cohort including DOA patients confirmed the decrease in mortality at 6 hours (25% vs. 11%, p=0.03), 24 hours (40% vs. 17%, p<0.01), and 30 days (52% vs. 34%, p=0.03). Mortality caused by exsanguination decreased in P2 (28% vs. 10%; p=0.01). Figure 4 compares survival curves between the periods displaying a pronounced drop in survival within 24 hours in P1 compared with P2 (log-rank (Mantel-Cox) p=0.02).

Table 1 Patient characteristics

	Period 1 (n=81)	Period 2 (n=60)	P value
Age (years)	36 (24–50)	52 (32–63)	**<0.01**
Male, n (%)	61 (75)	52 (82)	0.15
Blunt, n (%)	65 (81)	52 (85)	0.53
ASA 3&4, n (%)	7 (9)	12 (20)	0.06
SBP (mm Hg)	70 (60–92)	95 (80–123)	**<0.01**
GCS score	7 (3–13)	12 (3–14)	0.14
BD (mmol/L)	11.7 (5.5–17.7)	10.4 (5.6 to 17.2)	0.98
Lactate (mmol/L)	8.9 (4.7–13.9)	7.5 (4.6–13.9)	0.93
INR	1.3 (1.2–1.6)	1.2 (1.1–1.3)	**<0.01**
Fibrinogen (g/L)	1.3 (0.9–2.0)	2.0 (1.6–2.4)	**<0.01**
ISS	42 (30–50)	43 (29–54)	0.53
Ps	0.50 (0.20–0.84)	0.61 (0.20–0.87)	0.71
NISS	50 (36–57)	48 (36–59)	0.91
AIS head	2 (0–5)	0 (0–4)	0.13
AIS thorax	4 (3–4)	4 (2–4)	0.53
AIS abdomen	2 (0–4)	3 (0–4)	0.91
AIS head ≥3, n (%)	38 (47)	22 (37)	0.24
Time injury to admission (min)	90 (50–140)	63 (39–122)	0,16
Time admission to ICU (min)	217 (111–328)	250 (175–337)	0.11
Time injury to ICU (min)	357 (223–472)	350 (251–448)	0.76

Values are given as median (IQR) where not stated otherwise.
AIS, Abbreviated Injury Scale; ASA, American Society of Anesthesiologists; BD, base deficit; GCS, Glasgow Coma Scale; ICU, intensive care unit; INR, international normalized ratio; ISS, Injury Severity Score; NISS, New Injury Severity Score; Ps, probability of survival; SBP, systolic blood pressure.

Table 2 Transfusions within 24 hours

	Period 1 (n=81)	Period 2 (n=60)	P value
Transfusions first 6 hours			
U RBCs	15 (12–28)	14 (11–30)	0.59
U plasma	12 (7–19)	16 (12–28)	**<0.01**
U platelets	16 (8–26)	18 (12–30)	023
Plasma:RBC ratio	0.74 (0.54–0.90)	1.00 (0.90–1.23)	**<0.01**
Plasma:RBC ≥1, n (%)	17 (21)	41 (68)	**<0.01**
Platelets:RBC ratio	0.92 (0.65–1.19)	1.11 (0.93–1.29)	**<0.01**
Platelets:RBC ratio ≥1, n (%)	38 (47)	45 (75)	**<0.01**
Plasma:RBC & platelets:RBC ratios ≥1, n (%)	13 (16)	33 (55)	**<0.01**
Plasma:RBC or platelets:RBC ratios ≥1, n (%)	42 (52)	53 (88)	**<0.01**
Crystalloids, L	2.2 (1.0–3.7)	0.5 (0.3–1.2)	**<0.01**
Fibrinogen, g	0 (0–0)	1 (0–4)	**<0.01**
Transfusions first 24 hours			
U RBCs	19 (13–29)	16 (13–30)	0.70
U plasma	14 (8–23)	21 (15–33)	**<0.01**
U platelets	16 (8–32)	18 (12–35)	0.16
Plasma:RBC ratio	0.77 (0.55–0.95)	1.17 (1.00–1.40)	**<0.01**
Platelets:RBC ratio	0.97 (0.65–1.24)	1.13 (1.00–1.38)	**<0.01**
Crystalloids, mL	4.6 (2.6–6.6)	2.5 (1.1–4.7)	**<0.01**
Fibrinogen, g	0 (0–0)	1 (0–4)	**<0.01**
TXA <3 hours of injury, n (%)	30 (45)	45 (94)	**<0.01**
UMT 6 hours, n (%)	33 (41)	21 (35)	0.49
UMT 24 hours, n (%)	39 (48)	23 (37)	0.17

Values are given as median (IQR) where not stated otherwise.
RBCs, red blood cells; TXA, tranexamic acid; U, units; UMT, ultramassive transfusion.

Emergency thoracotomy was performed in 27% in P1 and 15% in P2 (p=0.09). The emergency laparotomy rate decreased from 62% to 37% in P2 (p<0.01). Patients who underwent laparotomy received more balanced transfusions in the acute phase (plasma:RBC ratio: 0.75 in P1 vs. 1.00 in P2; p<0.01) and at 24 hours (plasma:RBC ratio: 0.80 in P1 vs. 1.22 in P2; p<0.01) in P2 with a significantly decreased mortality at 24 hours (46% in P1 vs. 9% in P2; p<0.01) and 30 days (58% in P1 vs. 32% in P2; p=0.04). Angiographic interventions increased (12% in P1 vs. 36% in P2, p<0.01).

A multiple logistic regression model predicting overall 6-hour mortality in massively transfused patients was constructed with a purposeful selection of variables to determine demographic core variables. Table 4 presents the crude and adjusted ORs, identifying P1, high ISS, high lactate, and low GCS score to be independently correlated with increased 6-hour mortality. The logistic regression model predicted an OR of 0.27 (95% CI 0.08 to 0.93; p=0.03) for dying within 6 hours of injury when admitted in P2. The area under the curve for the score in the test data set was 0.85 (95% CI 0.79 to 0.92; p<0.01). The Hosmer-Lemeshow test statistic for model fit was acceptable ($\chi 2=9.76$, df=8, p=0.28). The OR remained low for P2 in multiple logistic regression models predicting 24-hour (OR 0.17, 95% CI 0.06 to 0.50; p<0.01) and 30 days (OR 0.34, 95% CI 0.15 to 0.79, p=0.01) mortality. The multiple logistic regression model including transfusion ratios for the whole population showed that plasma:RBC <1 and platelets:RBC <1 had a significant and independently increased OR of 21 (95% CI 1.97 to 235, p=0.01) for mortality at 6 hours.

Four percent of all patients included had missing data. None of the included variables had substantial missing data (>10% missing data). Variables most often missing were INR (3%)

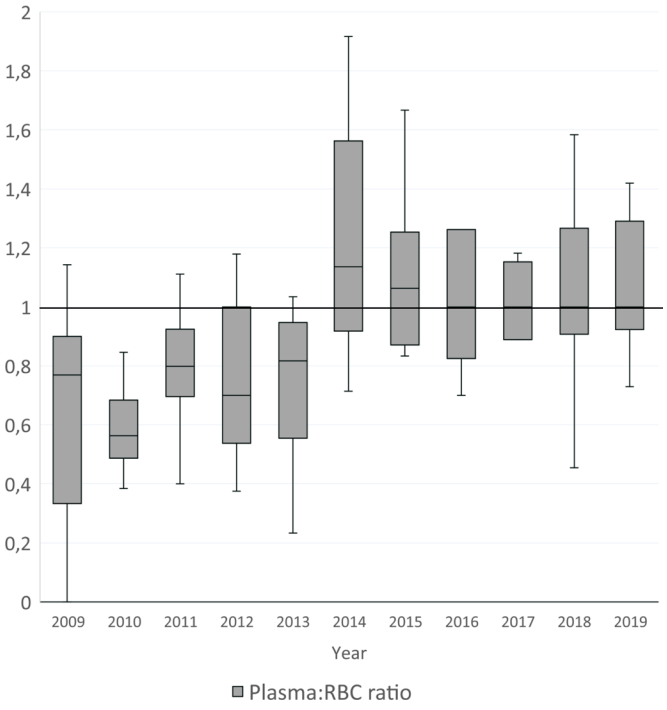

Figure 3 Annual plasma:RBC ratios during the first 6 hours after admission. RBC, red blood cell.

Table 3 Characteristics of outcome

	Period 1 (n=81)	Period 2 (n=60)	P value
6-hour mortality, n (%)	18 (22)	5 (8)	**0.03**
24-hour mortality, n (%)	29 (36)	8 (13)	**<0.01**
30-day mortality, n (%)	39 (48)	18 (30)	**0.03**
Death from hemorrhage, n (%)	23 (28)	6 (10)	**0.01**
Death before ICU, n (%)	25 (31)	6 (10)	**<0.01**
Emergency surgery			
Thoracotomy, n (%)	22 (27)	9 (15)	0.09
Laparotomy, n (%)	50 (62)	22 (37)	**<0.01**
Angiographic intervention, n (%)	10 (12)	22 (37)	**<0.01**
Ventilator-free days to day 28	0 (0–9)	0 (0–22)	0.11
Vasopressor-free days to day 28	3 (0–22)	11 (0–23)	0.14
Dialysis-free days to day 28	0 (0–28)	24 (0–28)	**0.04**
ICU-free days to day 28	0 (0–6)	0 (0–16)	0.19
VTE, n (%)	6 (7)	8 (13)	0.25

Values are given as median (IQR) where not stated otherwise.
ICU, intensive care unit; VTE, venous thromboembolism.

and fibrinogen (3%). Missing data were considered missing at random, and imputation of missing data was not performed.

DISCUSSION

This study describes a single institution's performance in DCR of severely injured trauma patients who received massive transfusion in the period from 2009 to 2019. Acute-phase resuscitation improved, achieving a 1:1:1 ratio, in P2 with an associated decrease in 6-hour mortality from 22% in P1 to 8% in P2 (p=0.03). The reduction in mortality remained significant at 24 hours and 30 days. The inclusion criteria excluded 7% of the total cohort; however, a sensitivity analysis was performed confirming the same pattern. Moreover, the multiple logistic regression model predicted an OR of 0.27 (95% CI 0.08 to 0.93; p=0.04) for dying within 6 hours when admitted in P2, and the OR remained low at 0.17 (p<0.01) at 24 hours and 0.34 (p=0.01) at 30 days for P2.

Compared with the rate of MHP within 24 hours of the general trauma population, the proportion of MHP within 6 hours was lower as expected (1.2% vs. 0.7%, respectively). The rates were comparable with a recently published large study from the American College of Surgeons Trauma Quality Improvement Program Database, including over 400 000 patients with a rate of 0.8% for MT in level 1 trauma centers.[22]

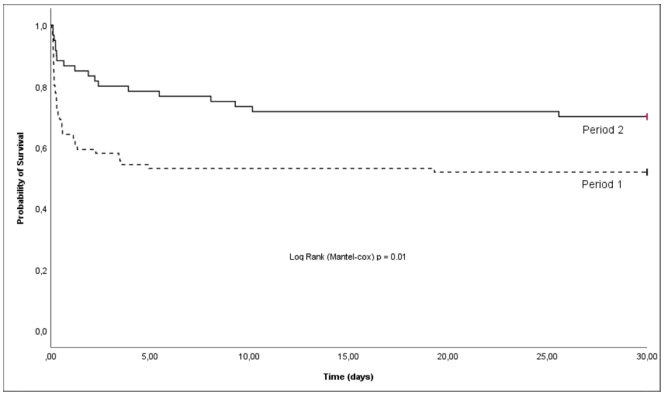

Figure 4 Kaplan-Meier plot for 30-day overall survival.

Table 4 Univariate and multiple logistic regression models for predicting 6-hour mortality

	Crude			Adjusted		
	OR	95% CI	P value	OR	95% CI	P value
Period 2	0.20	0.11 to 0.91	0.03	0.27	0.08 to 0.93	0.04
ISS	1.03	1.00 to 1.06	0.03	1.04	1.01 to 1.07	0.02
Lactate	1.14	1.04 to 1.25	<0.01	1.15	1.02 to 1.29	0.03
GCS	0.77	0.66 to 0.88	<0.01	0.82	0.70 to 0.95	0.01

GCS, Glasgow Coma Scale; ISS, Injury Severity Score.

Although the principles of DCR are well documented and practiced since the introduction in 2007 with balanced 1:1:1 transfusions as one of the main pillars in the treatment strategy,[12 13 35] achieving balanced transfusion rates remains a challenge. In a recently published analysis of 4427 massively transfused patients in the USA, Nederpelt *et al* demonstrated that 69% of the cohort were resuscitated with a plasma:RBC ratio ≤0.5 the first 24 hours, and the lowest ratios resulted in the highest mortality of 57%.[19] Similarly, in an Eastern Association for the Surgery of Trauma multicenter study, the authors uncovered that half of the trauma patients receiving UMTs in the recent period were transfused with RBC/FFP or RBC/platelets in unbalanced ratios ≥1.5:1 with a concomitant overall mortality of 43% at 24 hours.[20] Challenges to manage a balanced transfusion in the acute MT setting may have been underestimated and not conveyed properly. We think it is important to emphasize that the implementation of DCR with MHP in an institution takes time, and it is not given that institutions perform according to their protocol. From our data, we found that it took 6 years to reach the target of balanced transfusions according to our MHP. The alternative, whole blood (WB) resuscitation may reduce the logistical challenges of today's blood component therapy, and even improve hemostasis in bleeding patients. Although the current literature supports the safety and feasibility of WB use, the existing evidence is still limited.[36 37]

Our data demonstrate that massive transfusion with a balanced blood component ratio is achievable in the acute phase with reduced mortality at all time points from 6 hours to 30 days. From our experience, key factors contributing to an initial balanced transfusion are: strict adherence to protocol-based resuscitation, blood products available in the ED, effective blood bank logistics, and well-trained trauma teams, including the presence of attending level surgical and anesthesia competence. It is noteworthy that the abrupt change in transfusion ratio between 2013 and 2014 coincides with adding the presence of a dedicated trauma surgeon at all MHP activations.

The pathophysiology of TIC is a multifactorial complex process[38] which includes clotting factor consumption, hypothermia, acidosis, hypoperfusion, hemodilution and reduced clotting factor activity.[39 40] MHPs are meant to prevent and reverse these manifestations of TIC. Identification of trauma patients at risk of developing TIC is challenging due to the lack of scoring systems with good predictive performance but can be augmented by laboratory tests. In the current study, coagulation status at admission showed lower fibrinogen levels and higher INR in P1 (table 2), which may reflect a more liberal prehospital use of crystalloids in this period. INR variance is, however, not solely explained by decreased coagulation factor activities.[41] Baseline coagulation values at admission were comparable with recently published results on DCR by Cole *et al*.[21]

Critically injured hypotensive civilian trauma patients requiring laparotomy are still reported to have poor outcome with mortality rates up to 50%. In the UK, Marsden *et al* showed that the mortality rate for this population did not change between 2012 and 2016, with an average mortality rate of 48%, despite advances with the implementation of damage control strategies.[42] Harvin *et al* demonstrated that 82% of all deaths in the hypotensive group occurred within the first 24 hours.[43] Both studies lack data on transfusion ratios. In our study, 24-hour mortality decreased from 46% in P1 to 9% in P2 ($p<0.01$) for massively transfused patients undergoing laparotomy. The improved hemostatic resuscitation in P2 might have given the patients time to undergo angiographic interventions with concomitant decrease in need for hemostatic surgery (table 3). Also, the presence of an attending trauma surgeon does far more than improve DCR. For example, it might explain parts of the changed surgical treatment strategy between the periods.

This study has several limitations including those associated with its retrospective nature. During a period of 11 years, changes will occur gradually, which will not be easily quantifiable. During the study period, the MHP has been continuously updated following the growing body of evidence in this field. TXA was added to the MHP in August 2010, based on the Crash 2 trial.[29] Hypocalcemia and hypofibrinogenemia have been increasingly monitored and correction initiated with defined target levels defined as cCa^{2+} >1.2 mmol/L and fibrinogen >1.5–2.0 g/L, respectively.[1] The protocol for reversal of anticoagulants in bleeding trauma patients has gone through several adjustments. VHAs and other coagulation tests are integral parts of monitoring coagulation according to larger trials.[31] In February 2014, the trauma service got access to a dedicated trauma hybrid operating room in the ED. However, a dedicated operating room and access to interventional radiology were both readily available 24/7 throughout the study period, minimizing any indications for REBOA. The effects of an attending trauma surgeon are probably due to a combination of multiple variables including knowledge about physiology, clinical decision-making, surgical skills, focusing on DCR with adherence to the MHP with balanced transfusion. However, several of these variables are difficult to measure, whereas transfusions can be quantified. Moreover, the inclusion criterion of more than 10 RBCs during the first 6 hours of admission assumes survival until 6 hours and may therefore be subject to survival bias. Lastly, the institutional trauma registry was not created to answer this study's specific research question and the availability of some variables from the registry were limited which may have introduced bias.

In conclusion, achieving balanced transfusion rates at 6 hours facilitated by adding the presence of an attending trauma surgeon during all MHP activations coincided with a reduction in all-cause mortality and hemorrhage-related deaths in massively transfused trauma patients at 6 hours, 24 hours and 30 days.

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