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Effects of rotational thromboelastometry-guided transfusion management in patients undergoing surgical intervention for post-partum haemorrhage: an observational study

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ABSTRACT

BACKGROUND: Post-partum hemorrhage (PPH) can be associated with coagulopathy, which may be difficult to rapidly assess and may exacerbate blood loss. Rotational thromboelastometry (ROTEM) at the point of care can guide clinician choice of blood products and has been shown in some settings to reduce transfusions and improve outcomes. This hospital-based observational study aims to measure effects of a ROTEM-guided transfusion protocol on transfusion practice and clinical outcomes in patients with PPH managed in the operating theatre.

STUDY DESIGN AND METHODS: We compared a retrospective cohort of 450 consecutive patients with PPH treated in the operating theatre before the introduction of a ROTEM-guided transfusion algorithm in June 2016, with 450 patients treated after its introduction. Multivariate regression was used to evaluate the effect of ROTEM introduction on the primary outcome, patients requiring a packed red blood cell (PRBC) transfusion, adjusting for demographic and obstetric confounders. Secondary outcomes included other blood product transfusions, hysterectomy and intensive care unit (ICU) admission.

RESULTS: 90 (20%) of patients treated prior to ROTEM introduction received a PRBC transfusion, compared with 102 (22.7%) of those treated after ROTEM introduction (95% CI 1.0-2.0, p = 0.04). There was no difference in PRBC transfusion in patients undergoing caesarean section (95% CI 0.5-1.8, p=0.99). There was a trend towards increased use of cryoprecipitate and reduced use of platelets and fresh frozen plasma (FFP) after ROTEM introduction.

CONCLUSION: In our institution, the introduction of ROTEM-guided transfusion did not reduce PRBC transfusion in patients with PPH treated in the operating theatre.

Key words: rotational thromboelastometry, ROTEM, viscoelastic, postpartum haemorrhage, transfusion, coagulation

1. INTRODUCTION

Post-partum hemorrhage (PPH) is a common obstetric complication and a major cause of maternal mortality and morbidity in Australia.[1] Response to PPH requires early recognition, resuscitation, and treatment of the underlying cause:[1] uterine tone, retained tissue, trauma and coagulopathy. Massive PPH may also require hysterectomy to reduce ongoing blood loss, with admission to the intensive care unit (ICU) to monitor and treat multi-system complications.

PPH may be associated with, and exacerbated by, abnormalities of haemostasis. These abnormalities may be caused by a consumptive and/or dilutional coagulopathy, resulting from the haemorrhage itself and in combination with resuscitation measures. The type, severity and rate of onset of coagulopathy varies with the underlying cause.[2] Traditional coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT) lack sensitivity in predicting the severity of PPH and in guiding management,[2,3] and there is a paucity of evidence supporting use of these tests for transfusion management in the peri-operative setting.[4] While the fibrinogen level drops early in PPH and appears to be an early predictor of haemorrhage severity,[5,6] the utility of the standard Clauss assay in emergency settings is limited, due to the turnaround time of approximately one hour.[7,8]

Rotational thromboelastometry (ROTEM) is a point-of-care test of whole blood coagulation that rapidly measures time to clot formation, strength of clot and presence of fibrinolysis. In the perioperative setting, ROTEM can guide treatment choices for coagulopathy.

Observational studies in cardiac surgical settings have shown reduced utilisation of packed red blood cells (PRBC),[9–11] platelets[10,11] and fresh frozen plasma (FFP),[9,11] as well as reduced complications and costs,[9,10] following introduction of ROTEM-guided transfusion management. A systematic review of randomized controlled trials of ROTEM-guided transfusion management, largely in cardiac surgery, has shown reduction in need for blood products and reduced morbidity, although the number and quality of studies were low and the conclusions therefore uncertain.[12]

FIBTEM, a ROTEM measure of fibrinogen function, has been shown to have similar utility to Clauss fibrinogen in predicting severity of postpartum haemorrhage. Useful information is typically available within five minutes, and has been used to guide fibrinogen replacement in PPH.[8,13] Several observational studies found a reduction in blood product utilization in patients with severe PPH (estimated blood loss (EBL) greater than 1500ml) managed with ROTEM-guided protocols compared with traditional massive transfusion algorithms.[14–16] However, the utility of ROTEM in the wider spectrum of patients with PPH remains unclear. A randomised controlled trial of ROTEM-guided administration of early fibrinogen concentrate in PPH did not find a difference in transfusion outcomes,[17] a finding which may have resulted from the conservative threshold used for treatment. Questions remain regarding the precision of FIBTEM tests and thresholds,[18] and there is lack of consensus regarding clinical benefit of ROTEM use in PPH.[19,20] A recent systematic review called for further studies to compare ROTEM-guided transfusion management with standard approaches.[19]

Following the introduction of ROTEM-guided transfusion management for patients with PPH in the operating suite of our hospital, we aimed to assess its impact on the utilization of blood products – PRBC, platelets, FFP and fibrinogen – and on clinical outcomes. Our primary hypothesis was that ROTEM introduction would reduce the proportion of patients requiring PRBC transfusion.

2. MATERIALS AND METHODS

Ethics and study registration

Ethics approval for this study, including waiver of consent, was obtained from our Institutional Review Board (Reference Number: QA2017.74) in October 2017. The study protocol was registered with the Australian New Zealand Clinical Trials Registry (Registration Number: 12619001061123). Reporting of this study is in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[21].

Study design

Our study was conducted in a 600-bed general hospital providing obstetric care for more than 7000 births per year in Melbourne, Australia. Patients were screened for inclusion using our hospital obstetric database if they met criteria for PPH and had a theatre episode within 24 hours after delivery. PPH was defined as EBL within the first 24 hours of greater than 500ml following vaginal delivery or greater than 750ml following caesarean section, in accordance with institutional and state reporting guidelines.[22] The inclusion criterion was all women managed for PPH in the operating theatre, with no exclusions. The intervention was

the introduction of ROTEM (ROTEM Sigma, TEM international GmbH, Munich, Germany) as a point-of-care test in the operating suite in June 2016, alongside a transfusion algorithm developed by colleagues in Perth, Australia (Appendix 1) and clinical education on ROTEM-guided transfusion management. Each patient's treating anesthesiologist was responsible for their transfusion management in the operating theater, with access to standard laboratory investigations, and obstetric and hematology consultation as required. ROTEM was available as an additional tool in the post-ROTEM group and its use encouraged but not mandated. Utilization and timing of all tests performed, including ROTEM, were at the discretion of the treating anesthesiologist.

Our primary outcome was the proportion of patients in each cohort receiving PRBC transfusion during admission, which we hypothesized would be reduced in the post-ROTEM group. Secondary outcomes were proportions of patients receiving transfusions of platelets, FFP, and cryoprecipitate, total and average volumes of each blood product transfused, proportion of patients requiring hysterectomy, and proportion of patients requiring intensive care. Pre-planned subgroup analysis was performed according to mode of delivery.

Possible confounders were identified using a directed acyclic graph.[23,24] Confounders used in the model were demographic and obstetric risk factors known to increase risk of bleeding: country of birth, parity, multiple pregnancy, birthweight, prolonged labour, body mass index (BMI), and the presence of placental adhesive disorder.[22] We initially planned to adjust for labour ward blood loss for the vaginal delivery group to account for possible changes in labour ward management between the two cohorts separated in time. During analysis, finding that labour ward blood loss was unlikely to be an accurate surrogate for the quality

of ward management, we removed this covariate from the model. As this was a *post hoc* decision, sensitivity analyses including this variable were performed, and the effects were considered in the interpretation of our results.

Statistical analysis

Data were obtained from existing hospital databases and electronic medical records. Sample size calculation was performed prior to recruitment using STATA statistical software (Version 15, StataCorp LLC, USA). Minimum sample size was calculated to be 435 patients in each group, assuming a baseline rate of 10% transfusions in the control group, and 80% power to detect a 50% reduction in PRBC use in the post-ROTEM group. Data for the two cohorts were compared using logistic regression for categorical and linear regression for continuous variables, adjusting for confounders as described above.

3. RESULTS

Data were collected from 450 consecutive patients meeting the inclusion criterion treated from July 2015 to May 2016 ('pre-ROTEM cohort') and 450 consecutive patients from September 2017 to April 2018 ('post-ROTEM cohort'). Demographic and obstetric risk factors for PPH are shown in Table 1. Multiparity and caesarean deliveries were both more common in the post-ROTEM cohort. Volumes of blood loss were similar between the two groups (Table 2).

Study outcomes are shown in Table 3 for all patients, Tables 4 and 5 according to mode of delivery, and Figure 1. Overall, slightly more patients in the post-ROTEM cohort received a PRBC transfusion compared with the pre-ROTEM cohort, when adjusted for relevant demographic and obstetric characteristics (OR 1.4, 95% CI 1.0-2.0, p = 0.04). A sensitivity analysis also adjusting for labour ward blood loss according to the original protocol showed similar results (OR 1.6, 95% CI 1.1-2.4). For patients delivering via caesarean section, there was no difference in rates of PRBC transfusion between the pre- and post-ROTEM groups (OR 1.0, 95% CI 0.5-1.8, p=0.99).

In each of the subgroups and overall, there was a decrease in the percentage of patients receiving FFP and platelet transfusions, and an increase in those receiving cryoprecipitate transfusions, in the post-ROTEM group, although these were not statistically significant.

4. DISCUSSION

After the introduction of ROTEM-guided transfusion in our institution for patients requiring operative management for PPH, there was no reduction in the proportion of patients who received a PRBC transfusion. Slightly more patients who had a vaginal delivery were transfused following ROTEM introduction. There was no difference in PRBC transfusion rates pre- and post-ROTEM in patients delivering by caesarean section. These findings are in contrast to previously published observational studies in PPH that showed a reduction in PRBC transfusion post ROTEM introduction.[14,15]

We found that, regardless of mode of delivery, fewer patients in the post-ROTEM cohort received a platelet or FFP transfusion, and more received cryoprecipitate compared with those in the pre-ROTEM cohort. Although these differences were not statistically significant, the findings were consistent with those in other studies.[14,15] Our results support the role of ROTEM for early detection and management of fibrinogen depletion, a key event in PPH and its progression.[6] Additionally, ROTEM can help limit untargeted and unnecessary platelet and FFP transfusions.[14,15]

The increase in transfusion rates in patients who delivered vaginally was counter to our hypothesis. Approximately 80% of these patients delivered and received initial postpartum management on the ward, prior to transfer to theatre. It may be that changes in ward management that occurred between data collection periods for each cohort contributed to the difference in transfusion rates, rather than the introduction of ROTEM. For example, improvements in ward management may have resulted in those patients meeting the definition of PPH in the post-ROTEM group comprising a higher-risk population than those in the pre-ROTEM group. More proactive management of PPH in the later period may also have led to earlier administration of PRBC on the labour ward, and thus a greater percentage of patients receiving a PRBC transfusion in the post-ROTEM cohort.

Hypothesising that volume of blood loss on the ward might provide a surrogate measure for the quality of PPH ward management, we intended to use this parameter as a covariate. However, inclusion of this parameter in our model increased the positive association between ROTEM and PRBC transfusion, a finding we felt to be implausible and likely spurious. Labour ward blood loss was therefore removed as a covariate, meaning that

results for the vaginal delivery patient subgroup did not adjust for differences in labour ward management. Consequently, non-standardized ward management may have confounded our results in this subgroup, obscuring a true effect of ROTEM on PRBC transfusion.

In contrast, differences in PPH ward management would not have impacted patients delivered by caesarean section. Therefore, the lack of difference in PRBC transfusion between cohorts in this subgroup is more likely to be a true result. Focusing on this subgroup that receive more standardized management may be a useful strategy for future observational studies examining the effects of ROTEM in the operating theatre context.

A potential source of bias in our study is that only 32% of eligible patients in the post-ROTEM group received a ROTEM test. Although reflective of pragmatic clinical practice, this may have reduced the differences between the two groups and thus study power. Despite efforts made to encourage anesthesiologists to order a ROTEM test for all patients with PPH, in practice this often did not occur in patients with moderate, rather than severe, PPH. Further analysis of ROTEM use showed that 71% of patients with total blood loss > 1500ml received a ROTEM test, whereas only 18% of patients who bled $\leqslant$ 1500ml did so. This likely reflects anesthesiologists' perception that ROTEM is more useful at higher levels of blood loss, as it is then more likely to diagnose and guide treatment of a coagulopathy. This would attenuate the impact of low ROTEM use on our results, as patients in the post-ROTEM group who did not receive a ROTEM test despite its availability would have been less likely to have had severe PPH with suspected coagulopathy, and thus less likely to have had their blood transfusion status altered by the ROTEM results.

Our choice of PRBC transfusion as primary outcome may not have captured the potential benefits of ROTEM. We had hypothesized that early detection and management of coagulopathy might reduce blood loss, thus decreasing the need for PRBC transfusion. However, our patient population experienced low rates of suspected or confirmed coagulopathy; less than 4% in both pre- and post-ROTEM groups received FFP, platelets or cryoprecipitate. This may explain the lack of a positive finding in our study compared to Mallaiah[14] or McNamara[16], in which only coagulopathic patients were studied. Although our patient population was selected for pragmatic reasons – those patients requiring operative management for PPH would likely be a higher risk group, and our ROTEM machine is located in the operating theatre – their low rates of coagulopathy might suggest that the true benefit of ROTEM use was reducing unnecessary administration of FFP and platelets, and more targeted use of cryoprecipitate, rather than reducing PRBC transfusion.

Further research is needed to determine optimal ROTEM testing protocols, particularly in those patients who initially have a normal test result.[25] Questions remain regarding the most appropriate clinical triggers and timing intervals for repeat testing. Observational studies finding reduced blood product use with ROTEM, in contrast to our study, have been in populations with either established coagulopathy[14,16] or severe PPH greater than 1500ml.[15] Benefit from fibrinogen replacement has been shown when FIBTEM A5 < 12mm or fibrinogen < 2 g/L,[17] but only as few as 2.2% of patients experience this level of fibrinogen depletion.[26] To identify these patients, therefore, a high 'number needed to test' is required. It may be that ROTEM plays a more useful role to guide coagulopathy management in established or severe PPH, rather than as a screening tool for its early

detection. Even in severe PPH, the growing awareness of the importance of fibrinogen may reduce the relative benefit of ROTEM, as empirical 'shock pack' therapy is gradually phased out in favour of early fibrinogen replacement, in institutions without ROTEM. This may also have contributed to the lack of difference found in our study, compared to previous observational studies. Nonetheless, it has been argued that early ROTEM testing, even with a normal result, may deliver benefits by facilitating early involvement of senior staff and targeted escalation of obstetric care.[7]

Our study demonstrates a number of challenges in evaluating new diagnostic tools after they are introduced into clinical practice. As an observational study comparing two time periods, it was not possible to identify, measure and adjust for all potential confounders. There were multiple interdependent factors contributing to the primary outcome (PRBC transfusion) apart from ROTEM results. As a relatively new test, uncertainties exist regarding optimal testing strategies, thresholds for treatment and outcome measures.[7,17] Despite these challenges, we felt it was important to measure the effect of the introduction of ROTEM in our institution, aiming to reduce the risk of bias as much as possible and to present and discuss our results with clarity about their uncertainty. A large multi-centre study is likely required to further explore areas of uncertainty and clarify the role of ROTEM in managing patients with PPH.

5. CONCLUSION

In our observational study, the introduction of ROTEM-guided transfusion management in our institution did not reduce the proportion of patients with PPH treated in the operating theatre who received a PRBC transfusion. Although ROTEM offers a potentially significant advance in the management of obstetric haemorrhage by rationalising the use of specific blood products to treat specific coagulation pathway deficiencies, challenges remain to determine how it may best be utilized to benefit patients with PPH. It may have a dual role – firstly as a screening tool to exclude coagulopathy and secondly, as a diagnostic tool to identify specific coagulation deficiencies and guide the targeted use of blood products. Future trials assessing ROTEM may be best served to align outcomes with these two specific roles for ROTEM in the management of PPH.

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FIGURE LEGENDS

Figure 1. Percentages of patients receiving blood component transfusions.

VD: vaginal delivery; CS: caesarean section

TABLES

Table 1 – Relevant demographic and obstetric characteristics

	Pre-ROTEM cohort (n = 450)	Post-ROTEM cohort (n = 450)
Age (mean, SD)	30.5 (5.6)	30.7 (5.3)
Body mass index (mean, SD)	27.8 (8.1)	28.0 (8.2)
Country of birth		
Australia	226 (50.1%)	236 (52.4%)
Outside Australia	215 (47.7%)	206 (45.8%)
Not recorded	10 (2.2%)	8 (1.8%)
Parity		
Nulliparous	211 (46.9%)	116 (25.8%)
Multiparous	239 (53.1%)	334 (74.2%)
Multiple pregnancy	13 (2.9%)	20 (4.4%)
Birthweight		
High (>4000g)	62 (13.8%)	58 (12.9%)
Low (<1500g)	5 (1.1%)	6 (1.3%)
Prolonged labour	86 (19.1%)	74 (16.4%)
Placental adhesive disorder	11 (2.4%)	10 (2.2%)
Mode of delivery		
Vaginal	248 (55.1%)	201 (44.7%)
Caesarean section – elective	73 (16.2%)	99 (22%)

Caesarean section – emergency	129 (28.7%)	150 (33.3%)
Location of delivery		
Ward	201 (44.7%)	162 (36%)
Operating theatre	249 (55.3%)	288 (64%)

Table 2 - Volumes of estimated blood loss (mls)

	Pre-ROTEM cohort (n = 450)	Post-ROTEM cohort (n = 450)
All patients – total blood loss (mean, SD)	1223.3 (612.3)	1263.1 (723.0)
Vaginal delivery		
Labour ward blood loss (mean, SD)	774.7 (602.8)	715.4 (571.3)
Total blood loss (mean, SD)	1318.5 (652.3)	1373.4 (757.4)
Caesarean section		
Total blood loss (mean, SD)	1106.4 (538.3)	1174.0 (682.5)

Table 3 – Study outcomes, all patients

	Pre-ROTEM cohort (n = 450)	Post-ROTEM cohort (n = 450)	p-value
PRBC transfusion (%, n)	20.0 (90)	22.7 (102)	0.37
Other blood product transfusions (%, n)			

- Any	3.3 (15)	3.8 (17)	
- FFP	2.9 (13)	1.3 (6)	0.16
- Cryoprecipitate	2.4 (11)	3.3 (15)	0.55
- Platelet	2.0 (9)	1.1 (5)	0.42
Number of units transfused (mean, SD)			
- PRBC	0.5 (1.3)	0.6 (1.4)	0.66
- FFP	0.1 (0.5)	0.0 (0.5)	0.25
- Cryoprecipitate	0.3 (1.9)	0.3 (1.8)	0.80
- Platelet	0.0 (0.2)	0.0 (0.2)	0.53
Hysterectomy (%, n)	0.9 (4)	0.7 (3)	1.00
Intensive Care Unit admission (%, n)	2.4 (11)	4.9 (22)	0.08

Table 4 – Study outcomes in patients delivering vaginally

	Pre-ROTEM cohort (n = 248)	Post-ROTEM cohort (n = 201)
PRBC transfusion (%, n)	27.4 (68)	37.3 (75)
Other blood product transfusions (%, n)		
- Any	3.6 (9)	5.0 (10)
- FFP	3.2 (8)	1.5 (3)
- Cryoprecipitate	2.4 (6)	4.0 (8)
- Platelet	2.0 (5)	1.0 (2)
Number of units transfused (mean, SD)		

- PRBC	0.7 (1.3)	0.8 (1.3)
- FFP	0.1 (0.5)	0.0 (0.3)
- Cryoprecipitate	0.3 (2.2)	0.3 (1.7)
- Platelet	0.0 (0.2)	0.0 (0.2)
Hysterectomy (%, n)	0.8 (2)	0.0 (0)
Intensive Care Unit admission (%, n)	2.8 (7)	6.0 (12)

Table 5 – Study outcomes in patients delivering via caesarean section

	Pre-ROTEM cohort (n = 202)	Post-ROTEM cohort (n = 249)
PRBC transfusion (%, n)	10.9 (22)	10.8 (27)
Other blood product transfusions (%, n)		
- Any	3.0 (6)	2.8 (7)
- FFP	2.5 (5)	1.2 (3)
- Cryoprecipitate	2.5 (5)	2.8 (7)
- Platelet	2.0 (4)	1.2 (3)
Number of units transfused (mean, SD)		
- PRBC	0.3 (1.3)	0.3 (1.5)
- FFP	0.1 (0.5)	0.0 (0.5)
- Cryoprecipitate	0.2 (1.5)	0.3 (1.8)
- Platelet	0.0 (0.1)	0.0 (0.2)
Hysterectomy (%, n)	1.0 (2)	1.2 (3)

Intensive Care Unit admission (%, n)	2.0 (4)	4.0 (10)