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ORIGINAL PAPER

Impact of a prehospital discrimination between trauma patients with or without early acute coagulopathy of trauma and the need for damage control resuscitation: rationale and design of a multicenter randomized phase II trial

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ABSTRACT

Background: The evidence of the Trauma Induced Coagulopathy Clinical Score (TICCS) accuracy has been evaluated in several studies but the potential effect of its use on patient outcomes needs to be evaluated. The primary objective of this study is to evaluate the impact on mortality of a prehospital discrimination between trauma patients with or without a potential need for damage control resuscitation.

Methods: The trial will be designed as randomized phase II clinical trial with comparison of the experimental protocol against the standard of care. The TICCS will be calculated on the site of injury for the patients of the intervention group and treatment will be guided by the TICCS value. Seven days mortality, 30 days mortality, global use of blood products and global hospital length-of-stay will be compared.

Discussion: Many data suggest that a very early flagging of trauma patients in need for DCR would be beneficial but this need to be proved. Do we improve our quality of care by an earlier diagnosis? Does a prehospital discrimination between trauma patients with or without a potential need for DCR has a positive impact?

Abbreviations: TICCS: Trauma Induced Coagulopathy Clinical Score; EACT: Early Acute Coagulopathy of Trauma; DCR: Damage Control Resuscitation; MT: Massive Transfusion; COAST: Coagulopathy of Severe Trauma; COAST: Coagulopathy of Severe Trauma; TBI: Traumatic Brain Injury; TXA: Tranexamic acid; RBC: Red Blood Cells; TASH: Trauma Associated Severe Hemorrhage; ROTEM: Rotational thromboelastometry; EXTEM: Extrinsic thromboelastometry; FibTEM: Fibrinogen thromboelastometry; MTP: Massive Transfusion protocol; EP: Exsanguination Protocol

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KEYWORDS
Trauma; prehospital medicine; hemorrhagic shock; acute care surgery; blood products transfusion

Background and rationale

Uncontrolled exsanguinating hemorrhage is the leading cause of death within the first 48 hours after severe trauma [1–3]. Almost, 25% of major trauma patients present with a trauma-induced coagulopathy characterized by an initial hemorrhagic phenotype (early acute coagulopathy of trauma (EACT)) and a potential late procoagulant phenotype [4–6]. Initiating damage control resuscitation (DCR) as early as possible after severe trauma in patients with EACT is pivotal for patient survival [7]. This specific and aggressive therapeutic strategy and its components have been widely studied and debated [8–14], but one aspect remains essential for the patient's outcome: the treatment has to be initiated as early as possible to be efficient [8,9].

A large multicenter trial recently demonstrated that predicting the need for massive transfusion (MT) after trauma using clinical presumption continues to be a challenge [15]. The relative inability to reliably predict MT has resulted in the development of several algorithms to help to identify trauma patients in need for MT [16–18] or suffering from EACT [19–21]. To be predictive, these scores generally include weighted and complex systems,

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making them difficult to be used in routine practice. All of them, except the coagulopathy of severe trauma (COAST) score, the early blood transfusion needs score (EBTNS) and the Trauma Induced Coagulopathy Clinical Score (TICCS), require not only clinical data but also laboratory investigations or medical ultrasonic examinations [16], delaying their use at least a few minutes after hospital admission. The TICCS, the COAST and the EBTNS, for their part, allow a prehospital, on-site, flagging of trauma patients suffering from EACT and/or in need for DCR.

This early identification of trauma patients in need for DCR has potential to be beneficial for general emergency units that are not expected to be ready for this rare situation 24 hours per day, seven days per week. It could also be useful for high performing trauma centers to identify such patients earlier and be able to provide earlier adequate treatment.

By contrast, initiation of DCR in patients who do not require this aggressive therapy may negatively affect their survival [22]. An early identification of patients who do not require DCR would probably be beneficial (impact on cost-effectiveness and on patients' survival).

The evidence of TICCS accuracy has been evaluated in several studies [19,23,24] but the potential effect of its use on patient outcomes needs to be evaluated. Moreover, there has never been any evaluation of the impact of a prehospital discrimination of trauma patients with or without the need for DCR.

Objectives

The primary objective of this study is to evaluate the impact on mortality of a prehospital discrimination between trauma patients with or without a potential need for DCR. Secondary objectives include evaluation of the feasibility of such discrimination and its impact on cost-effectiveness. We hypothesize that the information will lead to improved quality of care with reduced mortality and morbidity.

Methods

Trial design

The trial will be designed as randomized phase II clinical trial with comparison of the experimental protocol (prehospital discrimination using the TICCS) against the standard of care. Patients will be allocated in a 1:1 ratio in two groups: the intervention group will benefit from a prehospital evaluation using the TICCS and from a specific treatment protocol regarding the TICCS value. The control group will benefit from the standard local care.

A completed Consolidated Standards of Reporting Trials (CONSORT) checklist for the trial is available in additional file 1.

Eligibility criteria

Adults suffering from trauma with paramedical or medical prehospital care who fulfill the following criteria will be eligible:

- Age $\geq$18 years.
- Prehospital intervention of paramedical or medical team involved in the present trial
- Admission in a hospital involved in this trial

Patients will not be eligible if they fulfill one of the following criteria:

- Age $<$18 years.
- Spontaneous admission without prehospital intervention
- Penetrating trauma

Study setting

The trial will involve several participating prehospital and hospital teams across Belgium.

Prehospital and in-hospital realities slightly differ from participating centers to others which will increase the generalizability of future findings and limits the bias, optimally focusing on the tested variables.

A complete list of study sites is presented in additional file 2.

Interventions

Control and intervention groups will only differ in the management of potential bleeding and coagulopathy. All patients will benefit from the recommended level of care regarding their situation, including airway management, traumatic brain injury (TBI) management, control of external bleeding, cervical spine and extremities immobilization if needed …

Control group

The patients allocated in the control group will be managed as recommended in the local guidelines and protocols. As the trial involves participating

centers with different prehospital and hospital realities and local practices, the control group will reflect a wide panel of levels of care and will not be limited to a unique approach.

Intervention group

The TICCS will be calculated on the site of injury for the patients taken in charge in the intervention group (Table 1). Those patients will be classified in two categories regarding their TICCS value. Patients with TICCS $\geq$10 will be classified as in need for DCR; while patients with TICCS $<$10 will be classified as not in need for DCR.

TICCS $<$10. This subgroup will be considered without a need for DCR and without EACT. There will not be any activation of the DCR components (no phone contact to the blood bank, to the surgical team, no prehospital transfusion). The use of a prehospital treatment/prevention of the hyperfibrinolysis using tranexamic acid (TXA) will not be recommended. Crystalloids infusion will be allowed. All patients will benefit from the recommended level of care regarding their situation (airway, TBI, etc.), including trauma team activation if locally recommended.

TICCS $\geq$10. This subgroup will be considered with a need for DCR and with EACT. They will be treated using the STTTOPPP the bleeding protocol. The STTTOPPP the bleeding protocol is the acronym for:

- Surgical team pre-activation
- Trauma team pre-activation
- Transfusion team pre-activation
- Tranexamic acid (administration of 1 g of TXA if documented hyperfibrinolysis)
- O negative RBC transfusion as soon as possible
- Plasma and platelets transfusion as soon as possible
- Permissive hypotension (restrictive use of crystalloids: no more than 500 ml before definitive control of the bleeding is achieved)
- Prophylaxis (initiate antithrombotic prophylaxis as soon as the bleeding is under control and coagulation tests are normal, first evaluation before the 24th hour after trauma).

Both subgroups of the intervention group will be evaluated at hospital admission for confirmation or invalidation of the need for DCR, using either local guideline, and/or the calculation of the trauma associated severe hemorrhage (TASH) score [17] and/or diagnosis of EACT using ROTEM® or conventional coagulation tests, especially to appreciate the absence or the presence of abnormal fibrinolysis (either hyperfibrinolysis or fibrinolysis shutdown).

The study design diagram is depicted in Figure 1.

Outcomes

The primary outcome is the difference in seven days mortality rate (all cause of mortality) between the intervention and the control groups.

Secondary outcomes will include: 30 days mortality rate, global hospital length-of-stay and the total number of blood products transfused after 30 days.

Sample size

The trial being designed as a randomized phase II trial, it will start with the intention of including all patients during two consecutive years. A preliminary analysis will be conducted after one year.

Table 1. Definition and scoring system of the Trauma Induced Coagulopathy Clinical Score (TICCS).

Criteria	Number of points attributed
General severity	
Critical (to be admitted in resuscitation room)	2
Non critical (regular ED room)	0
Blood pressure	
SBP below 90 mmHg at least once	5
SBP always above 90 mmHg	0
Extent of significant injuries	
Head and neck	1
Left upper extremity	1
Right upper extremity	1
Left lower extremity	1
Right lower extremity	1
Torso	2
Abdomen	2
Pelvis	2
Total possible score	0–18

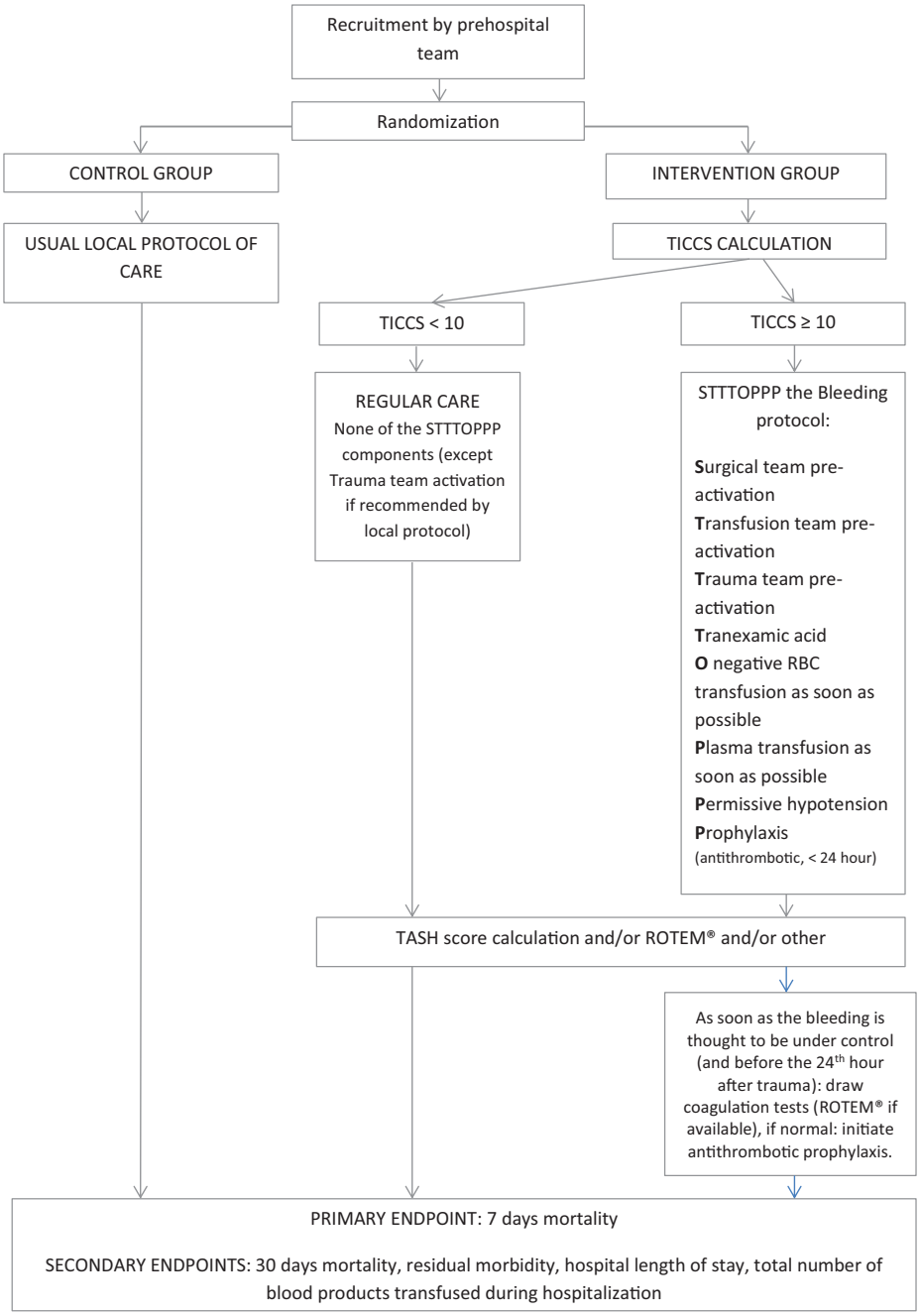

Figure 1. Randomization design.

Randomization

Randomization will take place at the initiation of the study. Prehospital intervention teams in each participating center will be equally randomized in two groups: one group will be trained to use the TICCS, the other will not be. Therefore, patients taken in charge by a prehospital intervention team trained to TICCS calculation will automatically be allocated to the intervention group; while those taken in charge by an untrained prehospital intervention team will be allocated to the control group.

Blinding

It will not be possible for participating medical teams to be blinded to which group the patients are assigned due to the nature of the intervention. The data analyst will be blinded to treatment assignment.

Data collection methods

Data will be collected locally in each participating center and will be anonymously recorded on the trial website by the local principal investigator or his research assistant. The website has been designed to avoid incomplete data, will give feedbacks (about the number of patients included) to this respective centers every six months. The participating centers will only have access to their own center database. The trial coordination team will have access to the whole database and will

not be able to record or change any data. After one year of inclusion and in the end of the 24 months period of inclusion, data will be extracted for interim and final analysis. All data will be anonymous.

Statistical methods

Results will be expressed as means and standard deviations (SPS) for quantitative variables with a Normal distribution and as medians and interquartile rage (IQR, P25–P72) for skewed distributed quantitative variables. Qualitative variables will be summarized using counts and percentages. Mean values between both groups (intervention vs. control) will be compared by Student's *t*-test or by the non-parametric Wilcoxon test when applicable. Proportions between both groups will be compared using the Chi-square test. For the primary endpoint, seven days mortality rate will be calculated in both groups with corresponding 95% confidence interval. Comparison will be tested using Chi-square test. Regarding the secondary endpoints, the same method will be applied to analyse the 30 days mortality rate. Survival methods, including Kaplan–Meyer's curve and log-rank test, will be applied to investigate global hospital length-of-stay between both groups. Student's *t*-test (or the non-parametric Wilcoxon test) will be considered to analyse the total number of blood products transfused after 30 days. If the descriptive statistical analysis revealed the presence of potential confounding factors between both groups, appropriate multivariate methods will then be considered. All results will be considered to be significant at the 5% critical level ($p < .05$). Statistical analyses will be carried out using SAS (Version 9.4 for Windows, SAS Inc., Cary, NC) and R Statistical packages (R Foundation, Vienna, Austria).

Protocol amendments

Any protocol amendments will be submitted to the university hospital (Centre Hospitalier Universitaire de Liège) ethics committee (as well as each participating center local ethics committee) for approval and noted in the registered protocol at the clinicaltrials.gov register. Trial participants will be notified should relevant protocol changes be made.

Access to data

All investigators, research assistants and data analysts will have access to the trial data.

Discussion

This study protocol presents the design of a randomized phase II clinical trial aiming to determine the impact of a prehospital discrimination of trauma patients with or without EACT and the need for DCR, using a prehospital scoring system.

Early identification of trauma patients suffering from active bleeding and/or from EACT remains challenging in clinical practice. The TICCS is an easy-to-calculate clinical score developed for identification of trauma patients in need for DCR and suffering from EACT. Its ability to predict those critical conditions has been previously evaluated but, so far, its potential impact on patients' care remains uncertain. The several components of DCR are widely debated in the literature but there is logical consensus that every one of those aspects has to be applied as early as possible. Massive transfusion protocols (MTPs) or exsanguination protocols (EPs) proved in several studies to be efficient partly by shortening the delay of transfusion [8,9,25]. The existence of an immediately available experienced trauma team at patient's arrival proved to be efficient partly by shortening the delay of decision and the delay of surgical control of the bleeding [8]. Studies also demonstrated that prolonged prehospital, on-scene, time has a strong negative impact on patients' outcome [26]. This suggests that a very early flagging of trauma patients in need for DCR would be beneficial but this need to be proved. Our study overcomes this medical need by proposing an original but crucial question: do we improve our quality of care by an earlier diagnosis? Does a prehospital discrimination between trauma patients with or without a potential need for DCR has a positive impact?

Additional strengths of our study include the fact that a various number and types of participating centers are involved. Thus, the control group is not limited to a specific type of care (non-trauma center regional hospital or level one trauma center or hospital in country or region without any trauma system, prehospital medical or paramedical teams). It increases the generalizability of our future findings and limits the bias, optimally focusing on the tested variable. Our intervention is relatively simple and easily applicable to the clinical

setting and can be reproducible in various local settings.

There are also limitations in our study design. The study is designed as a phase 2 trial (as opposed to a phase 3 randomized controlled trial (RCT)) because of the practical challenge to find a significant correlation between a diagnostic tool and patients' outcome. Particularly in the context of severe trauma, leading a phase 3 RCT is very challenging, especially when choosing mortality as a primary endpoint. Selecting another primary endpoint to allow practical realization of a phase 3 RCT would have, in our opinion, distanced ourselves from the essence of our work as clinicians and researchers: positively impact our patients 'outcome. On the other hand, conducting a proper phase 3 RCT to test our hypothesis would have been difficult to achieve. But this decision implies that our results will probably need to be interpreted with caution and might need replication and/or stronger validation using a phase 3 RCT.

Another limitation will result from the context of our study: it will involve both prehospital and in-hospital teams. Prehospital clinical trials are rare and challenging to conduct, there will probably be practical difficulties due to the context and, hence, possible missing data and patients.

Ethics approval and consent to participate

The study protocol has been submitted to and approved by the Ethics Committee of each participating center (the Comité d'éthique hospitalo-facultaire universitaire de Liège was designated as the central committee). Due to the nature of the critical and urgent condition of the patients, a third party consent to participate to the study will be first collected. As soon as the patient's condition will allow a individual a posteriori consent, it will be collected to.

Consent for publication: Consent for publication will be obtained from all participants.

Disclosure statement

No potential conflict of interest was reported by the authors.

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