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Effects of Baseline Platelet Reactivity on Thrombolysis in Myocardial Infarction Flow and Ischemic Time in Fibrinolysis-treated ST Elevation Myocardial Infarction Patients

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Abstract

Objective: Thrombolysis in Myocardial Infarction (TIMI) flow in ST-Elevation Myocardial Infarction (STEMI) is a prognostic predictor that is directly influenced by duration of culprit artery occlusion; ischemic time. It is unknown whether platelet reactivity measured by P2Y12 reaction unit (PRU) is affected by ischemic time or predictive of TIMI flow. Our objectives were to examine the effect of baseline PRU on TIMI flow and on ischemic time.

Methods: Between May 2014 and August 2016, the study included 144 patients between four sites undergoing percutaneous coronary intervention (PCI) within 24 hours of tenecteplase, aspirin and clopidogrel for STEMI. The VerifyNow® Assay measured baseline PRU prior to angiography. Ischemic time was defined as the duration between index symptom onset and tenecteplase administration. Kruskal-Wallis H test was conducted because the assumption of normality was violated to test differences in baseline PRU based on TIMI flow and based on time intervals prior to PCI.

Results: Median ischemic time was 172 minutes (IQR 115-285). Baseline PRU did not differ based on TIMI flow grade {$\chi^2(3)=3.00$, $p=0.39$}. Baseline PRU was not affected based on ischemic time {$\chi^2(3)=1.50$, $p=0.68$)}.

Conclusion: Platelet reactivity measured by PRU is not associated with TIMI flow or ischemic time. Future research is warranted to examine the association between baseline PRU and prognosis.

Abstract Key Points: Effect of baseline platelet reactivity measured by PRU on TIMI flow and on ischemic time was examined.

Between May 2014 and August 2016, 144 patients undergoing percutaneous coronary intervention within 24 hours of fibrinolysis for STEMI were included

In STEMI patients treated with fibrinolysis, baseline PRU at the time of angiography does not correlate with TIMI flow or ischemic time.

Keywords: Platelet reactivity; Fibrinolysis; Percutaneous coronary intervention; ST elevation myocardial infarction; Thrombolysis in Myocardial Infarction flow; Ischemic time; Clopidogrel

Introduction

Fibrinolytic agents are used to treat over one fifth of patients presenting with ST elevation myocardial infarction (STEMI) worldwide [1]. Although acute and long-term mortality in STEMI patients treated with fibrinolysis has declined, there continues to be an increased risk for both thrombotic and bleeding complications [2]. Pathways for improved outcomes in this patient population include optimizing antiplatelet agents, reducing ischemic time, a pharmaco-invasive approach, and peri-procedural anticoagulation [3].

Ischemia exerts a time-dependent effect on myocardial necrosis that is associated with impaired epicardial flow, inadequate myocardial perfusion and increasing infarct size [4]. Prolonged ischemic time is

represented by duration of culprit artery occlusion. It is demonstrated angiographically by lack of Thrombolysis in Myocardial Infarction (TIMI) 3 flow [5], and is independently associated with Major Adverse Cardiovascular Events (MACE) and higher mortality [6]. Fibrinolysis-induced paradoxical platelet hyperreactivity [2,4,7] is an independent predictor of MACE following acute coronary syndrome and percutaneous coronary intervention (PCI). It is not known whether platelet reactivity and TIMI flow are related or whether they are independent variables affecting final outcomes in the fibrinolytic-treated STEMI patient.

Ischemic time, TIMI flow and platelet hyperreactivity are all independently associated with MACE. Thus, we sought to determine if these variables are related. In this study, we examined the relationship between ischemic time, platelet reactivity and TIMI flow in the fibrinolytic-treated STEMI patient following aspirin and clopidogrel loading. We hypothesized that shorter ischemic time will be associated with lower baseline platelet reactivity, which may be associated with improved TIMI flow.

Methods

The methods of the main study have been reported elsewhere [8]. In brief, this was a prospective blinded end points study design performed at four Canadian centers coordinated by the Prairie Vascular Research Network.

Patients were eligible for enrollment if they were above the age of 18 and provided written informed consent. Patients were included in the study population if they presented within 12 hours after symptom onset, had acute STEMI on their qualifying electrocardiogram (ECG) (≥ 1 mV in ≥ 2 contiguous leads), and, due to anticipated delay to primary PCI, received tenecteplase (TNKase®, Genentech, South San Francisco, CA) for reperfusion. Consistent with current guidelines, all patients received both aspirin (162 to 325 mg loading dose) and clopidogrel (300 mg loading dose for patients ≤ 75 years of age, 75 mg dose for patients >75 years of age) as adjunctive therapy at the time of fibrinolysis [3]. All patients received a pharmaco-invasive strategy with an angiogram at a PCI-capable hospital within 24 hours of fibrinolysis. Major exclusion criteria were any contraindications for the use of P2Y12 receptor inhibitor, all patients who received GP IIb/IIIa receptor antagonist, a need for oral anticoagulation, atrial fibrillation, an increased risk of bradycardia, PCI or coronary artery bypass surgery during the previous 3 months, active bleeding or high risk of bleeding based on clinical assessment, known clinically important thrombocytopenia or anemia, concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer, and women of child-bearing age.

At angiography, baseline platelet reactivity was measured with the VerifyNow® P2Y12 assay once anatomy suitable for PCI was identified (Figure 1). Members of the clinical staff, who managed patient care, including the interventional cardiologists, were blinded to the results of the VerifyNow® P2Y12 assay. Staff performing platelet reactivity assessments were not involved in patient care to ensure that the results remained blinded. The study was approved by local ethics board of all the participating institutions and complied with the Declaration of Helsinki and with International Conference on Harmonization/Good Clinical Practice guidelines.

Primary endpoint and pharmacodynamic assessment

Baseline platelet reactivity was measured by P2Y12 reaction units (PRU) according to the VerifyNow® P2Y12 assay (Accriva, San Diego, California) after fibrinolytic administration, as previously described [9]. Level III board certified interventional cardiologists documented preprocedural TIMI flow based on visual assessment of the rate of contrast opacification of the infarct artery [10]. Ischemic time was measured as the duration between index symptom onset and tenecteplase administration.

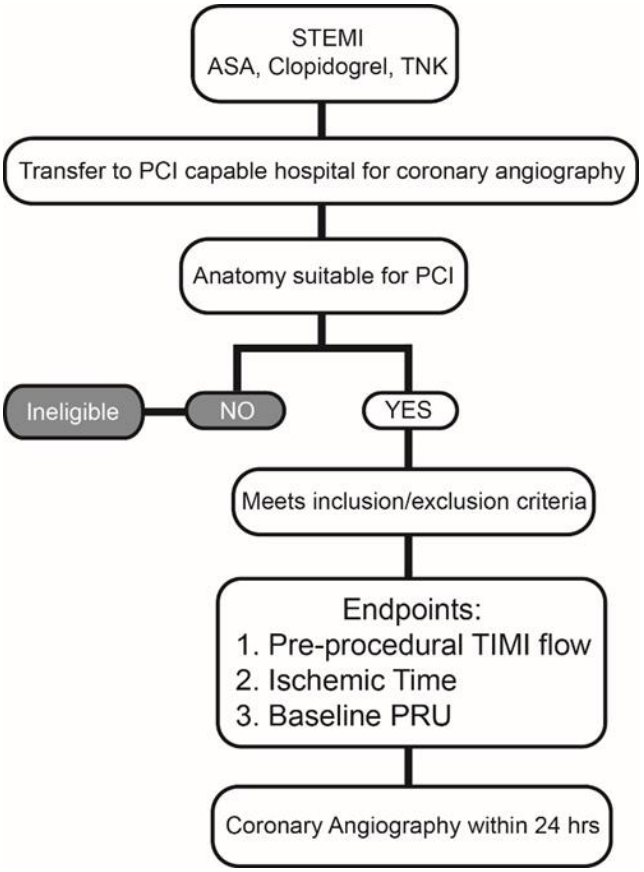

Figure 1: Study Flow Diagram. Abbreviations: ASA: Aspirin; hrs: hours; PCI: percutaneous coronary intervention; PRU: P2Y12 reaction units; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction; TNK: tenecteplase.

Statistical analysis

The purpose of this study was to evaluate the relation of PRU to ischemic time and TIMI flow. Statistical analyses were performed using SPSS software (version 23.0, SPSS Inc. Chicago). Sample size was calculated according to the primary endpoint of achieving therapeutic platelet inhibition, defined as PRU ≤ 208 [11], in the main study [8]. Based on data available for platelet inhibition determined by the VerifyNow® P2Y12 assay in patients with coronary artery disease, high platelet reactivity is typically observed in more than 50% of patients treated with a 300 mg loading dose of clopidogrel [9], and less than 30% of patients treated with a 180 mg loading dose of ticagrelor [11]. After accounting for inability to obtain follow-up VerifyNow® assay

measurements of 20% with 80% power and a 2-tailed α value of 0.05, 144 patients were estimated to detect a 25% increase in achieving the primary endpoint. Continuous variables were expressed as mean ± standard deviation (SD) and median (25^{th} and 75^{th} percentile) and categorical variables as frequencies (%). Because the assumption of normality was violated, a Kruskal-Wallis H test was conducted to test differences in baseline PRU based on grade of TIMI flow and based on time intervals prior to PCI. A probability level of <0.05 was adopted to determine statistical significance.

Results

Among the 212 patients screened at four sites, 144 patients were included. A significant proportion of patients were excluded due to our exclusion criteria, missing information, or erroneous data. Baseline characteristics, angiographic findings and procedural characteristics of the study population are as outlined (Table 1).

Characteristics	Patients (N = 144)
Demographic	
Age, mean (SD)	63.0 ± 12.1
Male, n (%)	107 (74.3)
White, n (%)	137 (95.1)
Medical History, n (%)	
Hyperlipidemia	69 (47.9)
Hypertension	74 (51.4)
Diabetes mellitus	25 (17.4)
Smoker	93 (64.6)
Prior MI	15 (10.4)
Prior PCI	10 (6.9)
Prior CABG	5 (3.5)
Baseline Platelet reactivity (PRU)	258.6 ± 54.5
Median time delay, min (interquartile range)	
Symptom onset to first ECG	137 (70-229)
ECG to TNK administration	28 (16-51)
TNK to cath lab arrival	293 (192-736)
Cath lab arrival to randomization	27 (19-41)
Time from randomization to artery open	10 (6-16)
Time from TNK to baseline PRU	337 (228-807)
Time from TNK to first balloon inflation	345 (234-832)
Successful PCI	141 (97.9)
In-Hospital Medications, n (%)	
ACE Inhibitor	73 (50.7)
Statin	103 (71.5)
Proton pump inhibitor	31 (21.5)
Beta-blocker	82 (56.9)
Nitrate	28 (19.4)
ASA	144 (100.0)

Table 1: Patients' Baseline, Peri-procedural and Procedural Characteristics.

Median ischemic time was 172 minutes (IQR 115-285). The median time from fibrinolysis to first balloon inflation was 345 (IQR 234-832) minutes. A consensus definition for platelet reactivity denoted by PRU ≥ 208 was used as a threshold associated with ischemic event occurrences [11]. Baseline PRU of the cohort was 258.6 ± 54.5. Thus, only 19.6% of patients demonstrated therapeutic platelet inhibition (8). At baseline, 18.8%, 4.9%, 4.2% and 72.2% of participants presented with TIMI flow grade 0, 1, 2 and 3 respectively (Figure 2).

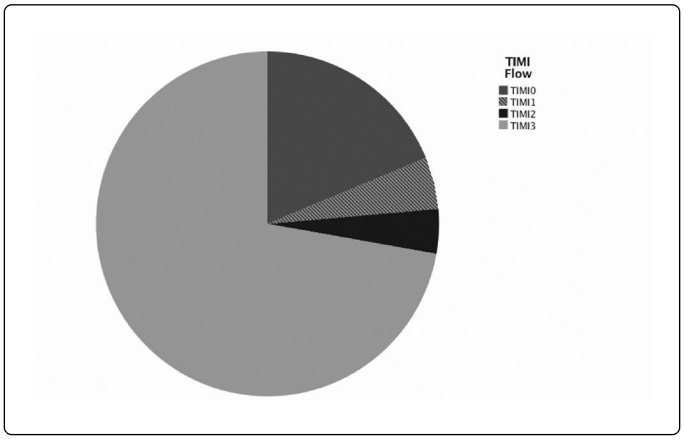

Figure 2: Baseline TIMI flow distribution. Distribution of Thrombolysis in Myocardial Infarction (TIMI) flow across study participants.

Platelet Reactivity and Ischemic Time

No statistically significant differences were noted for baseline PRU based on ischemic time (symptom to TNK time interval; Figure 3 {($\chi^2(3)=1.50$, p=0.68)}.

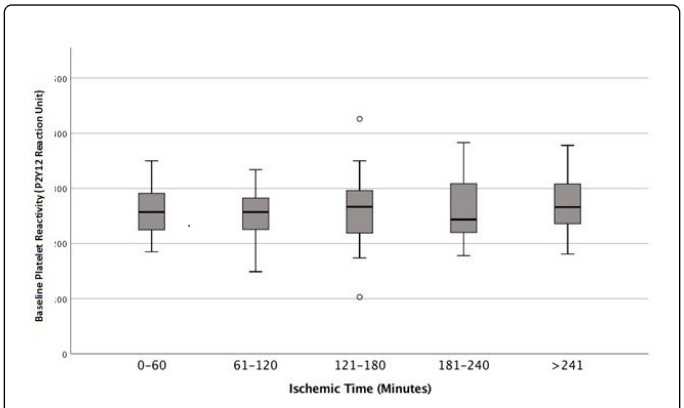

Figure 3: Baseline platelet reactivity and ischemic time. Comparison of median baseline platelet reactivity measured in P2Y12 Reaction Units (PRU) according to increasing ischemic time measured in minutes (min). The horizontal line within the box indicates the median, boundaries of the box indicate the 25th and 75th percentile, and the whiskers indicate the highest and lowest values of the results. Outliers are shown as a separately plotted point. Not significant.

Platelet reactivity and TIMI flow

No statistically significant differences were noted for baseline PRU based on grade of TIMI flow ($\chi^2(3)=3.00$, p=0.39) (Figure 4).

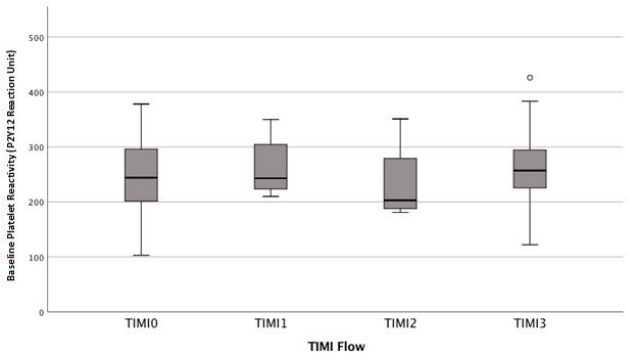

Figure 4: Baseline platelet reactivity and TIMI flow. Comparison of median baseline platelet reactivity measured in P2Y12 reaction units (PRU) with pre-procedural Thrombolysis In Myocardial Infarction (TIMI) flow. The horizontal line within the box indicates the median, boundaries of the box indicate the 25th and 75th percentile, and the whiskers indicate the highest and lowest values of the results. Outliers are shown as a separately plotted point. Not significant.

Discussion

In this study, we sought to determine whether a relationship exists between platelet reactivity and TIMI flow in fibrinolysis-treated STEMI patients undergoing a pharmaco-invasive approach. The results of our study show that baseline PRU did not correlate with TIMI flow or ischemic time. There are several potential explanations for our findings, including – fibrinolysis induced platelet hyperreactivity, heterogeneity in clopidogrel response, and prognostic variability of TIMI flow.

Fibrinolytic therapy in STEMI increases platelet hyperreactivity through P2Y12 ADP receptor inhibition; an effect corroborated by the main study [2]. We previously demonstrated that baseline PRU after fibrinolysis was above threshold: 258.6 ± 54.5 (Table 1). Further, there was no statistically significant difference in baseline PRU even with prolonged ischemic time (Figure 3). In contrast, baseline PRU was lower in a study by Alexopoulos et al. with STEMI patients who did not receive fibrinolytic therapy: 234.0 ± 61.6 [12]. Together, these findings suggested that fibrinolysis induced platelet hyperreactivity propagated a pro-thrombotic environment that overshadowed an effect from ischemic time on PRU [2].

Multiple recent studies highlight the range in clopidogrel pharmacodynamics due to inadequate P2Y12 ADP receptor inhibition that is accompanied by increased MACE [13,14]. This variability is mediated by a loss-of-function CYP2C19 allele conferring genetic resistance to clopidogrel that occurs in 25% to 30% of the population [13]. Fibrinolysis enhanced pro-thrombotic state may increase the variability of clopidogrel responsiveness [2]. Our main study revealed that 80% of patients still had inadequate platelet inhibition despite adjunctive antiplatelet therapy and fibrinolytic therapy [8]. Since our patients were pre-treated with clopidogrel, the expected proportion of

clopidogrel non-responders in our cohort potentially created enough variability to mask a relationship between platelet hyperreactivity and TIMI flow.

Reperfusion inhibits ischemic progression and limits infarct size [15,16]. Although fibrinolysis aims to achieve reperfusion, TIMI flow is a surrogate of myocardial recovery and survival [17]. While 72.2% of participants presented with TIMI 3 flow (Figure 2), there was no statistically significant difference in baseline PRU measured against grade of TIMI flow (Figure 4). However, the ischemic myocardium still exhibits delayed recovery of contractile function despite reperfusion [18]. Thus, even amongst patients with TIMI 3 flow, greater prognostic utility results from assessing myocardial reperfusion with myocardial blush grade or ST segment resolution as it is a strong predictor of mortality [17,19]. Myocardial blush grade should be considered with TIMI flow to define angiographic success [19].

Despite the association between MACE and platelet hyperreactivity measured with a point-of-care assay [2], PRU cannot be considered a risk factor requiring intervention [10,20]. Most patients exhibiting platelet hyperreactivity remain event-free, and no randomized controlled trial has demonstrated that PRU guided antiplatelet therapy improves outcome; thus, routine platelet function testing is not recommended [21]. On the other hand, demonstrating TIMI 2 or 3 flow [17], despite its limitations, has been associated with improved outcomes. Our demonstration of the lack of relationship between platelet hyperactivity and TIMI flow is consistent with the mentioned studies.

Limitations

There are several limitations to our study. Firstly, PRU measured with a point-of-care platelet function assay is a surrogate marker of platelet reactivity. Although PRU predicts high platelet reactivity; the prognostic value is not well defined [12]. Secondly, platelet reactivity thresholds used in pharmacodynamic studies were obtained from studies involving stable coronary artery disease. Thirdly, a single platelet function assay was used, and the results were not compared with other modalities. Residual platelet reactivity may vary depending on the assay used [11]. Given the lack of evidence in the fibrinolysis treated STEMI patient, the high platelet reactivity observed in this study should be interpreted cautiously. Next, TIMI flow was reported by interventional cardiologists in a catheterization laboratory and not assessed in a core laboratory. Further, although ischemic time was defined as onset of chest pain to tenecteplase administration, not all patients who received fibrinolysis achieved successful reperfusion. This was evidenced by the fact that up to 40% of the population still had an occluded coronary artery [8]. Additionally, given the administration of fibrinolytic therapy there was a disproportionate majority of the population who achieved TIMI 3 flow prior to angiography compared to TIMI 1 or 2. Lastly, tenecteplase was the only fibrinolytic employed in our study, which limits generalizability of our results in patients treated with other modalities.

Conclusion

In STEMI patients treated with fibrinolysis, clopidogrel and aspirin that undergo a pharmaco-invasive approach, PRU at the time of angiography does not correlate with TIMI flow or ischemic time.

Permissions

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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