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Early coagulation support protocol: A valid approach in real-life management of major trauma patients. Results from two Italian centres ☆

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ABSTRACT

Introduction: Early coagulation support (ECS) includes prompt infusion of tranexamic acid, fibrinogen concentrate, and packed red blood cells for initial resuscitation of major trauma patients. The aim of this study was to determine the effects, in terms of blood product consumption, length of stay, and in-hospital mortality, of the ECS protocol, compared to the massive transfusion protocol (MTP) in the treatment of major trauma patients.

Patients and methods: A retrospective analysis was conducted using the registry data of two Italian trauma centres. Adult major trauma patients with, or at risk of, active bleeding who were managed according to the MTP during the years 2011–2012, or the ECS protocol during the years 2013–2014 and were considered at risk of multiple transfusions, were enrolled. The primary endpoint was to determine whether the ECS protocol reduces the use of blood products in the acute management of trauma patients. Secondary endpoints were the outcome measures of length of stay in ICU, length of stay in hospital, and mortality at 24-hours and 28-days after hospital admission.

Results: Among the 518 major trauma patients admitted to the trauma centres during the study period, 235 patients (118 in the pre-ECS period and 117 in the ECS period) matched one of the inclusion criteria and were enrolled in the study. Compared with the pre-ECS period, the ECS period showed a reduction in the average consumption of packed red blood cells (−1.87 units, 95% confidence interval [CI], −2.40, −1.34), platelets (−1.28 units; 95% CI, −1.64, −0.91), and fresh frozen plasma (−1.69; 95% CI, −2.14, −1.25)

☆ This study was performed at the Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy) and at Azienda Ospedaliera San Camillo Forlanini (Rome, Italy).

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in the first 24-hours. Furthermore, during the ECS period, we recorded a 10-day reduction in the hospital length of stay (−10 days, 95% CI, −11.6, −8.4) and a non-significant 28-day mortality increase.
Conclusions: The ECS protocol was effective in reducing blood product consumption compared to the MTP and confirmed the importance of early fibrinogen administration as a strategy of rapid coagulation. This novel approach may be adopted in real-life management of major trauma patients.
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Introduction

Uncontrolled bleeding is the main cause of early death due to major trauma during the acute phase of trauma-induced critical illness; coagulopathy represents a severe complication yielding increased transfusion requirements and mortality [1–3]. Fibrinolysis plays a central role in the development of trauma-induced coagulopathy (TIC), which affects up to a third of major trauma patients at hospital admission [4–8]. Massive transfusion protocols (MTPs) were developed to foster the use of the damage-control protocol proposed by a pan-European group in 2013 [9,10], facilitating rapid blood product release and adherence to haemostatic resuscitation using a transfusion ratio of 1:1:1 for fresh frozen plasma (FFP), platelets (PLT) and packed red blood cells (pRBC), respectively [10,11]. Activation of the MTP is triggered by a scoring system comprised of objectifiable clinical indices, trauma severity, and laboratory data [12–14].

More recently, the Italian Trauma Centres Network developed a new algorithm for more restrictive blood product management in major trauma patients, defined as early coagulation support (ECS), which was introduced into the clinical practice of several institutions in Italy. The ECS protocol includes prompt infusion of tranexamic acid, fibrinogen concentrate, and pRBC for initial resuscitation, with FFP and PLTs subsequently administered only when indicated by the results of viscoelastic techniques via point-of-care analysis using either thromboelastometry (ROTEM) or thromboelastography (TEG) and/or laboratory/clinical findings (Fig. 1) [15,16]. Although most recent European guidelines are the most restrictive protocols among possible treatment options for bleeding management in trauma patients [17], to date, no study has systematically evaluated whether these novel approaches may reduce blood product consumption.

We conducted an analysis of two Italian trauma centres to determine whether the ECS protocol helped to reduce the amount of blood products administered to major trauma patients with, or at risk of, major haemorrhage, as compared to the previously used MTP.

Patients and methods

A retrospective analysis was conducted using the registry data from the emergency departments of two referral trauma centres in Rome, Italy (Fondazione Policlinico Universitario A. Gemelli and San Camillo Forlanini Hospital), where the ECS protocol was introduced as a standard of care in 2013.

The study was approved by the local Ethics Committees and the analysis plan was registered at clinicaltrials.gov (ID: NCT03354559). Requirement for informed consent was waived as all the procedures were considered a standard of care during both periods.

Patients

Between 2011 and 2014, patients who were consecutively admitted to participating centres from emergency departments with major trauma [11,18] who had, or were at risk of, active bleeding, were considered eligible and were added to the total group of study candidates and managed according to the MTP (years 2011–2012) or the ECS protocol (years 2013–2014).

For the purpose of this study, only major trauma patients who fulfilled one of the following criteria at the time of hospital admission were added to the study cohort:

- blood lactate level ≥5 mmol/L;
- arterial base excess (BE) <−6 mmol/L;
- blood haemoglobin (Hb) concentration ≤9 g/dL;
- systolic blood pressure (SBP) ≤90 mmHg.

According to international guidelines [11,15], this patient group was considered at risk of requiring multiple transfusions.

Exclusion criteria, irrespective of received treatments:

- age <18 years old;
- patients admitted to the emergency department >6 h after trauma;
- patients with cardiac arrest at hospital admission;
- patients who died within the first hour after hospital admission.

Study design

In 2011–2012 (pre-ECS group), all patients fulfilling the inclusion criteria were treated with an MTP providing FFP, PLT and pRBC according to a 1:1:1 ratio for the entire duration of the stabilization phase (tranexamic acid and fibrinogen are not provided by the MTP) [11].

In 2013–2014 (ECS group), patients were treated according to the ECS protocol (Fig. 1), which provided administration of an early coagulation treatment within 15–30 min after the patient's admission [15]. Therefore, all included patients, after hospital admission and before the first available coagulation result (coagulation screen, fibrinogen level and/or viscoelastic monitoring and platelet count), received initial haemostatic resuscitation with tranexamic acid 1 g intravenous bolus over 20-minutes followed by 1 g in continuous infusion over 8-hours and fibrinogen concentrate 2 g bolus (until to a maximum 4 g in the first hour) along with 2–4 units of pRBC. Both tranexamic acid and fibrinogen were administered within the first 15-minutes after hospital admission in accordance with the ECS protocol [15].

Since PLT transfusion was triggered by the platelet count [11] and FFP needed to be matched, thawed, and warmed before administration, neither of them was administered in the early treatment stage (i.e., within 30-minutes after the patient' admission). Point of care tests guided subsequent interventions, when they were available. Permissive hypotension (systolic arterial pressure 80–90 mmHg or mean arterial 50–60 mmHg) and a fluid restrictive strategy were applied until surgical bleeding control was achieved. However, when prolonged bleeding occurred and an increasing number of pRBCs (>4 units) and fluid volumes were required (>2000 mL), FFP was transfused for hemodynamic and haemostatic resuscitation according to a 1:1:1 ratio for the duration of the stabilization phase, as indicated by the MTP [11].

In both periods, trauma teams were comprised of a trauma team leader (a critical care physician), a trauma surgeon, a radiologist, an orthopaedic surgeon, a neurosurgeon, and a transfusion

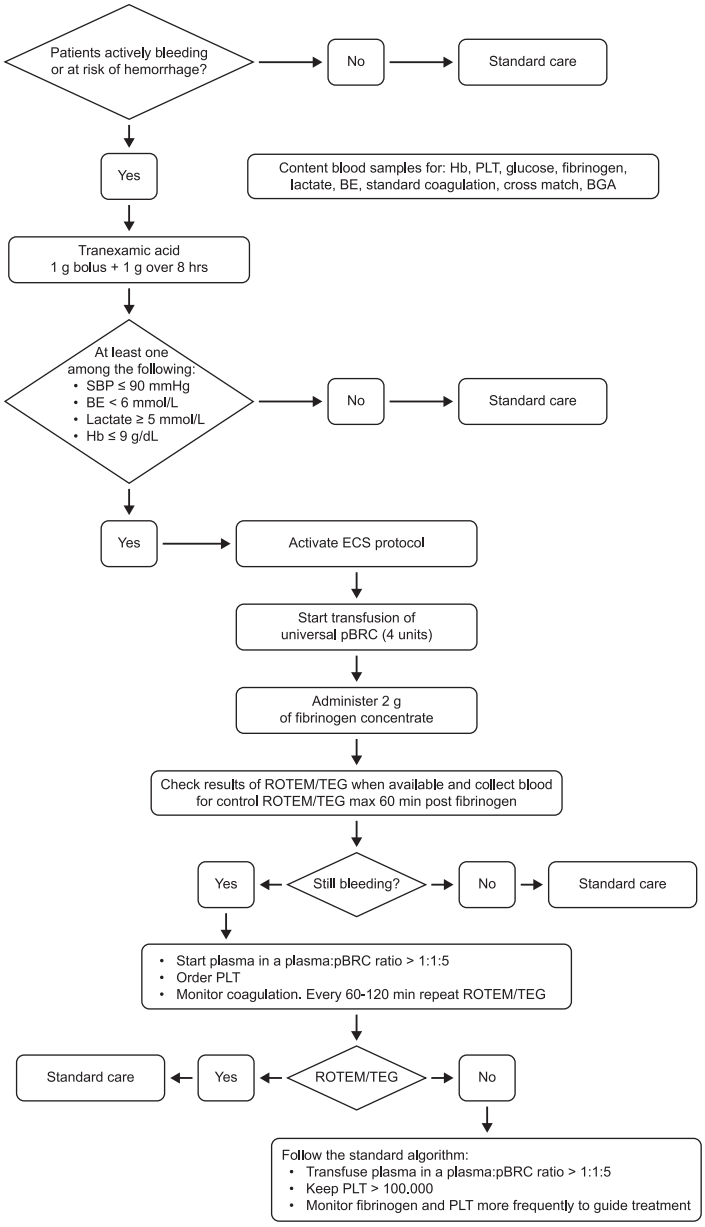

Fig. 1. The ECS protocol. Adapted from [16].
BE = base excess; BGA = blood gas analysis; ECS = early coagulation support; Hb = haemoglobin; pBRC = packed blood red cells; PLT = platelets; SBP = systolic blood pressure.

physician. Since the ECS protocol was introduced as a standard of care in both the centres, all the team members have received training on its application.

During the study period, standard care (diagnostic tests, antibiotic administration, fluid therapy, and hemodynamic management) was delivered according to the clinical practice of each institution in accordance with the international guidelines on trauma management [11].

Data from all major trauma patients with ISS >15 who were admitted to the ICU were included in each Trauma Centre's database and analysed (overall cohort), but only information about patients who met the study criteria was transferred into the multicentre database and included in the study cohort.

Data from the electronic records were matched with blood bank registries to confirm the number of blood units transfused within the study period. When patients were transferred from outside hospitals (in which the same protocols are applied), information regarding transfusion administration prior to admission was collected and matched with the blood bank's data.

The amounts of pRBC, FFP, and PLT units administered within 24-hours after admission were recorded.

Endpoints

The primary endpoint of the study was to determine whether the ECS protocol reduces the use of blood products in the acute management of trauma patients.

Secondary endpoints were the outcome measures of length of stay in ICU (LOS-ICU), length of stay in hospital (LOS-hospital), and mortality at 24-hours and 28-days after hospital admission.

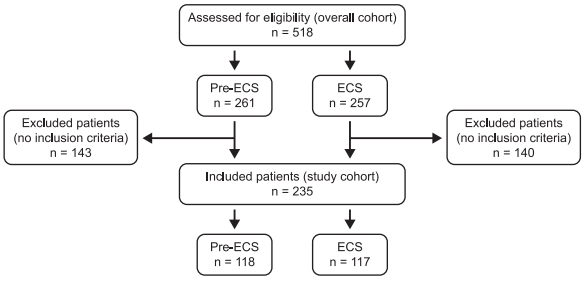

Fig. 2. Patients disposition.
ECS = early coagulation support.

Statistical analysis

Patient characteristics upon admission were described by mean and standard deviation for continuous variables. Median and interquartile range for scales, scores, and relative frequencies were used for discrete variables.

We tested the null hypothesis of no association between study period and patient characteristics using the *t*-test, Wilcoxon test, and chi-square test for three-types of variables. We estimated the mean difference in number of transfused units and LOS between ECS and pre-ECS from unadjusted Poisson models, using the delta method to estimate the 95% confidence interval (CI) for the mean difference. Findings were reinforced by replacing the Poisson model with a negative binomial distribution. For the mortality outcome, we estimated the relative risk (RR) with a 95% CI of death within the first 24-hours and within 28-days since admission for the post-ECS patients as compared to pre-ECS patients, from Poisson models without adjustment for other variables. Among those surviving the first 24-hours, we replicated the analysis by considering death between the 2nd and the 28th day of hospital stay. Propensity score matching, and a stratified analysis were performed [19]. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

Results

During the study period, 518 patients were admitted into the participating centres due to major trauma (overall cohort): 261 patients were treated in 2011–2012 (pre-ECS period) and 257 were treated in 2013–2014 (ECS period). A total of 235 patients with, or at risk of, active bleeding matched one of the inclusion criteria (study cohort) and were enrolled in the study (118 in the pre-ECS group and 117 in the ECS group) (Fig. 2).

Table 1 shows the baseline characteristics of the overall cohort at hospital admission (see Appendix A for further details).

The prevalence of inclusion criteria, which define the patients at risk of multiple transfusion (study cohort), is reported in Table 2 (see Table S1, Appendix A for further details). The patients who met at least one inclusion criteria and were included in the study cohort were 118 (45.2%) in the pre-ECS group and 117 (45.5%) in the ECS group ($p = 0.9$).

Table 1 shows the baseline characteristics of the study cohort at hospital admission, which, as in the overall cohort, are well balanced between the two groups (pre-ECS and ECS).

Table 3 shows the main results of resource absorption and mortality. Compared with the pre-ECS period, during the ECS period we observed a reduction in the average blood product consumption in the first 24-hours for pRBC, PLT, and FFP. The propensity-score matched analysis confirms these results [19].

Furthermore, during the ECS period, a significant 10-day reduction in the LOS-hospital was recorded, but no LOS-ICU reduction was found, and a non-significant 28-day mortality increase was observed. Such an increase was mainly due to the first 24-hours' increased mortality rather than mortality during days 1 through 28. In the propensity-matched population, a significant increase in the LOS-ICU was recorded, but at the same time both LOS-hospital and mortality at day-0 decreased [19]. Finally, ECS protocol seems to be a safe approach since 4 deep venous thrombosis (DVT) and 2 pulmonary embolisms (PE) have been observed in the pre-ECS groups vs 2 DVTs and 2 PEs in the ECS group (data not shown).

Discussion

Haemostatic resuscitation timing in major trauma patients is still an ongoing challenge. Our analysis showed that, among patients at risk of multiple transfusions, application of the ECS protocol was associated with a statistically significant reduction in the average blood product consumption within the first 24-hours after admission when compared to MTP.

The biggest change brought by the ECS protocol was early infusion, within 15–30 min after hospital admission, of tranexamic acid, fibrinogen concentrate and pRBC, instead of FFP, for early coagulopathy support and major bleeding control. This is in-line with the recent study of Moore et al. [20], which showed that an early plasma transfusion, administered within 30-minutes after injury, to trauma patients in haemorrhagic shock did not improve clinical outcomes.

The ECS protocol has some specific advantages. Firstly, the early use of fibrinogen acts as a targeted TIC therapy, as it has been identified as a key factor in TIC physiopathology and is consequently suggested as a first step in TIC management due to its haemostatic power [7,21]. Furthermore, in contrast to FFP, fibrinogen is promptly available and allows a reduction in fluid administration [4,7,22–24].

As reported in literature [7,25], fibrinogen level is essential to haemostasis and low concentrations upon hospital admission are independently associated with higher in-hospital mortality among major trauma patients.

Fibrinogen levels are not routinely measured during initial treatment, despite the fact that prompt identification of critically low levels and early supplementation could potentially correct trauma-induced coagulopathy. Early estimation of hypofibrinogenemia is possible using surrogate markers of shock and haemorrhage such as Hb and BE [3,7,21,22,26].

Currently, three different sources of fibrinogen are available: FFP, cryoprecipitate, and fibrinogen concentrate. The large amount of volume needed to restore fibrinogen levels via FFP can lead to haemodilution and subsequent worsening of coagulopathy. A faster and greater rise in fibrinogen level is achievable with the administration of fibrinogen concentrate [22,27–29], which showed superiority in reversing TIC compared to cryoprecipitate [4] and a favourable survival rate and lower transfusion requirements than FFP [28,29].

Recently, the RETIC trial [30] showed a prolonged haemostasis and an increased number of pRBC units transfused in major trauma patients at risk of major bleeding treated with FFP, compared to fibrinogen concentrate, confirming that FFP is poorly effective in reducing blood loss or in correcting TIC [30,31]. Moreover, since fibrinogen availability has a key role in platelet activation, this could explain why fibrinogen administration reduces not only pRBCs and FFP but also PLT requirements [24].

The PROPPR trial [32] showed that the use of a high ratio pRBC: FFP: PLT (i.e., 1:1:1), as provided by the MTP, reduced transfusion-related comorbidities due to immediate availability of blood products with a rapid haemostatic control and to a fluid-restrictive strategy. We agree with the application of restrictive fluid resuscitation as a relevant part of damage control resuscitation, but it is important to remember that in Italy cryoprecipitate

Table 1
Demographic and baseline information (overall and study cohort).

Baseline characteristic	Overall cohort ($n=518$)			Study cohort ($n=235$)		
	Pre ECS ($n=261$)	ECS ($n=257$)	p-value[a]	Pre ECS ($n=118$)	ECS ($n=117$)	p-value[a]
Inclusion criteria, *n* (25th, 75th percentiles)	–	–	–	1 (1, 2)	1 (1, 2)	0.8
Mean age, years (SD)	45.4 (19.9)	48.6 (19.8)	0.06	47.7 (20)	49 (19.8)	0.6
Men, *n* (%)	202 (77.4%)	191 (74.3%)	0.4	87 (73.7%)	85 (72.6%)	0.9
Mean SBP, mmHg (SD)	112.9 (30.7)	109.6 (31.5)	0.2	96.7 (32.2)	91.6 (34.6)	0.2
Median GCS (25th, 75th percentiles)	13 (7, 15)	14 (8, 15)	0.1	12 (7, 15)	13.5 (7, 15)	0.5
Median ISS (25th, 75th percentiles)	26 (19, 38)	25 (17, 34)	0.02	34 (25, 48)	29 (19, 41)	0.05
AIS head ≥4, *n* (%)	83 (31.8%)	74 (28.8%)	0.5	35 (29.7%)	32 (27.4%)	0.7
AIS chest ≥4, *n* (%)	95 (36.4%)	79 (30.7%)	0.2	53 (44.9%)	48 (41%)	0.5
AIS abdomen ≥4, *n* (%)	51 (19.5%)	37 (14.4%)	0.1	42 (35.6%)	28 (23.9%)	0.05
AIS pelvis and limbs ≥4, *n* (%)	46 (17.6%)	52 (20.2%)	0.4	30 (25.4%)	35 (29.9%)	0.4
AIS face ≥4, *n* (%)	24 (9.2%)	16 (6.2%)	0.2	14 (11.9%)	8 (6.8%)	0.2
AIS extremities ≥4, *n* (%)	8 (3.1%)	8 (3.1%)	1.0	5 (4.2%)	7 (6%)	0.5
Mean pH (SD)	7.3 (0.1)	7.3 (0.1)	0.9	7.3 (0.1)	7.3 (0.1)	0.8
Mean lactate, mmol/L (SD)	2.9 (1.9)	3.1 (2.5)	0.5	4 (2.3)	4.2 (3.2)	0.6
Mean BE, mmol/L (SD)	−4.7 (3.6)	−4.8 (3.7)	0.8	−6.9 (3.8)	−7.3 (3.7)	0.4
Mean fibrinogen, mg/dL (SD)	229 (99.4)	237.8 (100.3)	0.3	195.4 (90.1)	212.9 (108.1)	0.2
Mean INR (SD)	1.2 (0.3)	1.2 (0.4)	1.0	1.3 (0.3)	1.3 (0.5)	0.7
Mean haemoglobin, g/d (SD)	12.1 (2.4)	12.2 (2.4)	0.5	11.1 (2.6)	11.2 (2.6)	0.8
Mean PLT, x1000/dL (SD)	208.3 (77)	222.4 (78.7)	0.04	197.8 (83.9)	209 (87.6)	0.3

AIS = anatomical injury score; BE = base excess; GCS = Glasgow coma score; INR = international normalized ratio; ISS = injury severity score; PLT = platelets; SBP = systolic blood pressure.
[a] Chi-square, *t*-test and Wilcoxon rank test for dichotomic, continuous and injury scale variables, respectively.

Table 2
Prevalence of inclusion criteria at hospital admission (overall cohort).

Inclusion criteria	All patients ($n=518$)	Pre ECS ($n=261$)	ECS ($n=257$)	p-value[a]
Pts with at least one criteria, *n* (%)	235 (45.4%)	118 (45.2%)	117 (45.5%)	0.9
SBP ≤90 mmHg	125 (24.1%)	61 (23.4%)	64 (24.9%)	0.7
BE <−6 mmol/L	143 (27.6%)	67 (25.7%)	76 (29.6%)	0.3
Lactate ≥5 mmol/L	72 (13.9%)	38 (14.6%)	34 (13.2%)	0.7
Hemoglobin ≤9 mg/dL	60 (11.6%)	32 (12.3%)	28 (10.9%)	0.6

BE = base excess; SBP = systolic blood pressure.
[a] Chi-square test.

Table 3
Resources absorption and relative risk of in-hospital mortality (study cohort).

Study outcome	Pre ECS ($n=118$)	ECS ($n=117$)	Mean difference[a] (95% CI)	Relative Risk[b] (95% CI)
Resources absorption, median (25th, 75th percentiles)				
pRBC units 24 h	4 (1, 6)	1 (0, 4)	−1.87 (−2.4; −1.34)	–
FFP units 24 h	0 (0, 5)	0 (0, 3)	−1.69 (−2.14; −1.25)	–
PLT units 24 h	0 (0, 5)	0 (0, 0)	−1.28 (−1.64; −0.91)	–
LOS-ICU, days	9 (3, 20)	9 (3, 19)	0.77 (−0.2; 1.74)	–
LOS-hospital, days	34 (15, 52)	28 (14, 49)	−10 (−11.58; −8.42)	–
In-hospital mortality, *n* (%)				
Day 0	8 (6.8%)	11 (9.4%)	–	1.39 (0.56; 3.45)
Day 1–28	15 (13.6%)	16 (15.1%)	–	1.11 (0.55; 2.24)
Day 0–28	23 (19.5%)	27 (23.1%)	–	1.18 (0.68; 2.06)

FFP = fresh frozen plasma; LOS-hospital = lengths of hospital stay; LOS-ICU = lengths of intensive care unit stay; PLT = platelets; pRBC = packed red blood cells.
[a] A negative number indicates a reduction in the resources absorption during the ECS period.
[b] A number lower than 1 indicates a reduction in the mortality risk for patients in the ECS with respect to the pre-ECS period.

is often not available, leaving FFP as the only alternative to fibrinogen concentrate. This results in delays to administration time due to the thawing process [33].

Stanworth et al. [34], support the ECS strategy in terms of earlier delivery of pRBCs and delays in the administration of blood. The results showed that the majority of pRBCs were transfused in the first 4 h (35.0% in the first hour and 54.8% in the first 2 h) and that the first unit of pRBCs was administered at a median of 41 min after admission while the median time to first FFP transfusion was 87 and 67 min in patients with major (patients who received at least 4 units of pRBCs in the first 24 h) and massive (≥10 units) haemorrhage. Furthermore, only 15.6% of patients reached an FFP:RBC ratio of 1:2 or higher in the first hour; 41.0% and 55.4% reached the ratio within 4 h and 24 h, respectively [34].

The importance of an early administration of tranexamic acid and fibrinogen concentrate is provided by the study of Curry et al. [35] in which trauma patients with active bleeding received tranexamic acid either pre-admission or upon arrival to the hospital followed by fibrinogen concentrate, or placebo, as soon as possible. The results showed that the median administration time was about 40-minutes, and 69% of patients received fibrinogen concentrate (or placebo) within 45-minutes of admission. In the fibrinogen concentrate group an increase in fibrinogen levels (0.9 g/L vs. a reduction of 0.2 g/L in the placebo group), a higher

fibrinogen level at 2 h from admission, and a significantly higher proportion of patients who had fibrinogen levels ≥ 2 g/L during the first 2 h (75% vs. 47%) were observed [35].

In our analysis, the adoption of the ECS protocol led to a reduction in the average LOS-hospital, while no significant difference was observed in the LOS-ICU. The stratified analysis [19] showed that the reduction of the LOS-hospital is greater in patients >40 years of age; furthermore, the ECS protocol seems to significantly affect the LOS-ICU in older patients (>65 years) and in patients with more serious disease (≥3 inclusion criteria). This could possibly be due to a reduction in transfusion-related comorbidities. The overall reduction in LOS-hospital observed with the application of ECS protocol could be due not only to the prompt infusion of tranexamic acid, fibrinogen concentrate, and pRBC, but also, and perhaps above all, to the use of a defined and standardized protocol. This approach could indeed have increased the level of attention towards haemostatic resuscitation timing improving the clinical outcome of major trauma patients.

Literature reports a mortality rate of 25 to 50% in patients submitted to massive transfusion [36–39]. Previous studies showed how both viscoelastic guided-protocols and high fibrinogen-RBCs ratio protocols reduce mortality rates in trauma patients [4,17,28,29,40,41], while the PROPPR trial [31] showed a reduction in 24 h mortality (12.7% with a 1:1:1 ratio and 17% with a 1:1:2 ratio) and a reduction in 30-day mortality (22.4% vs 26.1%), albeit both were statistically non-significant.

In our study, during the ECS-period, a non-significant 28-day mortality increase was recorded. Since this increase was mainly due to the first 24-hour mortality and, as shown in the stratified analysis [19], in the ECS group, there was a higher number of patients with AIS head ≥4 who died during the first 24 h, it could be possible that the increase in deaths was due to severe head trauma rather than haemorrhage. The increased mortality in patients with severe head trauma has already been addressed [42] and in our study, no difference has been found in patients without head trauma. It must be noted that the mortality rate is very low in both groups and this not only decreased the statistical power of the data but also confirmed the importance and potential benefits of damage control resuscitation in major trauma. Both protocols (MTP and ECS) adhere to the concept of damage control strategy, with emphasis towards early administration of blood products, prevention, and immediate correction of coagulopathy and minimization of crystalloid fluid [10]. Furthermore, in both study periods (pre-ECS and ECS) the incidence of thrombotic complications was very low, confirming the safety of this approach.

The main limitations of the present study are related to the retrospective design and inherent biases associated with this methodology. Furthermore, even if both protocols are provided as standard procedures and the study is therefore reproducible, the results are not generalizable since only two centres were involved.

Another potential limitation is that the study was conducted in a time period during which coagulation support approaches were both an intense area of interest and subject to change. This might suggest that unmeasured practice changes made the major contribution to the observed outcomes. However, since the ECS protocol was a standard of care in both the centres and all the team members have received specific training on its application, we believe that the methodological rigor of the study has been guaranteed.

Conclusions

In our analysis, the ECS protocol was effective in reducing blood product consumption compared to the MTP, while guaranteeing early coagulation support in major trauma patients with high bleeding risk. ECS protocol seems to be a valid approach that may be adopted in real-life management of major trauma patients, since it is based on clinical parameters that are routinely assessed by the clinician at hospital admission. Further studies are necessary to show the effects on mortality and to confirm the aforementioned results.

Declaration of competing interest

GN is a member of the Task Force for Advanced Bleeding Care in Trauma (ABC-T), whose objective is to develop and update the European guidelines on management of bleeding following major trauma. The ABC-T meetings are supported by an unrestricted grant from CSL Behring (in the past by Novo Nordisk). GV has received honoraria from CSL Behring for statistical analysis. All of the other authors declare that they have no competing interests.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2019.09.032.

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