A pilot, randomised controlled trial of a rotational thromboelastometry-based algorithm to treat bleeding episodes in extracorporeal life support: the TEM Protocol in ECLS Study (TEMPEST)

Hergen Buscher, David Zhang and Priya Nair

ABSTRACT

Objectives: Minimal evidence to guide haemostatic therapy for bleeding in extracorporeal life support (ECLS) has resulted in wide variability in practice. We aimed to show that a goal-directed algorithm incorporating results from thromboelastometry (TEM) is feasible and safe for the timely management of bleeding episodes in adult patients receiving ECLS.

Design and participants: A pilot randomised controlled trial involving 16 adult patients who underwent ECLS, randomised over 10 months.

Intervention: The intervention group was treated according to a goal-directed algorithm based on TEM results during bleeding episodes. Apart from the intervention, both groups received standard care including conventional laboratory coagulation tests.

Outcome measures: Need for blood product transfusion, haemorrhagic and thromboembolic complications and survival.

Results: There was a statistically non-significant trend towards reduction in the amount of blood products transfused, occurrence of bleeding, and thrombotic complications, when comparing the intervention arm with the control arm. Survival to hospital discharge was 69%.

A significant correlation was found between fibrinogen levels and FIBTEM clot firmness at 10 minutes ($R = 0.812; P < 0.001$); activated partial thromboplastin time and clotting time HEPTEM/INTEM ratio ($R = -0.719; P < 0.001$); and platelet count and EXTEM clot firmness at 10 minutes ($R = 0.783; P < 0.001$).

Conclusion: TEM allows assessment for coagulation status in a timely manner and its use for the treatment of bleeding episodes in adult patients receiving ECLS appears feasible and safe. Clinical benefit should be investigated in larger multicentre randomised trials.
management of bleeding episodes in patients undergoing ECLS, and that results are comparable to those obtained using conventional laboratory coagulation tests.

**Methods**

**Setting**

Our study was carried out in an adult ECLS-enabled, cardiopulmonary transplant and mechanical circulatory support referral ICU in Sydney, Australia.

**Participants**

Consecutive patients were randomised. Eligible patients were aged 18 years or older, and received ECLS for cardiac and/or pulmonary support. Patients were excluded if they had a ventricular assist device in place; were pregnant; had contraindications to the administration of platelets, fresh frozen plasma (FFP), cryoprecipitate, tranexamic acid or desmopressin; had treatment limitations in place; or were not expected to survive the following 24 hours.

Informed consent for participation in the prospective arm was obtained from the patient or person responsible. The study was approved by St Vincent's Hospital Human Research Ethics Committee (HREC/15/SVH/439).

**Study design**

Patients were randomly assigned in a 1:1 ratio to management with an algorithm-guided intervention, based on repeated TEM measurements during bleeding episodes (intervention arm); or to standard care (control arm). The Research Electronic Data Capture (REDCap) randomisation module was used to conduct permuted-block randomisation, with stratification according to the mode of ECLS and whether ECLS occurred perioperatively.

Patients allocated to the intervention arm underwent daily TEM testing, conducted using the Sigma TEM device (ROTEM) in addition to standard care. TEM test results and methods have been described previously. In brief, whole blood is tested at the bedside to provide information on clotting time (affected by factor deficiency or heparin) and clot firmness (affected by fibrinogen and platelets). This is achieved through the oscillation of a pin in a well of whole blood after addition of a haemostatic activator.

During bleeding episodes, defined as the need for blood products (excluding red blood cells [RBCs]) or coagulation factors to treat clinically apparent bleeding, haemostatic therapy was guided by an algorithm based on TEM results (Figure 2). If the indication for further blood products (excluding RBCs) persisted, further algorithm-based therapy was administered. Follow-up TEM testing was conducted. If the bleeding episode persisted after the second algorithm-based treatment, further therapy was left to clinician discretion, as was the case if TEM testing did not reveal any abnormalities. Subsequent bleeding episodes were considered to be new episodes if they were more than 24 hours after the previous episode.

Patients allocated to the control arm received standard care, based on results of previous conventional coagulation tests which included activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen level and platelet count. Patients in both treatment arms underwent surgical and interventional treatments as clinically indicated.

**Figure 1. TEM algorithm for treatment of bleeding episodes**

![Figure 1](image1.jpg)

**Figure 2. Protocol for algorithm use during bleeding episodes in patients in the intervention arm**

![Figure 2](image2.jpg)
ECLS circuits used the Jostra Rotaflow or Cardiohelp centrifugal blood pump (Maquet), the Quadrox D oxygenator (Maquet) and heparin-bonded circuits. Anticoagulation therapy administered was unfractionated heparin infusions, with a targeted APTT of up to twice the reference range.

Data collection
Demographic data was recorded, including sex, age, ECLS indication, circuit configuration, ECLS duration, and Acute Physiology and Chronic Health Evaluation (APACHE) II score. Feasibility data collected included the type and dose of treatment for bleeding episodes, including the total volumes of blood products and coagulation factors administered and the results of TEM or conventional laboratory tests conducted. Data on safety included bleeding episodes; re-bleeding events; surgical interventions for bleeding; thrombotic complications (new cerebral, intestinal or limb ischaemia, deep vein thrombosis or pulmonary embolism); ECLS circuit failure in the 24 hours after therapy during a bleeding episode; and survival to ECLS weaning and ICU and hospital discharge. Feasibility and safety data were collected from randomisation to the end of ECLS treatment.

Statistical analysis
We tested continuous variables for normality using the Shapiro–Wilks test and show them as medians with interquartile ranges (IQRs), and show categorical variables as frequencies and percentages. The small dataset meant that non-parametric methods were necessary. The Mann–Whitney U test was used for comparison between two arms of the study. The χ² or Fisher exact tests were used to analyse categorical variables. Pearson correlation and regression analysis was used to compare TEM results with corresponding conventional coagulation test results. P < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 23.0 (SPSS) and Prism 6, version 6.0 (GraphPad).

Results
Over an 8-month period from June 2016 to January 2017, 16 patients were enrolled in the prospective arm of the study, and were randomised into the intervention group (n = 7) or standard care (n = 9). In total, 173 ECLS days were studied in 16 patients.

Table 1 shows baseline data. When comparing the intervention group and standard care group, there was no statistically significant difference in age, sex, ECLS configuration, indication, ECLS duration, APACHE-II score or conventional baseline coagulation parameters.

Sixteen patients (100%) received transfusion of packed RBCs (PRBCs), 10 (63%) received platelets, eight (50%) received FFP, and nine (56%) received cryoprecipitate.

Desmopressin was administered for three (19%) patients, tranexamic acid for two (13%) and protamine for two (13%) patients. The total volume of blood products transfused was 176 units of PRBCs, 56 units of platelets, 55 units of FFP and 118 units of cryoprecipitate. The amounts of each blood product transfused are compared in Table 2.

Patients in the intervention group received less transfusion of all four products compared with the control group, although the difference was not significant.

Comparison of the median values per ECLS day showed higher transfusion requirements in the standard care group, although the difference was not significant.

Table 3 shows safety data collected during the study. The intervention group had a non-significantly reduced haemorrhagic and thromboembolic complication rate compared with the control arm.

Of these thrombotic complications was one case of ischaemic stroke in the control group. There were two incidences of oxygenator failure, both in the control group.
Two patients (29%) in the intervention arm died after haemorrhagic strokes. Both patients showed a lower clot lysis index at 30 minutes (LI30) on their FIBTEM assay in the days before the stroke.

There was no significant difference in survival rates to ECLS decannulation, ICU discharge and hospital discharge. Overall, 135 TEM tests were conducted, which showed good correlation between these parameters and standard laboratory coagulation tests.

Discussion

Our results suggest that the use of a goal-directed algorithm based on TEM is feasible and safe and may have potential to reduce the transfusion of blood products, and reduce adverse outcomes related to haemostatic disturbances during ECLS.

In the control arm, when a bleeding episode is identified, clinicians could either act on formula-driven transfusion strategies, or depend on conventional laboratory tests to inform their therapy.24 In the case of a formula-driven approach, for example using a 1:1:1 fixed ratio of PRBCs:platelets:FFP,25 clinicians can bypass laboratory testing and promptly administer therapy. However, this approach may result in over-transfusion, adverse events and wastage of blood products.26

Table 2. Blood product usage

<table>
<thead>
<tr>
<th>Product</th>
<th>TEM group (n = 7)</th>
<th>Standard care group (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBCs</td>
<td>4 (3–13.5)</td>
<td>10 (8–13)</td>
<td>0.351</td>
</tr>
<tr>
<td>Platelets</td>
<td>1 (0–3.5)</td>
<td>3 (0–4)</td>
<td>0.408</td>
</tr>
<tr>
<td>FFP*</td>
<td>0 (0–3.5)</td>
<td>2 (0–8)</td>
<td>0.470</td>
</tr>
<tr>
<td>Cryoprecipitate*</td>
<td>0 (0–5)</td>
<td>4 (0–6)</td>
<td>0.536</td>
</tr>
</tbody>
</table>

Median volume/ECLS day/patient, units (IQR)

<table>
<thead>
<tr>
<th>Product</th>
<th>TEM group (n = 7)</th>
<th>Standard care group (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBCs</td>
<td>0.90 (0.59–0.99)</td>
<td>1.41 (0.65–1.41)</td>
<td>0.210</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.16 (0–0.22)</td>
<td>0.49 (0–0.69)</td>
<td>0.210</td>
</tr>
<tr>
<td>FFP*</td>
<td>0 (0–0.32)</td>
<td>0.06 (0–0.66)</td>
<td>0.408</td>
</tr>
<tr>
<td>Cryoprecipitate*</td>
<td>0 (0–0.33)</td>
<td>0.65 (0–0.71)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

TEM = thromboelastometry. ECLS = extracorporeal life support. IQR = interquartile range. PRBC = packed red blood cells. FFP = fresh frozen plasma. * FFP and cryoprecipitate shown as whole blood units.

Table 3. Adverse events and survival

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>TEM group (n = 7)</th>
<th>Standard care group (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding episode*</td>
<td>4 (57%)</td>
<td>7 (78%)</td>
<td>0.596</td>
</tr>
<tr>
<td>Re-bleeding†</td>
<td>2 (50%)</td>
<td>6 (86%)</td>
<td>0.491</td>
</tr>
<tr>
<td>Surgical intervention for bleeding</td>
<td>4 (57%)</td>
<td>5 (56%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Thrombotic complication</td>
<td>1 (14%)</td>
<td>5 (56%)</td>
<td>0.145</td>
</tr>
<tr>
<td>ECLS circuit change/failure</td>
<td>0</td>
<td>2 (22%)</td>
<td>0.475</td>
</tr>
<tr>
<td>Survival to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECLS weaning</td>
<td>5 (71%)</td>
<td>9 (100%)</td>
<td>0.175</td>
</tr>
<tr>
<td>ICU discharge</td>
<td>5 (71%)</td>
<td>9 (100%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>5 (71%)</td>
<td>6 (67%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

TEM = thromboelastometry. ECLS = extracorporeal life support. ICU = intensive care unit. * Defined as the need for blood products (excluding PRBCs) or coagulation factors to treat any clinically apparent bleeding or haemostatic disturbance. † Defined as bleeding episode in the 24 hours after the previous episode (% re-bleeding calculated from the number of patients who experienced bleeding episode).

There was a positive correlation between clot firmness at 10 minutes in the FIBTEM test with fibrinogen levels, with $R = 0.812$ and $P < 0.001$ (Figure 3).

There was a negative correlation between the HEPTEM/INTEM clotting time ratio and APTT, with $R = –0.719$ and $P < 0.001$ (Figure 4).

There was also good correlation between the clot firmness at 10 minutes in the EXTEM test and platelet count, with $R = 0.783$ and $P < 0.001$ (Figure 5). A quadratic relationship fits best with the data points.

Figure 3. Correlation and regression between A(10) FIBTEM and fibrinogen levels

A10 = clot firmness at 10 minutes.
In the other approach, clinicians await laboratory tests to inform their treatment, and test results may not supply specific information. Activated clotting time is less accurate with low heparin dosing compared with the higher doses used in cardiopulmonary bypass and may be prolonged by platelet diatheses, fibrinogen and other factor deficiencies, haemodilution and hypothermia. Other tests, such as APTT and PT, are unable to assess the contribution of cells to the coagulation process, as understood in recent times. Most importantly, turnaround times associated with laboratory tests can delay treatment by up to an hour.

In contrast, the use of TEM in the intervention arm of this study allowed results to become available within 5 minutes. They provided information on the underlying cause of the bleeding, such as differentiating coagulopathy from surgical causes, and identifying specific deficiencies through the use of various assays running concurrently. Blood products can usually be ordered within 10 minutes.

The nonparametric nature of data on the amount of blood products used made it hard to directly compare transfusion requirements, but comparison of the median units per ECLS run indicated that the intervention arm may have had reduced blood product usage. This suggests that targeted therapy was more effective in correcting the haemostatic defect, thus reducing the need for further transfusions. However, an alternative explanation may be that the algorithm simply reduced the amount of transfusions by placing constraints on the amount and type that could be prescribed, without being more effective. This non-blinded trial may also be biased towards a conservative transfusion practice in the intervention arm.

A difference in transfusion requirements was also seen when the length of the ECLS run was factored in. ECLS duration might affect the amount of blood products transfused but, conversely, management of bleeding episodes and transfusions may also affect ECLS duration.

Currently, there are no published studies on the use of TEM-guided ECLS therapy; however, a body of evidence exists regarding its use in cardiac surgery, with outcomes such as reduced transfusion rates, costs, and complications, with no adverse effect on mortality. Likewise, there has been growing evidence of its role in trauma, obstetrics and liver transplantation. The incidences of haemorrhage and thrombosis are similar to those in previously published observations. We defined a bleeding episode as the need for blood products (excluding PRBCs) or coagulation factors to treat any clinically apparent bleeding or haemostatic disturbance. Other ways of defining bleeding episodes include clinical observation of signs of bleeding, or analysis of haemoglobin levels.
A hyperfibrinolysis-like syndrome was observed in the FIBTEM assay of two patients in the intervention arm in the days before they experienced haemorrhagic strokes. Daily TEM testing for both patients showed greatly increased FIBTEM A(10) and maximum clot firmness, followed by signs of increased fibrinolysis (LI30 < 80%). Hyperfibrinolysis is usually assessed by the EXTEM assay, as reflected in the algorithm used in this study. The observed FIBTEM behaviour has not, to our knowledge, been previously described and may warrant further investigation.

The good correlation between TEM parameters with conventional laboratory tests supports the hypothesis that such POCT can validly assess coagulation status. This is consistent with studies investigating the use of TEM in various fields, such as cardiac and paediatric surgery, as well as adult ECLS patients. However, contrary to the existing literature, we found that a quadratic relationship fits best when comparing A(10) EXTEM with platelet count, as opposed to a linear relationship. A possible reason for this difference may be the narrower range of platelet count results included in their analysis (50–300 × 10^9/L), compared with the wider range in our analysis (30–470 × 10^9/L). This suggests that a linear relationship exists when the A(10) EXTEM and platelet count are within normal ranges, with linearity disappearing outside the normal range.

The algorithm allowed for some clinician discretion in choosing the dose of blood products or drugs, depending on the perceived severity of bleeding. The effect of having a dosage range has not been investigated previously, but may improve acceptability and adherence to the algorithm, improving the feasibility of this intervention.

A major limitation of our study was the small sample size. As our objective was a pilot study to demonstrate feasibility and safety, we were not able to clearly prove clinical benefit. Likewise, heterogeneity of the sample could only be mitigated in part by stratifying for variables such as the ECLS configuration and perioperative placement. Although there was no difference in coagulation status, the baseline bleeding risk is difficult to control for in a small sample size. A larger multicentre study is needed to evaluate meaningful clinical endpoints. Future trials should also evaluate the impact of platelet dysfunction by using point-of-care aggregometry, which was not available in our institution as a POCT at the time of the trial.

External validity was limited by a setting in which factor concentrates (fibrinogen and prothrombin complex) were not accessible because, ideally, a POCT should be paired with a point of care solution for optimum benefit. In addition, heparin was the only anticoagulant studied in our trial.

Conclusions

Although no statistical difference was shown, all safety and efficacy-related endpoints favoured the intervention, which justifies adequately powered trials. This intervention has the potential to improve patient outcomes, reduce expenditure on blood products, and contribute to recommendations for ECLS anticoagulation practices. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of extracorporeal life support in the critically ill.

Acknowledgement

Our trial was supported by a grant from the Extracorporeal Life Support Organization.

Competing interests
None declared.

Author details

Hergen Buscher1,2
David Zhang1,2
Priya Nair1,2
1 Intensive Care Unit, St Vincent’s Hospital, Sydney, NSW, Australia.
2 University of New South Wales, Sydney, NSW, Australia.

Correspondence: hergen.buscher@svha.org.au

References


