Evidence for Thromboelastometry/graphy-guided Patient Blood Management: Summary of Systematic Reviews and Meta-Analyses

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1. Introduction

In 2011, the first Cochrane analysis on thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion has been puplished and reported at this time that there is an absence of evidence that TEG or ROTEM improves morbidity or mortality in patients with severe bleeding. The authors concluded that the application of a TEG- or ROTEM-guided transfusion strategy seems to reduce the amount of bleeding but whether this has implications for the clinical condition of patients is still uncertain [1]. In 2016, an update of the Cochrane analysis with the title "Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding" has been published, stating that there is growing evidence that the application of TEG- or ROTEM-guided transfusion strategies may reduce the need for blood products, and improve morbidity in patients with bleeding [2]. Whereas the first Cochrane analysis included nine RCTs with a total of 776 participants, the Cochrane analysis from 2016 was based on 17 RCTs including in total 1493 participants. So the number of RCTs was nearly doubled within five years. This is in-line with an increase in ROTEM publications from 236 from 2000 to 2010 to 914 publications from 2011 to 2017 (PubMed Search, June 29, 2017). Accordingly, the evidence for ROTEM/TEG-guided Patient Blood Management (PBM) is significantly increasing. Based on the increasing number of publications, several systematic reviews and meta-analyses have been published in the last years. The aim of this mini-review is to summarize the evidence for ROTEM/TEG-guided PBM based on these systematic reviews and meta-analyses.

2. Systematic Reviews on ROTEM/TEG-guided PBM

In 2013, Mallett et al. [3] performed a systematic review of all relevant studies that have used viscoelastic tests (VET) of coagulation in patients with liver disease. The authors concluded that although many studies are observational and small in size, it is clear that VET provide additional information that is in keeping with the new concepts of how coagulation is altered in these patients.

In 2014, Müller et al. [4] published a systematic review on the utility of TEG/ROTEM in adults with sepsis. This systematic review included 18 studies (2 RCTs and 16 observational cohort studies). Here, the authors reported that compared with conventional coagulation tests, TEG/ROTEM can detect impaired fibrinolysis, which can possibly help to discriminate between sepsis and systemic inflammatory response syndrome (SIRS). A hypocoagulable profile is associated with increased mortality. Accordingly the authors concluded that TEG/ROTEM could be a promising tool in diagnosing alterations in coagulation in sepsis. Given that coagulopathy is a dynamic process, sequential measurements are needed to understand the coagulation patterns in sepsis, as can be detected by TEG/ROTEM.

Haas et al. [5] published a systematic review on ROTEM for guiding bleeding management of the critically ill patient. This systematic review included 6 trauma, 12 cardiovascular, and 4 liver transplant studies. Here, the authors stated that the published literature clearly demonstrates the usefulness of ROTEM in detecting coagulation disorders in severe trauma, cardiac and aortic surgery, liver transplantation, and postpartum haemorrhage reliably and within a clinically acceptable turn-around time. Accordingly, they concluded that in all of the above-mentioned scenarios, the transfusion of any allogeneic blood products could be reduced significantly using ROTEM-guided bleeding management, thereby minimising or avoiding transfusion-related side effects. Based on the current body of evidence as assessed by the GRADE system, the use of ROTEM may be recommended in particular for management of severe bleeding after trauma and during cardiac and aortic surgery. However, as laboratory

testing contributes only one part of severe bleeding management, the implementation of safe and effective treatment algorithms must be ensured at the same time.

Da Luz et al. [6] published a descriptive systematic review on the effect of TEG and ROTEMROTEM on diagnosis of coagulopathy, transfusion guidance and mortality in trauma. They analyzed 55 studies (12,489 patients) including 38 prospective cohort studies, 15 retrospective cohort studies, two before-after studies, and no randomized trials. Many TEG/ROTEM measurements were associated with early coagulopathies, including some (hypercoagulability, hyperfibrinolysis, platelet dysfunction) not assessed by routine screening coagulation tests. One observational study suggested that a ROTEM-based transfusion algorithm reduced blood-product transfusion, but TEG/ROTEM-based resuscitation was not associated with lower mortality in most studies. Accordingly, the authors concluded that limited evidence from observational data suggest that TEG/ROTEM tests diagnose early trauma coagulopathy and may predict blood-product transfusion and mortality in trauma.

In 2015, Hunt et al. [7] performed a Cochrane analysis to determine the diagnostic accuracy of TEG and ROTEM for trauma-induced coagulopathy (TIC) in adult trauma patients with bleeding, using a reference standard of prothrombin time ratio ≥ 1.2 or an INR ≥ 1.5. They found no evidence on the accuracy of TEG, and three ROTEM studies were included in the final analysis. Here, EXTEM A5, A10, and A15 showed a sensitivity for TIC between 70 and 100% and a specificity between 58 and 100%.

In 2015, Whiting et al. [8] published a systematic review and cost-effectiveness analysis (health technology assessment) on viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis. Thirty-one studies were included in the clinical effectiveness review. Eleven RCTs (1089 participants) assessed viscoelastic devices in patients undergoing cardiac surgery; six assessed TEG and five assessed ROTEM. The authors concluded that vicoelastic testing is cost-saving and more effective than standard laboratory tests (SLTs), in both patients undergoing cardiac surgery and trauma patients. However, there were no data on the clinical effectiveness of Sonoclot.

Inaba et al. [9] reported on the 2014 consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation in Philadelphia, Pensylvania. This panel included trauma surgeons, hematologists, blood bank specialists, anesthesiologists, and the lay public. The recommendations of this consensus conference have also been included in the recently published AWMF S3-Leitlinie Polytrauma/Schwerverletzten-Behandlung [10-11].

In 2016, Veigas et al. [12] publishe another systematic review on the ROTEM values for the diagnosis of coagulopathy, prediction and guidance of blood transfusion and prediction of mortality in trauma patients. A total of 13 observational studies involving 2835 adult trauma patients met the inclusion criteria. Nine studies were prospective and four were retrospective. There were no randomized controlled trials. The authors concluded that most of the evidence indicates that abnormal EXTEM and FIBTEM early clot firmness amplitudes (A5, A10) or maximal clot firmness (MCF) diagnose coagulopathy, and predict blood transfusion and mortality. The presence of fibrinolysis was also associated with mortality. ROTEM thus, may be of value in the early management of trauma patients.

3. Meta-Analyses on ROTEM/TEG-guided PBM

Since 2011, eight meta-analyses on ROTEM/TEG monitoring of haemostatic treatment in bleeding patients have been published [1-2, 13-18] and one meta-analysis on viscoelastic testing for hepatic surgery is just under preparation [19]. The impact of ROTEM/TEG-guided PBM on transfusion requirements, morbidity, and mortality is summarized in the flowing table. Since the different meta-analyses considered different studies in their meta-analyses and focused on different outcomes, the results and conclusions were not exactly the same.

In addition, Corredor et al. [14] focused on the role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery. The authors included 30 observational studies incorporating 3044 patients in the qualitative assessment, and nine randomised controlled trials including 1057 patients in the meta-analysis. Here, the use of platelet function testing within a blood transfusion algorithm demonstrated a significant reduction in blood loss, transfusion of packed red cells and fresh frozen plasma. The combined use of viscoelastic testing and platelet function testing

even achieved a significant greater reduction in blood loss compared with their use alone. Accordingly, the authors concluded that - due to the multifactorial nature of postoperative bleeding in cardiac surgery - the incorporation of point-of-care platelet function testing into viscoelastic testing-guided transfusion management algorithms is associated with a reduction in blood loss and transfusion requirements in cardiac surgery patients.

Author Year [Ref]	**Afshari 2011 [1] & Wikkelsø 2011 [13]**	**Corredor 2015 [14] (VET + PFT)**	**Deppe 2016 [15]**	**Wikkelsø 2016 [2]**	**Wikkelsø 2017 [16]**	**Fahrendorff 2017 [17]**	**Serraino 2017 [18]**
Studies (n)	9	9	17	17	17	15	15
Patients (n)	776	1057	8332	1493	1493	1238	8737
Dichotomous Variables	RR (95% CI); I^2	RR (95% CI); P	OR (95% CI); P	RR (95% CI); P; I^2	RR (95% CI); P; I^2	OR (95% CI); P; I^2	RR (95% CI); P; I^2
Allogenic Blood Transfusion	NA	NA	0.63 (0.56-0.71); P<0.0001	NA	NA	NA	NA
PRBC Transfusion	0.88 (0.76-1.02); I^2=26%	0.86 (0.79-0.94); P=0.001	0.63 (0.50-0.78); P<0.0001	0.86 (0.79-0.94); P=0.001; I^2=0%	0.86 (0.79-0.94); P=0.001; I^2=0%	NA	0.88 (0.79-0.97); P=0.01; I^2=43%
Plasma Transfusion	0.64 (0.29-1.42); I^2=70%	0.42 (0.30-0.59); P<0.001	0.31 (0.13-0.74); P<0.0001	0.57 (0.33-0.96); P=0.034; I^2=86%	0.57 (0.33-0.96); P=0.034; I^2=86%	NA	0.68 (0.46-1.00); P=0.05 I^2=79%
Platelet Transfusion	0.77 (0.47-1.26); I^2=47%	0.81 (0.55-1.18); P=0.27	0.62 (0.42-0.92); P=0.0292	0.73 (0.60-0.88); P=0.0012; I^2=0%	0.73 (0.60-0.88); P=0.0012; I^2=0%	NA	0.78 (0.66-0.93); P=0.004; I^2=0%
Plasma & Platelet Transf.	0.39 (0.27-0.57); I^2=0%	NA	NA	0.44 (0.24-0.81); P=0.008; I^2=0%	0.44 (0.24-0.81); P=0.008; I^2=0%	NA	NA
Fibrinogen Concentrate	NA	NA	NA	0.94 (0.76-1.17); P=0.59; I^2=22%	0.94 (0.76-1.17); P=0.59; I^2=22%	NA	0.94 (0.76-1.17); P=0.59; I^2=0%
Prothrombin Complex (PCC)	NA	NA	NA	0.39 (0.07-2.16); P=0.28; I^2=91%	0.39 (0.07-2.16); P=0.28; I^2=91%	NA	0.39 (0.07-2.16); P=0.28; I^2=91%
Recombinant FVIIa	NA	NA	NA	0.19 (0.03-1.24); P=0.083; I^2=33%	0.19 (0.03-1.24); P=0.083; I^2=33%	NA	NA
Massive Transfusion	0.82 (0.38-1.77); I^2=34%	NA	NA	0.82 (0.38-1.77); P=0.61; I^2=34%	0.82 (0.38-1.77); P=0.61; I^2=34%	NA	NA
Re-exploration due to bleeding	0.91 (0.44-1.87); I^2=11%	0.68 (0.36-1.26); P=0.22	0.56 (0.45-0.71); P<0.0001	0.75 (0.50-1.10); P=0.14; I^2=0%	0.75 (0.50-1.10); P=0.14; I^2=0%	NA	0.82 (0.55-1.23); P=0.34; I^2=0%
Postoperative AKI / Dialysis	NA	NA	0.77 (0.61-0.98); P=0.0278	0.46 (0.28-0.76); P=0.0028; I^2=0%	0.46 (0.28-0.76); P=0.0028; I^2=0%	NA	0.42 (0.20-0.86); P=0.02; I^2=26%
Thromboembolic Events	NA	NA	0.44 (0.28-0.70); P=0.0005	1.04 (0.35-3.07); P=0.94; I^2=0%	1.04 (0.35-3.07); P=0.94; I^2=0%	NA	NA
Cerebrovascular Accident/Stroke	1.66 (0.46-5.93); I^2=0%	NA	0.64 (0.31-1.30); P=0.1345	NA	NA	NA	1.73 (0.41-7.23); P=0.47; I^2=0%
Mortality (in hospital/30 d/ longest follow-up)	0.77 (0.35-1.72); I^2=0%	0.66 (0.31-1.39); P=0.27	0.92 (0.74-1.16); P=0.4520	0.52 (0.28-0.95); P=0.033; I^2=0% ROTEM: 0.44 (0.21-0.93); P=0.031; I^2=15% TEG: 0.72 (0.25-2.07); P=0.54; I^2=0%	0.52 (0.28-0.95); P=0.033; I^2=0%	0.60 (0.34-1.07); P=0.08; I^2=11%	0.55 (0.28-1.10); P=0.09; I^2 = 1%
Continuous Variables							
Drainage Volume (mL/24 h)	-85.1 (-140.7 to -29.4); I^2=0%	-103.0 (-149.9 to -56.1); P<0.0001	-175 (-376 to 26); P=0.0873	NA	NA	-1.40 (L) (-2.57 to -0.23); P=0.02; I^2=97%	NA
PRBC Transfusion (U with 250 mL/U)	NA	NA	NA	NA	NA	-0.64 (-1.12 to -0.15); P=0.01; I^2=82%	NA
Plasma Transfusion (U with 270 mL/U)	NA	NA	NA	NA	NA	-1.98 (-3.41 to -0.54); P=0.007; I^2=97%	NA
Platelet Transfusion (U with 340 mL/U)	NA	NA	NA	NA	NA	-1.62 (-0.92 to 0.24); P=0.25; I^2=87%	NA
Ventilation Time (h)	9.54 (-28.9 to 47.9); I^2=0%	NA	-7.24 (-26.2 to 11.7); P=0.4546	NA	NA	NA	-0.28 (-0.66 to 1.23); P=0.56; I2=0%
ICU LOS (h)	-2.03 (-4.35 to 0.29); I^2=0%	NA	-2.28 (-7.58 to 3.02); P=0.3995	NA	NA	NA	-31.8 (-94.7 to 31.1); P=0.32; I^2=59%
Hospital LOS (d)	0.07 (-0.40 to 0.26); I^2=0%	-2.1 (-4.3 to 0.2); P=0.08	-0.06 (-0.29 to 0.16); P=0.5899	NA	NA	NA	-3.1 (-9.6 to 3.3); P=0.34; I^2=69%

Table: Impact of ROTEM/TEG-guided Patient Blood Management. CI =confidence interval; I2 = degree of heterogeneity; n = number; NA = not analyzed; OR = odds ratio; PFT = platelet function testing; PRBC = packed red blood cells; RR = risk ratio; VET = viscoelastic testing; red = statistically significant

In contrast to the Cochrane analysis published in 2016 [2], Serraino & Murphy [18] reported that the reduction in mortality (RR 0.55, 95% CI 0.28-1.10) did not reach statistical significance (p=0.09). Furthermore, Serraino & Murphy wrote in their abstract that viscoelastic point-of-care testing did not improve important clinical outcomes beyond transfusion. In contrast, they report later in their meta-analysis a significant reduction in severe acute kidney injury (RR 0.42, 95% CI 0.20-0.86). Surprisingly and in contast to all other meta-analyses published in 2016 [2, 15-17], the authors hypothesized that viscoelastic testing lacks clinical effectiveness and further large trials are unlikely to demonstrate clinical benefits for current viscoelastic point-of-care tests. These discrepancies have been addressed by an editorial by Ranucci [20] as well as by a comment by Kozek-Langenecker et al [21]. Both authors pointed out inappropriate blood transfusion is still and issue and that a significant reduction in actute kidney injury is an important clinical outcome since it is associated with a significant increase in long-term mortality. In contrast to Serraino & Murphy, Ranucci and Kozek-Langenecker recommend focussing future research on adequate surgery-specific viscoelastic testing supported treatment algorithms.

Notably, the Cochrane analysis published in 2016 [2], differentiated also between viscoelastic testing- and standard laboratory testing-driven protocols as well as between TEG- and ROTEM-driven protocols. Here, viscoelastic testing-guided algorithms were associated with a significant lower mortality (RR 0.36, 95% CI 0.16-0.84; p=0.02). Trials using ROTEM reached statistical significance for reducing mortality (RR 0.44, 95% CI 0.21-0.93; p=0.03), whereas trials using TEG did not (RR 0.72, 95% CI 0.25-2.07; p=0.54). Here, it cannot be concluded whether this is based on differences in the devices or differences in the algorithms used. However, even taking both devices - ROTEM and TEG – together, the reduction in mortality was still significant (RR 0.52, 95% CI 0.28-0.95; p=0.03). This shows again, that the conclusion done by Serraino & Murphy is at least rashly.

Further RCTs have already been published in between [22-26] or are actually running [NCT01402739 (HEART-PoC), NCT01826123 (MultiPOC), NCT02311985 (POCKET), NCT02416817 (STATA Trial), NCT02457403 (SCARLET), NCT02461251 (ROTEM-PPH), NCT02593877 (iTACTIC), NCT02740374 (ROTEM_SPINE), NCT02729974 (Placenta Accreta), NCT02745041 (FEISTY), NCT02758184 (Major Spine Surgery), NCT03064152 (PPH)].

4. Viscoelastic Testing as a Mandatory Part of Patient Blood Management

The value of point-of-care viscoelastic testing has to be assessed as an essential part of Patient Blood Management in order to improve patient safety [27]. Here, it plays a major role in the second pilar – focusing on minimization of bleeding and blood loss. The single diagnostic and therapeutic interventions of Patient Blood Management should not be assessed in isolation since it is well known that bundles of interventions are more effective than each single intervention [10, 28-32]. Accordingly, Meybohm et al. [33-34] and Leahy et al. [35-36] could demonstrate in their large multicenter PBM cohort studies including 129,719 and 605,046 patients, respectively, significantly decreased transfusion requirements, improved patient outcomes (acute renal failure, hospital-aquired infections, acute myocardial infarction and stroke), reduced hospital costs, hospital length of stay and hospital mortality (OR 0.72, 95% CI 0.67-0.77; p<0.001). Accordingly, the European Commission recently published guidance for health authorities and hospitals supporting PBM implementation in the EU [37-38].

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