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ORIGINAL

Thromboelastometry in neonates and infants undergoing cardiac surgery

GORAZD KALAN • ENVER MELKIC • MOJCA GROSELJ-GRENC

MOJCA GROSELJ-GRENC (✉)
GORAZD KALAN
Department of Paediatric Surgery
and Intensive Care
University Medical Centre
Bohoriceva 20, 1525 Ljubljana, Slovenia
Phone: +38615228135
Fax: +38614301714
E-mail: mojca.groselj@kclj.si

ENVER MELKIC
Institute of Clinical Chemistry
and Biochemistry, University Medical Centre
Zaloska 7, 1525 Ljubljana, Slovenia

ABSTRACT

Introduction. Rotational thromboelastometry (ROTEM) in monitoring coagulation in children undergoing cardiac surgery has been studied with promising results. Since the data about ROTEM in infants and neonates undergoing cardiac surgery are scarce, the aim of our study was to asses ROTEM abnormalities in this patient group.

Methods. Infants and neonates undergoing cardiac surgery on cardiopulmonary bypass were included in this prospective, observational study conducted in a level III multidisciplinary neonatal and pediatric intensive care unit (ICU) between May 2011 and January 2012. ROTEM analysis, together with determination of platelet count, international normalized ratio of prothrombin time (INR), activated partial thromboplastin time (PTT), and fibrinogen concentration, was done in all neonates and infants before surgery (t_1), after admission to ICU (t_2) and 24 hours after surgery (t_3).

Results. Twenty infants and neonates were operated on during the time of the study. ROTEM abnormalities seen after surgery (t_2) were: thrombocytopenia 14, hypofibrinogenemia 1, mixed hypofibrinogenemia and coagulation factor deficiency 1, and mixed thrombocytopenia with mild hyperfibrinolysis 1. Three patients were found to have normal ROTEM results. The median values of all except one of the ROTEM tests, as well as platelet count, INR, PTT, and fibrinogen concentration, showed significant prolongation or deterioration after admission to ICU and these deteriorations persisted in several parameters for 24 hours.

Conclusions. In our neonates and infants, cardiac surgery on cardiopulmonary bypass predominantly affects platelets, although most of the ROTEM parameters deteriorated after admission to ICU.

Key words: thromboelastometry, cardiac surgery, neonate, infant, thrombocytopenia, hypofibrinogenemia.

Introduction

Rotational Thromboelastometry (ROTEM) graphically represents the fibrin polymerization process in a thromboelastogram and provides a complete evaluation of the process of clot initiation, formation, and stability. (1) The original one-trace ROTEM was recently upgraded with the addition of new different coagulation-inducing agents and platelet-inhibiting agents, which allow detection of specific coagulation defects like hypofibrinogenemia, factor deficiency, thrombocytopenia, heparin influence and hyperfibrinolysis. (2,3)

The causes of bleeding in patients undergoing cardiac surgery on cardiopulmonary bypass are multifactorial, and involve hemodilution, anticoagulation (heparin), activation of coagulation and fibrinolytic systems and impairment of platelet function. (4) ROTEM provides a tool to specifically asses some of these changes and furthermore, it is a faster method than standard laboratory tests of coagulation. (5,6) First results with ROTEM can be obtained within 10-30 minutes. (1,7) ROTEM has already been successfully used as a point of care test in adult cardiac surgery (2,8,9) and there is growing evidence of its usefulness in paediatric cardiac surgery. (4,7,10-12) Since the coagulation system in infants and neonates has some unique characteristics (4,13,14) and the data about thromboelastometry in infants and neonates after cardiac surgery are scarce, we decided to asses ROTEM abnormalities in neonates and infants undergoing cardiac surgery.

Methods

Infants and neonates undergoing cardiac surgery on cardiopulmonary bypass

Table 1. Patients' characteristics.

Gender	
Male	11
Female	9
Number of neonates (<29 days)	9
Number of infants on prostaglandin E_1	7
Age	
Median (range)	103 days (9-302 days)
Diagnoses	
Ventricular septal defect	4
d-Transposition of great arteries (arterial switch)	3
Truncus arteriosus	3
Aortopulmonary window	3
Pulmonary atresia (BT shunt and unifocalization or PA repair)	2
Atrioventricular canal	1
Tetralogy of Fallot (total repair)	1
Double outlet right ventricle	1
Hypoplastic left heart syndrome (Norwood procedure)	1
Pulmonary veins stenosis	1
Median time of cardiopulmonary bypass	98 min (60-217 min)
Median time of circulatory arrest	73 min (0-118 min)
Median time of hypothermia <32°C	48 min (0-170 min)
Median postoperative blood loss in first hour	9 mL/kg (0.7-36 mL/kg)
Median postoperative blood loss in first 24h	34 mL/kg (10-160 mL/kg)
No of patients receiving blood products in ICU	
Packed red blood cells	19
Fresh frozen plasma	17
Packed platelets	6
Median packed red blood cells in ICU in first 24h	29 mL/kg (0-149 mL/kg)
Median fresh frozen plasma in ICU in first 24h	29 mL/kg (0-99 mL/kg)
Median packed platelets in ICU in first 24h	0 mL/kg (0-36 mL/kg)
Deaths	1

BT, Blalock-Taussig; ICU, intensive care unit; PA, pulmonary artery.

between May 2011 and January 2012, and postoperatively admitted to a level III, multidisciplinary neonatal and paediatric intensive care unit (ICU), were included in this prospective, observational study. Infants and neonates with previously known coagulopathies or thrombocytopathies were excluded from the study. The study protocol encompassing patient data and surgery data was completed for each patient. Administration of blood products and the amount of bleeding were recorded hourly during the first 24h.

Blood samples for ROTEM® analysis were obtained before surgery (t_1), after admission to ICU (t_2) and 24 hours after surgery (t_3) together with platelet count, international normalized ratio of prothrombin time (INR), activated partial thromboplastin time (PTT), and fibrinogen concentration. Whole blood citrate-anticoagulated samples (1.8 mL) were immediately transported to the central hospital laboratory, where ROTEM analysis by Rotem delta analyzer (Penthapharm GmbH) was performed. ROTEM analysis was done by measuring clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), and maximum lysis (ML). Separate analyses were performed for EXTEM (extrinsic screening test), INTEM (intrinsic screening test), FIBTEM (fibrinogen screening test), HEPTEM (heparin screening test) and APTEM (hyperfibrinolysis screening test). Each test required 300 μL of citrate-anticoagulated whole blood. The sample preparation and Rotem analyzer setup were based on the manufacturer's instructions.

Data were presented as the median and range. The Mann-Whitney U test was used to compare ROTEM parameters for different time points (t_1 vs. t_2, t_1 vs. t_3) and between groups (neonates younger than 29 days versus infants older than 28 days; and infants receiving continuous infusion of prostaglandin E_1 (PGE_1) before surgery vs. infants without PGE_1 infusion). Differences were considered to be statistically significant at a level of $P < 0.05$. Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS INC., Chicago, IL, USA).

The study was approved by the National Medical Ethics Committee of the Ministry of Health, Republic of Slovenia, and written consent was obtained from parents before blood sampling.

Results

Twenty infants and neonates were operated on during the time of the study. The

patients' characteristics are summarized in table 1. None of the operated infants and neonates had known coagulopathy or thrombocytopathy. No surgical reexplorations due to postoperative bleeding were needed. One patient died on the fifth postoperative day. The majority of patients received packed red blood cells and fresh frozen plasma (table 1), 6 patients received packed platelets and 2 patients received fibrinogen concentrate in ICU. No prothrombin complex concentrate or activated factor VII were given in ICU. According to the ROTEM analysis after admission to ICU (t_2) patients were classified into one of the following groups: thrombocytopenia 14, hypofibrinogenemia 1, mixed hypofibrinogenemia and coagulation factor deficiency 1, and mixed thrombocytopenia with mild hyperfibrinolysis 1. Three patients showed normal ROTEM results. The median values of all except one of the ROTEM tests, as well as platelet count, INR, PTT, and fibrinogen concentration, showed significant prolongation or deterioration after surgery, and these deteriorations persisted for several parameters over the next 24h (table 2).

Median EXTEM-CT, FIBTEM-CT, and APTEM-CT before surgery (t_1) and 24 h after surgery (t_3) were shortened in our patients in comparison to our hospital laboratory reference values. The prolongation of median INTEM-CFT and HEPTEM CFT was recorded after admission to ICU (t_2), as well as a decrease of EXTEM-MCF, INTEM-MCF, APTEM-MCF, and HEPTEM-MCF, in comparison to our hospital laboratory reference values. HEPTEM-MCF was the only value that dropped 24h after surgery (t_3) in comparison to our hospital laboratory reference values (table 2).

The following laboratory tests differentiated between neonates younger than 29 days and infants older than 28 days: before surgery (t_1): HEPTEM-CT (median 140 s vs. median 105 s; Mann-Whitney U test, P = 0.040); 24 hours after surgery $_{(t3)}$: EXTEM-CT (median 25 s vs. median 35 s; Mann-Whitney U test, P = 0.014); EXTEM-ML(median 1% vs. median 5%; Mann-Whitney U test, P = 0.029); INTEM-CT (median 136 s vs. median 164 s; Mann-Whitney U test, P = 0.012); APTEM-ML (median 0% vs. median 3%; Mann-Whitney U test, P = 0.02); HEPTEM-ML (median 0.5% vs. median 2%; Mann-Whitney U

Table 2. Median values and ranges of platelet count (x109/L), INR, PTT, fibrinogen concentration (g/L) and ROTEM parameters, before surgery (t_1), after admission to the intensive care unit (t_2) and 24h after surgery (t_3). The median values outside our hospital laboratory reference values are in bold.

ROTEM Parameter	t_1 median (range)	t_2 median (range)	t_3 median (range)	p_1 (t_1 vs. t_2)	p_2 (t_1 vs. t_3)
Platelet count	393 (137-742)	112 (33-261)	147 (79-270)	0.0000*	0.0000*
INR	1.06 (0.97-1.25)	1.33 (1.06-2.77)	1.23 (1.06–2.40)	0.0000*	0.0002*
PTT	33 s (26-41)	37 s (19-67)	38 s (27-61)	0.0053*	0.0599
Fibrinogen	2.25 (1.8-3.31)	1.76 (0.7-2.44)	2.48 (0.50-3.16)	0,0001*	0,4175
EXTEM-CT	25 s (7-47)	36 s (22-144)	27 s (13-43)	0.0001*	0.1131
EXTEM-CFT	70 s (33-103)	155 s (54-500)	110 s (69-155)	0.0000*	0.0001*
EXTEM-MCF	63 mm (52-79)	48 mm (29-64)	57 mm (45-62)	0.0000*	0.0001*
EXTEM-ML	3% (0-10)	0% (0-13)	3% (0-14)	0.0089*	0.9342
INTEM-CT	144 s (14-242)	186 s (128-330)	150 s (122-200)	0.0009*	0.2834
INTEM-CFT	59 s (32-90)	143 s (74-538)	83 s (54-181)	0.0000*	0.0001*
INTEM-MCF	63 mm (48-77)	48 mm(28-56)	55 mm (45-64)	0.0000*	0.0001*
INTEM-ML	2% (0-9)	0% (0-8)	3% (0-14)	0.0253*	0.6089
FIBTEM-CT	21 s (15-41)	35 s (15-59)	30 s (3-46)	0.0005*	0.0087*
FIBTEM-MCF	17 mm (11-50)	11 mm (5-49)	18 mm (12-24)	0.0003*	0.9176
FIBTEM-ML	3% (0-33)	3% (0-18)	1% (0-8)	0.7148	0.4478
APTEM-CT	23 s (5-43)	40 s (13-65)	34 s (22-47)	0.0003*	0.0002*
APTEM-CFT	68 s (35-124)	158 s (87-771)	99 s (67-183)	0.0000*	0.0045*
APTEM-MCF	62 mm (49-79)	47 mm (26-81)	57 mm (43-61)	0.0000*	0.0003*
APTEM-ML	1% (0-10)	0% (0-4)	1% (0-11)	0.0174*	0.7048
HEPTEM-CT	126 s (33-178)	165 s (121-316)	129 s (50-311)	0.0010*	0.6637
HEPTEM-CFT	61 s (33-117)	154 s (90-653)	106 s (67-234)	0.0000*	0.0001*
HEPTEM-MCF	61 mm (46-76)	44 mm (27-52)	48 mm (39-57)	0.0000*	0.0003*
HEPTEM-ML	2% (0-7)	0% (0-12)	1% (0-12)	0.0370*	0.5016

APTEM, hyperfibrinolysis screening test; CFT, clot formation time; CT, clotting time; EXTEM, extrinsic screening test; FIBTEM, fibrinogen screening test; HEPTEM, heparin screening test; INR, international normalized ratio of prothrombin time; INTEM, intrinsic screening test; MCF, maximum clot firmness; ML, maximum lysis; PTT, activated partial thromboplastin time; ROTEM, Rotational thromboelastometry.

* – statistically significant p values ($p < 0.05$)

test, P = 0.03). Duration of hypothermia (below 32°C) was longer in neonates, and neonates received more fresh frozen plasma than infants, although differences did not reach statistical significance (median 68 min vs. median 0 min; Mann-Whitney U test, P = 0.054; and median 48 mL vs. median 15 mL; Mann-Whitney U test, P = 0.062). No differences were found between neonates and infants for platelet count, INR, PTT, fibrinogen concentration, time of cardiopulmonary bypass and circulatory arrest, postoperative blood loss in the first hour and in the first 24h, and volume of transfused packed red blood cells (Mann-Whitney U test, P >0.1 for all comparisons). The only laboratory test that differentiated between infants receiving PGE_1 and infants without PGE_1 was EXTEM-CT 24h following surgery (median 24 s vs. median 34 s; Mann-Whitney U test, P = 0.023).

Discussion

Cardiac surgery on cardiopulmonary bypass can affect different aspects of coagulation. (15-17) Although most of the ROTEM parameters showed significant deterioration following surgery, thrombocytopenia was the predominant ROTEM abnormality seen in our group of neonates and infants.

Straub et al. found in 10 infants undergoing cardiac surgery on cardiopulmonary bypass prolongation of CT in INTEM and HEPTEM and a decrease in INTEM, HEPTEM, EXTEM and FIBTEM amplitude which represented a measure for clot firmness and is similar to our MCF. (7) The authors concluded that these changes reflected the defect in plasmatic coagulation together with platelet damage. (7) In our group of patients CT was significantly prolonged after admission to ICU (t_2) in comparison to baseline (t_1), but the median CT result in all ROTEM tests was still within normal range according to our reference values. This shows that a plasmatic coagulation defect was not the most important cause of bleeding in our patients. Meanwhile, prolongation of median CFT in INTEM and HEPTEM, when compared to our reference values, together with reduction of median MCF in all ROTEM tests except FIBTEM, were found in our patients after admission to ICU (t_2). In addition, significant prolongation of CFT and reduction of MCF in all ROTEM tests were found in our patients after admission to ICU (t_2). Since CFT and MCF, except from factor XIII, are mainly based on platelets and fibrinogen, and furthermore, fibrinogen dysfunction can be excluded with FIBTEM-MCF in the normal range, we concluded that the most important cause of bleeding in our patients was thrombocytopenia. This finding was also supported by lowered median platelet count after surgery (t_2). However, we cannot exclude the influence of lower fibrinogen concentration after surgery (t_2) on the drop in MCF in EXTEM, INTEM, HEPTEM and APTEM. According to the ROTEM results, there was only one case of mild hyperfibrinolysis and two cases of hypofibrinogenemia in our patients.

Tirosh-Wagner et al. found a significant increase in CT and a decrease in MCF in 15 children undergoing cardiac surgery 24h after surgery. (4) Unfortunately, the authors did not compare the values to their references values. Median postoperative loss in their study (4), in the first 24h, was very similar to ours, but they used far less blood products than we did. We used fresh frozen plasma in the majority of our patients, which explains the return of CT toward baseline values (t_1) in our patients 24h after surgery (t_3), despite bleeding.

Hayashi et al. found no significant changes in ROTEM tests 24h after cardiac surgery in 21 children, but ROTEM analysis in their study was not done immediately after surgery. (11) Interestingly, only four children received fresh frozen plasma and only two children received red cell transfusion within 24h after surgery in their study, (11) but children in their study were comparatively older and the surgical procedures were different than the ones in our patients.

Comparison of ROTEM tests between neonates and older infants showed prolonged HEPTEM-CT in neonates before surgery (t_1), but median HEPTEM-CT was still in the range of our adults' references values. Interestingly, 24h after surgery (t_3) neonates showed shorter EXTEM-CT, and INTEM-CT, and less fibrinolysis than infants. These differences could be partly explained by more fresh frozen plasma being given to our neonates, but a similar "hypercoagulability state" in 1-3 month old infants has already been described by other authors. (18) Recently, age-related reference values in children in comparison to reference ranges in adults were published. (14) According to these reference values, CT values in EXTEM but not in INTEM are slightly shorter in 1-3 month old infants, than in older infants. (14) Since our adult reference ranges differ from their values, (14) these values cannot be absolutely compared to our values. The reason is inter-laboratory variation of ROTEM tests.

Although PGE_1 can have an inhibitory effect on platelet aggregation, (19) we found no differences between infants receiving PGE_1 and those without PGE_1 before surgery (t_1) and after admission to ICU (t_2). Since platelet function cannot be measured by ROTEM, the specific tests for platelet function should be used to measure the influence of PGE_1 on platelets. (20) Shortened EXTEM-CT in infants receiving PGE_1 24h after surgery (t_3) can be explained by the comparatively younger age of infants receiving PGE_1 and by the already described "hypercoagulability state" in the first three months of life. (14,18)

In conclusion, cardiac surgery on cardiopulmonary bypass in our neonates and infants predominantly affected platelets, although most of the ROTEM parameters deteriorated. ROTEM might be especially useful in evaluation of neonates and infants after cardiac surgery on cardiopulmonary bypass, who bleed excessively and in whom standard therapy in our ICU (packed red blood cells and fresh frozen plasma) is insufficient.

REFERENCES

1. Luddington RJ. Thrombelastography/thromboelastometry. Clin Lab Haematol 2005;27:81-90.
2. Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W. An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. Transfus Med 2006;16:31-9.
3. Lang T, Bauters A, Braun SL, Pötzsch B, von Pape KW, Kolde HJ, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 2005;16:301-10.
4. Tirosh-Wagner T, Strauss T, Rubinshtein M, Tamarin I, Mishaly D, Paret G, et al. Point of care testing in children undergoing cardiopulmonary bypass. Pediatr Blood Cancer 2011;56:794-8.
5. Haas T, Spielmann N, Mauch J, Madjdpour C, Speer O, Schmugge M, et al. Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery. Br J Anaesth 2012;108:36-41.
6. Ogawa S, Szlam F, Chen EP, Nishimura T, Kim H, Roback JD, et al. A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 2012;52:14-22.
7. Straub A, Schiebold D, Wendel HP, Hamilton C, Wagner T, Schmid E, et al. Using reagent-supported thromboelastometry (ROTEM) to monitor haemostatic changes in congenital heart surgery employing deep hypothermic circulatory arrest. Eur J Cardiothorac Surg 2008;34:641-7.
8. Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U, et al; EACTS Audit and Guidelines Committee. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008;34:73-92.
9. Mittermayr M, Velik-Salchner C, Stalzer B, Margreiter J, Klingler A, Streif W, et al. Detection of protamine and heparin after termination of cardiopulmonary bypass by thrombelastometry (ROTEM): results of a pilot study. Anesth Analg 2009;108:743-50.
10. Andreasen JB, Hvas AM, Christiansen K, Ravn HB. Can RoTEM® analysis be applied for haemostatic monitoring in paediatric congenital heart surgery? Cardiol Young 2011;21:684-91.
11. Hayashi T, Sakurai Y, Fukuda K, Yada K, Ogiwara K, Matsumoto T, et al. Correlations between global clotting function tests, duration of operation, and postoperative chest tube drainage in pediatric cardiac surgery. Paediatr Anaesth 2011;21:865-71.
12. Groselj-Grenc M, Kalan G, Melkic E. Thromboelastometry for detection of specific coagulation defects in children after cardiac surgery – a pilot study. The Pediatric Cardiac Intensive Care Society European Conference & Annual Scientific Meeting of PICS (UK). Programme & Abstract Book. Cambridge, UK. 2011 Sep 21-23; p. 30.
13. Strauss T, Levy-Shraga Y, Ravid B, Schushan-Eisen I, Maayan-Metzger A, Kuint J, et al. Clot formation of neonates tested by thromboelastography correlates with gestational age. Thromb Haemost 2010;103:344-50.
14. Oswald E, Stalzer B, Heitz E, Weiss M, Schmugge M, Strasak A, et al. Thromboelastometry (ROTEM) in children: age-related reference ranges and correlations with standard coagulation tests. Br J Anaesth 2010;105:827-35.
15. Arnold P. Treatment and monitoring of coagulation abnormalities in children undergoing heart surgery. Paediatr Anaesth 2011;21:494-503.
16. Besser MW, Klein AA. The coagulopathy of cardiopulmonary bypass. Crit Rev Clin Lab Sci 2010;47:197-212.
17. Jaggers J, Lawson JH. Coagulopathy and inflammation in neonatal heart surgery: mechanisms and strategies. Ann Thorac Surg 2006;81:S2360-6.
18. Haizinger B, Gombotz H, Rehak P, Geiselseder G, Mair R. Activated thrombelastogram in neonates and infants with complex congenital heart disease in comparison with healthy children. Br J Anaesth 2006;97:545-52.
19. Koga T, Az-ma T, Yuge O. Prostaglandin E1 at clinically relevant concentrations inhibits aggregation of platelets under synergic interaction with endothelial cells Acta Anaesthesiol Scand 2002;46:987-93.
20. Toth O, Calatzis A, Penz S, Losonczy H, Siess W. Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. Thromb Haemost 2006;96:781-8.