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Is pre-hospital coagulation management in trauma feasible?

Coagulation management remains a formidable challenge in severely bleeding trauma patients. A strong rationale suggests starting treatment of trauma-induced coagulopathy in the pre-hospital phase.

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The burden of trauma is increasing worldwide, particularly in less well-resourced nations. There are an estimated 5 million deaths per year, more than TB, malaria and HIV combined. Trauma particularly affects young adult males, seeing a disproportionate long-term morbidity and loss of income (Hay et al. 2017). Despite advances in trauma care, haemorrhage remains the leading cause of trauma-associated preventable death in mature trauma systems in developed countries (Tien et al. 2007). About half of these deaths occur in the first hour, with many occurring pre-hospital (Oyeniyi et al. 2017). To aim for and achieve earliest haemorrhage control is literally vital for bleeding patients in any context.

Trauma-induced coagulopathy (TIC) (Johansson et al. 2017) consists of acute trauma coagulopathy (ATC) and resuscitation coagulopathy (RC). ATC occurs in around 1 in 4 patients with major trauma and is a consequence of injury and occurs within minutes of the event (Floccard et al. 2012). Shock seems to exacerbate TIC (Kushimoto et al. 2017). TIC RC is a consequence of resuscitation fluids, acidosis and hypothermia and is near universal in trauma requiring blood transfusion.

The currently most comprehensive pathophysiological model of ATC is conceptualised as systemic endothelial damage or *endotheliopathy* (Johansson et al. 2017). This concept credits the destruction of the proteoglycan layer (glycocalyx), covering all endothelial surfaces in the body, with a pivotal role in mechanism of TIC. Among the main drivers of this endotheliopathy are inflammatory cascades and sympathoadrenal activation. The degradation products of this endotheliopathy, such as syndecan-1, can be measured in the pre-hospital phase and are correlated with mortality (Ostrowski et al. 2017). The treatment of this endotheliophathy may become a new therapeutic target.

Conventional TIC management starts on admission to the resuscitation room and consists of intravenous tranexamic acid, the only current specific treatment for ATC, and blood product resuscitation. The latter includes fresh frozen plasma, platelets and fibrinogen, usually given in a 1:1:1:1 ratio (Holcomb et al. 2015; Harris et al. 2018) but targeted therapy may be an alternative (Gonzalez et al. 2016). The rapid deterioration and mortality associated with trauma haemorrhage sees the early treatment of TIC in the pre-hospital environment to be of paramount importance (Spinella and Cap 2017). The pre-hospital use of blood products in this context is the focus of this mini-review.

Detecting pre-hospital trauma-induced coagulopathy

The first challenge for pre-hospital TIC Management is to detect it. **Clinical scores** have been described and could be applied to pre-hospital use to predict TIC (**Table 1**). The first generation of scores predicted massive transfusion (Brockamp et al. 2012). However, massive transfusion is not consistently associated with TIC, concerns only a minority of patients and became less frequently required (Cantle and Cotton 2017). Other scores use specific pre-hospital parameters to predict TIC (**Table 1**). Scores may offer the advantage of easily identifying patients that will not require blood products. Overall, scores appear to be used infrequently (Hamada et al. 2015) and their impact on management has not been prospectively evaluated. Clinical gestalt remains probably equivalent to the aforementioned scores to detect TIC (Pommerening et al. 2015).

Deployment of **point-of-care (POC)** devices (Gauss et al. 2014; Mistral et al. 2017) in the pre-hospital setting theoretically offers an objective alternative for TIC detection. Their level of agreement compared to laboratory-based results is variable and the value of POC-measured variables remains a matter of debate (Hagemo 2013). Furthermore, most POC devices measure international normalised ratio (INR), probably not a reliable indicator of TIC. Determination of

Table 1. Clinical scores to predict massive transfusion (MT) and trauma-induced coagulopathy (TIC)

Score	Variables	Predictive performance
Prediction of massive transfusion scores (selection)		
ABC [Nunez et al. 2009] Acute Blood Consumption	Penetrating trauma, HR >120 b/min, systolic pressure <90 mmHg, FAST positive	AUC 0.76 Sensitivity 76.1% Specificity 70.3% LHR+ 2.5 LHR- 0.34
TASH [Yücel et al. 2006] Trauma-Associated Severe Haemorrhage	Unstable pelvis, open femur, FAST positive, HR >120 b/min, systolic pressure < 100mmHg, Hb <12, BE < -2	AUC 0.89 Sensitivity 84.4% Specificity 78.4% LHR+ 3.8 LHR- 0.21
Clinical gestalt to predict massive transfusion and bleeding		
GESTALT [Pommerening et al. 2015]	At discretion of physician in charge	AUC 0.66 Sensitivity 66% Specificity 64% LHR+ 1.53 LHR- 0.53
Prehospital prediction of coagulopathy		
COAST [Mitra et al. 2011] Coagulopathy of Severe Trauma INR >1.5	Entrapment, systolic pressure 90-100 mmHg, likely pelvic or abdominal injury, thoracic decompression, temperature <35	AUC 0.83 Sensitivity 60.0% Specificity 96.6% LHR+ 15 LHR- 0.42
TICCS [Tonglet et al. 2017] Trauma-Induced Coagulopathy Clinical Score Viscoelastic parameters, INR >1.3, Fib <1.5 g/dl	Critical, systolic pressure <90 mmHg, extent of injury (torso, abdomen, pelvis)	AUC 0.70 Positive predictive value 48% Negative predictive value 89%
PACT [Peltan et al. 2016] Prediction of Acute Coagulopathy of Trauma INR >1.5	Pre-hospital: age, GCS, shock index, intubation, traumatic arrest, mechanism	AUC 0.80 Sensitivity 69% Specificity 74% Score >/= 5 factors: LHR+ 23, LHR- 0.55
Prediction of coagulopathy components		
FIbAT [Gauss et al. 2017] Fibrinogen on Admission in Trauma Fibrinogen <1.5g/dl	Age <33y, pre-hospital HR >100, pre-hospital systolic pressure <100 mmHg, FAST positive, lactate >2.5mmol/l, temperature <36, delta Hb >2 g/dl, admission Hb <12 g/dl	AUC 0.87 Sensitivity 46.0% Specificity 96.6% Score >/= 5 factors: LHR+ 23, LHR- 0.55

AUC area under curve BE base excess FAST focused assessment with sonography in trauma GCS Glasgow Coma Scale Hb haemoglobin HR heart rate INR international normalised ratio LHR +/- likelihood ratio positive and negative

Table 2. Lyophilised plasma types

Type of Plasma	Properties	Current use
German lyophilised Plasma (LyoPlas N-w) *(DRK Blutspendedienst West, Germany)*	Single donor AB-Plasma, no pathogen inactivation, delivered after 4 months, lyophilised in glass bottle, storage 25 months 12–25 °C, use in sterile aqua	RePHILL trial, some civil units and Israeli Special Forces
French lyophilised plasma (FLyP®) *(Centre de Transfusion Sanguine des Armées, France)*	Pool of > 10 donors, different ABO groups, pathogen inactivation (Amotosalen-UV- irradiation), inactivated leucocytes, storage two years at 14–25°C, use in sterile aqua	French and US special forces, French military, some French civilian centres
Bioplasma FDP® *(National Bioproducts Institute, Pinetown, South Africa)*	Pooled ABO-Universal-Plasma pathogen inactivation (S/D-method) and lyophilised	No data

their role and potential benefit, in particular in comparison to clinical judgment, requires more research.

Managing pre-hospital trauma-induced coagulopathy

Current pre-hospital TIC management relies on blood component therapy. However, the recombination via transfusion results in a coagulopathic product with an estimated INR of 1.5. Whole blood is favoured by some pre- and in-hospital providers and may be less coagulopatic and more simple to administer (Spinella et al. 2016). The strategy has not been assessed in a randomised trial. For the time being pre-hospital TIC management relies on currently available component therapy which shall be considered.

> ❮❮ knowledge and familiarity of use required for pre-hospital TIC-targeted resuscitation suggest it may require delivery by enhanced care teams ❯❯

Tranexamic acid (TXA) remains a fundamental element of any TIC strategy based on the results of the Crash-II trial (CRASH-2 trial collaborators et al. 2010). Some groups question standard and routine administration without prior documentation of hyperfibrinolysis, because of a potential negative influence in patients with physiological fibrinolysis (Moore et al. 2016). Its beneficial effect on overall and 24-hour mortality seems reproducible after pre-hospital administration in patients with bleeding or a high likelihood of transfusion (Wafaisade et al. 2016; Morrison et al. 2012). The earlier TXA is administered the safer and more effective it is (Gayet-Ageron et al. 2018).

Red blood cells (RBC) are a crucial element of TIC management, mainly because RBC improve the rheological properties of blood-facilitating clot formation. The Mayo Clinic helicopter emergency medical service in the USA and French physician-staffed emergency medical systems have practised pre-hospital RBC transfusion since the 1980s. Various and

Table 3. Lists of ongoing trials, investigating the components of pre-hospital TIC Management or their combination

Trial	Intervention	Outcome
COMBAT Control of Major Bleeding After Trauma **ClinicalTrials.gov NCT01838863**	Randomised administration of 2 units of AB-plasma vs. normal saline	Primary: 28-day mortality Secondary: Multi-organ failure
FinTIC ClinicalTrials.gov **NCT01818427**	Randomised high-dose fibrinogen concentrate administration vs standard care	Primary: Fibrinogen polymerisation on viscoelastic test Secondary: Viscoelastic test and laboratory parameters, thromboembolic events
PAMPer Pre-hospital Air Medical Plasma **ClinicalTrials.gov NCT01818427**	Randomised pre-hospital air ambulance 2 units plasma administration of 2 units of plasma vs standard care	Primary: 28-day mortality Secondary: transfusion organ failure
PATCH Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage **ClinicalTrials.gov NCT02187120**	Randomised pre-hospital administration of TXA vs placebo	Primary: Glasgow Extended Outcome Scale at 6 months Secondary: transfusion, coagulopathy, mortality, etc,
PREHO-PLYO Pre-hospital Plasma lyophilised **ClinicalTrials.gov NCT02736812**	Randomised pre-hospital administration of lyophilised Plasma vs normal saline	Primary: change in Prothrombin level Secondary: INR, ROTEM
PRO-COAG Prothrombin Concentrate Complex Trauma Hemorrhage **ClinicalTrials.gov NCT03218722**	Randomised intra-hospital PCC administration vs placebo	Primary: transfusion requirements Secondary: INR, ROTEM parameters
RePHILL Resuscitation with Pre-Hospital blood products **IRAS ID: 179484**	Randomised pre-hospital administration of 2U blood and FFP vs normal saline	Primary: Survival Secondary: organ perfusion, lactate levels,

ROTEM rotational thromboelastometry

heterogenous reports shared observational data on the clinical impact of pre-hospital RBC use (Lockey et al. 2013; Lyon et al. 2017), some with promising results (Brown et al. 2015). A meta-analysis of these studies did not indicate a benefit (Smith et al. 2016), but did not include a recent publication (Rehn et al. 2018) that indicates increased survival to hospital.

Fresh frozen plasma (FFP) is available and carried by pre-hospital providers as cooled thawed plasma, useable for up to 3 days. Lyophilised plasma was widely used in the 1950s and has regained interest recently (Martinaud et al. 2012) (**Table 2**). Lyophilised plasma solves logistical issues associated with thawed FFP. Plasma may attenuate TIC-associated endotheliopathy, maybe by restoring the proteoglycan layer (Kozar et al. 2011). Lyophilised plasma contains higher fibrinogen concentrations and is associated with quicker correction of coagulopathy compared to FFP (Garrigue et al. 2018). Lyophilised plasma is an ideal pre-hospital component of TIC management, easy to carry and administer, and its use is feasible in the pre-hospital context (Jenkins et al. 2014).

Fibrinogen concentrate (FC) is the key substrate of the coagulation cascade (Maegele et al. 2015), and low levels are associated with increased mortality (Inaba et al. 2013; McQuilten et al. 2017). Low plasma fibrinogen leads to reduced clot firmness (Ostrowski et al. 2011) and is the first coagulation factor to reach critically low levels (Schöchl et al. 2014). The fibrinogen-to-RBC ratio was independently associated with improved survival (Stinger et al. 2008), and only high-dose fibrinogen substitution appears to correct TIC (Khan et al. 2014). FC presents the advantage of easy carry, use and low-volume administration. Currently there are no randomised trials demonstrating efficacy or improvements in mortality.

Prothrombin complex concentrate (PCC) can consist of either three- or four-factor preparations. The composition can vary substantially and contain pro-coagulant factors, mainly factors II, IX, and X, with or without factor VII, and anti-coagulant factors such as Protein S and C and Antithrombin III (Grottke and Levy 2015). Preclinical studies suggest an appealing pathophysiological rationale (Hansson et al. 2017). Small clinical studies suggest PCC used in combination with FC to be associated with lower mortality and reduced blood product use (Schöchl et al. 2010; Innerhofer et al. 2013); the main risk is associated thromboembolic events (Grottke and Levy 2015). PCCs are easy to carry, use and allow low-volume administration. A prospective trial (PRO-COAG) is currently ongoing in France (**Table 3**).

There are no published pre-hospital trials, which assess the efficacy of TIC-targeted resuscitation strategies that include blood product delivery. The pre-hospital environment carries specific organisational, logistical and physiological constraints. The time window to identify TIC and administer treatment such as blood products is limited in the pre-hospital environment and increasing scene time may increase mortality. The level of knowledge and familiarity of use required for pre-hospital TIC-targeted resuscitation suggest it may require delivery by enhanced care teams. There may be insufficient time for clinicians to assess for TIC and deliver the large volumes of component blood therapy (2-4 RBC, 2-4 FFP, 4g of Fibrinogen). This will require the teams to identify the key interventions for pre-hospital care delivery in terms of efficacy, cost and ease of delivery.

Pre-hospital TIC strategy

Grounded upon the preceding observations and concepts a pre-hospital TIC strategy could comprise the first-line administration of tranexamic acid, lyophilised plasma and FC. All three are easy to use, carry and store; combined they represent a reasonable volume load that is feasible to administer within the pre-hospital time frame. Pre- and in-hospital treatment should be integrated and seamless as part of a unified pathway. This should include agreed triggers, algorithms and treatment at a network or preferably national level. Examples include so-called 'code red' protocols (Weaver et al. 2012; Hamada et al 2018). An integrated, interrelated pathway would reduce still-existing barriers to timely blood product administration (Stanworth et al.

2016). A synergy between clinical judgement and machine learning algorithms embedded into patient monitors might improve detection of TIC in the near future.

In summary, initiation of pre-hospital TIC management is feasible and ongoing prospective trials will define the most appropriate treatment strategies.

Conflict of interest

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Abbreviations

ATC acute trauma coagulopathy
FC fibrinogen concentrate
FFP fresh frozen plasma
INR international normalised ratio
PCC prothrombin complex concentrate
POC point-of-care
RBC red blood cells
RC resuscitation coagulopathy
TIC trauma-induced coagulopathy
TXA tranexamic acid

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