Prehospital detection of traumatic coagulopathy

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Increased focus on traumatic coagulopathy over the last decade has led to more aggressive use of hemostatic agents in resuscitation of the massively bleeding patient. Novel formulations of plasma factors and other therapeutics have opened for early intervention to prevent coagulopathy and may even be utilized in the prehospital setting. Careful selection of patients to receive hemostatic agents early during the resuscitation is of great importance due to the potential detrimental effects of this treatment.

Several studies have identified coagulation parameters as reliable predictors of massive transfusion, even very early after trauma. Prothrombin time international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen concentration, and viscoelastic tests such as thrombelastography (TEG) and rotational thrombelastometry (RoTEM) have proved to be of value in predicting massive transfusion when performed in-hospital. PT/INR appears to be slightly more accurate than the other parameters, with a reported sensitivity of 84.8% and an area under the receiver operating curve of 0.87. Comparison studies on PT/INR, aPTT, and viscoelastic assays do suggest that caution should be taken when point-of-care (POC) methods, as opposed to conventional laboratory analyses, are used. Novel techniques for POC measurement of fibrinogen levels are currently being developed, and preclinical data suggest acceptable agreement with conventional methods.

A number of factors should be considered regarding the feasibility of POC tests in the prehospital environment. In addition to environmental factors such as temperature, altitude, and humidity, electromagnetic interference issues and operators' skills must be taken into account. Coagulation parameters appear to be a useful tool in identifying patients with increased risk of massive bleeding at an early stage. Further studies are needed to determine if prehospital intervention based on POC analyses improves outcome.

INTRODUCTION

Along with recent advances in the understanding of acute coagulopathy, a number of hemostatic agents have become subjects of interest in management of massive hemorrhage.[1-3] Aggressive transfusion of plasma factors in the form of fresh frozen plasma is widely implemented in modern hemostatic resuscitation guidelines.[4-6] Specific factor concentrate such as fibrinogen, factor XIII, and recombinant factor VIIa, as well as factor combination such as prothrombin complex concentrates, have so far been less studied.[5,7] Dried plasma formulations have recently been developed,[8] and are currently being used in combat settings.[9,10]

An interesting aspect of utilizing factor concentrates in acute bleeding is the circumvention of the logistical challenges associated with the administration of fresh frozen plasma. The possibility to administer coagulation support closer to the time of injury in the prehospital environment may be of importance. This would be of particular interest in situations where transportation times are long, patients are entrapped, or for any other reason evacuation to a trauma center is delayed. However, the potential of negative side effects from hemostatic agents cannot be neglected, and a careful selection of patients who should receive this treatment is of great importance.

A number of scoring systems have been developed to identify the patients that require massive transfusion.[11-14] Even though these scoring systems perform relatively accurately, they have limitations in that they require diagnostic instruments that are rarely available outside hospitals. Moreover, they lack the ability to distinguish between strictly surgical cause of bleeding, and bleeding worsened by traumatic coagulopathy.

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The existence of coagulopathy in massively bleeding patients has been known for decades. However, in 2003 Macleod and Brohi almost simultaneously described coagulopathy very early after injury and found it to be an independent predictor of mortality.[15,16] Their findings indicate that conventional coagulation tests such as prothrombin time international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) may give additional information about potential perturbations in coagulation. One recent study confirms the existence of early coagulopathy in samples collected in the prehospital setting.[17] On the basis of these findings, it is tempting to try to identify early traumatic coagulopathy in order to determine which patients need hemostatic support in transit to a medical facility. The question is, however, whether prehospital coagulation tests are suitable for this purpose.

PREDICTING MASSIVE TRANSFUSION FROM COAGULATION TESTS

Several studies confirm the prognostic value of coagulation tests in predicting massive transfusion and mortality. In a recent study Schöchl et al.[18] reviewed the predictive value of several coagulation tests, including rotational thrombelastometry (RoTEM) analyses. The highest area under receiver operating curves (ROC-AUCs) for massive transfusion was found for PT/INR (0.87), aPTT (0.85), and hemoglobin (0.87). With thresholds set for best sensitivity and specificity, PT/INR showed a markedly higher sensitivity than aPTT and hemoglobin, with 84.8% compared with 71.6% and 77.5%, respectively. Fibrinogen concentration also proved to be a sensitive test (84.2%) with ROC-AUC of 0.83. The RoTEM analyses had comparable, but slightly lower ROC-AUCs than PT/INR, with 0.84 for the maximum clot firmness (MCF) in the FibTEM assay. Interestingly, base deficit as a surrogate measure of amount of bleeding performed markedly worse than most of the coagulation tests, supporting the hypothesis that coagulopathy has a distinctively different mechanism than simply blood loss and acidosis.

Caution must be used though when interpreting data where massive transfusion is used as a surrogate for coagulopathy. The amount of units transfused is dependent upon physician behavior, which frequently is influenced by laboratory test results. The use of laboratory parameters to predict massive transfusion is clearly confounded by this fact. Studies that analyze predictors of death from hemorrhage would be a more valid approach. Unfortunately, even those studies that have evaluated values present upon admission for prediction of death have not analyzed only patients with death secondary to hemorrhage.[15,16,19]

RELIABILITY OF POINT-OF-CARE (POC) TESTS

The reliability of POC analysis of coagulopathy has been questioned when carried out by nonlaboratory personnel in a stressful environment compared with the in-hospital laboratory setting.

Our center has for the past 2 years been performing POC PT/INR analyses in the trauma room by anesthetist nurses. The analyses are performed on a handheld device (Coaguchek XS Plus, Roche, Grenzach-Wyhlen, Germany), giving the PT/INR value in a matter of a few seconds. Agreement of these measurements compared with laboratory measurements are similar to that reported by Davenport et al.[20] with 95% Limits of Agreement (LoA) of –0.20 to 0.17. Even though this seems to be an acceptable level of agreement, some caution should be taken since the agreement tends to worsen with lower hematocrit levels in their study. The predictive value of POC PT/INR for massive transfusion and death from hemorrhage is still to be investigated.

POC aPTT measurements are not widely available. Nevertheless, one study did compare the results from a clinician-operated POC aPTT (Coaguchek Pro, Roche) device to standard laboratory assay in surgical intensive care patients.[21] The results revealed poor agreement with 95% LoA of –83.2 to 49.2 seconds. Even in healthy controls, agreement was considered to be too low for use in clinical practice.

Viscoelastic tests for hemostatic function, such as thrombelastography (TEG) and RoTEM have increasingly been used in detection of traumatic coagulopathy over the past few years. Even though they are both utilized as POC devices, this would not be feasible in the prehospital environment. However, modifications of the RoTEM device have been developed to allow for use in the field. A prototype of a portable device also exists, and may be available in the near future.

A few studies have examined the reproducibility and agreement of viscoelastic tests such as TEG and RoTEM.[22-25] Venema and colleagues conducted repeatability analyses for both TEG and RoTEM in healthy volunteers. They conclude that the clot reaction time and clot kinetics parameters (denoted R-time and K-time in TEG, CT and CFT in RoTEM) had a variability that rendered them unacceptable for clinical purposes. Maximum amplitude and MCF was found to be more consistent. They even found this parameter to be interchangeable between the two devices.

In a multicenter study on trauma patients including our own institution, it appears that agreement between TEG and RoTEM is reduced when the devices are operated by clinicians rather than laboratory personnel (Hagemo et al., unpublished data). This should be taken into consideration in prehospital implementation of the assay.

Fibrinogen may be the one factor that first falls to critical levels in traumatic bleeding,[26] and a POC test for fibrinogen concentration may be very valuable. Since fibrinogen concentration measurements is a plasma-based analysis and requires centrifugation, the prehospital feasibility of its measurement is reduced. POC fibrinogen measurement is, however, possible in a prototype device utilizing lateral flow microfluidic technique, as described by Dudek and colleagues.[27] Interestingly, the analyses by this technique may also be performed on whole blood, and is therefore promising as a prehospital utility. Preclinical data show very good correlations with the conventional Clauss method (r2 = 0.97).

Some studies show there is a significant relationship between fibrinogen concentration measured by the Clauss method and the TEG/RoTEM assays with correlation coefficients ranging from 0.75 (Spearman rho) to 0.85 (Pearson) with the amplitude of the clotting trace.[18,28] It is, however, important to acknowledge the fact that the viscoelastic assays depend on several other factors (particularly Factor XIII) and do not necessarily reflect fibrinogen function specifically.

FEASIBILITY IN THE PREHOSPITAL ENVIRONMENT

In addition to validity and reliability, the practical and logistical aspects of POC tests must be carefully considered. Even a well-established use of a POC test in-hospital does not necessarily mean it is suitable for prehospital use. Size of equipment and weight is of importance. Power supply and storage of reagents must also be taken into consideration.

POC devices for measuring PT/INR have been developed for domestic use in patients taking oral anticoagulation. PT/INR measurements are also available on systems allowing multiple blood analyses aimed for use by health professionals. Studies on the feasibility of these devices in the trauma patients are still lacking. Recent advances have paved the way for thromboelastometry in field hospitals, and in the near future even portable devices may be available. As for PT/INR measurements, the feasibility of these devices for prehospital use in trauma patients requires study.

It is crucial also to consider the physical environment in which the device is to be operated. Ambient temperature and humidity may in certain parts of the world be way beyond what the equipment is constructed and certified for. In air ambulance services, the equipment should be tested for hypobaric conditions. Also, for in-flight operation of POC devices, one should make sure that the equipment is thoroughly tested for electromagnetic interference, in order to maintain flight safety.

CONCLUSION

A number of hemostatic agents and plasma formulations are available, many of which may be used in the prehospital setting. Identifying the right patients for these treatments is challenging. Current literature suggests that basic coagulation tests predict massive bleeding and death secondary to traumatic injury accurately. Data also suggest that coagulation changes are detectable early on scene. Studies to document that early intervention based on POC measurements improve outcome are still lacking. As technology improves, we may see possibilities in the near future to identify even more accurately the specific type of hemostatic intervention needed for the individual patient in the prehospital setting.

CONFLICT OF INTEREST

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