Original Article

Relationship between Maximum Clot Firmness in ROTEM® and Postoperative Bleeding after Coronary Artery Bypass Graft Surgery in Patients Using Clopidogrel

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Abstract

Background: The aim of the present study was to investigate the relationship between maximum clot firmness (MCF) in rotational thromboelastometry (ROTEM®) and postoperative bleeding in patients on clopidogrel after emergency coronary artery bypass graft surgery (CABG). **Methods:** This observational study recruited 60 patients posted for emergency CABG following unsuccessful primary percutaneous coronary intervention (PCI) while on 600 mg of clopidogrel. The study population was divided into 2 groups on the basis of their MCF in the extrinsically activated thromboelastometric (EXTEM) component of the (preoperative) ROTEM® test: patients with MCF <50 mm (n = 16) and those with MCF ≥50 mm (n = 44). Postoperative chest tube drainage amount, need for blood product transfusion, postoperative complications, and duration of mechanical ventilation after CABG were recorded. **Results:** No significant differences were observed between the two groups regarding duration of surgery, cardiopulmonary bypass, and aortic cross-clamp time. Chest tube drainage at 6, 12, and 24 h after Intensive Care Unit admission were significantly higher in the patients with MCF below 50 mm. The need for blood product transfusion was higher in the group with MCF <50 mm. In patients who experienced postoperative bleeding of 1000 mL or more, the ROTEM® parameters of INTEM (Intrinsically activated thromboelastomery) α and MCF, EXTEM α and MCF, and HEPTEM (INTEM assay performed in the presence of heparinase) MCF (but not FIBTEM (Thromboelastometric assay for the fibrin part of the clot) values) were significantly lower than those with postoperative bleeding <1000 mL ($P \leq 0.05$). **Conclusions:** When platelet aggregometry is not available, the ROTEM® test could be useful for the prediction of increased risk bleeding after emergency CABG in patients who have received a loading dose of clopidogrel.

Keywords: *Bleeding, clopidogrel, coronary artery bypass grafting, thromboelastometry*

Introduction

Patients with the acute coronary syndrome often have ruptured atherosclerotic plaques, which could lead to platelet activation and coronary obstruction secondary to thrombosis. Antiplatelet drugs often reduce mortal complications. In these patients, coronary artery bypass graft surgery (CABG) is imperative for revascularization.[1,2] Although antiplatelet drugs such as aspirin are well known for primary and secondary prevention in coronary artery disease,[3] the increasing prevalence of postoperative bleeding is still a concern.[4] Newly introduced antiplatelet drugs such as clopidogrel, prasugrel, and ticagrelor have conferred similar relative benefits among these patients.

Clopidogrel (Plavix®) is a drug with selective and irreversible inhibition of the binding of adenosine diphosphate (ADP) to its receptor.[5] Given its antiplatelet properties, the combination of clopidogrel with aspirin contributes to maintain patency of stents.[6] Moreover, this drug is used in carotid and peripheral stenosis as well.[7] Many patients with intracoronary stents benefit from the antiplatelet properties of clopidogrel. However, risk of postoperative bleeding and need for surgical re-exploration have been increasingly reported in these patients.[8-11] Despite the recent rise in the perioperative use of clopidogrel, literature contains conflicting reports on the results. A study suggested that clopidogrel consumption in a period of 5 days preceding surgery could increase morbidity and mortality, and if used in the preceding 48 h, it might increase the risk of postoperative bleeding.[8] Another study showed that clopidogrel used 4 days before

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surgery increased the risk of bleeding, blood transfusion, and duration of Intensive Care Unit (ICU) stay.[12] Conversely, a clinical trial carried out on 106 patients showed that clopidogrel only slightly increased the risk of bleeding and concluded that the advantages of clopidogrel outweighed its side effects.[13] Clopidogrel has irreversible effects on platelet function.[14,15] Some studies have suggested that the drug be discontinued 5 days preceding surgery,[16] whereas others have maintained that a 7-day period is safe.[17] Rotational thromboelastometry (ROTEM®) is drawn upon for viscoelastic diagnosis and noninvasive measurement of the hemostatic and coagulopathy state, degree of lysis, and platelet dysfunction.[18] ROTEM® represents an efficient evaluation for the hemostatic state of the clot.[19] Patients with abnormal ROTEM® exhibit a high incidence rate of postoperative bleeding[20] and the use of ROTEM® intraoperatively reduces the need for blood transfusion.[21] One of the usual tests employed for the evaluation of platelet activity is multiple electrode aggregometry using a Multiplate® analyzer. Although this technique has long been applied in interventional cardiology to evaluate the result of antiplatelet therapy, it is not available at departments of cardiac surgery as a standard assessment tool.[22] When platelet aggregometry is not available, patients posted for emergency CABG on full-dose clopidogrel following failed percutaneous coronary intervention (PCI) may benefit from the ROTEM® test insofar as it can help to evaluate the coagulation status, to provide information on the increased risk of bleeding, and to determine transfusion requirements.

The present study was designed to evaluate the role of the ROTEM® test parameters such as maximum clot firmness (MCF) in the prediction of bleeding postemergency CABG, in patients on clopidogrel.

Methods

In this observational study, 60 patients aged between 18 and 85 years who were posted for emergency CABG following unsuccessful primary PCI who had been administered 600 mg loading dose of clopidogrel were assigned to 2 groups on the basis of their MCF in the extrinsically activated thromboelastometric (EXTEM) assessment of the ROTEM® test. The time interval between PCI and CABG was between 6 and 24 h. The ROTEM® tests were conducted when consultations were sent for emergent CABG. We chose "50 mm" for the minimum normal value of EXTEM MCF as our study cutoff point to divide our patients into two groups: those with MCF <50 mm (n = 16) and those with MCF ≥50 mm (n = 44). The study was approved by the local ethics committee and informed consent was obtained from all the participating patients.

Patients with anemia with hematocrit <30%, platelet count <120000/mL, patients with renal failure (creatinine clearance <30 mL/min), patients with active liver disease, and patients with severe coagulopathy or under anticoagulation (warfarin or heparin) therapy before surgery were excluded from the study. Demographic data and intraoperative values were recorded for all the patients.

The ROTEM® test comprising of EXTEM, INTEM, FIBTEM, and HEPTEM was conducted for all the patients before surgery. The patients were given lorazepam (1–2 mg) as premedication on the night of surgery and intramuscular morphine sulfate (3–5 mg) on the morning of surgery. All the patients received 5–15 cc/kg body weight of crystalloids for compensating intravascular volume expansion and they underwent standard monitoring (i.e. pulse oximetry, invasive blood pressure, electrocardiography, and central venous pressure measurement). After the patients were given 5 μg of sufentanil, an arterial line was placed. The patients received 0.1–0.15 mg/kg of midazolam, 1–2 μg/kg of sufentanil, and 0.2 mg/kg of cisatracurium for the induction of anesthesia. After tracheal intubation, a central venous line was placed, and sufentanil, atracurium, midazolam, or propofol were used for the maintenance of anesthesia. The cardiopulmonary bypass and surgery techniques were similar in all the individuals. All the patients were transferred intubated to the ICU after surgery. The cardiac surgeons who evaluated postoperative drainage of the patients were not aware about the values of preoperative ROTEM test that was performed by the anesthesiologist.

Drain from the chest tube, need for blood product transfusion, cardiac (i.e., myocardial infarction and arrhythmia), respiratory, renal, and cerebral complications, tracheal intubation time, and ICU stay time were measured and recorded for all the participants. The collected data were entered into IBM SPSS® Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). The one-sample Kolmogorov–Smirnov test was utilized to evaluate the normal distribution of the data. The Chi-square test was applied for the analysis of the categorical variables and Mann–Whitney U-test for the statistical analysis of the nonparametric data. In addition, the independent samples t-test was used to compare the mean values of the continuous variables between the study groups. $P \leq 0.05$ was considered statistically significant in this study.

Results

As is shown in Table 1, the demographic variables and the surgical data were similar in both groups. Concerning the consumption of drugs such as nitrates, beta-blockers, angiotensin-converting enzyme inhibitors, aspirin, and proton pump inhibitors, there were no significant differences between the two groups. The laboratory parameters, recorded for all the patients, showed no statistically significant difference between the study groups. Table 2 summarizes the complications on the basis of the MCF values: below 50 mm and ≥50 mm (in the 2 study groups). No significant differences were observed regarding cardiopulmonary bypass, aortic cross-clamp time, and

Table 1: Demographic characteristics and clinical variables data in the study groups

	MCF <50 mm (*n*=16) (%)	MCF ≥50 mm (*n*=44) (%)	*P*
Gender			
Male	16 (100)	38 (86.4)	0.179
Female	0	6 (13.6)	
Age (year)	60.56±7.38	61.11±10.58	0.849
Operating room working shift			
Morning 8:00-14:00	5 (31.3)	11 (25)	0.021
Evening 14:00-19:00	1 (6.3)	19 (43.2)	
Night 19:00-8:00	10 (62.5)	14 (31.8)	
Cigarette smoking	7 (43.8)	19 (43.2)	1.000
Diabetes mellitus	9 (56.3)	17 (38.6)	0.252
Dyslipidemia	1 (6.3)	19 (43.2)	0.011
Hypertension	3 (18.8)	31 (70.5)	0.001
Recent myocardial infarction (<1 months)	5 (31.3)	23 (52.3)	0.242
Nitrates	11 (68.8)	21 (47.7)	0.242
β-blockers	12 (75)	28 (63.6)	0.567
Angiotensin-converting enzyme inhibitors	7 (43.8)	17 (38.6)	0.771
Aspirin	13 (81.3)	39 (88.6)	0.429
Proton pump inhibitors	3 (21.4)	3 (6.8)	0.145
Preoperative ejection fraction	34.64±11.174	40.12±11.288	0.121
Mitral regurgitation severity			
No	7 (50)	25 (59.5)	0.793
Mild	5 (35.7)	13 (31)	
Moderate	2 (14.3)	4 (9.5)	
Severe	0	2 (14.3)	
Number of vessels with stenosis			
2	0	2 (14.3)	1.000
3	6 (100)	12 (85.7)	

All data are expressed as means±SDs or *n* (%). MCF in the EXTEM component of the (ROTEM®) test. MCF: Maximum clot firmness, EXTEM: Extrinsically activated thromboelastometric, ROTEM: Rotational thromboelastometry, SD: Standard deviation

operation times between the two groups. The measurement of chest tube drainage amounts at 6, 12, and 24 h after admission to the ICU revealed that the values were higher in the group with MCF <50 mm; the difference was statistically significant.

Five (31.3%) patients with MCF below 50 mm needed surgical re-exploration, while there were only 4 (6.8%) cases of re-exploration among those with MCF ≥50 mm (P = 0.026). Need for inotropic agents in the operating room and the ICU did not show any statistically significant difference between the groups; however, the postoperative complications of the patients with MCF <50 mm before CABG were fewer than those of the patients with MCF of 50 mm or higher (P = 0.017).

The patients were also allocated to two subgroups according to their postoperative bleeding volumes: more and <1000 mL. Fifty-two patients had postoperative bleeding <1000 mL, while postoperative bleeding in 8 patients exceeded that. The ROTEM® parameters in these two subgroups are displayed in Table 3. Our data analyses showed significant statistical differences between the patients bleeding <1000 mL and those bleeding at least 1000 mL vis-à-vis the ROTEM® parameters, comprising INTEM α, EXTEM MCF, EXTEM α, INTEM MCF, and HEPTEM MCF (all Ps < 0.05).

Discussion

Our study results showed that EXTEM MCF <50 mm in the ROTEM® test in patients who received full dose (600 mg) of clopidogrel before CABG correlated with higher rates of postoperative bleeding, re-exploration, complications, and need for blood product transfusion. We found that the patients who experienced postoperative bleeding of 1000 mL or more had more complications and were more likely to undergo reoperation and require inotropic drugs. In addition, we observed associations between lower values of the ROTEM® test parameters such as INTEM α, EXTEM MCF, EXTEM α, INTEM MCF, HEPTEM MCF, and postoperative bleeding more than 1000 mL.

In 2010, approximately 492,000 PCI procedures were carried out in the United States. Researchers suggest that patients should be given the loading dose of clopidogrel (i.e., 600 mg orally) and then 75 mg daily for 2 months after PCI.[23] Approximately 15% of patients presenting with coronary artery disease will need CABG in the future.[24] On the other hand, it is well known that more postoperative complications and higher blood transfusion rates are correlated with poor outcomes.[25]

Clopidogrel is the main antiplatelet drug used after PCI; it should, nevertheless, be discontinued 5–7 days before surgery so that platelet activity reaches normal levels and the risk of intraoperative bleeding decreases.[26] Knowing the appropriate time to discontinue platelet receptor inhibitor drugs such as clopidogrel which block the P2Y12 receptor for patients who undergo CABG is crucial inasmuch as it may lessen the risk of bleeding and need for massive transfusion.[27,28]

Thromboelastograph (TEG®) demonstrates an integral evaluation for coagulation pathways and hemostasis. A study carried out in 2010 showed that TEG® along with platelet mapping (PM) immediately before surgery was able to predict severe bleeding after surgery; furthermore, the authors of that article concluded that aspirin consumption did not affect postoperative bleeding.[29] Another study which used TEG-PM® in patients under antiplatelet therapy demonstrated more drainage from chest tubes in those using clopidogrel and there was a positive correlation between reductions in maximum amplitude ADP and a

Table 2: Operative variables and postoperative complications in patients with maximum clot firmness <50 mm and ≥50 mm

	MCF <50 mm (%)	MCF ≥50 mm (%)	*P*
Aortic cross-clamp time (min)	43.75±7.41	48.68±28.79	0.504
Cardiopulmonary bypass time (min)	81.44±15.16	88.03±41.44	0.0541
Operation time (h)	5.01±1.11	4.83±1.31	0.645
Chest tube drainage 6 h after ICU admission (mL)	718.75±377.22	222.73±97.92	<0.0001
Chest tube drainage 12 h after ICU admission (mL)	1031±547.08	338.1±106.96	<0.0001
Chest tube drainage 24 h after ICU admission (mL)	1258.75±555.19	446.93±165.42	<0.0001
ICU stay (day)	8.29±3.99	4.32±2.25	<0.0001
Intubation time (h)	17.45±11.26	11.25±4.73	0.004
Packed RBC transfusion in the OR (units)			
0	3 (18.8)	19 (43.2)	0.021
1	7 (43.8)	13 (29.5)	
1<	6 (37.5)	13 (28.88)	
FFP transfusion in the OR (units)			
0	3 (18.8)	27 (61.4)	0.003
1	0	6 (13.6)	
1<	13 (81.25)	11 (25)	
Platelet transfusion in the OR (units)			
0	6 (37.5)	22 (50)	0.175
1	1 (6.3)	5 (11.4)	
1<	9 (56.25)	17 (38.63)	
Packed RBC transfusion in the ICU (units)			
0	2 (12.5)	20 (47.6)	0.005
1	6 (37.5)	12 (28.6)	
>1	8 (50)	10 (23.80)	
FFP transfusion in the ICU (units)			
0	9 (56.3)	37 (88.1)	0.013
1	0	0	
>1	7 (43.75)	5 (11.90)	
Platelet transfusion in the ICU (units)			
0	8 (50)	40 (92.5)	<0.0001
1	2 (12.5)	0	
>1	6 (37.5)	2 (4.76)	
Re-exploration	5 (31.3)	3 (6.8)	0.026
Postoperative complications	6 (37.5)	4 (9.1)	0.017
Inotrope use in the OR	8 (50)	14 (31.8)	0.234
Inotrope use in the ICU	6 (37.5)	14 (31.8)	0.760

All data are expressed as means±SDs or *n* (%), >1: More than one unit, MCF in the EXTEM component of the (ROTEM®) test. EXTEM: Extrinsically activated thromboelastometric, ROTEM: Rotational thromboelastometry, RBC: Red blood cell, FFP: Fresh frozen plasma, ICU: Intensive Care Unit, OR: Operating room

higher percentile of platelets blocked. In that study, a 1 mm reduction in maximum amplitude ADP showed increased drainage by up to 6%.[30]

Mahla *et al*.[31] suggested a strategy for preoperative platelet function testing to time CABG in a better manner in patients under clopidogrel therapy. In another study performed in 2014, platelet inactivity measured by TEG-PM® with a 34% cutoff ADPPRI (inhibition of adenosine 5-diphosphate platelet receptor inhibition) was able to help prevent inappropriate cancellation of surgeries.[32] Görlinger *et al*.[33] concluded that given the ability of the ROTEM® analysis to assess heparin effects and fibrinogen-platelet interaction, this test was applicable to perioperative coagulation management for the monitoring of platelet function in cardiac patients. In addition, the authors reported that the ROTEM® test allowed a rapid evaluation of platelet function and prediction of postoperative bleeding.

Serraino and Murphy discussed the use of "viscoelastic blood tests" for the management of coagulopathy in cardiac surgery patients and concluded that routine usage

Table 3: Relationship between the values of the rotational thromboelastometry parameters (including FIBTEM) and the amount of postoperative bleeding

	Bleeding <1000 mL (*n*=52)	Bleeding ≥1000 mL (*n*=8)	*P*	Normal values
INTEM CT (s)	207.69±99.15	216.75±51.79	0.802	100-240
INTEM α (degree)	72.62±10.32	53.00±4.00	<0.0001	70-83
INTEM MCF (mm)	63.63±9.89	47.88±4.29	<0.0001	50-72
EXTEM CT (s)	55.35±13.40	47.50±18.83	0.151	38-79
EXTEM α (degree)	73.73±10.69	51.38±4.50	<0.0001	63-83
EXTEM A10 (mm)	58.02±13.14	34.63±3.66	<0.0001	43-65
EXTEM MCF (mm)	65.08±10.64	45.38±2.33	<0.0001	50-72
FIBTEM A10 (mm)	20.72±6.54	22.00±4.84	0.606	7-23
FIBTEM MCF (mm)	23.32±8.49	23.50±4.69	0.953	9-25
HEPTEM CT (s)	187.00±65.54	198.25±45.01	0.649	100-240
HEPTEM MCF (mm)	63.59±6.88	55.50±2.67	0.002	50-72

All data are expressed as means±SDs. CT: Clotting time, MCF: Maximum clot firmness; A10: Amplitude in minute 10, SD: Standard deviation, EXTEM: Extrinsically activated thromboelastometric, ROTEM: Rotational thromboelastometry, INTEM:Intrinsically activated thromboelastomery; FIBTEM: Thromboelastometric assay for the fibrin part of the clot; HEPTEM:INTEM assay performed in the presence of heparinase

of viscoelastic point-of-care tests did not decrease mortality or complications.[34] This review, however, addressed "cardiac surgery patients" in general and when faced with a high risk subgroup of these patients, i.e., those with unsuccessful PCI, having taken loading dose of clopidogrel and undergoing emergency CABG, the clinical scenario may be somewhat different.

New generations of ROTEM® test apparatus such as "ROTEM PM system" allow simultaneous analysis of thromboelastometry and platelet aggregation. These platelet aggregometry tests are Aratem (arachidonic acid), Traptem (thrombin-activating peptide), and Adptem (ADP).[35] Furthermore, new techniques and simulators help anesthesiologists to train medical personnel with essential skills to face the real clinical scenarios.[36]

Conclusions

In summary, we conclude that when platelet aggregometry is not available, the ROTEM® analysis could be useful for the prediction of increased risk of bleeding after emergency CABG in patients on loading dose of clopidogrel. MCF <50 mm in the EXTEM component of the ROTEM® test could be promising in the identification and evaluation of coagulation parameters as well as in the determination of the appropriate time for CABG in patients on clopidogrel. Nonetheless, further controlled and interventional (clinical trial) studies with larger sample sizes are needed to confirm this relationship strongly.

Limitations

The main limitation of the current study is its noninterventional design. We conducted only an observational research mainly considering ethical issues. Being fully aware that EXTEM MCF is the product of platelet function and fibrinogen activity, we included the FIBTEM analysis in the ROTEM® test to differentiate fibrin activity from platelet function although this is an indirect measurement. We did not measure plasma fibrinogen levels. Another notable weakness of our work is its limited number of patients, especially in the group with MCF <50 mm (n = 16). The main reason for this limited patient recruitment was difficulty in waiting and finding patients who were subjected to emergent CABG following unsuccessful primary PCI.

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Conflicts of interest

There are no conflicts of interest.

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