Evaluation of ROTEM-guided therapy in the management of major haemorrhage

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Introduction

- A major haemorrhage is a potentially fatal bleeding event defined by; loss of > 1 blood volume in 24hrs, 50% of total blood volume loss within 3 hours or a bleeding rate of > 150mls/min (Hunt et al., 2015).
- Current treatment is via transfusion "shock packs" with additional treatment directed by standard laboratory tests (SLTs) or clinical judgement.
- However, allogeneic transfusions are associated with adverse events (Pandey and Vyas, 2012; Yang et al., 2012).
- SLTs do not evaluate *in vivo* haemostasis, are not validated to monitor haemostasis in major haemorrhage and have long turnaround times (TATs) (Rossaint et al., 2016).
- Rotational thromboelastometry (ROTEM) is a rapid point-of-care test that measures all aspects of haemostasis accurately reflecting the process *in vivo* (Carll and Wool, 2020). The mechanism of action is illustrated in figure 1.

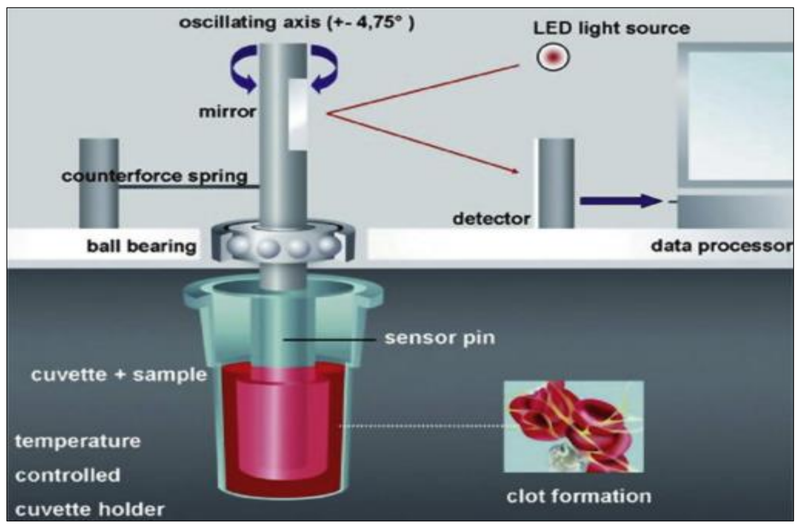

Figure 1: Whole blood is pipetted into 5 cuvettes in a cartridge containing the reagents for a particular aspect of haemostasis plus quality control. As the clot forms, the oscillating pin in the cuvette becomes restricted, and freed during fibrinolysis. This change is detected by a change in light reflectance, captured by the photodetector and plotted as a trace (Curry et al., 2018; McNamara and Mallaiah, 2019).

- An example of a ROTEM trace is outlined in figure 2.

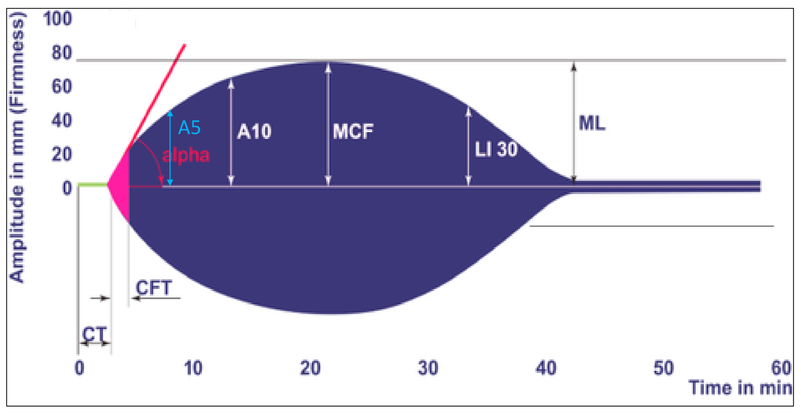

Figure 2: Example of a ROTEM trace (CT = clotting time (s), CFT = clot formation time (s), alpha = angle representing speed of clot formation (°), A5 = clot amplitude at 5 mins (mm), A10 = clot amplitude at 10 mins (mm), MCF = maximum clot firmness (mm), LI 30 = amplitude of lysis at 30 mins (%), ML = maximum lysis (%)) (Whiting and DiNardo, 2014; Cruz et al., 2017).

- The transfusion triggers used to direct treatment in this study are included in the algorithm developed by this trust, depicted in figure 3.

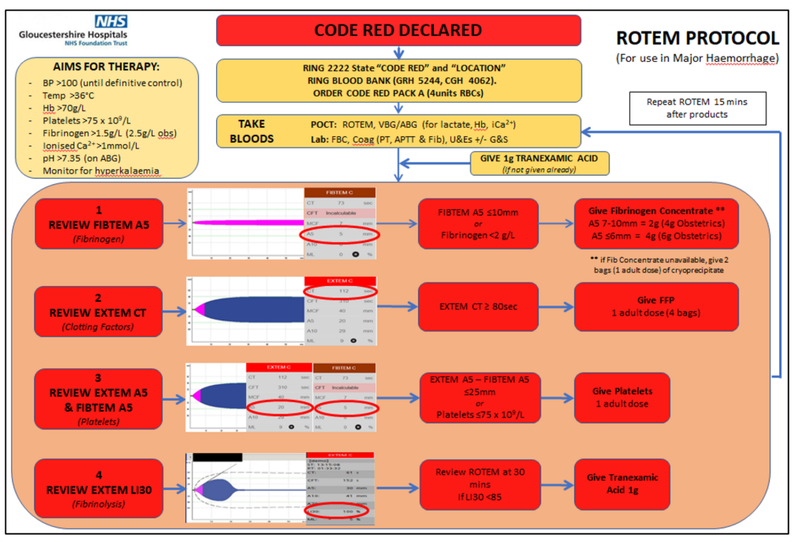

Figure 3: Algorithm included in the major haemorrhage protocol (MHP) used to direct treatment in a major haemorrhage.

- Numerous benefits of ROTEM use in treating bleeding have been identified from several studies (Schöchl et al., 2011; Mallaiah et al., 2015; Mace et al., 2016).
- However, international and local guidelines do not recommend it as a gold standard due to limitations of these studies and a lack of consensus regarding the instrumentation, treatment thresholds and therapy. So, further research is required.

Aims

- The impact of ROTEM-guided component therapy when treating major haemorrhage cases vs shock pack treatments was investigated.
- The number of blood components transfused and disposed, and patient outcomes were compared.
- The ROTEM was assessed by comparing the results and TATs to SLTs.

Methods

- The study was conducted at Gloucestershire Hospitals NHS Foundation Trust. Data was collected from 26 patients January-June 2020 (pre-ROTEM group). The post-ROTEM group consisted of 206 patients and data collection took place June 2020-December 2021.
- Patient demographics, blood component data and clinical outcomes were compared.
- ROTEM results and TATs were compared to SLTs, all data were collected from the sources illustrated in table 1.
- A post-hoc power calculation was performed.

Table 1: The data collected and sources (LIMS = laboratory information system, EPR = electronic patient record, Blood360 = blood tracking system).

Patient Information	**Source**
Patient Age and Sex	LIMS
Haemorrhage Aetiology	LIMS
SLT Results and their Turnaround Times	LIMS
ROTEM Results	ROTEM Analyser
Blood Component Data	**Source**
Number of Red Cells, FFP, Platelet and Cryoprecipitate Units Transfused/Disposed	LIMS/Blood360
Concentration of Fibrinogen Concentrate Transfused	LIMS
Volume of Cell Salvage Transfused	Patient notes
Patient Outcomes	**Source**
Estimated Blood Loss (EBL)	Patient Notes
Intensive Therapy Unit (ITU) Admission	LIMS
Length of Hospital Stay (LOS)	EPR
Mortality	LIMS

- Approval was granted by the Trust Research & Development department and the University Science and Engineering Research Ethics & Governance Committee.
- Kolmogorov-Smirnov tested the data for normality. IBM SPSS statistics software was used; Mann-Whitney U, Fisher's exact and Spearman's Correlation analysis compared the data and significance was set at $p<0.05$.

Results

- Patient demographics and cell salvage were consistent across the groups.
- There was a statistically significant reduction in the median number of fresh frozen plasma (FFP) units transfused for the post-ROTEM group (p=0.002), illustrated in figure 4.

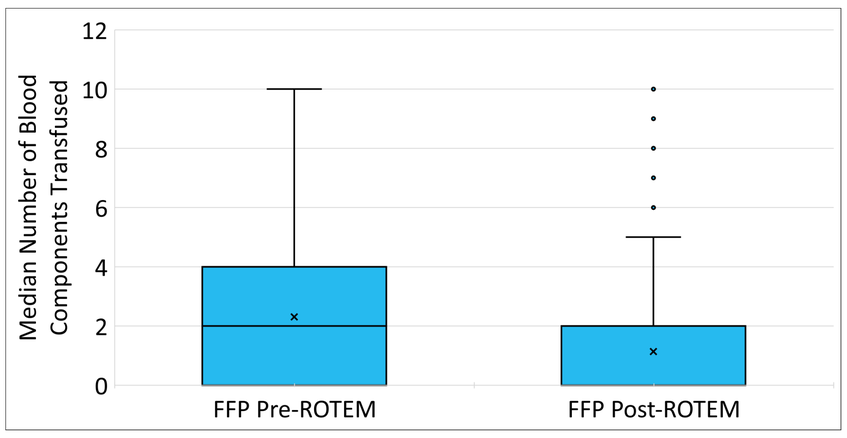

Figure 4: A comparison of the median number of FFP units transfused between the pre and post-ROTEM groups.

- There were slight changes in the median number of red cell (p=0.585), cryoprecipitate (p=0.226) and platelet (p=0.768) units transfused between the groups but none of the data were statistically significant (data not shown but discussed later).
- There was a statistically significant increase in the median concentration of fibrinogen concentrate issued in the post-ROTEM group (p=0.006) (data not shown).
- There was a statistically significant reduction in the median number of blood components disposed (p<0.0001), depicted in figure 5.

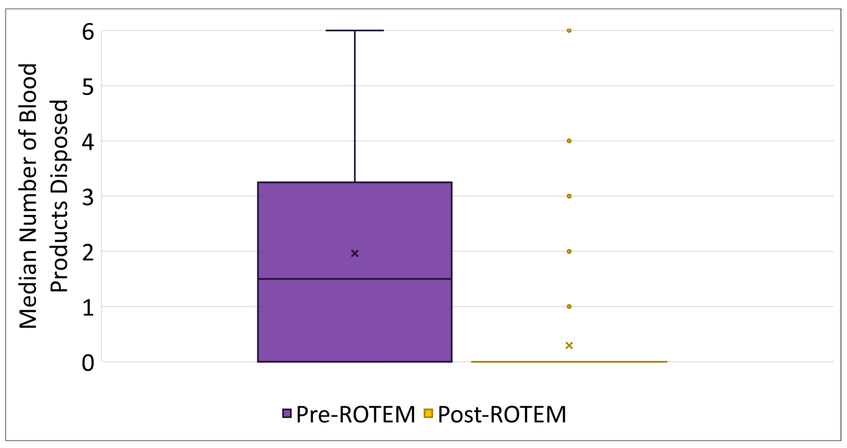

Figure 5: A comparison of the median number of blood products disposed pre- and post-ROTEM implementation.

- There was a slight reduction in the Obstetric & Gynaecology EBL data in the post-ROTEM group but it was not statistically significant (p=0.266) (data not shown).
- There were slight increases in the median LOS (p=0.819), ITU admission (p=0.624) and mortality rate (p=0.691) for patients in the post-ROTEM group, although the data were not statistically significant (data not shown).
- The ROTEM results were produced rapidly and showed strong correlation with the full blood count (FBC)-derived platelet count ($r=0.619$, $p<0.0001$) and the Clauss fibrinogen result ($r=0.859$, $p<0.0001$), the latter is illustrated in figure 6.
- The post-hoc power calculation was 0.67 (calculation not shown).

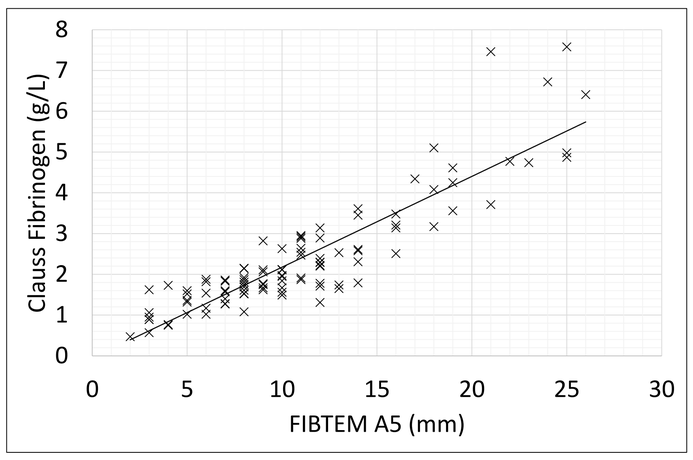

Figure 6: The correlation between the FIBTEM A5 and the Clauss fibrinogen result.

Discussion & Concluding Remarks

- The reduced median number of FFP units transfused was likely due to a change in shock pack contents and FFP was only required in 26% of cases in the post-ROTEM group. This almost entirely accounted for the reduction in the median number of blood components disposed.
- Although not statistically significant, the slight reduction in the median number of red cell transfusions was likely due to quicker cessation of bleeding, observed in similar studies (Hanke et al., 2012; Leon-Justel et al., 2015).
- The insignificant increase in median platelet transfusions was likely due to quicker identification of haemostatic deficiency by the ROTEM compared to SLTs (Haas et al., 2012).
- The insignificant reduction in median number of cryoprecipitate units transfused was due to the availability of fibrinogen concentrate in the post-ROTEM group.
- This study identified no improvements in ITU admission or mortality with fibrinogen concentrate vs cryoprecipitate, in contrast to benefits observed in other studies (Fenger-Eriksen et al., 2009; Wafaisade et al., 2013). This is either due to the small sample sizes or the multifactorial nature of clinical outcome data.
- ROTEM results were produced rapidly providing clinicians more time to prevent or reverse an already established coagulopathy. These results correlated strongly with SLTs which is in keeping with findings from other studies (Olde Engberink et al., 2014; Mace et al., 2016).

Novel aspects of this study:

- The impact of ROTEM-guided treatment of patients with a major haemorrhage was studied across several disciplines.
- One treatment algorithm was developed for all patients enabling simplification and standardisation.
- ROTEM-guided blood component therapy was compared to another treatment method.
- The inclusion of Fibryga (Octapharma) as a method of fibrinogen replacement as it is the only fibrinogen concentrate product licensed in the UK for the treatment of acquired hypofibrinogenaemia.

Unfortunately there were several limitations of this study:

- It was conducted at one hospital Trust so results, reference ranges and treatments were population-specific.
- The project was retrospective and observational so some confounding variables could not be accounted for.
- The sample sizes were small so the study may not have been sufficiently powered to give confidence in the outcomes.
- There were issues with MHP compliance; the ROTEM was not always used, SLTs weren't always performed and blood components were inappropriately requested at times.

Future Work:

- Given the limitations of this study, large randomised controlled trials are required to assess the impact of ROTEM-guided treatment on patients with a major haemorrhage.
- Further work is needed to assess the benefit of fibrinogen concentrate in treating those with acquired hypofibrinogenaemia due to blood loss.

References

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