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The clinical effect of hemostatic resuscitation in traumatic hemorrhage; a before-after study

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1. Introduction

Trauma carries a large burden on health care resources. It is the leading cause of death among adults under the age of 50 years and represents a global mortality of 5 million people annually. Despite preventive measures and advances in critical care medicine, the number of traumatic deaths is not decreasing [1,2]. Hemorrhage accounts for 30–40% of traumatic mortality and is only surpassed by neurologic injuries as most common cause of death [3]. The physiological hemostatic response to injury comprises a complex series of reactions, with activation of the coagulation cascade to minimize blood loss [4]. Through various anticoagulation and hyperfibrinolysis pathways however, this may result in trauma-induced coagulopathy (TIC) [5,6]. TIC is diagnosed in 25–35% of trauma patients and is directly related to mortality [7]. Iatrogenic factors such as acidosis and hypothermia may further impede coagulation and together with TIC form a 'lethal triad' [8,9].

In order to manage these coagulation disorders, damage control resuscitation has been developed [10,11]. This strategy aims to achieve rapid control of the source of bleeding, in combination with permissive hypotension and hemostatic resuscitation. Permissive hypotension guarantees an adequate systolic perfusion pressure while avoiding dilutional coagulopathy [12]. Hemostatic resuscitation combines blood product transfusion and administration of coagulation factor concentrates to correct trauma-induced coagulopathy. Recent literature shows that the hemostatic effect of this strategy is most favourable with transfusion of red blood cell concentrate, plasma and platelet filtrate in a proportional ratio of 1:1:1 [13,14].

Coagulation management in hemostatic resuscitation can be guided by conventional laboratory assays (CLA) or viscoelastic hemostatic assays (VHA). Conventional laboratory assays such as prothrombin time (PT) and activated partial thromboplastin time (APTT) have limitations, since they only assess plasmatic coagulation and have prolonged turnaround times. Consequently, they are insufficient for correction of trauma-induced coagulopathy [15,16]. Viscoelastic hemostatic assays such as thromboelastometry (ROTEM) and thromboelastography (TEG) can be used as point-of-care monitoring and provide insight in the complete process of plasmatic and cellular clot formation, firmness and dissolution. VHA-guided coagulation management has shown to reduce bleeding, transfusion requirements and possibly mortality in cardiothoracic and transplantation surgery [17]. The level of evidence for its use in the traumatic population is however limited [18]. Trauma guidelines currently recommend to combine CLA and VHA for coagulation monitoring and resuscitation in these patients [19].

The aim of this study was to evaluate the clinical effect of hemostatic resuscitation in the traumatic population. We conducted a before-after study that allowed us to compare the outcome in patients treated with this strategy with a pre-intervention cohort. We hypothesized that hemostatic resuscitation would result in a beneficial clinical outcome.

2. Material and methods

2.1. Study design and setting

This observational study was conducted after implementation of a hemostatic resuscitation protocol in January 2015 at the Erasmus University Medical Center in Rotterdam, the largest level I trauma center in The Netherlands. This protocol introduced the use of massive transfusion packages with subsequent thromboelastometry-guided coagulation management for patients with traumatic blood loss. The standardized massive transfusion packages consisted of three units of 270 mL red blood cell concentrate, three units of 200 mL plasma, one combined unit of 350 mL platelet filtrate from five donors, 2000 mg fibrinogen concentrate and 2000 mg calcium gluconate. Furthermore, all patients received a dose of tranexamic acid upon presentation (1000 mg for patients <70 kg, 1500 mg for patients >70 kg). Thromboelastometry analysis was performed by laboratory personnel

Abbreviations: APTT, activated partial thromboplastin time; CLA, conventional laboratory assays; ISS, Injury Severity Scale; PT, prothrombin time; RBC, red blood cell concentrate; ROTEM, thromboelastometry; TEG, thromboelastography; TIC, trauma-induced coagulopathy; VHA, viscoelastic hemostatic assays.

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using the ROTEM Delta device (TEM International GmbH, Munich, Germany). Real-time thromboelastometry results were displayed through the ROTEM Secure Viewer software (TEM International GmbH, Munich, Germany). Physicians were trained in interpretation of the thromboelastometry results and a flowchart guided further coagulation correction. This flowchart was based on protocols from comparable trauma centers and corresponds with recently published treatment algorithms [20-23]. Supplemental administration of fibrinogen concentrate, prothrombin complex concentrate, platelet filtrate or tranexamic acid was given after interpretation of FIBTEM clot amplitude at 10 min, EXTEM clotting time, EXTEM clot amplitude at 10 min and EXTEM maximum lysis at 60 min respectively (Supplementary Fig. 1). Activation of the protocol was carried out at discretion of the attending trauma surgeon or anesthesiologist. This combined transfusion strategy replaced a traditional protocol, where patients were primarily treated with red blood cell concentrate (RBC) and crystalloids. In this traditional strategy, administration of plasma, platelet filtrate or coagulation factor concentrates was only performed after extensive RBC transfusion.

Both protocols focused on prompt control of hemorrhage through hemostatic interventions, in combination with permissive hypotension and prevention of hypothermia, acidosis and hypocalcemia. After hemodynamic stabilisation, RBC transfusion was performed at a hemoglobin level of 8.1 g/dL in both protocols (9.7 g/dL for patients with underlying cardiovascular disease). For platelet transfusion, the threshold was 75×10^9/L in hemostatic resuscitation and 60×10^9/L in the traditional protocol. The hemostatic resuscitation protocol was implemented simultaneously with the nationwide transition from single donor fresh frozen plasma (310 mL Q-plasma, Sanquin, The Netherlands) to pooled multi-donor solvent detergent plasma (200 mL Omniplasma, Sanquin, The Netherlands).

The study was approved by the Medical Ethical Committee of the Erasmus University, Rotterdam, The Netherlands. The need for informed consent was waived due to the observational design of the study in which patients were treated in adherence to routine institutional guidelines.

2.2. Study population

Adult polytrauma patients were included in the study population if they were primarily presented at the emergency department and received ≥1750 mL of blood transfusions (equivalent to the volume of one massive transfusion package) within 24 h of admission. Polytrauma was defined as an Injury Severity Score (ISS) >15 resulting from injury of at least two body regions. Patients admitted between January 2013 and December 2014 were compared to patients who presented between January 2015 and December 2016.

2.3. Data collection

All consecutive polytrauma patients were registered by the Trauma Research Unit Department of the Erasmus University Medical Center. Patients eligible for inclusion were anonymously registered in a study database. The following variables were collected from their medical records: patient characteristics, vital parameters, mechanism of trauma, Injury Severity Score, time between injury and presentation, Helicopter Emergency Medical Services consultation, anticoagulant medication, conventional laboratory assays, thromboelastometry results, blood transfusion type and volume, coagulation concentrates, procoagulant medication, mortality, length of stay on the intensive care, ventilation days, renal replacement therapy, transfusion complications, thromboembolic complications and length of stay in the hospital. Mechanism of trauma was categorized as fall from height, traffic accidents, gunfire incidents, stabbing incidents or other injuries. Cause of death was categorized as exsanguination, neurologic and others. Laboratory results of the assays performed shortest after emergency department presentation were documented in the database, with a maximum interval of one hour after arrival. Calculated APACHE IV mortality was provided by the national critical care registry. Mortality data were verified in the national civil registration database.

2.4. Outcomes

The primary outcome was defined as 30-day mortality. Secondary outcomes were transfusion requirements in the first 24 h of admission, ICU length of stay in 30-day survivors and exsanguination as cause of death.

2.5. Statistical analysis

Statistical analysis was performed using SPSS Statistics 25 (IBM, Armonk, United States). Continuous data were checked for normal distribution by inspection of Q-Q plots and the Shapiro-Wilk test. Data were presented as median with interquartile range (IQR) and frequencies with percentages. Differences between populations were analyzed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorial variables. Effect on primary outcomes are presented by univariate odds ratios with 95% confidence intervals. Thirty-day survival was assessed with Kaplan-Meier analysis and log-rank test. Statistical significance was set at a p-value of <0.05 for all analyses.

3. Results

During 2013–2014, 822 polytrauma patients were presented at the Erasmus University Medical Center compared to 845 patients in 2015–2016. After exclusion of pediatric patients, interhospital transfers and patients not directly presented after injury, 611 and 595 patients remained in both groups respectively. Evaluation of blood transfusion requirement provided a study population of 57 patients in 2013–2014 and 65 patients in 2015–2016 who received transfusion of ≥1750 mL blood products within 24 h.

The baseline characteristics (Table 1) show that patients had a median overall age of 48 years [IQR 32–60]. The 2013–2014 pre-intervention population included a significantly larger portion of male patients (85% vs 65%, $p < 0.001$) and demonstrated a lower heart rate at presentation (100 bpm [IQR 86–129] vs 117 bpm [IQR 100–130], $p = 0.046$). Blood pressure, temperature and Glasgow Coma Scale did not significantly differ between groups. Traffic accidents and fall from height were the most common mechanisms of injury (45% and 29% respectively). Traumatic brain injury was present in 67% of cases. The median ISS was 34 [IQR 26–45] in both populations, with an overall calculated APACHE IV mortality of 52% [IQR 7–77]. Eighty-one percent of patients needed emergency surgery or embolization. Time to presentation at the emergency department was 48 min [IQR 42–63] in the pre-intervention group and 54 min [IQR 47–60] post-intervention ($p = 0.85$). Consultation of Helicopter Emergency Medical Services was not different between groups (92% vs 86%, $p = 0.20$). Prehospital transfusion of red blood cell concentrate, however, was significantly more frequently administered in the post-intervention population (0% vs 16%, $p < 0.001$).

Laboratory results (Table 2) demonstrate that the hemoblogin level at emergency department presentation did not significantly differ between groups (10.6 g/dL [IQR 8.9–12.4] vs 11.3 g/dL [IQR 9.3–13.1], $p = 0.18$). The median platelet count was lower in the pre-intervention population (178×10^9/L [IQR 136–219] vs 203×10^9/L [IQR 147–283], $p = 0.025$). Nevertheless, thrombocytopenia was not significantly more frequently observed (31% vs 25%, $p = 0.52$). Thromboelastometry was performed in 2% of patients in the pre-intervention population versus 49% post-intervention ($p < 0.001$). Sixty-nine percent of these cases had abnormal thromboelastometry results, most frequently due to a limited FIBTEM clot amplitude (59%) or prolonged EXTEM clotting time (52%). The Clauss fibrinogen assay was performed more frequently in the post-intervention population

Table 1
Baseline population characteristics at emergency department presentation.

Characteristics	Pre-intervention ($n = 65$)	Post-intervention ($n = 57$)	p-Value
Age (years)	47 (33–60)	49 (32–59)	0.78
Male	55 (85%)	35 (61%)	< 0.001
Heart rate (beats per minute)[a]	100 (86–129)	11 (100−130)	0.046
Tachycardia (≥100 beats per minute)	35 (55%)	43 (80%)	< 0.001
Systolic blood pressure (mmHg)[b]	105 (80–128)	96 (80–138)	0.54
Hypotension (≤90 mmHg)	25 (42%)	22 (45%)	0.85
Temperature (Celsius)[c]	35.4 (34.0–36.0)	35.5 (34.5–36.2)	0.23
Hypothermia (≤35.0C)	20 (45%)	13 (32%)	0.27
Maximum Glasgow Coma Scale	8 (3–14)	7 (3–14)	0.72
Glasgow Coma Scale ≤8	35 (54%)	29 (51%)	0.86
Mechanism of trauma			
Fall from height	19 (29%)	17 (30%)	1.00
Traffic accident	28 (43%)	27 (47%)	0.72
Stabbing incident	6 (9%)	7 (12%)	0.77
Gunfire incident	3 (5%)	2 (4%)	1.00
Other	9 (14%)	4 (7%)	0.25
Blunt trauma	55 (85%)	48 (84%)	1.00
Traumatic brain injury	42 (65%)	40 (70%)	0.57
Injury Severity Score	34 (25–44)	34 (27–48)	0.48
APACHE IV mortality (%)	49 (6–76)	63 (11–80)	0.64
Helicopter Emergency Medical Services	60 (92%)	49 (86%)	0.20
Time to presentation (minutes)	48 (42–63)	54 (47–60)	0.85
Prehospital intubation	44 (68%)	37 (65%)	0.45
Prehospital transfusion	0	9 (16%)	< 0.001
Transfusion on emergency department	49 (75%)	43 (75%)	0.84
Emergency surgery or embolization	52 (80%)	47 (82%)	0.82
Anticoagulant medication			
Antiplatelet therapy	3 (5%)	1 (2%)	0.62
Vitamin K antagonists	0	3 (5%)	0.10

Categorial variables presented as numbers (%) with p-values from Fisher's exact test; continuous variables presented as median (interquartile range) with p-values from Mann-Whitney U test.

[a] Excluding patients with missing variables; pre-intervention: 1 patient (2%), post-intervention: 3 patients (5%).

[b] Excluding patients that were lost to follow-up; pre-intervention: 5 patients (8%), post-intervention: 8 patients (14%).

[c] Excluding patients that were lost to follow-up; pre-intervention: 21 patients (32%), post-intervention: 16 patients (28%).

Table 2
Laboratory analysis results.

Laboratory results	Pre-intervention ($n = 65$)	Post-intervention ($n = 57$)	p-Value
Hemoglobin (g/dL)	10.6 (8.9–12.4)	11.3 (9.5–13.1)	0.18
Analyzed patients	61 (94%)	54 (95%)	1.00
Anemia (<9 g/dL)	16 (26%)	8 (15%)	0.17
pH	7.16 (7.09–7.26)	7.21 (7.01–7.28)	0.65
Analyzed patients	49 (75%)	48 (84%)	0.27
Acidosis (<7.30)	42 (86%)	38 (79%)	0.44
Lactate (mmol/L)	4.5 (2.9–7.1)	4.0 (3.0–8.3)	0.71
Analyzed patients	47 (72%)	44 (77%)	0.68
Hyperlactatemia (>2 mmol/L)	39 (83%)	39 (89%)	0.55
Base deficit (mEq/L)	10 (7–13)	9 (6–15)	0.99
Analyzed patients	47 (72%)	47 (82%)	0.20
Elevated (>4 mEq/L)	41 (87%)	38 (81%)	0.57
Platelet count (10^9/L)	178 (136–219)	203 (147–283)	0.025
Analyzed patients	54 (83%)	52 (91%)	0.28
Thrombocytopenia (<150 × 10^9/L)	17 (31%)	13 (25%)	0.52
INR[a]	1.4 (1.3–1.6)	1.3 (1.1–1.6)	0.08
Analyzed patients	46 (71%)	47 (82%)	0.14
Prolonged (>1.5)	12 (26%)	14 (30%)	0.82
APTT (seconds)	30 (25–45)	35 (24–50)	0.68
Analyzed patients	41 (63%)	40 (72%)	0.45
Prolonged (>60 s)	5 (12%)	9 (23%)	0.25
Fibrinogen (g/L)	1.0 (0.6–2.2)	1.6 (1.2–1.8)	0.34
Analyzed patients	3 (5%)	34 (60%)	< 0.001
Hypofibrinogenemia (<1.5 g/L)	2 (67%)	14 (41%)	0.57
Thromboelastometry			
Analyzed patients	1 (2%)	28 (49%)	< 0.001
Abnormal EXTEM / FIBTEM	1 (100%)	19 (68%)	1.00

Categorial variables presented as numbers (%) with p-values from Fisher's exact test; continuous variables presented as median (interquartile range) with p-values from Mann-Whitney U test.

[a] Excluding patients using vitamin K antagonists; pre-intervention: no patients, post-intervention: 3 patients (5%).

(5% vs 60%, $p < 0.001$). The measured fibrinogen activity, however, was not significantly different between groups (1.0 g/L [IQR 0.6–2.2] vs 1.6 g/L [IQR 1.2–1.8], $p = 0.34$). Other conventional laboratory results did neither reveal significant difference. The prevalence of any type of coagulation disorder at the moment of presentation was 40% in the pre-intervention population versus 56% post-intervention ($p = 0.12$).

Adherence to the hemostatic resuscitation protocol in 2015–2016 was 65%. Table 3 provides the results for blood transfusion and coagulation management in the first 24 h of admission. Patients received red blood cell concentrate transfusion in a median dose of 2160 mL [IQR 1350–3645] in both groups. The volume of plasma transfusion was significantly lower in the post-intervention population (2170 mL [IQR 1240–5580] vs 1400 mL [IQR 700–2100], $p < 0.001$). Meanwhile, the post-intervention population was more frequently treated with platelet filtrate (65% vs 96%, $p < 0.001$) and fibrinogen concentrate (20% vs 74%, $p < 0.001$). The median volume of platelet filtrate administration was 700 mL [IQR 350–1400] in the pre-intervention cohort compared to 350 mL [IQR 350–1050] post-intervention ($p = 0.27$). For patients that received fibrinogen concentrate, median doses were 4000 mg [IQR 2500–6000] and 2000 mg [IQR 2000–4000] respectively ($p = 0.16$). Furthermore, the median administered dose of calcium gluconate was higher in the post-intervention population (2000 mg [IQR 1000–4000] vs 3000 mg [IQR 2000–6000], $p = 0.034$). Treatment with tranexamic acid and prothrombin complex concentrate did not

Table 3
Blood transfusion and coagulation treatment within the first 24 h.

Therapy	Pre-intervention ($n = 65$)	Post-intervention ($n = 57$)	p-Value
Red blood cell concentrate			
Treated patients	65 (100%)	57 (100%)	1.00
Dose (mL)	2160 (1350–4995)	2160 (1350–3240)	0.67
Plasma			
Treated patients	63 (97%)	57 (100%)	0.50
Dose (mL)	2170 (1240–5580)	1400 (700–2100)	< 0.001
Platelet filtrate			
Treated patients	42 (65%)	55 (96%)	< 0.001
Dose (mL)	700 (350–1400)	350 (350–1050)	0.27
Fibrinogen concentrate			
Treated patients	13 (20%)	42 (74%)	< 0.001
Dose (mg)	4000 (2500–6000)	2000 (2000–4000)	0.16
Tranexamic acid			
Treated patients	51 (78%)	47 (82%)	0.65
Dose (mg)	2000 (1000−3000)	2000 (1000–3000)	0.87
Calcium gluconate			
Treated patients	54 (83%)	52 (91%)	0.28
Dose (mg)	2000 (1000–4000)	3000 (2000–6000)	0.034
Prothrombin complex concentrate			
Treated patients	7 (11%)	12 (21%)	0.14
Dose (IU)	2000 (750–2500)	1125 (625–2000)	0.54

Categorial variables presented as numbers (%) with p-values from Fisher's exact test; continuous variables presented as median (interquartile range) with p-values from Mann-Whitney U test.

significantly differ between study groups.

All cause 30-day mortality was 43% in the pre-intervention population versus 51% post-intervention ($p = 0.47$; Table 4). Kaplan-Meier analysis did not show significant difference in 30-day survival (Fig. 1, log-rank $p = 0.41$). Causes of death were similarly distributed in both study populations, with exsanguination representing 32% of cases pre-intervention versus 24% post-intervention ($p = 0.57$). After excluding patients with a neurologic cause of death, 30-day mortality did not change (23% vs 26%, $p = 0.80$, log-rank $p = 0.74$). Secondary outcome ICU length of stay in 30-day survivors was not significantly different between groups (6.0 vs 8.0 days, $p = 0.30$), nor was the amount of ventilation days (3.0 vs and 5.5 days, $p = 0.53$) or hospital length of stay (31.0 vs 27.0 days; $p = 0.25$). Post-hoc analysis only comparing patients that were treated in adherence to the hemostatic resuscitation protocol did not change primary or secondary outcomes (Supplementary Table 1 and Supplementary Fig. 2). Renal replacement therapy, thromboembolic complications and transfusion reactions were infrequently reported and did not show significant difference in distribution between groups.

4. Discussion

This study was performed to evaluate the effect of a hemostatic resuscitation strategy that combines the use of massive transfusion packages and thromboelastometry-guided coagulation management in patients with trauma-induced coagulopathy. Our findings demonstrate that in a population with 65% protocol adherence, application of hemostatic resuscitation increases the frequency of platelet filtrate and fibrinogen concentrate administration, while reducing the volume of plasma transfusion. The outcome results observed in our population do not indicate a favourable trend with regards to mortality, exsanguination or ICU length of stay.

Our study underlines the difficulty of adequate hemostatic management in the traumatic population. The multifactorial causes of bleeding together with problematic source control and trauma-induced coagulopathy make traumatic hemorrhage incomparable to other types of bleeding. Results from studies performed in patients with hemorrhage due to other conditions do therefore not necessarily translate to the traumatic population. The beneficial effect of hemostatic resuscitation described in cardiothoracic surgery was not reproduced in our trial [17]. A previous study by Johannson et al. demonstrated a decrease in 30-day mortality after implementation of a hemostatic resuscitation protocol similar to the one used in this study [24]. Their population, however, included a relatively large fraction of vascular and cardiothoracic surgery patients, with trauma representing only 14.5% of cases. Our results exclusively in patients with traumatic hemorrhage do not indicate a similar trend. A multicenter randomized controlled trial is currently being undertaken to further clarify the potential clinical effect of thromboelastometry-guided hemostatic resuscitation in trauma patients [23].

Approximately half of the patients in our study population suffered from coagulation disorders upon presentation at the emergency department. This corresponds to the prevalence of trauma-induced coagulopathy previously reported [25,26]. These findings emphasize the importance of expeditious coagulation analysis in trauma patients. As stated in trauma guidelines, point-of-care thromboelastometry monitoring may shorten turnaround times and thereby improve insight in patient coagulation status compared to conventional laboratory assays [19].

Considering the pathophysiological effects of trauma-induced coagulopathy, we anticipated an increase in platelet filtrate transfusion as observed in our post-intervention population. Nevertheless, this does not correspond to the results of a recent trial by Gonzalez et al. [27]. Their study evaluated the effect of a massive transfusion protocol where suppletion of coagulation factor concentrates was either directed by conventional laboratory assays or thromboelastography. Patients treated with the thromboelastography-guided protocol demonstrated a significant reduction in both plasma and platelet filtrate transfusion and had improved 28-day survival.

The reduction in plasma transfusion volume observed after implementation of the hemostatic resuscitation protocol may be the result of adequate coagulation factor concentrate utilization. However, the simultaneous nationwide transition from single-donor fresh frozen plasma in a volume of 310 mL per unit to multi-donor solvent detergent plasma in a volume of 200 mL per unit presumably affected these findings. The frequency of treatment with plasma, platelet filtrate and coagulation factor concentrates observed in the pre-intervention population indicates a more liberal administration of these products than instructed in the protocol applicable at that time. Most likely, evidence from studies on hemostatic resuscitation prior to implementation of our protocol stimulated physicians to already adopt parts of this strategy in their clinical practice. This may have led to a potential underestimation of the effect of hemostatic resuscitation in our patients. Furthermore, the time of blood product administration was

Table 4
Primary and secondary outcome variables comparing patients treated before versus after implementation of hemostatic resuscitation.

Outcome	Pre-intervention (n = 65)	Post-intervention (n = 57)	*p*-Value	Odds ratio (95% CI)
Mortality				
24 h	20 (31%)	17 (30%)	1.00	0.96 (0.44–2.07)
7 days	25 (39%)	26 (46%)	0.47	1.34 (0.65–2.77)
30 days	28 (43%)	29 (51%)	0.47	1.37 (0.67–2.80)
Cause of death				
Neurologic injury	17 (61%)	19 (66%)	0.79	1.23 (0.42–3.61)
Exsanguination	9 (32%)	7 (24%)	0.57	0.67 (0.21–2.15)
Other	2 (7%)	3 (10%)	1.00	1.50 (0.23–9.73)
Mortality neurology excluded				
24 h	9 (19%)	7 (18%)	1.00	0.92 (0.31–2.74)
7 days	11 (23%)	10 (26%)	0.80	1.20 (0.45–3.22)
30 days	11 (23%)	10 (26%)	0.80	1.20 (0.45–3.22)
ICU length of stay in 30-day survivors (days)[a,b]	6.0 (2.0–15.8)	8.0 (3.0–14.5)	0.30	
Ventilation support in 30-day survivors (days)[a,b]	3.0 (1.3–12.8)	5.5 (2.0–9.8)	0.53	
Hospital length of stay in 30-day survivors (days)[a,c]	31.0 (22.5–56.8)	27.0 (16.0–51.0)	0.25	
Renal replacement therapy[b]	2 (3%)	1 (2%)	1.00	
Thromboembolic complications[c]	2 (3%)	3 (5%)	1.00	
Transfusion reactions	0	1 (2%)	0.48	

Categorial variables presented as numbers (%) with *p*-values from Fisher's exact test; continuous variables presented as median (interquartile range) with *p*-values from Mann-Whitney *U* test.

[a] Excluding patients that died at the emergency department or operating theatre prior to clinical admission; 6 patients in 2013–2014, 5 patients in 2015–2016.

[b] Excluding patients that were lost to follow-up; 1 patient in 2013–2014, no patients in 2015–2016.

[c] Excluding patients that were lost to follow-up; 5 patients in 2013–2014, 1 patient in 2015–2016.

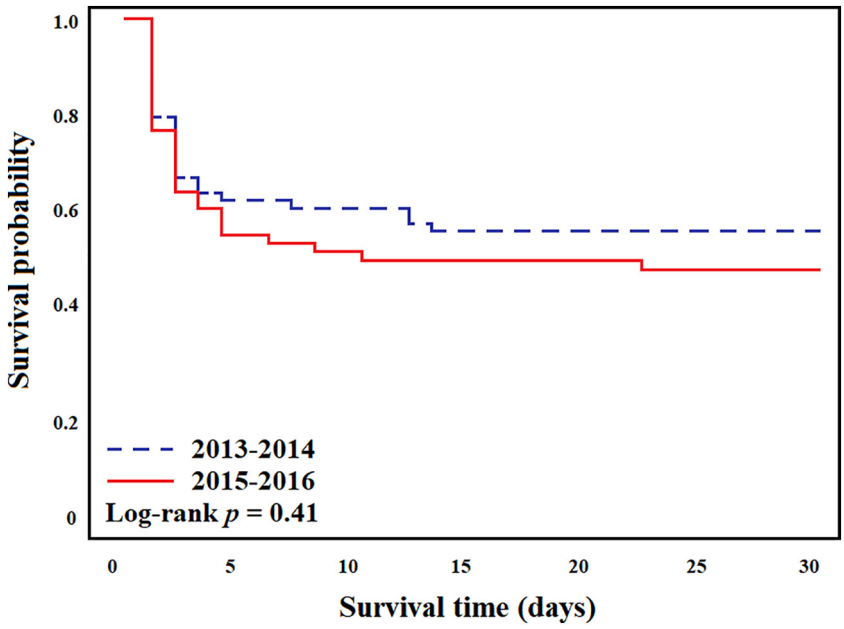

Fig. 1. Cumulative survival rate for patients treated before (2013–2014) versus after (2015–2016) implementation of hemostatic resuscitation.

unfortunately not documented during the trial. The necessary thawing of plasma may have delayed the logistic distribution of this product, thereby affecting the sequence of blood product transfusion. The volume of crystalloid and colloid administration could neither reliably be collected from the medical records of our patients. A possible transition in treatment with these products could therefore not be assessed. Due to these limitations, the definite effect of plasma transfusion in trauma patients cannot be addressed with this study. Results from previous trials, however, indicate that due to processing and storage, the effectiveness of plasma transfusion on reversal of coagulation disorders is probably limited [28]. Innerhofer et al. recently reported a reduction of blood transfusion requirement and morbidity in trauma patients treated with fibrinogen concentrate, prothrombin complex concentrate and factor XIII, compared to treatment with plasma [29]. Taking all results into account, we believe that the use of coagulation factor concentrates should be stimulated in patients with trauma-induced coagulopathy.

Adherence to treatment protocols in the emergency department is highly variable, mostly due to time constraints and the clinical setting of unscheduled patient care [30]. In order to optimize compliance, we developed an extensive implementation program, which included congress meetings, poster reminders and educational visits with audit and feedback at all involved departments. The adherence rate observed in our study population is consistent with previously described results in trauma patients [31]. There seems to be a correlation between guideline compliance and in-hospital mortality in the traumatic population [32]. Future studies should therefore focus on optimization of strategies for emergency department protocol implementation, in order to further improve the quality of trauma care.

A major limitation to our study is the population size, due to our single center design. Despite thorough selection of our study population, exsanguination only represented cause of death in a limited group of patients. The infrequency of this clinical endpoint affects the reliability of our findings and therefore the effect of hemostatic resuscitation on exsanguination cannot be determined with this study. Post-hoc power calculations are not recommended by literature [33]. We emphasize that a statistical type II error is not excluded and might impede our study results.

Another limitation is a potential chronological bias due to the before-after design of our study. This would however most likely benefit the post-intervention population, for example reflected by the increase in prehospital blood transfusions. Since the results of hemostatic resuscitation in our post-intervention population lack an outcome benefit, it is relatively unlikely that undocumented confounding factors significantly constrain this conclusion. A multicenter study with consecutive protocol implementation at each site would be necessary in order address both these restrictions.

5. Conclusion

This study emphasizes the problematic management of hemorrhage in trauma patients and demonstrates the difficulty of implementing a protocolized resuscitation strategy. Our results do not indicate that the use of a hemostatic resuscitation protocol with massive transfusion packages and thromboelastometry-guided coagulation management causes a favourable trend in 30-day mortality or intensive care length of stay. Due to the limitations of our study, the optimal resuscitation strategy in traumatic hemorrhage will have to be determined by future research.

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Authors' contribution statement

RZ conceptualized the study, carried out retrospective inclusion of patients, performed statistical analysis of the data and drafted the manuscript. He took part in development and implementation of the hemostatic resuscitation protocol. Furthermore, he took care of the application for approval by the medical ethical committee.

HE contributed in interpretation of the data, helped to draft the manuscript and revised the manuscript critically for important intellectual content.

SH participated in the design of the study and supervised statistical data analysis. Furthermore, she helped to draft the manuscript and revised the manuscript critically for important intellectual content.

MM took part in development and implementation of the hemostatic resuscitation protocol, helped to draft the manuscript and revised the manuscript critically for important intellectual content.

DH facilitated the data for inclusion of patients and contributed in interpretation of the data. Furthermore, he helped to draft the manuscript and revised the manuscript critically for important intellectual content.

RS made contributions in conception and coordination of the study and contributed in interpretation of the data. Furthermore, he helped to draft the manuscript and revised the manuscript critically for important intellectual content.

Declaration of Competing Interest

None.

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