Head to Head Comparison of Two Point-of-care Platelet Function Tests Used for Assessment of On-clopidogrel Platelet Reactivity in Chinese Acute Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Background: Platelet function tests are widely used in clinical practice to guide personalized antiplatelet therapy. In China, the thromboelastography (TEG) test has been well accepted in clinics, whereas VerifyNow, mainly used for scientific research, has not been used in routine clinical practice. The aim of the current study was to compare these two point-of-care platelet function tests and to analyze the consistency between the two tests for evaluating on-clopidogrel platelet reactivity in Chinese acute myocardial infarction patients undergoing percutaneous coronary intervention (PCI).

Methods: A total of 184 patients admitted to Fuwai Hospital between August 2014 and May 2015 were enrolled in the study. On-clopidogrel platelet reactivity was assessed 3 days after PCI by TEG and VerifyNow using adenosine diphosphate as an agonist. Based on the previous reports, an inhibition of platelet aggregation (IPA) <30% for TEG or a P2Y12 reaction unit (PRU) >230 for VerifyNow was defined as high on-clopidogrel platelet reactivity (HPR). An IPA >70% or a PRU <178 was defined as low on-clopidogrel platelet reactivity (LPR). Correlation and agreement between the two methods were analyzed using the Spearman correlation coefficient (r) and kappa value (κ), respectively.

Results: Our results showed that VerifyNow and TEG had a moderate but significant correlation in evaluating platelet reactivity ($r = -0.511$). A significant although poor agreement ($\kappa = 0.225$) in identifying HPR and a significantly moderate agreement in identifying LPR ($\kappa = 0.412$) were observed between TEG and VerifyNow. By using TEG as the reference for comparison, the cutoff values of VerifyNow for the Chinese patients in this study were identified as PRU >205 for HPR and PRU <169 for LPR.

Conclusions: By comparing VerifyNow to TEG which has been widely used in clinics, VerifyNow could be an attractive alternative to TEG for monitoring on-clopidogrel platelet reactivity in Chinese patients.

Key words: Blood Platelets; Clopidogrel; Thromboelastography; VerifyNow

INTRODUCTION

Antiplatelet therapy is the cornerstone treatment for patients with acute coronary syndrome or those undergoing percutaneous coronary intervention (PCI).[1] However, considerable interindividual variability in platelet reactivity has been observed during clopidogrel therapy: patients with a low response to clopidogrel tend to have high on-clopidogrel platelet reactivity (HPR) and ischemic adverse events,[2,3] whereas patients exhibiting a high response to clopidogrel

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typically have low on-clopidogrel platelet reactivity (LPR) and adverse bleeding events.[4] Thus, for patients at high risk of adverse events (e.g., history of stent thrombosis, suspicion of drug resistance, and high bleeding risk), platelet function tests are administered in clinical practice[1,5] to help guide personalized antiplatelet therapy.

In China, a point-of-care platelet function test based on thromboelastography (TEG) has been widely accepted in clinical practice; however, appropriately trained technicians and a laboratory facility are required. VerifyNow is a new and speedy point-of-care platelet function test which is more user-friendly than TEG.[6,7] However, in China, VerifyNow has been mainly used for scientific research and not for routine clinical practice because the test is relatively expensive and is not included in the China medical insurance system. Thus, the aim of the present study was to conduct a head-to-head comparison between TEG and VerifyNow and to analyze the consistency between the two tests in evaluating on-clopidogrel platelet reactivity in Chinese patients with acute myocardial infarction (AMI) and providing information on the utility of the VerifyNow test for clinical application in China.

METHODS

Study population

Patients admitted to the coronary care unit of Fuwai Hospital between August 2014 and May 2015 were enrolled in the study. The decision to use PCI was based on coronary angiography results, and all interventions were conducted according to the appropriate guidelines.[5,8] All patients received a 300 mg loading dose of aspirin and 300 mg of clopidogrel orally before PCI, followed by 100 mg of aspirin and 75 mg of clopidogrel daily. The inclusion criteria for patient enrollment were the occurrence of AMI followed by primary PCI, using TEG and VerifyNow for platelet function test. The exclusion criteria were a platelet count <100,000/mm³ or >500,000/mm³, a hemoglobin level <100 g/L, hemodynamic instability, active bleeding, use of intensified antiplatelet agents other than standard dual antiplatelet therapy, and contraindication to antiplatelet therapy. The study was approved by the Fuwai Hospital Institutional Ethical Review Board, and all patients were provided with written informed consent for participation. The study conformed to the principles outlined in the *Declaration of Helsinki*.

Blood sampling

Blood samples were collected 3 days after PCI by peripheral venipuncture. For samples used for the VerifyNow test, 2 ml Greiner Bio-One Vacuette tubes (Greiner Bio-One Vacuette North America Inc., Monroe, NC, USA) were partially filled with 3.2% sodium citrate and the tubes were filled with blood to the tube black line and gently inverted five times to ensure complete mixing of the contents. For samples used for the TEG test, blood was collected into two Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ, USA), one filled with 3.2% trisodium citrate anticoagulation and the other with lithium heparin anticoagulation. The Vacutainer tubes were filled to capacity and inverted three to five times to ensure complete mixing of the anticoagulant. All assays were performed within 4 h of blood sampling.

Thromboelastography

TEG (Haemonetics, Braintree, MA, USA) consisted of the TEG Hemostasis Analyzer and automated analytical software, and all tests were performed according to the manufacturer's instructions (www.haemonetics.com). Data were recorded as inhibition of platelet aggregation (IPA): $100–100 \times ([MA_{ADP} − MA_{FIBRIN}]/[MA_{THROMBIN} − MA_{FIBRIN}])$, where MA_{ADP} is the adenosine diphosphate (ADP)-induced clot strength (measurement of clopidogrel effect), MA_{FIBRIN} is the fibrin induced clot strength (measurement of fibrin contribution), and $MA_{THROMBIN}$ is the thrombin-induced clot strength (maximum clot strength). IPA <30% was defined as HPR[9] and IPA >70% was defined as LPR.[10] The cutoff values of IPA used were based on the previous studies which showed that IPA <30% was associated with ischemic events, whereas IPA >70% was associated with increasing requirement for blood transfusion.

VerifyNow

VerifyNow (Accumetrics, San Diego, CA, USA) is a whole-blood assay based on light transmission measurement. A P2Y12-specific cartridge was used to assess platelet function caused by clopidogrel. Data are expressed as P2Y12 reaction unit (PRU). Tests were performed according to the manufacturer's recommendations (www.accumetrics.com). Based on previous studies, PRU >230 was defined as HPR,[11] and <178 was defined as LPR.[12]

Statistical analysis

Sample size was calculated (software: PASS 11 [NCSS, Kaysville, UT, USA]) based on the statistical power ($[1−β] = 0.9$, $a = 0.05$) and the assumption that the correlation (r) between TEG and VerifyNow was $− 0.3$, which resulted in a required sample size of $n = 112$. Continuous variables were presented as the mean ± standard deviation (SD) for normally distributed values. Otherwise, data are presented as the median (interquartile range [IQR]). Categorical variables were reported as counts (percentages) and were compared using the Chi-square test. Nonparametric Spearman correlation coefficient (r) was adopted to evaluate the relationship between TEG and VerifyNow. Agreement between the two tests was determined by the kappa statistic (κ). Receiver operating characteristic (ROC) curve analyses were used to determine the cutoff values of VerifyNow using TEG as a reference. All statistical analyses were performed using the SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and a two-tailed $P < 0.05$ was considered to be statistically significant.

RESULTS

Study population

A total of 184 AMI patients who underwent primary PCI and dual antiplatelet treatment with aspirin and clopidogrel

were enrolled in the study. Among them, 165 (89.67%) had ST-segment elevation myocardial infarction and 19 (10.33%) had a non-ST-segment elevation myocardial infarction. The mean age was 60.9 ± 11.3 years, and 147 (79.89%) of the patients were male. The median IPA was 68.50% (IQR: 41.60–90.05%), and the median PRU was 185.00 (IQR: 120.25–233.75). The clinical and laboratory characteristics of the patients are listed in Table 1.

Correlation between thromboelastography and VerifyNow

Our study found a moderate negative correlation ($r = -0.511$, $P < 0.001$) between TEG and VerifyNow in evaluating platelet reactivity. The result is shown in Figure 1.

Table 1: Clinical and laboratory characteristics of patients enrolled ($n = 184$)

Patients characteristics	Values
Age (years)	60.9 ± 11.3
Male	147 (79.89)
BMI (kg/m²)	25.88 ± 3.35
Risk factor	
Current smoking	60 (32.61)
Current alcohol drinking	48 (26.09)
Diabetes mellitus	59 (32.07)
Hypertension	100 (54.35)
Hyperlipemia	126 (68.48)
Type of AMI	
STEMI	165 (89.67)
NSTEMI	19 (10.33)
Platelet function test	
TEG (IPA %)	68.50 (41.60–90.05)
VerifyNow (PRU)	185.00 (120.25–233.75)
Laboratory measurements	
Platelet (×10⁹/L)	205.00 ± 54.48
Hemoglobin (g/L)	142.98 ± 18.11
ALT (U/L)	42 (27–63)
AST (U/L)	122.50 (50.00–249.00)
Serum creatinine (μmol/L)	77.48 (69.24–89.83)
BUN (mmol/L)	5.86 (4.82–7.09)
Glucose (mmol/L)	7.16 (5.77–9.77)
LDL (mmol/L)	2.84 ± 0.98
HDL (mmol/L)	1.01 ± 0.29
LVEF (%)	55.00 (47.00–59.25)
Concomitant medications	
ACEI or ARB	114 (61.96)
Beta-blocker	160 (86.96)
Nitrates	181 (98.37)
Statin	175 (95.11)
PPI	168 (91.30)

The data was presented as *n* (%), median (IQR), or mean ± SD. SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; AMI: Acute myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; TEG: Thromboelastography; IPA: Inhibition of platelet aggregation; PRU: P2Y12 reaction unit; ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood urea nitrogen; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LVEF: Left ventricular ejection fraction; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; PPI: Proton pump inhibitor.

Agreement between thromboelastography and VerifyNow in identifying high on-clopidogrel platelet reactivity

IPA <30% or PRU >230 was defined as HPR. Based on the cutoff values, 29 patients were identified as HPR by the TEG test, whereas 50 patients were identified as HPR by the VerifyNow test (29 [15.76%] vs. 50 [27.17%], $\chi^2 = 7.108$, $P = 0.008$). In relation to the presence or absence of HPR, out of 184 patients, 135 (73.37%) were concordant, with 15 being HPR and 120 without HPR, whereas among 49 (26.63%) discordant results, 14 samples were found to be HPR by TEG alone and 35 by VerifyNow alone. A significant although weak agreement between TEG and VerifyNow was observed ($\kappa = 0.225$, $P < 0.001$). Results are shown in Table 2.

Agreement between thromboelastography and VerifyNow in identifying low on-clopidogrel platelet reactivity

IPA >70% or PRU <178 was defined as LPR. Based on the cutoff values, TEG and VerifyNow identified 90 and 84 patients as LPR (90 [48.91%] vs. 84 [45.65%], $\chi^2 = 0.393$, $P = 0.531$), respectively. Among 130 samples (70.65%) showing concordant results, 60 samples were associated with LPR and 70 without LPR. Among 54 (29.35%) discordant results, 30 were found to be LPR by TEG alone and 24 by VerifyNow alone. A significant moderate agreement was observed between the two tests ($\kappa = 0.412$, $P < 0.001$). Results are shown in Table 3.

Cutoff values of VerifyNow in identifying high on-clopidogrel platelet reactivity and low on-clopidogrel platelet reactivity

Using TEG as the reference method with the cutoff values shown above, ROC curve analysis revealed that the cutoff value in identifying HPR by Verifynow was PRU >205, and the area under the curve (AUC) was 0.784 (95% confidence interval [*CI*]: 0.703–0.865, $P < 0.001$) with a sensitivity of 82.80% and a specificity of 62.60% [Figure 2]. For LPR,

Table 2: Agreement between TEG and VerifyNow in identifying HPR

VerifyNow	TEG		κ
	HPR ($n = 29$)	No HPR ($n = 155$)	
HPR ($n = 50$)	15	35	0.225
No HPR ($n = 134$)	14	120	

TEG: Thromboelastography; HPR: High on-clopidogrel platelet reactivity.

Table 3: Agreement between TEG and VerifyNow in identifying LPR

VerifyNow	TEG		κ
	LPR ($n = 90$)	No LPR ($n = 94$)	
LPR ($n = 84$)	60	24	0.412
No LPR ($n = 100$)	30	70	

TEG: Thromboelastography; LPR: Low on-clopidogrel platelet reactivity.

the cutoff value was PRU <169 with an AUC of 0.768 (95% CI: 0.700–0.836, P < 0.001), a sensitivity of 80.90% and a specificity of 63.30% [Figure 3].

DISCUSSION

VerifyNow is a new point-of-care platelet function test which holds great potential for use in clinical practice. VerifyNow has many advantages over TEG. First, it is a faster test compared to TEG. Second, it is user-friendly and does not need a laboratory facility. Third, the required blood volume is less than that required with TEG.[6,7] However, whether VerifyNow can be used as an alternative test to TEG in clinical practice for evaluating HPR and LPR remains to be seen. The current study analyzed the consistency and agreement between TEG and VerifyNow in Chinese coronary heart disease patients and showed the cutoff values of VerifyNow suitable for Chinese patients in predicting HPR and LPR, thus providing evidence of the utility of VerifyNow in guiding personalized antiplatelet therapy in China.

In the present study, we showed that TEG and VerifyNow had a moderate but significant correlation in evaluating platelet reactivity. Further statistical analysis revealed a moderate agreement in identifying LPR, but a poor agreement in identifying HPR between the two tests. So far, only a few studies with small sample sizes have been conducted to compare TEG and VerifyNow for evaluating platelet function in patients on-clopidogrel therapy. Madsen et al.[9] reported that TEG and VerifyNow had a poor correlation in evaluating on-clopidogrel platelet reactivity ($r = 0.11$), and there was no agreement in identifying HPR in Canadian patients ($n = 33$) after PCI. Lv et al.[11] also showed that TEG and VerifyNow had a poor correlation ($r = -0.0139$) and agreement in identifying HPR ($\kappa = -0.0349$) in acute ischemic stroke patients ($n = 58$) treated with clopidogrel. The reasons for the inconsistency might be due to differences between the ethnic groups of the study populations and clinical factors. For example, in the Madsen et al.[9] study, for Canadian PCI patients, the cutoff value for HPR using VerifyNow was PRU >264, whereas Lv et al.[11] focused on acute ischemic stroke patients.

The TEG test has been widely used in China, and its utility in evaluating platelet function is well accepted by many clinical researchers. For example, Kwak et al.[10] reported that an IPA response to clopidogrel of <70% measured by TEG could be used as a value for the safety assessment of patients who undergo off-pump coronary artery bypass graft surgery without increased risk of transfusion requirement. Bliden et al.[13] pointed out that an IPA of <30% provided a positive predictive value of 73% and a negative predictive value of 91% for combined ischemic outcome. By using TEG as the reference, we determined the cutoff values of VerifyNow for our study subjects in evaluating on-clopidogrel platelet reactivity. Using ROC curve analysis, we showed that PRU >205 for HPR and PRU <169 for LPR were optimal. Similar to our study, a consensus[14] on the definition of on-treatment platelet
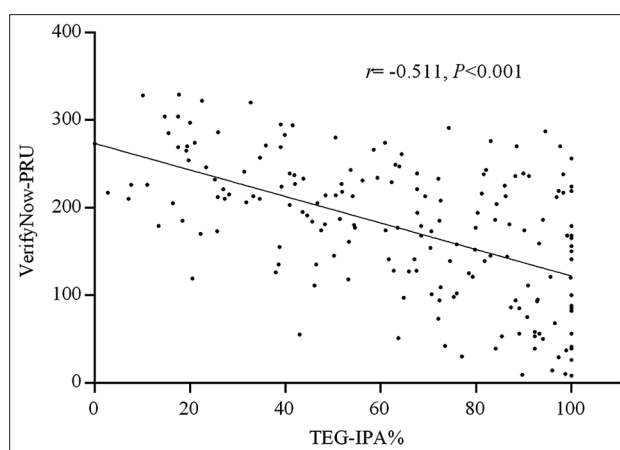

Figure 1: Linear regression model representing the correlation between TEG and VerifyNow ($n = 184$). TEG: Thromboelastography; IPA: Inhibition of platelet aggregation; PRU: P2Y12 reaction unit.
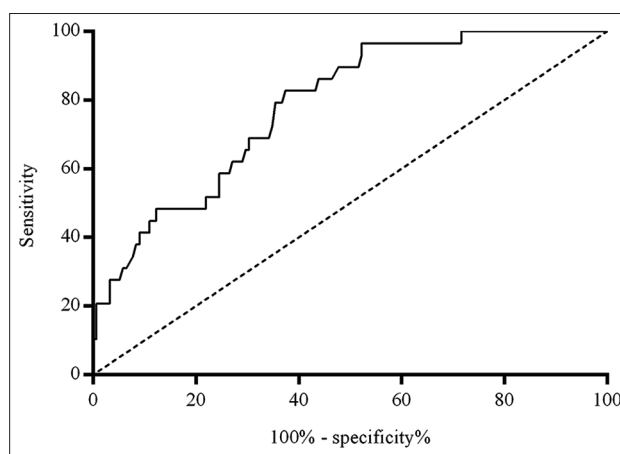

Figure 2: ROC curve for VerifyNow with HPR ($n = 184$). AUC: 0.784 (95% CI: 0.703–0.865, P < 0.001); cutoff value: PRU >205. HPR: High on-clopidogrel platelet reactivity; ROC: Receiver operating characteristic; AUC: Area under curve; CI: Confidence interval; PRU: P2Y12 reaction unit.

Figure 3: ROC curve for VerifyNow with LPR ($n = 184$). AUC: 0.768 (95% CI: 0.700–0.836, P < 0.001); cutoff value: PRU <169. LPR: Low on-clopidogrel platelet reactivity; ROC: Receiver operating characteristic; AUC: Area under curve; CI: Confidence interval; PRU: P2Y12 reaction unit.
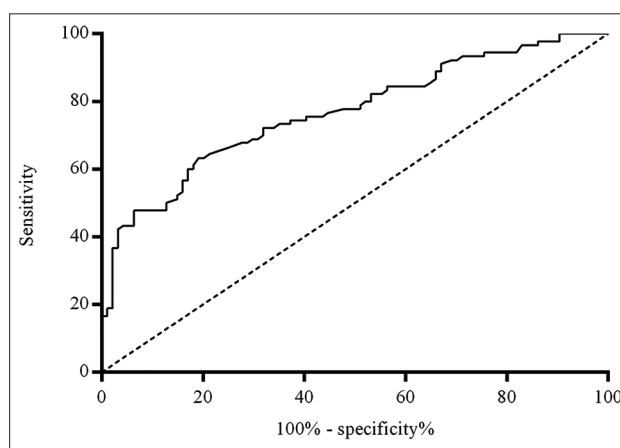
reactivity to ADP indicated that PRU >208 could be used for predicting ischemic events. Nishi *et al.*[15] showed that PRU ≤ 175 could discriminate between patients with and without hemorrhagic complications within 1 week following neurointervention (AUC 0.63). Multivariate analysis identified low platelet reactivity (PRU ≤175) as an independent predictor for hemorrhagic complications. Patti *et al.*[16] indicated that a pre-PCI PRU value of <189 was the optimal cutoff value to predict 30-day incidence of major bleeding complications after PCI. Mangiacapra *et al.*[12] showed that PRU ≥239 and PRU ≤178 using VerifyNow were the optimal cutoff values to predict ischemic events and bleeding events at 30-day follow-up after elective PCI, respectively. Using multivariate analysis, normal platelet reactivity (PRU 179–238) was an independent predictor of reduced risk of 30-day net adverse clinical events (odds ratio: 0.47, 95% *CI:* 0.27–0.81). The discrepancy in cutoff values among different studies may be influenced by differences between the ethnic groups of the study populations, clinical factors, laboratory conditions, and environmental factors.[6,7,14]

The results of our study showed that a significantly lower proportion of HPR was identified by TEG than VerifyNow (29 [15.76%] vs. 50 [27.17%], χ^2 = 7.108, P = 0.008), whereas there was no difference in identifying LPR (90 [48.91%] vs. 84 [45.65%], χ^2 = 0.393, P = 0.531) between the two tests. The results were similar to Lv *et al.*[11] who reported that VerifyNow showed a larger proportion of low responses to clopidogrel (namely HPR) than TEG (17 [29.31%] vs. 9 [15.52%], P = 0.075). The reasons underlying the disagreement may be due to the different methodologies of the two point-of-care systems.[6,17] First, TEG measures the physical properties of a forming clot using an oscillating cup that holds a sample of whole-blood and the strength of fibrin-platelet bonding as the clot is reflected by the magnitude of pin motion. In contrast, VerifyNow is a turbidimetry-based optical detection device where platelet aggregation is reflected by changes in light transmission. Furthermore, TEG only uses ADP as the sole agonist to evaluate the antiplatelet effect of clopidogrel mediated by the P2Y12 receptor, whereas VerifyNow uses the combination of ADP and prostaglandin E1 (PGE1). PGE1 is used as a suppressor of intracellular free calcium to reduce the nonspecific contribution of ADP binding to P2Y1 receptors.

There are several limitations of the current study. First, platelet reactivity was only evaluated by TEG and VerifyNow and not by other available platelet function tests for monitoring clopidogrel responsiveness. Second, although the present study contained a sufficient number of patients for platelet reactivity analysis, it did not allow for an evaluation of the consistency of TEG and VerifyNow in predicting clinical adverse events. Third, the patients investigated were from a single center which may not be representative of the population at large. Multicenter clinical studies using a larger sample size with multiple platelet function tests focusing on both platelet reactivity and clinical outcome are required.

In conclusion, TEG and VerifyNow have a moderate correlation in evaluating platelet reactivity. By comparing VerifyNow to TEG which has been widely used in the clinic, VerifyNow may be an attractive alternative platelet function test for monitoring the responsiveness to clopidogrel.

Conflicts of interest

The equipment of VerifyNow (Accumetrics, San Diego, CA, USA) was provided by Beijing Huikang Jianyi Medical Instrument Company.

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