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Massive Transfusion/Hemorrhage Protocols Versus Goal-Directed Bleeding Management: Science Gone Eerie?

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ABSTRACT

Key questions in bleeding management are "Why does my patient bleed?" and "How to fix it?" To answer the first question, the high negative predictive value of viscoelastic testing can be used to identify coagulopathic bleeding. Accordingly, goal-directed bleeding management (GDBM) guided by viscoelastic testing has been shown to be an effective and essential part of the second pillar of patient blood management (PBM) with the aim to improve patients' outcomes and safety. Patient's medical and drug history – with a focus on medication with oral anticoagulants and antiplatelet drugs – are important in emergency, urgent, and elective surgery. Furthermore, risk scores have been developed and validated for traumatic and obstetric hemorrhage and can be helpful tools to predict severe hemorrhage and the need for massive transfusion. Acidosis, hypocalcemia, anemia, and hypothermia ("diamond of death in trauma") are important basic conditions for hemostasis and good predictors of coagulopathy and should be closely monitored by blood gas analysis and corrected in bleeding patients. Earlier time to hemostasis was associated with decreased mortality in trauma studies. Therefore, GDBM aims to stop the bleeding as soon as possible and avoid the main killers in blood transfusion: Transfusion-associated circulatory overload, transfusion-related acute lung injury, transfusion-related immune modulation, and thrombosis. Thromboelastometry-guided bleeding management follows the concepts of Good Medical Practice and Precision Medicine. Here, rotational thromboelastometry (ROTEM)-guided bleeding management algorithms are using a stepwise approach based on the sequence "Treat first what kills first:" (1) Fibrinolysis management, (2) clot firmness management, (3) thrombin generation management, and (4) avoidance of hypercoagulability and thrombosis. Here, thromboelastometry can not only identify patients with hypercoagulability and increased risk of thrombosis but also ROTEM-guided bleeding management can avoid thromboembolic complications, too. This may support the idea of personalized antithrombotic therapy guided by viscoelastic testing in the postoperative period. Finally, PBM is not about blood transfusion: It is about patients' outcomes. Accordingly, several meta-analyses based on more than 20 randomized controlled trials on the effect of viscoelastic testing-guided perioperative bleeding management did not only demonstrate a significant reduction in transfusion requirements but also a significant reduction in mortality and postoperative acute kidney injury. The reduction in postoperative acute kidney injury again has a significant impact on long-term survival. Accordingly, recent PBM guidelines recommend the implementation of viscoelastic testing-guided bleeding management algorithms with a 1B or 1A recommendation. This is also addressed in the World Health Organization policy brief about the urgent need to implement PBM in all member states in a timely manner. However, even if the number of national activities is increasing, there is still a long way to go.

Keywords: Bleeding management algorithms, Goal-directed bleeding management, Massive transfusion protocols, Patient blood management, Thromboelastometry

ASK THE RIGHT QUESTIONS IN BLEEDING MANAGEMENT

Key questions in bleeding management are "Why does my patient bleed?" and "How to fix it?" To answer the first question, the high negative predictive value of viscoelastic testing can be used to identify coagulopathic bleeding. Notably, only about 25% of bleeding in severe trauma and post-partum hemorrhage (PPH) is associated with coagulopathy defined as Extrinsic TEM A5 ≤35 mm (definition of trauma-induced coagulopathy as reported by Davenport *et al.*) or Fibrinogen TEM A5 <12 mm (definition of coagulopathy in PPH as reported by Collins *et al.*),[1-4] To treat massive hemorrhage, several therapeutic strategies are used. The first option – mainly used in the US – is the implementation of "Massive Transfusion Protocols" with the aim to provide sufficient blood products in certain ratios or shock packages to keep the blood volume and hemodynamics stable.[5-7] The second option – mainly used in Europe – is the implementation of "Massive Hemorrhage Protocols" with the aim to stop the bleeding as soon as possible to avoid transfusion and particularly massive transfusion (therefore also called "Massive Transfusion Avoiding Protocols").[8-10] A hybrid approach starting with shock packages and then moving to goal-directed bleeding management (GDBM) as soon as viscoelastic testing results are available is a third strategy – mainly used in Scandinavia.[11-14]

However, in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) randomized controlled trial (RCT) among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days.[15] Moreover, a study published in 2011 even showed that plasma transfusion in trauma patients who did not require massive transfusion was not associated with improved survival but a substantial increase in complications, particularly acute respiratory distress syndrome (ARDS) (12-fold), multiple organ dysfunction (6-fold), pneumonia (4-fold), and sepsis (4-fold).[16] Similarly, platelet transfusion in patients with traumatic brain injury (TBI) and concomitant antiplatelet use was associated with a higher mortality (risk ratio 1.5) in a meta-analysis based on ten studies.[17] Notably, the non-infectious blood transfusion reactions transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury, and transfusion-related immune modulation with an increased risk of nosocomial infections are responsible for 66% of transfusion-associated mortality and are mainly triggered by plasma-rich blood products.[18,19] Therefore, liberal plasma and platelet transfusion should be considered carefully in bleeding trauma patients.[20]

In contrast, GDBM guided by viscoelastic testing has been shown to be an effective and essential part of the second pillar of patient blood management (PBM) with the aim to improve patients' outcomes and safety ("First do no harm!" Hippocrates, 460–370 B.C.).[21,22] GDBM follows the concept of good medical practice and precision medicine using a control loop with fast diagnosis first, appropriate therapy, and reassessment.[8,23-25] Accordingly, the implementation of thromboelastometry-guided bleeding management algorithms has demonstrated significant benefits in several clinical settings.[4,8,10,26-32]

PATIENT'S MEDICAL AND DRUG HISTORY (ANTICOAGULATION AND ANTIPLATELET DRUG MANAGEMENT)

For traumatic and obstetric hemorrhage, risk scores (e.g., ABC or TASH score) have been developed and validated and can be helpful tools to predict severe hemorrhage and the need for massive transfusion. However, the predictive value of these scores is low, and 40% of all PPH events occur in low-risk patients, emphasizing the need for early vigilance and treatment regardless of categorization.[33-35]

Medical and drug history are important in emergency, urgent, and elective surgery. In elective and urgent surgery, oral anticoagulants (Vitamin K-antagonists [VKAs] and direct oral anticoagulants [DOACs]) and antiplatelet drugs (P2Y12-receptor inhibitors) may be paused preoperatively dependent on the underlying disease, the bleeding risk of the planned surgical intervention, the half-life time of the drug, and/or functional testing.[36-40] In emergency surgery, particularly if medical and drug history is not available, drug monitoring may be helpful to define the best strategy in bleeding, including postponing surgery, drug elimination by dialysis (dabigatran) or hemoperfusion (direct factor Xa-inhibitors by CytoSorb), and specific (idarucizumab for dabigatran, andexanet alfa for direct factor Xa-inhibitors, and prothrombin complex concentrate (PCC) and Vitamin K for VKAs) or unspecific reversal agents (PCC for direct factor Xa-inhibitors).[41-51]

In patients treated with VKAs (e.g., warfarin), EXTEM clotting time (CT) correlates well with the international normalized ratio (INR) and can be used to guide PCC therapy.[52,53] In contrast, point-of-care (POC) tests using ellagic acid (intrinsic TEM and Heparin TEM), kaolin (kaolin-thromboelastography [TEG], heparinase-TEG, and Quantra CT), or kaolin plus tissue factor as activators (rapid-TEG) are unreliable to detect VKAs.[54-56] Accordingly, the Hemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anesthesiology recommends a tissue factor-activated, factor VII-dependent, and heparin-insensitive POC test for perioperative monitoring and guidance of prothrombin complex therapy.[57] Notably, EXTEM CT can be prolonged by fibrinogen deficiency, too, which must be excluded before treating with PCC.[8,10,58]

Patients treated with DOACs may be identified by prolonged EXTEM and HEPTEM CT, but detection of low levels of apixaban may require more sensitive assays (low tissue factor TEM [TFTEM] or Russel Viper Venom test) and differentiation between direct thrombin inhibitors (DTIs) and direct factor Xa inhibitors may require a DTI specific assay (ecarin TEM or ECA-test or ECATEM/TFTEM CT-ratio).[59-63]

Plasma concentrations of intravenous DTIs, such as argatroban and bivalirudin, correlate well with EXTEM and ECATEM CT.[64,65]

Finally, the effects of unfractionated heparin and protamine can be assessed by INTEM CT and, more precisely, by INTEM/HEPTEM CT-ratio.[66-69] The latter correlates well with anti-Xa activity.[70,71]

PRECONDITIONS OF HEMOSTASIS

Acidosis (pH < 7.3; BE < −6 mmoL/L), hypocalcemia (Ca_i^{2+} <1 mmoL/L), anemia (Hb <7–9 g/dL), and hypothermia (T_{Core} <34°C) ("diamond of death in trauma") are important basic conditions for hemostasis and good predictors of coagulopathy and should be closely monitored by blood gas analysis and corrected in bleeding patients.[72-75] Notably, ionized calcium levels in major trauma patients on arrival at the emergency department have a parabolic relationship with coagulopathy, need for transfusion, and mortality.[76] This means that overcorrection should be avoided.

TIME MANAGEMENT

A sub-analysis of the PRPOPPR RCT showed that earlier time to hemostasis was associated with decreased mortality (3% for every 15-minute decrease in time to hemostasis) and complication rates (2–6% for acute kidney injury, ARDS, multiple organ failure, and sepsis).[77] Gratz *et al*. demonstrated in a sub-study of the Collaborative European Neuro Trauma Effectiveness Research in TBI study, that it is feasible to achieve a time-to-treat after hospital admission of in median 50 min by implementing a thromboelastometric-guided hemostatic algorithm in patients with TBI.[78] Rimaitis *et al.* confirmed that the implementation of a thromboelastometry-guided algorithm for coagulation management in isolated TBI patients undergoing craniotomy with adhesion to the protocol of 85.3% was associated with improved outcomes (decreased progressive hemorrhagic injury and need for neurosurgical re-intervention).[79] This is in line with the results of the implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy (iTACTIC) RCT, which showed in the predefined subgroup of patients with severe TBI an odds ratio for 28-day mortality of 0.28 (95% confidence interval [CI], 0.10–0.74; P = 0.016) in patients treated according to viscoelastic testing-guided algorithms.[80]

CONCEPT OF THROMBOELASTOMETRY-GUIDED BLEEDING MANAGEMENT (2ND PILLAR OF PBM) – PERSONALIZED AND PRECISE

Thromboelastometry-guided bleeding management algorithms are based on the following concept and steps:

1. Don't treat numbers in the absence of clinically relevant bleeding! (low positive predictive value (15–25%) of conventional coagulation tests and viscoelastic testing).[8,10,81]
2. Identify patients with coagulopathic bleeding (using cutoff values defined in large observational studies to predict bleeding or (massive) transfusion).[1-4,8,82]
3. Use cutoff values adapted to the patient population, clinical setting, and procedure.[8,32,83-85]
4. Use the high negative predictive value (90–96%) of viscoelastic testing to exclude reasons for bleeding ("not-to-do" algorithms = avoid what is not needed).[8]
5. Treat first what kills first! (according to the Advanced Trauma Life Support concept [sequence matters!]).[8,86]
6. Perform the right hemostatic intervention in the right dose, at the right time, and in the right sequence.[8,87]
7. Stop the bleeding as soon as possible, but avoid any inappropriate blood transfusion or hemostatic intervention.[8]

FIBRINOLYSIS MANAGEMENT

Hyperfibrinolysis is associated with increased mortality in trauma and PPH and must be treated early (at best within 1, latest within three hours after injury or delivery) with tranexamic acid in severe bleeding without waiting for lab results.[88-96] In contrast, tranexamic acid should be considered carefully in gastrointestinal bleeding and liver transplantation since it did not reduce mortality but was associated with an increased incidence of deep vein thrombosis and pulmonary embolism in patients with chronic liver disease.[97-99] Notably, FIBTEM is the most sensitive and specific thromboelastometric assay for hyperfibrinolysis and detected hyperfibrinolysis (FIBTEM maximum lysis (ML) >15%) in 33% of trauma patients (injury severity score [ISS] >15) in the study published by Wang *et al.*[100-102] Hospital mortality was 22% in this subgroup compared with 81% in the subgroup with EXTEM ML >15% (9% of trauma patients) and 10% mortality in trauma patients with ML ≤15% in both FIBTEM and EXTEM.

Recent studies demonstrated that platelet-mediated clot retraction, characterized by "clot instability with decreased lysis indices (LI60) in EXTEM and Aptitude TEM but no clot instability in FIBTEM, is associated with good platelet function and improved survival in patients undergoing liver transplantation.[103-105]

Notably, fibrinolysis shutdown (EXTEM LI60 ≤2%) is also associated with increased mortality due to multiple organ failure in trauma, particularly if it is still present 24 hours after trauma.[106-108] Fibrinolysis shutdown with a cutoff value of LI60 <3.5% is also associated with thrombosis and increased mortality in bacterial sepsis and COVID-19.[109-113]

CLOT FIRMNESS MANAGEMENT

EXTEM and FIBTEM clot firmness parameters A5, A10, and maximum clot firmness (MCF) are predictive for bleeding, transfusion, and massive transfusion in trauma, PPH, and other bleeding scenarios.[1-4,8,10,114-116] Here, the amplitude 5 min after CT (A5) provides the fastest results with the same diagnostic performance as A10 and MCF.[82,117] Whereas EXTEM clot firmness represents both fibrin and platelet contribution to clot firmness, FIBTEM eliminates platelet contribution to clot firmness by cytochalasin D (and tirofiban in rotational thromboelastometry [ROTEM] *sigma*) and, therefore, represents fibrin contribution to clot firmness, only. Accordingly, FIBTEM clot firmness correlates well with the plasma fibrinogen concentration and factor XIII activity.[8,118-121] Here, "platelet noise" (interference of platelet count with FIBTEM, TEG Functional Fibrinogen, or Quantra Fibrinogen Contribution to Clot Stiffness results) is dependent on the effectiveness of platelet inhibition in the assay Cytochalasin D + tirofiban > cytochalasin D > abciximab.[122-125] A low "platelet noise" is crucial for adequate differentiation between fibrin and platelet contribution to clot firmness and fibrinogen dosing.[8,10,126-128] Platelet contribution to clot firmness (PLTEM in ROTEM and PCS in Quantra) can be calculated as the difference between EXTEM and FIBTEM clot firmness and predicts the need for platelet transfusion.[129-132]

Notably, plasma is not an adequate source for fibrinogen replacement and is associated with worse outcomes, particularly in PPH and variceal hemorrhage.[4,8,29,133-135] Cryoprecipitate and fibrinogen concentrate administration are appropriate interventions to increase the plasma fibrinogen concentration and FIBTEM clot firmness and are associated with improved outcomes in bleeding patients with fibrinogen deficiency.[136-144]

THROMBIN GENERATION MANAGEMENT

Thrombin generation is not an issue in early trauma and PPH if the patients have not been treated with oral anticoagulants. Since factor VIII activity and von Willebrand factor increase early after trauma and during major surgery but plasma activity of factor II, VII, and X are decreasing over time, the activity of Vitamin K-dependent factors may be limited in prolonged bleeding.[145] Here, EXTEM CT is more sensitive to detect low factor X activity compared with rapid-TEG.[146] However, EXTEM CT can be prolonged by fibrinogen deficiency, too, which must be excluded before treating with PCC.[8,10,58] In bleeding patients with normal FIBTEM clot firmness but prolonged EXTEM CT, PCC may be the better option to stop bleeding compared with plasma and may be safer compared to rFVIIa.[8,57,98,147-154]

AVOIDANCE OF HYPERCOAGULABILITY AND THROMBOSIS

Thromboelastometry can not only predict bleeding and transfusion and guide hemostatic interventions in bleeding patients but also can identify hypercoagulability and predict thrombosis, too. Here, the ROTEM triad of hypercoagulability is characterized by:[113]

1. Reduced CT in non-activated tests (NAHEPTEM) due to tissue factor expression on circulation cells and microparticles
2. Increased clot firmness (A5, A10, MCF) in NAHEPTEM, INTEM, EXTEM, and/or FIBTEM
3. Hypofibrinolysis or fibrinolysis shutdown (LI60 < 3.5%) in NAHEPTEM and/or EXTEM.

In non-cardiac surgery, preoperative EXTEM and INTEM A10, with a cutoff of 61.5 mm, were the best predictors of postoperative thromboembolic complications with an receiver operating characteristic Area under the curve (ROC AUC) of 0.751. In the same study, aPTT, INR, and platelet count were not predictive of thrombosis.[155] In a study in patients undergoing hip fracture surgery, the pre-operative EXTEM MCF was higher in patients with clinically evident venous thromboembolic events compared with patients without thrombotic complications (median [Interquartile range], 70 mm [68–71] vs. 65 mm [61–68]; $P < 0.001$).[156] Hypercoagulability as detected by ROTEM (increased EXTEM and INTEM MCF and decreased EXTEM and INTEM CT) following hip fractures was undetectable by conventional coagulation assays.[157] In patients with hip fractures and COVID-19, hypercoagulability is aggravated by fibrinolysis shutdown with increased EXTEM LI60 (98.5 ± 1.2% vs. 91.6 ± 5.4%; $P < 0.001$).[158] In two trauma RCTs, the RETIC and iTACTIC trial, thromboembolic events were reduced by 36% and 50%, respectively, in the group with viscoelastic testing-guided bleeding management.[80,127]

In adult patients with cardiovascular disease, an EXTEM MCF cutoff >68 mm has a sensitivity and specificity of 94%, and a FIBTEM MCF cutoff >24 mm has a sensitivity of 77% and a specificity of 88% for thrombosis.[159] Very similar EXTEM MCF (>69 mm) and FIBTEM MCF (>22 mm) cutoff values at admission to intensive care unit in neonates and infants undergoing cardiac surgery have been reported to be predictive for postoperative thrombotic complications.[160] In this prospective observational study, a significant association was found between uncritical transfusion of blood products and an increased incidence of thrombotic complications in the absence of intraoperative coagulation monitoring.

In contrast, big cohort studies, RCTs, and meta-analyses demonstrated a reduction in thromboembolic events by more than 50% after implementation of ROTEM-guided bleeding management.[161-163]

In patients with cirrhosis and hepatocellular carcinoma, a FIBTEM MCF >25 mm was associated with a 5-fold increase in portal vein thrombosis.[164] Furthermore, a postoperative FIBTEM MCF >23 mm on postoperative day 3 (ROC AUC 0.779) and a FIBTEM MCF >28 mm on postoperative day 7 (ROC AUC 0.706) were associated with thromboembolic complications in adult living donor liver transplant recipients with a pre-existing tendency to hypercoagulability.[165] Accordingly, any thromboembolic events (3.7% vs. 6%) and hepatic artery thrombosis (1.9 vs. 6%) could be reduced after the implementation of ROTEM-guided bleeding management in liver transplantation.[166]

To that effect, thromboelastometry can not only identify patients with hypercoagulability and increased risk of thrombosis but also ROTEM-guided bleeding management can avoid thromboembolic complications, too. This may support the idea of personalized antithrombotic therapy guided by viscoelastic testing in the postoperative period.[167]

EVIDENCE AND GUIDELINES FOR GOAL-DIRECTED BLEEDING MANAGEMENT

PBM is not about blood transfusion: It is about patients' outcomes.[168] Accordingly, several meta-analyses based on more than 20 RCTs on the effect of viscoelastic testing-guided perioperative bleeding management did not only demonstrate a significant reduction in transfusion requirements but also a significant reduction in mortality and postoperative acute kidney injury.[27,169] The reduction in postoperative acute kidney injury again has a significant impact on long-term survival.[170,171] Most of these RCTs have been performed in cardiac surgery.

However, another meta-analysis confirmed that viscoelastic testing reduced intraoperative blood loss as well as plasma and platelet transfusion requirements in the assessment and reversal of coagulopathy in patients with cirrhosis.[172] Accordingly, thromboelastometry-guided bleeding management allowed for the implementation of an enhanced recovery after surgery protocol for fast-track liver transplantation with improved patient outcomes.[173]

The Eastern Association for the Surgery of Trauma (US) published a meta-analysis in their practice management guidelines demonstrating a risk ratio for mortality of 0.75 (95% CI, 0.59–0.95) for the implementation of viscoelastic testing in bleeding trauma patients with coagulopathy.[28] This positive effect of viscoelastic testing on mortality could be confirmed by a big US military trauma study in 3,320 patients. After adjusting for confounders, viscoelastic testing during initial resuscitation was independently associated with decreased mortality (odds ratio [OR], 0.63; $P = 0.04$; overall mortality after propensity analysis, 7.3% vs. 13.1%; $P = 0.001$).[174]

A recently published meta-analysis on the role of POC ROTEM in the management of primary PPH demonstrated a significant reduction in emergency hysterectomy (OR = 0.55; 95% CI, 0.32–0.95), TACO (OR = 0.03; 95% CI, 0.00–0.50), FFP transfusion (OR = 0.07; 95% CI, 0.04–0.14), platelet transfusion (OR = 0.51; 95% CI, 0.28–0.91), PRBC transfusion (OR = 0.70 (95% CI, 0.55–0.88), and had better cost-effective treatment (mean cost difference = − 357.5 US$ (95% CI, −567.75– −147.25 US$). POC thromboelastometry-guided bleeding management was associated with reduced morbidity. No mortality was detected across the studies.[29]

CONCLUSION

Recent PBM guidelines recommend the implementation of viscoelastic testing-guided bleeding management algorithms with a 1B or 1A recommendation.[175-181] This is also addressed in the World Health Organization policy brief about the urgent need to implement PBM in all member states in a timely manner.[182] However, even if the number of national activities is increasing, there is still a long way to go.[183]

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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