Efficacy of rotational thromboelastometry for diagnosis and correction of coagulopathy in massive postpartum hemorrhage: a cohort retrospective multi-center DiPTEM study

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Abstract

INTRODUCTION: Continuous monitoring of the hemostasis system during postpartum hemorrhage is an essential aspect of intensive care. Rotational thromboelastometry (ROTEM) provides rapid and differentiated detection of hemostasis system disorders. **OBJECTIVE:** To evaluate the effect of implementing the rotational thromboelastometry on the need for blood transfusion in massive postpartum hemorrhage in the practice of perinatal centers. **MATERIALS AND METHODS:** A retrospective cohort multicenter study was conducted in two perinatal centers. The BEFORE group included females with massive postpartum hemorrhage (PPH) (>30 % of circulating blood volume (CBV) or > 2 L) within 2 years prior to ROTEM implementation in tertiary care hospitals; the AFTER group included females with massive postpartum hemorrhage within 2 years after ROTEM implemen-

Эффективность ротационной тромбоэластометрии для диагностики и коррекции коагулопатии при массивном послеродовом кровотечении: когортное ретроспективное многоцентровое исследование «ДиПТЭМ»

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Реферат

АКТУАЛЬНОСТЬ: Динамическая оценка системы гемостаза во время послеродового кровотечения (ПРК) является важным моментом интенсивной терапии родильниц. Использование ротационной тромбоэластометрии (РОТЭМ) позволяет быстро и дифференцированно определить нарушения в системе гемостаза. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Оценить эффект внедрения методики ротационной тромбоэластометрии на потребность в трансфузионных компонентах крови при массивных послеродовых кровотечениях в клинической практике перинатальных центров. **МАТЕРИАЛЫ И МЕТОДЫ:** В ретроспективном когортном многоцентровом исследовании приняли участие два перинатальных центра. В группу ДО вошли роженицы с массивным ПРК (> 30 % от объема циркулирующей крови (ОЦК) или > 2 л) в течение 2 лет до внедрения РОТЭМ в ста-

tation. The primary endpoint of the study was a comparative evaluation of the frequency of fresh frozen plasma (FFP) transfusion for hemostasis correction in massive PPH before and after ROTEM implementation as an urgent method for coagulopathy diagnosis. **RESULTS:** A total of 97 patients were included in the study: 48 in the BEFORE group and 49 in the AFTER group. A significant relative risk (RR) of reduced frequency of FFP transfusion RR = 0.53 (0.32, 0.85; $p = 0.009$) with NNT = 3.6 after implementation of ROTEM into clinical practice was found. The frequency of cryoprecipitate transfusion increased. Analysis of cases of PPH over 50 % of the CBV (PPH in the BEFORE and AFTER groups 68.2 ± 12.4 and 72.3 ± 35.9, respectively, p = 0.673) showed a twofold significant risk of reducing the number of parturient women requiring FFP transfusion: RR = 0.5 (0.25, 0.99); $p = 0.049$), with NNT = 2. **CONCLUSION:** Rapid information on the status of the hemostasis system can reduce unnecessary FFP transfusion. Introducing the ROTEM method into the clinical practice of obstetric hospitals will improve the outcomes of intensive care for one of the most challenging categories of patients — postpartum women with massive postpartum hemorrhage.

KEYWORDS: postpartum hemorrhage, hemorrhagic disorders, thrombelastography, fresh frozen plasma, fibrinogen

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ционары третьего уровня, в группу ПОСЛЕ — роженицы с массивным ПРК в течение 2 лет после внедрения РОТЭМ. Первичными конечными точками исследования были: сравнительная оценка частоты трансфузии свежезамороженной плазмы (СЗП) для коррекции гемостаза при массивном ПРК до и после внедрения РОТЭМ как метода ургентной диагностики коагулопатии. **РЕЗУЛЬТАТЫ:** В исследование было включено 97 пациенток, группу ДО составили 48, группу ПОСЛЕ — 49 рожениц. Был выявлен статистически значимый относительный риск (ОР) снижения частоты трансфузии СЗП ОР = 0,53 (0,32, 0,85; $p = 0,009$) со значением показателя числа больных, которых необходимо лечить (number needed to treat — NNT), NNT = 3,6 после внедрения РОТЭМ в клиническую практику. Увеличилось количество случаев трансфузии криопреципитата. Анализ случаев ПРК более 50 % от ОЦК (ПРК в группах ДО и ПОСЛЕ 68,2 ± 12,4 и 72,3 ± 35,9 соответственно, $p = 0,673$) выявил двукратный статистически значимый риск снижения количества рожениц, которым потребовалось проведение трансфузии СЗП ОР = 0,5 (0,25, 0,99; $p = 0,049$), со значением NNT = 2. **ВЫВОДЫ:** Возможность быстро получать информацию о состоянии системы гемостаза позволяет снизить количество необоснованно переливаемой СЗП. Внедрение метода РОТЭМ в клиническую практику акушерских стационаров позволит улучшить исходы интенсивной терапии одной из самых тяжелых категорий пациентов (родильниц) — с массивными ПРК.

КЛЮЧЕВЫЕ СЛОВА: послеродовое кровотечение, геморрагические расстройства, тромбоэластография, свежезамороженная плазма, фибриноген

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Introduction

Postpartum hemorrhage remains in the top three leading causes of maternal mortality [1–3]. Coagulopathy can be both the main cause of abnormal blood loss and develop due to massive blood loss. Therefore, continuous monitoring of the hemostasis system during postpartum hemorrhage is an essential aspect of intensive care for postpartum women. Rotational thromboelastometry (ROTEM) provides rapid and differentiated detection of hemostasis system disorders and is part of the point-of-care coagulation testing technology. It uses whole blood with no need to centrifuge it, and hemostasis is tested considering blood temperature and acid-base status directly at the bedside of a parturient woman [4]. These features of the method allow for rapid assessment of most parts of the hemostasis system and, if necessary, targeted therapy to replenish coagulation factors. ROTEM use reduces unnecessary FFP transfusion and provides a guide for the prompt correction of fibrinogen deficit; many studies showed the essential role of fibrinogen in coagulopathy pathogenesis [5]. Despite the wide use of integral methods for assessing the hemostasis system in various fields of medicine, the effectiveness and necessity of ROTEM in obstetric practice remains a matter of debate [6–7].

Objective — to evaluate the effect of implementing the technique of rotational thromboelastometry (ROTEM) on the need for blood transfusion in massive postpartum hemorrhage in the practice of perinatal centers.

Materials and methods

The study design was elaborated by the scientific committee of the Association of Obstetric Anesthesiologists. A retrospective cohort multicenter study was conducted in two perinatal centers in the Russian Federation: Regional Clinical Perinatal Center named after E.M. Bakunina (evaluation period from 01.10.2017 to 30.09.2021) and Krasnoyarsk Regional Maternal and Pediatric Clinical Center, evaluation period from 01.01.2015 to 31.12.2018). Patients were divided into groups before and after the introduction of ROTEM into clinical practice according to the following principle: BEFORE group — females with massive PPH within two years prior to ROTEM implementation in a tertiary care obstetric facility, AFTER group — females with massive PPH within two years after ROTEM implementation. The name of our study (ДиПТЭМ — DiPTEM) was based on this principle.

EXTEM and FIBTEM tests were performed using ROTEM to assess hemostasis. The indications for FFP transfusion included ongoing bleeding and increased clotting time (CT) in the EXTEM test above 70 seconds. When the clot density at 5 min (A5) in the FIBTEM test was less than 12 mm, 10 doses of cryoprecipitate were transfused at a time (1 dose contained 40 ml of cryoprecipitate). Subsequent transfusions depend on the results of repeated tests and the effectiveness of the initial therapy. The use of coagulation factors (prothrombin complex concentrate (PCC), recombinant activated factor seven (rFVIIa)) depended on the clinical presentation of ongoing bleeding.

The inclusion criteria for the study were: females with massive postpartum hemorrhage > 30 % of the circulating blood volume (CBV) or > 2000 mL during cesarean section (CS) [8]. The blood loss was determined by the gravimetric method. The exclusion criteria for the study were: massive postpartum hemorrhage associated with sepsis, amniotic fluid embolism, acute fatty liver of pregnancy, or congenital coagulopathies. The withdrawal criteria for the study were: no hemostasis test using ROTEM performed in the "AFTER" period.

The patients were divided into two groups: BEFORE group included patients with hemostasis correction performed based on standard coagulometric tests (thrombin time (TT), activated partial thrombin time (aPTT), fibrinogen, platelet count), clinical presentation, and physician's decision; AFTER group included patients with hemostasis correction performed based on ROTEM parameters, clinical presentation, and physician's decision.

CBV (mL) was calculated based on the formula = body weight × 100 mL; patients' body weight during pregnancy was used [9].

The primary endpoints of the study were: comparative assessment of the transfusion volume of donor erythrocytes (DE), blood components (FFP, cryoprecipitate, donor platelet concentrate), reinfusion of washed red blood cells (RWRBC), and coagulation factors (PCC, rFVIIa) for hemostasis correction in massive PPH before and after implementation of ROTEM as an acute coagulopathy diagnostic method.

The secondary endpoints of the study were: quantitative and qualitative changes in the ratios of infusion and transfusion media, postpartum bleeding volume, and autologous blood transfusion volume using reinfusion of washed red blood cells before and after ROTEM implementation. The effect of acute diagnostics of the hemostasis status on the rate of relaparotomy, hysterectomy and on the rate of such complications as acute respiratory failure, acute kidney injury, length of stay in an intensive care unit (ICU), and duration of mechanical ventilation (MV) after CS was of interest.

Statistical analysis

Statistical analysis of the first stage data included checking the series of numerical and quantitative indicators for the significance of differences with the normal distribution using the Kolmogorov—Smirnov test and descriptive statistics methods selected for each indicator according to the results of the above check. Unless the data had a significant deviation of the sample distribution from the normal probability distribution, the mean (M)

and standard deviation (± m) were used to report the data. If the study data had a significant deviation of the sample distribution from the normal probability distribution, the median (Me) and interquartile range (Q1; Q3) were used to report the data. Statistical hypotheses were formulated about the difference between the samples, which were tested using the parametric Student's *t*-test and the nonparametric Mann—Whitney *U*-test for the two groups under comparison. The relative risk (RR, 95% CI) was determined to assess the effectiveness of ROTEM in reducing transfusion volume. The significance level of accepting the hypothesis that the differences in the mean or other statistical parameters and the significance of the effects or correlation coefficients were significant was taken to be 0.05 with a power of 0.80. All data from the study were processed using IBM SPSS Statistics 25 for Windows (SPSS, Chicago, IL) and Microsoft Office Excel 2013.

Results

A cohort retrospective multicenter ДиПТЭМ study included 97 parturient women from two tertiary care perinatal centers. The BEFORE group included 48 patients, and the AFTER group included 49 patients.

The assessment of anthropometric data, age, and gestational age revealed a statistical difference in the age of parturient women: the median age in the BEFORE group was 38 years, and the median age in the AFTER group was 34 years. There was a significant difference in body weight and body mass index (BMI) (Table 1).

The leading cause of bleeding was placenta increta, followed by uterine atony, mainly caused by premature separation of the placenta. Combined data from the two perinatal centers showed no significant difference in blood loss and blood loss in relation to CBV (%) (Table 2).

Table 1. Characteristics of parturient women in the study groups

	BEFORE group (*n* = 48)	AFTER group (*n* = 49)	*p*-value
Age, years	38.0 (33.0; 41.8)	34.0 (30.0; 38.0)	0.006*
Gestational age, weeks	35.5 ± 3.2	35.1 ± 2.9	0.532**
Body weight, kg	76.0 ± 14.4	82.1 ± 15.4	0.049**
BMI, kg/m^2	27.82 ± 4.84	30.43 ± 5.50	0.015**

* Mann—Whitney *U*-test.
** Student's *t*-test for two independent samples.
BMI — body mass index.

Table 2. The cause and volume of blood loss in the study groups

Bleeding cause	BEFORE group	AFTER group	Total
Uterine atony, *n* (%)	19 (39.6)	18 (36.7)	37 (38.1)
Myomectomy during CS, *n* (%)	5 (10.4)	3 (6.1)	8 (8.2)
Placenta increta, *n* (%)	24 (50)	28 (57.1)	52 (53.6)
			p-value
Blood loss, mL	3356.3 ± 1302.9	3146.9 ± 1395.7	0.447*
Blood loss in relation to CBV, %	45.7 ± 19.2	39.5 ± 21.2	0.137*

* Student's *t*-test for two independent samples.
CBV — circulating blood volume; CS — cesarean section.

Although there was no significant difference in the volume of transfusion of FFP, a significant difference in the volume of FFP transfused per kilogram of body weight, and the total volume of transfused FFP was observed in the BEFORE group, which was 2 times greater than in the AFTER group (Table 3).

A significant relative risk (RR) of reduced frequency of FFP transfusion RR = 0.53 (0.32, 0.85; $p = 0.009$) with NNT = 3.6 after implementation of ROTEM into clinical practice was found. There was a significant difference in cryoprecipitate transfusion, the total volume of which increased almost 5-fold.

Assessment of the qualitative composition of infusion therapy showed a significant difference in crystalloid volume (Table 4).

Assessment of the ratio of infusion and transfusion therapy to the volume of blood loss showed a significant decrease in the latter after the implementation of ROTEM (Table 5).

Table 3. Transfusion volume of blood components and coagulation factors

Blood components	BEFORE group	AFTER group	*p*-value
Number of patients who received FFP, *n*	28	15	–
Mean volume of FFP, mL	1242.3 ± 380.8	1114.5 ± 648.7	0.419*
FFP, mL/kg	16.8 (14.9; 22.0)	13.2 (6.8; 15.3)	0.015**
Total volume of FFP, mL	34,783	16,718	–
Number of patients who received cryoprecipitate, *n*	5	12	–
Mean volume of cryoprecipitate, mL	100 (90; 130)	200 (142.5; 390)	0.009**
Total volume of cryoprecipitate, mL	540	2950	–
Number of patients who received DE, *n*	26	23	–
Mean volume of DE, mL	726.8 ± 321.2	918.9 ± 647.4	0.206*
Number of patients who received PCC, *n*	2	4	0.633*
Mean volume of PCC, mL	900.0 ± 424.3	1050.0 ± 300.0	–
Number of patients who received rFVIIa, *n*	4	3	–
Mean dose of rFVIIa, mg	2.1 ± 1.2	4.0 ± 2.8	0.261*
Number of patients who received RWRBC, *n*	35	39	–
Mean volume of RWRBC, mL	765.0 (330; 1200)	587 (160; 800)	0.023**

* Student's *t*-test.

** Mann—Whitney *U*-test for two independent samples.

DE — donor erythrocytes; FFP — fresh frozen plasma; PCC — prothrombin complex concentrate; RWRBC — reinfusion of washed red blood cells.

Table 4. Qualitative composition of infusion therapy

Infusion solutions	BEFORE group	AFTER group	*p*-value*
	n = 48	***n*** = 49	
Crystalloids, mL	3000 (2250; 3750)	2500 (2000; 3000)	0.005
	n = 44	***n*** = 40	
Colloids, mL	500 (50; 1000)	500 (200; 687)	0.628

* Mann—Whitney *U*-test.

Table 5. The ratio of infusion and transfusion therapy to the volume of blood loss

	BEFORE group (*n* = 48)	AFTER group (*n* = 49)	*p*-value*
Ratio	1.76:1	1.70:1	0.005

* Mann—Whitney *U*-test.

Evaluation of the length of stay in ICU in the BEFORE and AFTER groups (56.9 ± 32.5 and 52.4 ± 33.4 hours) and the MV duration (9.3 ± 5.8 and 7.5 ± 3.3 hours) after surgery showed no significant difference (Student's *t*-test $p = 0.505$ and 0.365, respectively). However, a significant reduction in the number of patients who required postoperative MV was observed: RR = 0.39 (0.21, 0.72; $p = 0.002$), with NNT = 3 (Table 6).

Table 6. Number of complications

	BEFORE group (*n* = 48)	AFTER group (*n* = 49)	RR (95 % CI)	*p*-value
Relaparotomy	8	0	0.06 (0.01, 0.97)	0.047
Hysterectomy	16	9	0.55 (0.27, 1.12)	0.101
Mechanical ventilation	26	10	0.39 (0.21, 0.72)	0.002

CI — confidence interval; RR — relative risk.

Assessment of the RR for hysterectomy rates showed no significant difference between the groups, in contrast to the RR for relaparotomy, which showed a significant decrease (Table 6).

Analysis of PPH cases up to 50 % of the CBV (PPH in the BEFORE and AFTER groups 33.3 ± 7.1 and 33.1 ± 7.3, respectively, $p = 0.912$) showed no significant RR reduction in the number of parturient women requiring FFP transfusion, RR 0.76 (0.38, 1.51; $p = 0{,}43$). However, analysis of cases of PPH over 50 % of the CBV (PPH in the BEFORE and AFTER groups 68.2 ± 12.4 and 72.3 ± 35.9, respectively, $p = 0.673$) showed a twofold significant RR of reducing the number of parturient women requiring FFP transfusion: RR = 0.5 (0.25, 0.99; $p = 0.049$), with NNT = 2.

Discussion

The current strategy for intensive care of massive obstetric hemorrhage is based on reducing the infusion volume to avoid hemodilution and increasing the volume of cryoprecipitate transfusion to replenish fibrinogen as a major predictor of postpartum bleeding. This approach avoids severe complications (e.g., dilutional coagulopathy) and allows proper correction of fibrinogen deficiency [10, 11]. Before implementing ROTEM at both centers, evaluation and decision-making on administering medications and transfusion media affecting the hemostasis system were usually based on four routine coagulation tests: aPTT, INR, fibrinogen level, and platelet count. Given the long waiting time required to obtain the results of these tests for ongoing bleeding, the decision to initiate therapy was made by the anesthesiologist/intensivist, usually empirically, without waiting for results, based on the volume of blood loss and/or clinical presentation. Usually, the therapy started with FFP, as it was considered a universal blood product containing almost all coagulation factors. Recently, the paradigm of infusion and transfusion therapy for obstetric hemorrhage has been changing, and according to international studies, using ROTEM for massive postpartum hemorrhage reduces the need for transfusion of blood components and coagulation factors [12–14]. P.W. Collins et al. showed that limiting FFP transfusion based on clinical assessment of blood loss and ROTEM data does not result in significant coagulopathy [9]. Our data also indicated that the introduction of ROTEM into clinical practice reduced the number of parturient women receiving FFP for massive PPH by almost half, thereby reducing the theoretical risk of infectious complications, TACO (transfusion-associated circulatory overload) and TRALI (transfusion-related acute lung injury) syndromes.

Despite the initial hypercoagulation and hyperfibrinogenemia in pregnant and parturient women [15], plasma fibrinogen plays a major role in the intensive care of PPH; its level should be maintained above 2 g/L [16–19]. It is important to note the correlation between a fibrinogen level (Clauss) of 2.0 g/L and an A5 FIBTEM index of 12 mm [20], which allows the use of ROTEM for the early detection of hypofibrinogenemia [21]. The ROTEM provides information on the hemostasis system status in a short time (about 5–10 minutes from the test start in the operating room) and can be used to diagnose fibrinogen deficiency and guide therapy. In our study, due to the FIBTEM test (functional fibrinogen) and targeted correction of hypofibrinogenemia, both the number of parturient women receiving cryoprecipitate and the volume of cryoprecipitate in the transfusion therapy for massive PPH increased, which is an important factor in the treatment of postpartum bleeding. These findings are consistent with the fundamental understanding of an impaired hemostasis system in PPH, where the leading role is given to a decrease in fibrinogen levels in the early stages of PPH [11].

The advantage in time to hemostasis test results using ROTEM, within the first 5 minutes, compared to waiting for platelet count, fibrinogen, and INR/PTT results, is paramount. However, recent European intensive care guidelines make a weak argument for the routine use of viscoelastic

tests, compared to routine tests (platelet count, fibrinogen, INR/PTT) [22]. This further highlights the relevance of additional and large-scale research in this area.

Study limitations

The study has several limitations: retrospective study design, no unified ROTEM protocol for the decision to administer coagulation factors, and different timing of the tests.

Conclusion

The study showed that the ROTEM method could detect a critical decrease in the fibrinogen level and guide its correction quickly, thus reducing the number of traumatic methods of surgical hemostasis, such as relaparotomy. Rapid information on the status of the hemostasis system can reduce unnecessary FFP transfusion. Introducing the ROTEM method into the clinical practice of obstetric hospitals will improve the outcomes of intensive care for one of the most challenging categories of patients — postpartum women with massive postpartum hemorrhage.

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Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

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