

Effects of modification of trauma bleeding management: A before and after study

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EFFECTS OF MODIFICATION OF TRAUMA BLEEDING MANAGEMENT:

A BEFORE AND AFTER STUDY

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ABSTRACT (240 words)

Objective

We hypothesised that the association of tranexamic acid (TXA) administration and thromboelastometry-guided haemostatic therapy (TGHT) with implementation of *Damage Control Resuscitation* (DCR) reduced blood products (BP) use and massive transfusion (MT).

Methods

Retrospective comparison of 2 cohorts of trauma patients admitted in a university hospital, before (Period 1) and after implementation of DCR, TXA (first 3-hours) and TGHT (Period 2). Patients were included if they received at least 1 BP (RBC, FFP or platelet) or coagulation factor concentrates (fibrinogen or prothrombin complex) during the first 24-hours following the admission.

Results

380 patients were included. Patients in Period 2 (n= 182) received less frequently a MT (8% vs. 33%, p<0.01), significantly less BP (RBC: 2 units [1-5] vs. 6 [3-11]; FFP: 0 units [0-2] vs. 4 [2-8]) but more fibrinogen concentrates (3.0 g [1.5-4.5] vs. 0.0 g [0.0-3.0], p<0.01). Multivariate logistic regression analysis identified Period 1 as being associated with an increased risk of receiving MT (OR: 26.1, 95% CI: 9.7-70.2) and decreased survival at 28 days (OR: 2.0, 95% CI: 1.0-3.9). After propensity matching, the same results were observed but there was no difference for survival and a significant decrease for the cost of BP (2370 ± 2126 vs. 3284 ± 3812 €, p: 0.036).

Conclusion

Following the implementation of a bundle of care including DCR, TGHT and administration of TXA, we observed a decrease to the use of blood products, need for MT and an improvement of survival.

Keywords: tranexamic acid, thromboelastometry, trauma, coagulopathy, blood products, coagulation factor concentrates, damage control.

INTRODUCTION

In order to improve the outcome of injured patients, *Damage Control* strategies have been implemented throughout the world during the last 15-years. *Damage Control Resuscitation* (DCR) seeks to minimise blood loss until definitive haemostasis is achieved. It includes permissive hypotension with restrictive fluid administration and early correction of the three components of the lethal triad: hypothermia, acidosis and the *Trauma induced coagulopathy* (TIC) [1]. TIC is a frequent phenomenon observed in 20 to 30 % of the injured patients [2], it reflects the severity of injury and bleeding, increases the requirement for blood and directly impacts outcome [2]. Treatment of TIC may involve administration of blood products (BP) at a fixed-ratio or the administration of BP combined with coagulation factors concentrates (CFC) according to an individualised goal-directed algorithm based on viscoelastic techniques, such as rotational thromboelastometry (ROTEM®, TEM international, Munich, Germany) [3-5]. Whereas several studies have found that the use of thromboelastometry-guided haemostatic therapy (TGHT) decreases the administration of BP and the rate of massive transfusion (MT) [6-8], only one study has suggested that the use of thromboelastography improves the outcome [9].

Together with implementation of DCR, it is now recommended, since the publication of the Crash-2 study in 2010, to give tranexamic acid (TXA) in the first three hours following the injury in order to reduce the bleeding and improve the outcome [10].

The objective of this before-and-after study was to evaluate in trauma patients the impact of the implementation of a bundle of care including DCR, TXA administration and TGHT, on blood consumption, MT and outcomes.

MATERIALS AND METHODS

Study objectives:

The primary goal of the study was to demonstrate a reduction of the BP consumption and MT with the combination of TXA administration, DCR and TGHT.

The secondary objectives were to determine the effects on the outcome, length of ICU stay and the impact on the overall cost of blood products and CFC.

Study design

This is a retrospective comparison between 2 groups of patients admitted to the same trauma centre located in an academic hospital (Centre Hospitalier Lyon Sud, Pierre Benite, France) before and after implementation of TXA administration (prehospital setting and the trauma resuscitation unit, 2010-2011), DCR and ROTEM® analysis, which was introduced in our hospital in march 2011 with several months dedicated to staff in-servicing.

We used 2 cohorts of patients for the study. The first cohort (Period 1) is retrospective, included patients admitted from January 1, 2005 to December 31, 2008 and was done for a previous unpublished work. The second cohort (Period 2) was identified from a trauma registry in which data were prospectively collected from January 1, 2012 to December 31, 2015. The registry is supervised by the regional network "RESUVAL" (www.resuval.fr) and is officially approved by the national data protection commission (*Commission Nationale Informatique et Liberté*, N°2009-674) [11]. In the registry, both prehospital and in hospital data are recorded. All patients (or their next of kin) were provided with information about the registry. According to French law, this non-interventional study did not need to be approved by a research ethics committee and specific written informed consent was not required.

Study groups and patients

Patients were included if they had a severe injury [injury severity score (ISS) > 8] and received during the first 24 hours following the admission, at least one BP (red blood cell, RBC; fresh frozen plasma, FFP; platelet concentrate, PC) or coagulation factors (fibrinogen concentrates, Clottafact®, or PCC Kanokad®, both from LFB, Les Ullis, France). Patients were excluded because of anticoagulant treatment, the absence of transfusion or CFC administration, the absence of ROTEM® analysis during the second period, the administration of blood products other than RBC (such as RBC) prior to the admission (**Figure 1**).

In Period 1, conventional coagulation tests (CCT) were used to diagnose and guide the treatment of TIC. In this group, BP or CFC were given according to physician's judgment or if the prothrombin time (PT) was less than 40 % or the fibrinogen was less than 1.0-1.5 $g.L^{-1}$.

In Period 2, coagulopathy was diagnosed and haemostatic products were given according to an algorithm developed in our hospital (**Figure 2**). ROTEM® analysis was performed using the ROTEM® coagulation analyser (Delta, Pentapharm, Munich, Germany) at admission and/or during the follow-up according to the judgment of the treating physician.

Blood products, CFC and tranexamic acid administration

In both study groups, the same category of BP and CFC were used. FFP and PCC were used during the 2 periods of time and the choice to used one or the other was let at the discretion of the attending physician. TXA was given only in Period 2. If not given in the prehospital setting, TXA was administered at admission. In both study time periods, RBC units were

administered to maintain a haemoglobin between 7 and 9 $g.dL^{-1}$. MT was defined as the administration of at least 10 RBC units during the first 24 hours. Platelet concentrates were utilized to maintain counts up to $50.10^9.L^{-1}$ (> $100.10^9.L^{-1}$ in patients with severe brain injury (GCS < 9) or haemorrhagic shock) as suggested by the French and European guidelines [4, 12].

Data Collection

From the patient's chart and trauma registry, we retrieved demographic data, including age and gender, Glasgow Coma Scale (GCS) at initial medical evaluation, systolic blood pressure (SBP) at hospital admission, mechanism of injury, blood product administration at 24 hours, and TXA administration. The ISS was calculated from the *abbreviated injury scale* (2005 version) after the imaging survey had been completed [13]. Length of intensive care unit stay was collected and the outcome (death/survival) was determined at 24 hours and at day 28.

Standard laboratory testing and ROTEM® analysis

We abstracted the results of conventional coagulation test (CCT) including standard coagulation (prothrombin time ratio (PT_{ratio}) and fibrinogen), ROTEM® analysis, haemoglobin and platelet count, base deficit and lactate. A lactate at admission > 3.9 $mmol.L^{-1}$ was used to categorise patients and define shock [14]. These tests are performed routinely in the trauma bay for all patients, at admission and throughout the resuscitation.

Blood samples were collected by venipuncture into Vacutainer tubes (Becton Dickinson, Plymouth, UK) containing EDTA for platelet and haemoglobin counts (XE-2100, XN-90000; Sysmex, Kobe, Japan) or citrate (0.129M trisodium citrate) for standard tests (Star Evolution; Diagnostica Stago, Asnieres, France): prothrombin time (PT) (STA-Neoplastin CI

plus), activated partial thromboplastin time (STA-PTT automat), fibrinogen (Clauss technique, STA-Fibrinogen), and thromboelastogram.

For the ROTEM® analysis, blood samples were collected at admission (<15 minutes) and then analysed within 30 minutes of blood sample collection. The ROTEM® coagulation analyser (Delta, Pentapharm, Munich, Germany) has been described previously in detail [15, 16]. In the ROTEM® analyser, coagulation is partially activated with recombinant human tissue factor (EXTEM test). In addition to the EXTEM screening tests, cytochalasin D (FIBTEM) is used in order to study the EXTEM with inhibition of platelets for fibrin polymerization evaluation. The ROTEM® analysis was performed at 37°C, in parallel, on two channels (EXTEM and FIBTEM). The following ROTEM® parameters were analysed: clotting time (CT), maximum clot firmness (MCF), and the amplitude of clot at 5 minutes (A5). ROTEM® analyses were performed in a standardized fashion throughout the study timeframe in the haemostasis laboratory where the ROTEM® is located. The results were immediately available on the computer located in the trauma resuscitation unit.

Cost calculation

The cost of BP and CFC was calculated for each group. The cost estimates were retrieved from the French blood bank and from the pharmacy of the *Hospices Civils de Lyon* (fibrinogen concentrates and PCCs). The following costs, including tax, were used for calculation: RBC (1U: 179,7 €), FFP (1U: 97.3 €), PC (1 unit: 82.1 €), fibrinogen concentrate (1g: 499,3 €), PCC (1U: 0.48 €).

Statistical Analysis

Results are expressed as median [interquartile range] or number (%) with 95% confidence

interval (95% CI). Normality of the distribution was tested using the Kolmogorov-Smirnov test. The Mann-Whitney U-test and Student t-test were used for continuous variables as appropriate. Statistical differences between groups were evaluated by $\chi 2$ test or by Fisher exact test when appropriate. A 2-tailed $p < 0.05$ was considered significant. In the whole cohort, data were missing for SBP, GCS, BE, lactate, PT, fibrinogen, haemoglobin and platelet. However, the incidence of missing data was less than 10% except in Period 1 for the GCS and BE, that were missing respectively in 45% and 25% of the case.

Univariate logistic regression models were performed with MT or mortality (at 24 hours and at day 28) as the dependent variable. Variables that were significantly associated with mortality at the level $p < 0.05$ were entered into stepwise logistic regression analysis to identify those variables that were independent predictors of mortality or MT. Odds ratios (ORs) and 95% CI were calculated. Calibration of the model was assessed using *Hosmer-Lemeshow* statistics. We used *Mahalanobis* metric matching within propensity score caliper to build a controlled match group. We matched one-by-one Period 1 and Period 2 patients according to the closest *Mahalanobis* distance using propensity score as caliper. Propensity score was estimated by the equation of logistic regression including Age, initial SBP, initial GCS and ISS. We selected covariables in a parsimonious way including well-known confounders. We were careful to include only baseline covariables. Statisticians subsequently reviewed statistical methods and results. All statistical tests were performed using commercially available statistical software (NCSS 9 Statistical Software (2013). NCSS, LLC. Kaysville, Utah, USA; MedCalc 14, Ostend, Belgium) and Stata software (Stata 14.0; Stata Corp, College Station, Tx, USA).

RESULTS

A total of 372 patients were included (190 in Period 1 and 182 in Period 2, **Figure 1**). Patients in Period 2 had a higher ISS, more frequently sustained a severe TBI and conventional coagulation tests showed a lower fibrinogen level at admission (**Table 1**). ROTEM® analysis at admission showed for the patients in Period 2 the following characteristics: (median [IQR]) for the EXTEM (CT: 79 s [62-117]; MCF EXTEM: 54 mm [46-59]; ML EXTEM: 4 [2-6]) and FIBTEM (MCF: 7 mm [4-10]).

We matched 102 patients in Period 2 with 102 patients in Period 1. Standardized differences for each covariable between group before and after matching were significantly reduced. Standardised difference for ISS was reduced from 27% to 2%, for Age from 18% to 5%, for SBP from 11% to 7% and for GCS from 6% to 0%. After matching, only the platelet number was different among groups (**Table 2**).

Blood products and TXA administration during the first 24 hours

TXA was given to 171 patients (95%) in Period 2, 109 (61%) in the prehospital phase and 62 (39%) at admission.

Patients in Period 2 received significantly less RBC, FFP and platelet but more PCCs and fibrinogen concentrates leading to an increase of the FIB:RBC ratio and the total FIB:RBC ratio (including fibrinogen from the FFP) (**Table 2**). The FFP:RBC ratio was not significantly different but significantly fewer patients received a combination of FFP and RBC in Period 2 (**Table 2**). After matching, the same results were observed.

When the comparison was made according to the ISS or in case of shock (lactate > 3.9 mmol.l^{-1}), these differences were also observed for the RBC, FFP, platelet and fibrinogen concentrates (**Figure 3**).

Massive Transfusion

A massive transfusion was utilised in 15 patients (8%) in Period 2 and 62 patients (33%) in Period 1 ($p< 0.01$). Stepwise regression analysis on unmatched cohorts showed that the following parameters were independent predictors of MT: Period 1, ISS, base deficit and haemoglobin (**Table 3**).

After matching, MT was observed for 3 patients (3%) in Period 2 as compared to 35 patients (34%) in Period 1 (odd ratio (OR): 5.39 (95% CI (95% confidence interval): 1.08-2.29, $p<0.001$).

Outcome

Survival at 24-hours was not different between groups (**Table 1**). Regression analysis showed that after adjustment, independent predictors of survival at 24-hours were base deficit, ISS, and GCS < 9 but not Period 1 (OR: 1.46 (95% CI: 0.69-3.11), $p= 0.326$). The same result was observed on matched data.

Survival at day-28 was not different between groups (**Table 1**). However, stepwise regression analysis showed that the variable "Period 1" was an independent predictor of death as well as the following parameters: age, GCS < 9, ISS and the base deficit (**Table 4**). However, after matching, there was no significant difference between groups.

Comparison of blood products and CFC Cost between groups

The mean ($\pm$ standard deviation) overall cost, including blood products and CFC was not different between study groups: 3190 $\pm$ 3448 euro (Period 1) vs. 3126 $\pm$ 2142 euro (Period 2, $p=0.861$). The cost of blood products only was diminished in Period 2 (939 $\pm$ 1468 € vs. 2394

± 2531 €, p<0.001) but it was associated with an increase to the cost of CFC (2192 ± 2367 € vs. 796 ± 1243 €, p<0.001).

After matching, a significant decrease to the overall cost of blood products and CFC was observed in Period 2 (2370 ± 2126 vs. 3284 ± 3812 €, p: 0.036).

DISCUSSION

In the present study, we observed that the incidence of massive transfusion and the use of blood products were dramatically reduced following the implementation of a bundle of care including thromboelastometry-guided haemostatic therapy, TXA administration and *Damage Control Resuscitation*. As well, we observed an improvement in survival at day-28 but not at 24-hours, and a decrease to the overall cost of blood products and CFC after matching.

For over a decade, thromboelastometry has been used to guide haemostatic treatment in a wide range of clinical situations such as liver transplantation, cardiac surgery, post-partum haemorrhage and trauma [16, 17]. It has been advocated, in trauma patients, as a method of early and accurate diagnosis of the coagulopathy and has been associated with a decrease in BP administration, as reported herein. A decrease of BP use was previously reported [6-8]. However, in these studies, the authors reported the effect of the association of ROTEM® analysis and CFC versus FFP and conventional coagulation test. In our study, in both group, CFC were used and we observed that the use of the ROTEM® in Period 2 leaded to an increase of fibrinogen concentrates administration and then to the FIB:RBC ratio. Fibrinogen concentrates is currently used as the first-line haemostatic agent in our trauma centre for TIC management, which is in agreement with what has been recently reported by Innerhofer et al. [8, 18]. It is suggested that increasing clot firmness by administering fibrinogen concentrates may help to decrease bleeding, reduce blood product consumption and the rate of MT. A significant reduction of MT was recently reported in a randomised study and in a before and after study [8, 19]. In both studies, factor XIII has been used but contrary to what has been reported in these studies, we observed a similar or even greater reduction in MT without its administration and with the use of FFP, even though the administration of FFP was dramatically reduced [8, 19, 20]. However, the reduction of blood

products use cannot be solely attributed to TGHT and is probably also in relation with implementation of TXA administration and DCR, including massive transfusion protocols (MTP). For example, it has been shown that following implementation of MTP, a decrease of BP use can be observed [21]. As well, Cotton BA et al. have shown that DCR is associated with a reduction in BP use in *Damage Control* laparotomy patients [22].

The second finding of this study was the improvement of survival at day-28. The interpretation of this result is complex because an improvement of prognosis has been shown for each components of the bundle of care implemented in this study [9, 10, 22, 23]. Damage control resuscitation that includes permissive hypotension, low volume resuscitation and *Damage Control Surgery* is currently recommended as standard of care in bleeding trauma patients and by itself improve the outcome [4, 24]. As well, a survival advantage has been demonstrated for TXA use and its administration in the first three hours after an injury is currently recommended [4, 10]. Moreover, the safety and effectiveness of TXA has been recently confirmed in a meta-analysis [25]. As recommended, a vast majority of patients in Period 2 received TXA. Therefore, we cannot exclude that the large administration of TXA in Period 2 may have contributed to our results, as in the RETIC study [8]. Recently, an improvement in survival has been reported with TGHT, as compared to CCT guided haemostatic treatment, in a population of injured patients meeting criteria for MTP activation [9]. In this trial, where the authors did not show any difference in blood products administration, it was suggested that TGHT allowed for more judicious use of blood products that were given earlier in patients in the TEG group than in the CCT group. It should nevertheless be note that patients in this study had received only a very low amount of fibrinogen (cryoprecipitate), which is quite different than European practices and findings from the present study. We observed an improvement of survival at day 28 and not at 24-

hours. This result is difficult to explain, but it is conceivable that the decrease in the number of blood products administered have led to a decrease in the number of transfusion-related complications such as infections, pulmonary embolism and TRALI [26, 27]. Unfortunately, we did not record this information in the study.

Finally, as reported by Nardi et al. and in other setting, we observed a reduction in the overall cost of transfusion and CFC in Period 2 after patients have been matched [7, 28]. This was attributable mainly to the significant and important decrease in the use of blood products. The decrease of the cost was not observed before matching probably because patients in Period 2 were more severely injured. It should also be observed that these results did not take into account the cost of consumables material for conventional coagulation tests or ROTEM® analysis. However, as compared to the costs of blood products or factor concentrates, the cost of biological testing is probably negligible and would probably not have change the results. For example, the cost of CCT is actually 14 euros as compared to 19 euros for VET analysis.

Limitations

Our study had several limitations. First, the present study was not randomised and reporting bias may have been induced because data from the first period were collected retrospectively from the patient's charts, whereas data from the second period were collected via standardised forms. Second, between the 2 study periods, multiple changes were introduced into clinical practice and it is not possible to determine the individual impact of each one. Only a randomised study would allow this to be done or, more pragmatically, a study comparing contemporary periods. Third, fibrinogen concentrates are not available everywhere which limits the extrapolation of the results. It is also important to

note that in the first period of the study, the lower threshold (1.0-1.5 $g.L^{-1}$) for the correction of fibrinogen deficit may have explained at least in part of the lower rate of fibrinogen concentrates administration. As well, fibrinogen concentrates were not immediately available in the trauma resuscitation unit contrary to the second period of time. This may have contributed to the results seen. Forth, patients in this study were cared by prehospital physician and the results of the present study may not apply into a prehospital paramedic based system even though we had shown in a previous study that the survival of injured patient was not different [11, 29].

CONCLUSION

In this study, following the implementation of a bundle of care including DCR, TGHT and administration of TXA, we observed a decrease to the use of blood products and need for MT as well as survival improvement. These results will nevertheless have to be confirmed by prospective studies.

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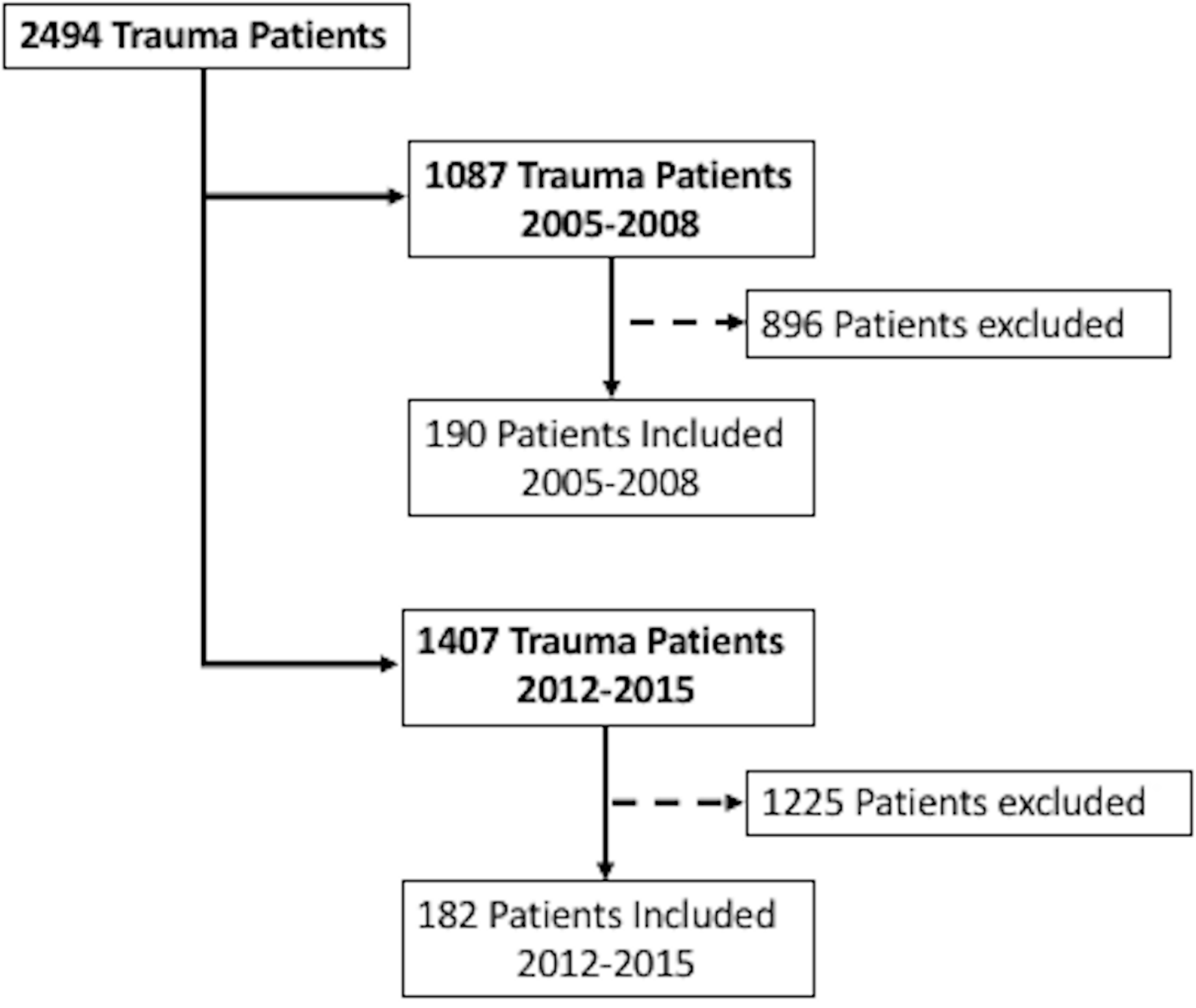
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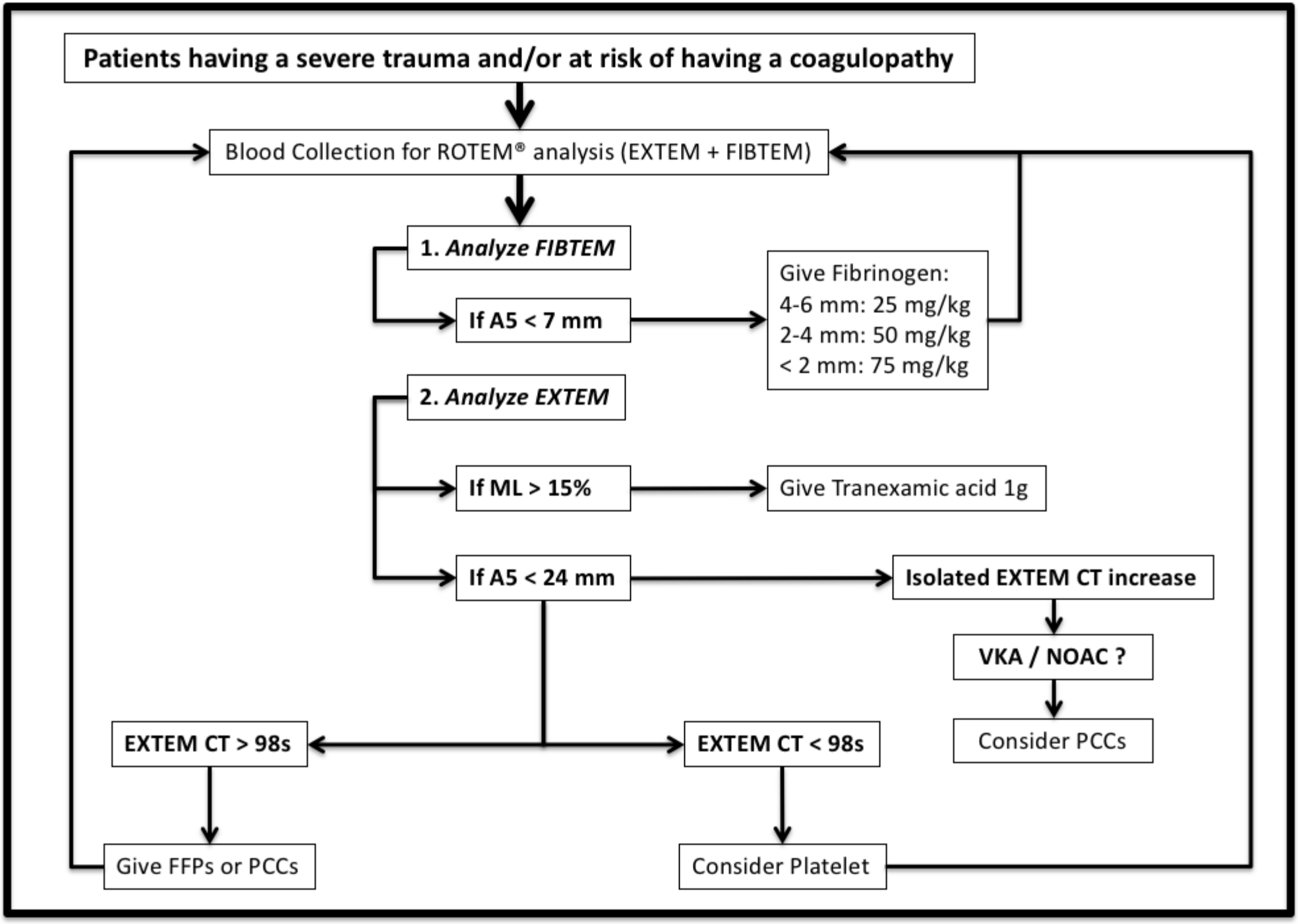
Legend of the Figures

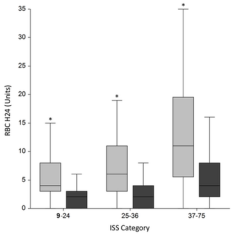
Figure 1. Flowchart of the study. Patients were excluded because of anticoagulant treatment, the absence of transfusion or CFC administration, the absence of ROTEM® analysis during the second period, the administration of blood products other than RBC prior to the admission.

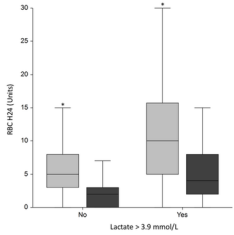
Figure 2. Algorithm used in Period 2.

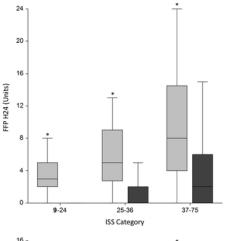
Figure 3. Distribution of blood products on unmatched cohorts according to the ISS and the presence of a shock (lactate > 3.9 $mmol.l^{-1}$). * $p < 0.05$ for the difference between study groups (ANOVA with Tukey-Kramer multiple comparison test). Data are median [interquartile range].

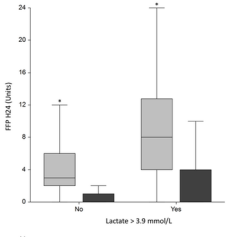

2494 Trauma Patients
1087 Trauma Patients
2005-2008
896 Patients excluded
190 Patients Included
2005-2008
1407 Trauma Patients
2012-2015
1225 Patients excluded
182 Patients Included
2012-2015

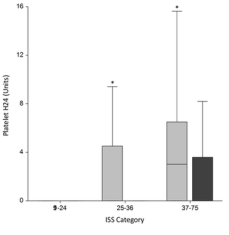

Patients having a severe trauma and/or at risk of having a coagulopathy
Blood Collection for ROTEM® analysis (EXTEM + FIBTEM)
1. Analyze FIBTEM
If A5 < 7 mm
Give Fibrinogen:
4-6 mm: 25 mg/kg
2-4 mm: 50 mg/kg
< 2 mm: 75 mg/kg
2. Analyze EXTEM
If ML > 15%
Give Tranexamic acid 1g
If A5 < 24 mm
Isolated EXTEM CT increase
VKA / NOAC ?
Consider PCCs
EXTEM CT > 98s
EXTEM CT < 98s
Give FFPs or PCCs
Consider Platelet

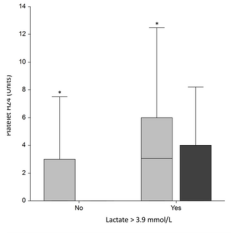

RBC H24 (Units)
ISS Category
9-24
25-36
37-75
Study_Group
Period 1
Period 2

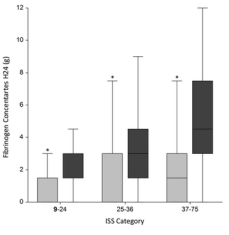

RBC H24 (Units)
Lactate > 3.9 mmol/L
No
Yes
Study_Group
Period 1
Period 2

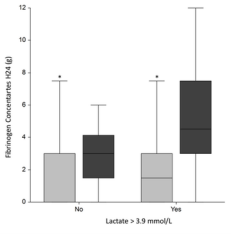

FFP H24 (Units)
ISS Category
9-24
25-36
37-75
Study_Group
Period 1
Period 2

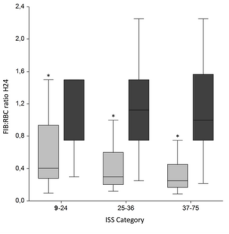

FFP H24 (Units)
Lactate > 3.9 mmol/L
No
Yes
Study_Group
Period 1
Period 2


Platelet H24 (Units)
ISS Category
9-24
25-36
37-75
Study_Group
Period 1
Period 2


Platelet H24 (Units)
Lactate > 3.9 mmol/L
No
Yes
Study_Group
Period 1
Period 2


Fibrinogen Concentartes H24 (g)
ISS Category
9-24
25-36
37-75
Study_Group
Period 1
Period 2


Fibrinogen Concentartes H24 (g)
Lactate > 3.9 mmol/L
No
Yes
Study_Group
Period 1
Period 2


FIB:RBC ratio H24
ISS Category
9-24
25-36
37-75
Study_Group
Period 1
Period 2

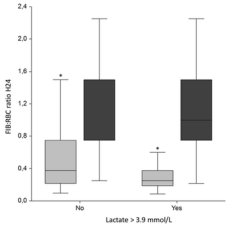

FIB:RBC ratio H24
Lactate > 3.9 mmol/L
No
Yes
Study_Group
Period 1
Period 2

Table 1. Demographic and injury characteristics at hospital admission.

	Period 1		Period 2	
	Unmatched	Matched	Unmatched	Matched
N	190	102	182	102
Demographic characteristics and vital signs at admission				
Age (years)	35 [22-54]	37 [24-54]	39 [25-53]	38 [25-53]
Sex male	144 (76)	76 (75)	129 (71)	71 (70)
SBP (mmHg)	105 [85-120]	109 [85-126]	106 [84-125]	107 [90-120]
GCS	13 [3-15]	13 [3-15]	11 [3-15]	13 [3-15]
GCS < 9	47 (26)	42 (41)	78 (43)*	39 (38)
Injury characteristics				
Injury Severity Score	28 [18-38]	28 [18-38]	30 [24-45]*	29 [22-38]
Blunt trauma	170 (89)	95 (93)	169 (93)	94 (92)
Trauma mechanism				
MVC	102 (54)	57 (56)	86 (47)	55 (54)
Pedestrian	14 (7)	8 (8)	23 (13)	8 (8)
Fall from a Height	44 (23)	24 (24)	48 (26)	28 (27)
Other	10 (5)	6 (6)	12 (7)	3 (3)
GSSW	12 (6)	4 (4)	11 (6)	6 (6)
Other penetrating	8 (4)	3 (3)	2 (1)	2 (2)
Outcome				
ICU LOS (days)	3 [1-9]	4 [1-17]	3 [1-13]	3 [1-12]
Survival at 24 hours	161 (85)	90 (88)	141 (77)	85 (83)
Survival at day 28	130 (68)	68 (50)	115 (63)	69 (50)

Data are n (%) or median [interquartile range]. P value refers to comparison between patients in Period 1 and 2. HD: hospital discharge; SBP: systolic blood pressure; GCS: Glasgow coma scale; MVC: motor vehicle crash; GSSW: gunshot and stab wound; ICU LOS: intensive care unit length of stay. * $p < 0.05$: unmatched patients in Period 1 vs. unmatched patients in Period 2.

Table 2. Laboratory analyses and blood product administration at 24 hours following admission.

	Period 1		Period 2	
	Unmatched	Matched	Unmatched	Matched
N	190	102	182	**102**
Laboratory analyses				
BD ($mEq.L^{-1}$)	6.2 [3.7-11.7]	6.6 [3.9-12.1]	8.0 [4.9-13.4]	7.4 [5.2-11.7]
Lactate ($mmol.L^{-1}$)	3.1 [2.1-6.6]	3.3 [2.1-6.8]	3.3 [2.1-5.9]	3.2 [2.0-5.0]
PT_{ratio}	1.3 [1.1-1.7]	1.3 [1.1-1.7]	1.4 [1.2-1.6]	1.3 [1.2-1.6]
Fibrinogen ($g.L^{-1}$)	1.6 [0.9-2.2]	1.6 [0.9-2.2]	1.5 [0.9-1.8]*	1.6 [1.1-2.0]
Hemoglobin ($g.dL^{-1}$)	10.6 [8.6-12.3]	10.6 [8.5-12.3]	10.1 [8.7-12.3]	11.0 [9.1-12.6]
Platelet ($10^9.L^{-1}$)	176 [123-233]	169 [130-225]	188 [146-227]	197 [151-241]‡
Blood products administered				
RBC (U)	6 [3-12]	6 [2-12]	2 [1-5]*	2 [0-4]‡
n (%)	181 (95)	96 (94)	137 (75)*	72 (71)‡
FFP (U)	4 [2-9]	5 [2-9]	0 [0-2]*	0 [0-2]‡
n (%)	163 (86)	84 (82)	60 (33)*	28 (27)‡
Platelets (U)	0 [0-4]	0 [0-4]	0 [0-0]*	0 [0-0]‡
n (%)	76 (40)	39 (38)	33 (18)*	17 (17)‡
FibCon (g)	0 [0-3]	0 [0-3]	3 [2-5]*	3 [2-5]‡
n (%)	76 (40)	46 (45)	153 (84)*	85 (83)‡
Total Fibrinogen (g)	2.4 [1.2-5.7]	2.9 [1.2-6.5]	3.0 [1.5-6.0]	3.0 [1.5-4.5]
n (%)	168 (88)	86 (84)	158 (87)	88 (86)
PCCs (UI)	1000 [900-1500]	1000 [875-1125]	2000 [1500-2000]*	2000 [1500-2000]‡
n (%)	10 (5)	6 (6)	37 (20)*	16 (16)‡
FFP:RBC ratio	0.8 [0.5-1.0]	0.9 [0.6-1.0]	0.7 [0.5-1.0]	0.8 [0.6-1.0]
n (%)	155 (82)	78 (76)	55 (30)*	26 (25)‡
FIB:RBC ratio	0.3 [0.2-0.5]	0.3 [0.2-0.5]	1.1 [0.8-1.5]*	1.1 [0.8-1.5]‡
n (%)	74 (39)	45 (44)	109 (60)*	55 (54)
Total FIB:RBC ratio	0.4 [0.3-0.7]	0.5 [0.4-0.8]	1.3 [0.9-1.6]*	1.4 [0.9-1.5]‡
n (%)	159 (84)	80 (78)	113 (62)	58 (57)‡

Data are median (interquartile range). BD: base deficit; CT: clotting time; clot amplitude at 5 min (A5) or maximum clot firmness (MCF). FibCon: fibrinogen concentrate; Total Fibrinogen: total amount of fibrinogen received by patients including fibrinogen from FibCon or FFP. ‡ $p < 0.05$: matched patients in period 1 vs. matched patients in period 2; * $p < 0.05$: unmatched patients in period 1 vs. unmatched patients in period 2.

Table 3. Stepwise regression analysis for massive transfusion.

	OR	95% CI	AUC	P		OR	95% CI	p
Univariate Analysis					**Multivariate Analysis**			
Period 1 (yes)	5.39	2.93-9.92	0.686	<0.001	**Period 1 (yes)**	25.92	9.66-69.51	<0.001
Injury Severity Score	1.06	1.04-1.08	0.723	<0.001	**Injury Severity Score**	1.06	1.03-1.10	<0.001
Base Deficit	0.88	0.84-0.92	0.732	<0.001	**Base Deficit**	0.88	0.83-0.94	<0.001
Hemoglobin	0.98	0.97-0.99	0.662	<0.001	**Hemoglobin**	0.97	0.96-0.99	<0.001
SBP < 90 mmHg (yes)	3.27	1.94-5.51	0.634	<0.001	-			
PT_{ratio} > 1.2 (yes)	4.17	2.16-8.07	0.641	<0.001	-			

The parameters that were significantly associated with massive transfusion are shown in the univariate analysis. For the multivariate regression analysis, calibration was assessed by the *Hosmer and Lemeshow* test (p: 0.18), AUC was 0.903 and the percentage of patients correctly classified was 87 %. OR: odds ratio. SBP (systolic blood pressure) and PT_{ratio} were not included in the final model.

Table 4. Univariate and multivariate stepwise regression analysis to predict death at day 28.

	OR	95% CI	AUC	P		OR	95% CI	P
Univariate Analysis					**Multivariate Analysis**			
Period 1 (yes)	0.79	0.52-1.22	0.529	0.196	**Period 1 (yes)**	2.12	1.06-4.24	0.033
Age	1.02	1.00-1.03	0.574	0.004	**Age**	1.04	1.02-1.08	<0.001
GCS < 9	12.67	7.50-21.39	0.775	<0.001	**GCS < 9 (yes)**	14.48	6.92-30.30	<0.001
Injury Severity Score	1.10	1.07-1.12	0.806	<0.001	**Injury Severity Score**	1.05	1.02-1.08	0.002
Base Deficit	0.85	0.82-0.89	0.741	<0.001	**Base Deficit**	0.86	0.81-0.91	<0.001
SBP < 90 mmHg (yes)	2.63	1.65-4.18	0.604	<0.001	**-**			

The parameters that were significantly associated with death at day 28 are shown in the univariate analysis. For the multivariate regression analysis, calibration was assessed by the Hosmer and Lemeshow test (p: 0.63), AUC was 0.896 and the percentage of patients correctly classified was 81%. Systolic blood pressure was not included in the final model. OR: odds ratio. The variable “study group” was forced into the model.