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Point-of-care testing of coagulation and fibrinolytic status during postpartum haemorrhage: developing a thrombelastography®-guided transfusion algorithm

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SUMMARY

Thrombelastography® is a monitor of coagulation and fibrinolytic status, with point-of-care applications in managing haemorrhaging patients. Advocates have suggested a possible role in managing obstetric haemorrhage. This study aims to develop a pregnancy-specific thrombelastography-guided transfusion algorithm, which could be integrated into the management of postpartum haemorrhage.

In this prospective observational study, 57 healthy, term-parturients provided pre-caesarean whole blood specimens for thrombelastography analyses. Specimens were processed according to a standardised protocol involving simultaneous analyses using three assays: native (non-activated); kaolin-activated; and kaolin and tissue factor-activated (RapidTEG®). For each assay, the following thrombelastography parameters were measured: reaction time (minutes); clot formation kinetics time (minutes); maximum amplitude (mm); and α angle (degree). Subsequent reference values were used to establish assay-specific reference intervals.

For all thrombelastography parameters studied, reference values obtained using a non-activated assay differed from the corresponding values obtained using activated assays, and also demonstrated greater inter-sample variability. From the assay-specific reference intervals obtained, it was possible to establish a pregnancy-specific thrombelastography-guided transfusion algorithm. Specific features of this transfusion algorithm included the preferential use of activated assays, the need for duplicates and a recommendation that an initial baseline thrombelastography measurement is established for subsequent serial comparisons. This transfusion algorithm has been developed to assist with assessment of coagulation and fibrinolytic status during postpartum haemorrhage.

Key Words: thrombelastography, obstetrics, reference intervals, point-of-care systems

Thrombelastography (TEG®)[1] and thromboelastometry (ROTEM®) are used to monitor the coagulation and fibrinolysis status of whole or activated blood. When a blood sample is oscillated in a heated cup with a suspended pin, the torsion developed during clot formation is graphically represented by a thromboelastogram (Figure 1). These thromboelastograms generate measured or derived parameters, providing useful in vitro information pertaining to clot properties (kinetics, strength and stability), fibrinolysis and platelet function[1,2].

Unlike conventional tests of coagulation, TEG devices can be used for point-of-care testing. This ensures that turnover in processing and reporting of specimens is kept to a minimum. This can be advantageous during rapid critical bleeding, such as in major obstetric haemorrhage. Other benefits of point-of-care testing using TEG include indirect assessment of platelet function, assistance with identifying causes of perioperative bleeding and guidance for pro and anticoagulant therapy[3]. There are limited reports regarding the use of TEG for point-of-care testing in the obstetric setting. Othman et al cited several examples where TEG proved valuable in the diagnosis and management of pregnancy complications[4]. In an editorial discussing the monitoring of transfusion requirements during major obstetric haemorrhage, Stocks acknowledged the potential advantages of TEG and non-invasive haemoglobin concentration monitoring. He did not see this newer technology supplanting current monitoring, rather proving an adjunct to conventional coagulation tests[5].

Having acquired a TEG 5000 Thrombelastograph® Hemostasis Analyzer (Haemoscope, Niles, IL, USA)

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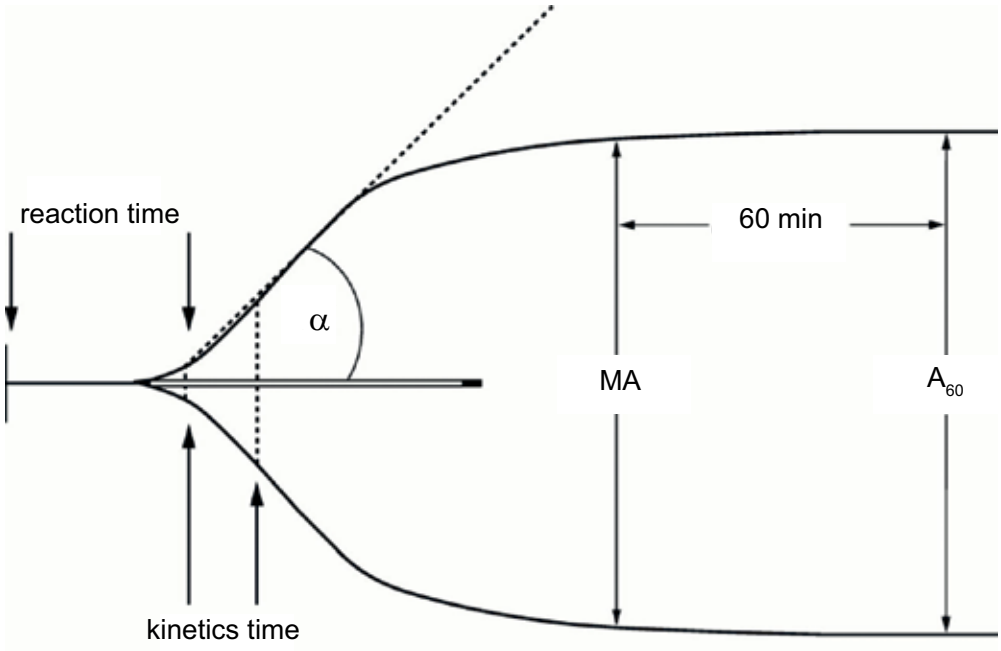

FIGURE 1: Standard thrombelastography parameters (used with permission of Haemoscope Corporation and Medtel NZ Ltd). Reaction time (influenced by clotting factors) is from the start to detectable clot formation (2 mm). Kinetics time (influenced by fibrinogen, less so platelets) is a measure of the speed or clot kinetics to reach 20 mm. Alpha angle (influenced by fibrinogen, less so platelets) measures the rapidity of fibrin build-up and cross-linking (clot strengthening). Maximum amplitude (influenced by platelets, less so fibrinogen) represents ultimate strength of developed fibrin clot. α =alpha angle, MA=maximum amplitude, A_{60}=amplitude 60 minutes.

and with access to a second device, we integrated this new technology into clinical practice. One potential point-of-care testing application was the development of a TEG-guided transfusion algorithm specifically for the management of postpartum haemorrhage. To achieve this primary objective, it was necessary to determine reference intervals (RI) for TEG in term parturients, using both activated and non-activated assays.

METHODS

Following local ethics committee approval (NTX/09/12/113), all parturients presenting at pre-assessment clinics for elective caesarean delivery over a two-month period were screened. Potential recruits were mailed a copy of the participant information sheet before their clinic appointment. Exclusion criteria included a history of excessive bleeding, coagulation abnormalities, pregnancy-induced hypertension, haematocrit <0.31, platelet count $<100\times10^9$/l, abnormal liver function tests, recent anti-platelet therapy or recent anticoagulant therapy. Written consent was obtained. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12612000867897).

All TEG analyses were performed by anaesthetic technicians who had completed a one-day, in-service course, which was overseen by a representative of the manufacturer. Operators were assessed for their knowledge and skills and were observed performing simulated runs. Specimens were analysed using two available TEG 5000 Thrombelastograph Hemostasis Analyzers. These analysers are calibrated every six months by an authorised engineer. Quality control, involving daily e-tests and weekly two-level liquid control tests, ensured all channels were standardised according to accepted laboratory standards.

The collection and processing of blood occurred in the following order. Following intravenous access sited in the operating suite, an initial 2 ml of blood was drawn into a plain syringe, which was then discarded to ensure any potential contamination during drawing was removed. A second sample of 4 ml of blood was drawn into a second plain syringe and used for TEG testing. A stopwatch was used to ensure samples were processed within the manufacturer's recommended time of four minutes. One millilitre of whole blood was placed into a kaolin vial and gently inverted five times, with the remainder of the whole blood sample from the plain syringe being placed in a plain plastic test tube. For the kaolin test, 360 μl of blood was pipetted from the mixed kaolin vial into a plain TEG cup and

testing commenced. For the RapidTEG® test, 10 μl of RapidTEG reagent, comprising lyophilised kaolin and tissue factor (reconstituted with 20 μl of sterile water five minutes prior to the testing), was placed in a plain TEG cup, followed by 360 μl of blood pipetted from the plastic test tube. For the native test, 360 μl of blood from the plastic test tube was transferred into a plain TEG cup, and testing commenced four minutes after the initial drawing of blood. Real-time results were presented on a networked monitor using TEG analytical software V4.2.97.

STATISTICAL ANALYSES

To establish or validate a reference interval for new or current laboratory tests, our laboratory service follows recommendations published by the Clinical and Laboratory Standards Institute (CLSI)[6]. The CLSI provides guidance regarding the selection of appropriate statistical methodology to determine reference intervals. Both parametric and non-parametric methods are discussed, as well as alternative statistical techniques. The choice of methodology depends on data distribution (Gaussian versus non-Gaussian), sample size and the presence of outliers. When sample sizes are less than 120, the CLSI recommends a technique called the 'robust method' as an alternative to parametric or non-parametric methods. The principles and application of this statistical technique and how it compares with other methodologies has been described by Horn et al[7]. Given our sample size of 57, we chose to use the 'robust method'[6,7] and estimated the median, 95% confidence intervals (CI) and upper/lower limits of the 95% reference intervals (RI). Three pairing combinations (native versus kaolin, native versus RapidTEG and kaolin versus RapidTEG) were analysed using Wilcoxon signed-ranks tests. A P value <0.05 was considered significant. Data analyses were performed using MedCalc® software V11.6.1 (MedCalc, Mariakerke, Belgium).

TABLE 1
*Patient characteristics and obstetric details**

Age, y	35.3 (4.6)
Height, cm	166.3 (7.5)
Weight, kg	84.5 (19.2)
BMI, kg/m²	30.4 (5.9)
Parity	
0	14%
1	54%
2	22%
>2	10%
Platelet count, ×109/l	200 (46)

* Values are mean (SD) except for parity (n=57) where percentage of total is reported. y=years, BMI=body mass index.

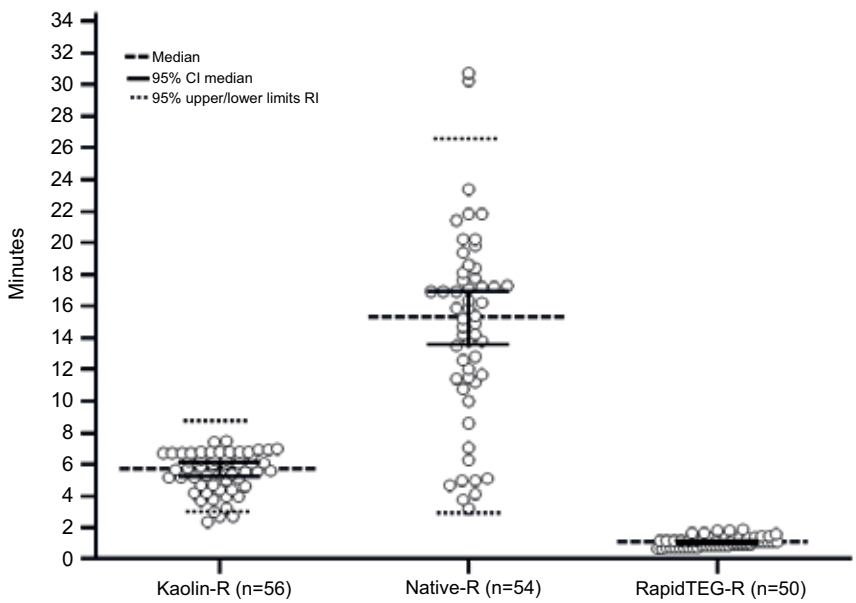

FIGURE 2: Reference values for reaction time using three different assays. Medians, 95% confidence intervals for medians and 95% reference intervals were estimated using the robust method[6,7]. CI=confidence intervals, RI=reference intervals, R=reaction time, TEG=thrombelastography.

RESULTS

A total of 57 patients provided blood specimens for analyses and the number of valid thromboelastograms was kaolin (n=56), native (n=54) and RapidTEG (n=50). Patient characteristics and obstetric details are summarised in Table 1.

Due to unidentified technical reasons, one kaolin, three native and seven RapidTEG specimens failed to clot, resulting in inability to generate a TEG profile. These were subsequently identified as artefact, on the basis that at least one matched analysis generated a valid TEG profile.

Reference values obtained for TEG parameters are presented in Figures 2–5. A consistent feature, highlighted graphically in Figures 2–5, was the propensity for the non-activated native assay to demonstrate greater inter-sample variability, particularly in comparison with corresponding reference values using activated assays. Assay-specific reference intervals for TEG parameters are summarised in Table 2.

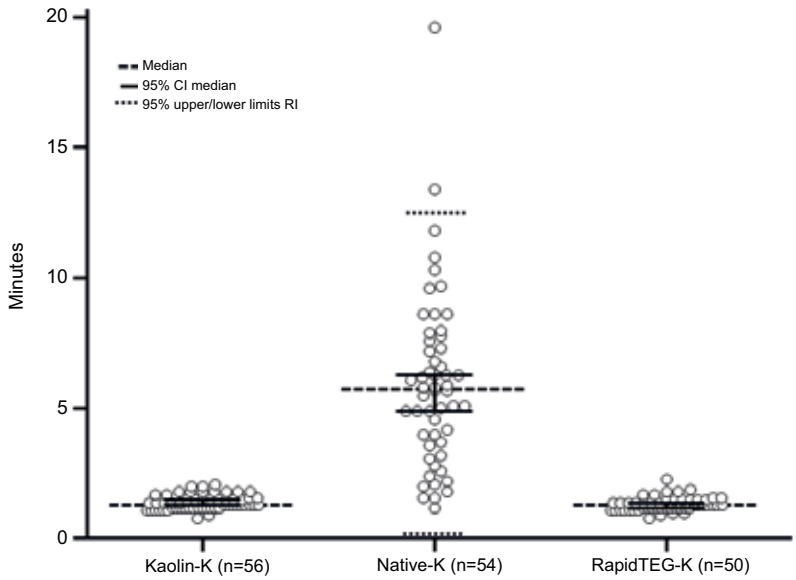

FIGURE 3: Reference values for kinetics time using three different assays. Medians , 95% confidence intervals for medians and 95% reference intervals were estimated using the robust method[6,7]. CI=confidence intervals, RI=reference intervals, K=kinectics time, TEG=thrombelastography

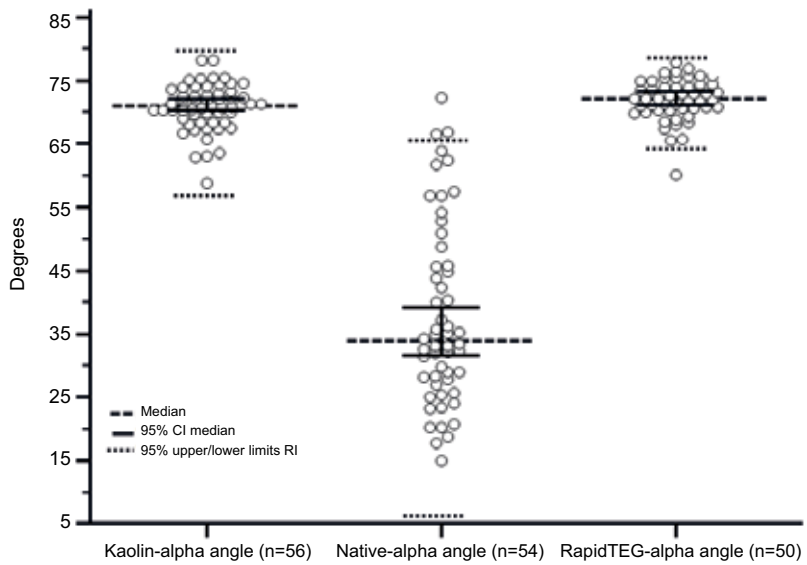

FIGURE 4: Reference values for alpha angle using three different assays. Medians, 95% confidence intervals for medians and 95% reference intervals were estimated using the robust method[6,7]. CI=confidence intervals, RI=reference intervals, TEG=thrombelastography

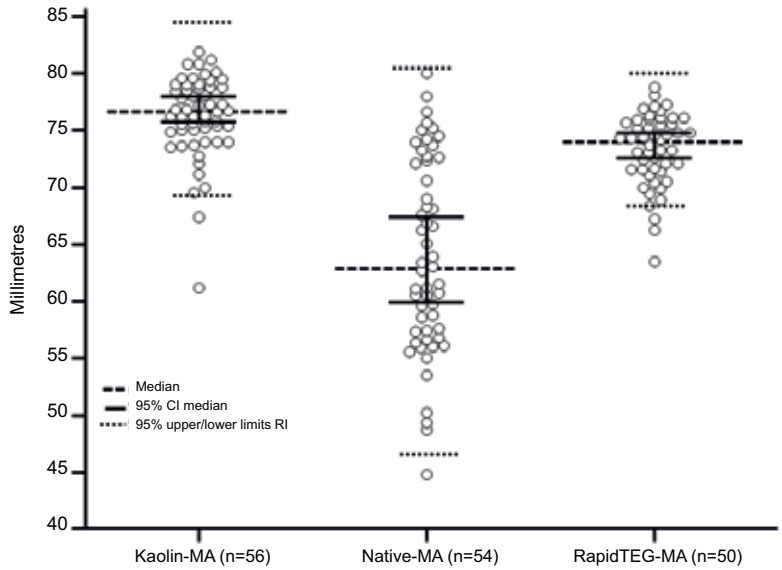

FIGURE 5: Reference values for maximum amplitude using three different assays. Medians, 95% confidence intervals for medians and 95% reference intervals were estimated according to the robust method[6,7]. CI=confidence interval, RI=reference interval, MA=maximum amplitude, TEG=thrombelastography.

TABLE 2

Reference Intervals for TEG parameters

	TEG assay*		
Parameter	Kaolin, n=56	Native, n=54	RapidTEG, n=50
r time, min	5.75 (2.97–8.31)	15.30 (2.38–27.03)	1.10 (0.47–1.73)
k time, min	1.30 (0.77–1.99)	5.75 (0.01–12.26)	1.30 (0.74–1.85)
α angle, deg	71.00 (63.80–78.68)	33.90 (5.23–65.78)	72.15 (65.67–79.10)
MA, mm	76.65 (69.44–84.20)	62.85 (46.54–81.28)	73.95 (67.13–80.25)

Median and upper/lower limits estimated using the robust method for determining reference intervals (Clinical and Laboratory Standards Institute)[6,7], upper and lower limits set to include 95% of reference values; results reported as median (lower limit–upper limit). * n=number of reference values used to estimate reference interval. TEG=thrombelastography, r time=reaction time, k time=kinetics time, MA=maximum amplitude.

TABLE 3

Calculated P values using the Wilcoxon signed-rank test when comparing paired reference values between two assays

Parameter	Kaolin vs native*, n=53	RapidTEG vs native**, n=48	Kaolin vs RapidTEG†, n=45
r time	P <0.0001	P <0.0001	P <0.0001
k time	P <0.0001	P <0.0001	P=0.41 (ns)
α angle	P <0.0001	P <0.0001	P=0.16 (ns)
MA	P <0.0001	P <0.0001	P <0.0001

Wilcoxon signed-rank test, two-tailed probability. P <0.05 considered statistically significant. * (n=number of valid pairs of matched reference values using the kaolin and native assays.) For all TEG parameters observed, reference values obtained using the kaolin assay were significantly different to those obtained using the native assay. ** (n=number of valid pairs of matched reference values using the RapidTEG and native assays.) For all TEG parameters observed, reference values obtained using the RapidTEG assay were significantly different to those obtained using the native assay. † (n=number of valid pairs of matched reference values using the kaolin and RapidTEG assays.) Reference values obtained for the r time and maximum amplitude were significantly different between the kaolin and RapidTEG assays. No differences were observed in reference values for k time and α angle. TEG=thrombelastography, r time=reaction time, k time=kinetics time, MA=maximum amplitude.

FIGURE 6: TEG-guided transfusion algorithm during a primary postpartum haemorrhage. TEG=thrombelastography, PT=prothrombin time, INR=international normalised ratio, APTT=activated partial thromboplastin time, R=reaction time, K=kinetics time, α =alpha, MA=maximum amplitude, PPH=postpartum haemorrhage, PRBC=packed red blood cells, HR=heart rate, BP=blood pressure, DIC=disseminated intravascular coagulopathy, FFP=fresh frozen plasma.

When samples failed to clot, it was not possible to pair data, so the number of valid pairs analysed was: kaolin versus native (n=53), RapidTEG versus native (n=48) and kaolin versus RapidTEG (n=45). The corresponding *P* values for these comparisons are summarised in Table 3. These results highlight the differences between non-activated RI and activated RI. When paired reference values for the two activated assays were compared, the RI for reaction time and maximum amplitude were significantly different. No differences were observed between the RI for kinetics time and α angle.

DISCUSSION

Our study measured TEG parameters using three different assays in a cohort of healthy term parturients. This data was used to establish assay-specific reference intervals for our newly acquired TEG devices. This practice is recommended for new TEG installations[8].

In a study which compared kaolin-activated TEG in a group of 60 pregnant versus 43 non-pregnant subjects, Polak et al demonstrated the relative hypercoagulable state within their pregnant group[9]. Macafee et al, using kaolin-activated TEG from 50 pregnant subjects, established several perioperative reference ranges[10]. When comparing their pre-operative reference range with the manufacturer's non-pregnant reference range, they also found evidence of hypercoagulability. Due to differences in statistical methods used, we chose not to make a direct comparison of our findings with the previously mentioned studies. However, we confirmed the presence of relative hypercoagulability within our cohort of pregnant subjects. Hypercoagulability is a physiological attribute of normal pregnancy[11], verified by other TEG and ROTEM studies[12–14]. This supports the need to establish pregnancy-specific TEG reference intervals.

This study confirmed that the reference interval for TEG-parameters is assay-dependant. This was especially evident when comparing corresponding results between non-activated and activated assays. These findings are consistent with those reported by Sharma et al[15], who, in a study of 45 healthy pregnant subjects, reported reduced inter-sample variability and increased reliability with the use of activated TEG assays.

Some differences observed between assays are easy to explain. Rapid clot initiation in the presence of potent surface activator(s) explains the shortened reaction time observed with the use of activated assays. Hence, the significant difference with respect to the comparison of reaction times between activated and non-activated assays, comes as no surprise. However, other differences noted are less intuitive. Differences of reference interval for the α angle suggest nonuniformity with in vitro fibrin formation. If matched specimens are assumed to possess the same concentration of fibrinogen and pro-haemostatic factors, and conditions of testing were similar at the time of processing, then observed differences are likely to be attributable to the type of assay used. These observations highlight two important principles. First, when utilising TEG, assay-specific reference intervals are required. Second, in vitro tests can never truly replicate what occurs in vivo.

The study objective was the integration of TEG, as a point-of-care testing application, into a TEG-guided transfusion algorithm. Similar algorithms are currently employed within our institution in cardiac and transplantation surgery. Shore-Lesserson et al reported a reduction in blood product use in cardiac surgery when they used a TEG-guided transfusion algorithm[16]. There are a limited number of reports of TEG-guided transfusion algorithms being applied in the obstetric setting. Bolton et al studied 66 patients who had massive obstetric haemorrhages involving >1.5 l blood loss[17]. They compared standard laboratory tests to a generic ROTEM-guided algorithm. They found that ROTEM had excellent sensitivity and specificity for identifying coagulopathy; good sensitivity and excellent specificity for predicting fresh frozen plasma transfusion; and identified two cases of hyperfibrinolysis that would not have otherwise been detected. However, the sensitivity for identifying platelet requirements was poor. In a study which established reference ranges for an obstetric population using ROTEM, Armstrong et al identified the need for "the introduction of protocol-based algorithms to aid in the management of the coagulopathic or bleeding parturient"[14]. We agree that more development and research of pregnancy-specific TEG-guided transfusion algorithms is required.

In designing and implementing our pregnancy-specific TEG-guided transfusion algorithm (Figure 6), we considered several factors. Any such algorithm needs to be consistent with our institution's multi-disciplinary protocols, clinical guidelines and recommended best practices. Particular consideration needs to be given to our institution's massive transfusion protocol. This protocol is an adaptation of a template developed by the National Blood Authority of Australia[18]. This template was formulated by an expert working committee and is based on

best evidence or consensus. In a review regarding the logistics of massive transfusion, DeLoughery suggested how TEG parameters could be used to guide transfusion decisions[19].

Any valid TEG-guided transfusion algorithm requires the selection of appropriate TEG triggers. Our selection was predicated on the basis of establishing normal reference intervals. We have assumed that any deviation outside the normal reference interval could be clinically significant. In considering the statistical process needed to establish these, we worked on the premise that our TEG devices were part of our laboratory and thus subject to current laboratory standards. In our opinion, this process was best based on recommendations suggested by the CLSI[6]. We acknowledge that other statistical methodologies can be employed to determine TEG reference ranges in obstetric populations[9,10,14].

Technical issues such as choice of assays, duplicate specimens and presentation of results in real-time must be considered. Resource, operator and time requirements pose technical pressures when performing TEG. Up to 12% of participants (seven of 57) had at least one invalid specimen. All seven specimens were subsequently proven to represent artefact. By running duplicate specimens using two channels, we believe most artefacts are likely to be detected. Given the limitation of having only two channels, we chose not to incorporate the native assay in our algorithm because of the greater inter-sample variability and reduced reliability. To provide real-time presentation of thromboelastograms on our in-theatre monitors, we used TEG analytical software V4.2.97. This allows serial TEG to be superimposed on the same screen. This graphical representation may prove useful in detecting hyperfibrinolysis, as well indicating the effect of pro-haemostatic therapy.

In operating our TEG device, we believe it is essential that our laboratory is actively involved with quality control and maintenance issues. Clinicians are unlikely to have the necessary expertise and experience to ensure these devices adhere to accepted laboratory standards.

We accept that limitations of our TEG-guided transfusion algorithm exist. Reference intervals for our healthy, non-labouring cohort of women cannot be directly extrapolated to all parturient cohorts. Physiological states (e.g. pregnancy, labour, puerperium)[12,13,20,21], pathological states (e.g. thrombocytopaenia,pre-eclampsia)[22–25],pharmacological(e.g. concurrent anti-platelet therapy)[26,27] and perioperative states (mode of anaesthesia, intravenous fluid therapy)[28–30] have been shown to affect TEG. However, we would maintain that our reference intervals provide a valid approximation for most pregnant patients presenting with a postpartum haemorrhage within our institution. In regards to interpreting point-of-care testing TEG, we believe monitoring dynamic changes in serial TEG parameters is as important as the identification of deviations outside the reference intervals.

Further studies or audits are required to determine how our algorithm TEG-triggers correlate with known risk factors such as hypofibrinogenaemia[31–33]. Also, further studies or audits will be required to show whether our TEG guidelines influence perioperative outcomes such as use of blood and blood products[16,17] or admission to an intensive care unit. We have yet to formally validate our algorithm. Our group is currently negotiating a prospective audit under the auspices of our institution's multidisciplinary transfusion committee.

In summary, we believe that there is a role for the systematic use of TEG devices to assist with the management of postpartum haemorrhage. When used as a point-of-care test, these devices provide a useful means of assessing dynamic changes in coagulation and fibrinolysis. Further research is required to determine what role this technology has in the management of postpartum haemorrhage. Until then, all available clinical and laboratory information should be used in clinical decision-making.

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