Does the level of myocardial injury differ in primary angioplasty patients loaded first with clopidogrel and the ones with ticagrelor?

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Abstract

Objective: In daily clinical practice, we encounter ST segment elevation myocardial infarction (STEMI) patients loaded with clopidogrel upon admission to primary angioplasty. These patients are loaded with ticagrelor, if there is no contraindication. This study aimed to compare the level of injury between STEMI patients who were first loaded with clopidogrel and the ones first loaded with ticagrelor. Although patients were switched from clopidogrel to ticagrelor at the first hour of angioplasty, antiplatelet action may still be lower than the others.

Methods: This study included STEMI patients with angina onset of ≤3 h and who had primary angioplasty to proximal segment of one coronary artery. All patients had total thrombotic occlusion at the proximal segment. Δtroponin level (6th-hour troponin–admission troponin) was calculated to compare the level of myocardial injury.

Results: A total of 105 patients were included; 52 were loaded with ticagrelor and 53 with clopidogrel first and switched to ticagrelor. Baseline characteristics were similar in the two groups, except from type B2 lesions being more common in the ticagrelor-loaded group. Δtroponin levels were significantly higher in the clopidogrel-loaded group compared with the ticagrelor-loaded group (p=0.013). Major bleeding and in-hospital MACE rates were similar in both groups.

Conclusion: In STEMI patients, the degree of troponin rise was more prominent in clopidogrel-loaded patients, despite the switch to ticagrelor in the first hour of intervention. Clopidogrel is slow and modest, and variable platelet inhibition may continue to be a negative factor for protection from myocardial injury, even after switching to ticagrelor. *(Anatol J Cardiol 2020; 24: 107-12)*

Keywords: clopidogrel, STEMI, ticagrelor, myocardial injury

Introduction

Current guidelines on ST segment elevation myocardial infarction (STEMI) recommend treatment with novel P2Y12 inhibitors, prasugrel, or ticagrelor, if there is no contraindication (1). However, we encounter patients in routine daily practice of primary angioplasty loaded with clopidogrel, without contraindication to novel agents. This is mostly due to initial presentation to a nonpercutaneous coronary intervention (PCI)-capable center, no access to novel agents, or possible hesitation of the first-contact doctor about the safety profile of novel agents. Whatever the reason is, we prefer reloading with 180-mg ticagrelor in these STEMI patients first loaded with clopidogrel if there is no contraindication, as recommended by the recent dual antiplatelet guidelines (2). Clopidogrel is a prodrug that requires activation with a large interindividual variability in platelet response. Majority of the variation in platelet response to clopidogrel still remains unexplained. CYP2C19 polymorphisms account for only 12% of variability in clopidogrel platelet response (3). On the other hand, ticagrelor is a novel reversible rapid antiplatelet agent that does not require metabolic activation (4). In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was superior to clopidogrel in primary efficacy end points in 18.624 acute coronary syndrome patients (5).

Trials have shown high levels of platelet reactivity in clopidogrel-loaded patients at a range of 5–44% (6). Prasugrel and ticagrelor reloading after administering clopidogrel was shown to further decrease high platelet reactivity effectively (7-9). This difference gained by the novel antiplatelet agents led us to search if clopidogrel-loaded patients who were then switched to ticagrelor can gain the advantages of patients first loaded with ticagrelor. No trials have compared the possible myocardial damage difference in this frequently encountered patient group in clinics.

This study aimed to compare the level of myocardial injury between STEMI patients who were first loaded with clopidogrel and then switched to ticagrelor and the ones first loaded with

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and continued on ticagrelor. Although patients loaded with clopidogrel were switched to ticagrelor at the first hour of angioplasty, antiplatelet action may still be lower compared to those loaded with ticagrelor. Major bleeding rates and in-hospital major adverse cardiac events (MACE) were also determined in these two groups.

Methods

This nonrandomized study retrospectively enrolled 105 STEMI patients who underwent primary angioplasty from January 2016 to May 2017 and was approved by the Ethical Committee of our institution. Patients between 18 and 80 years old who were admitted to the catheterization laboratory with STEMI diagnosis within the first 3 h of symptom onset were evaluated for the study. STEMI diagnosis was made based on the recent universal definition of MI at that period, with at least 20 min of chest pain and ST elevation in two contiguous ECG leads of at least 1 mm (10). Only patients with total thrombotic occlusion at the proximal segment of one coronary artery were included in the study. Patients with the following conditions were excluded: left bundle branch block upon admission, paced rhythm, coronary artery bypass grafting, complete atrioventricular block, cardiogenic shock, history or sign of a previous MI, loaded with prasugrel, loaded with P2Y12 inhibitors at an outside clinic prior to being transferred to our clinic, need of cardiopulmonary resuscitation or defibrillation, renal failure (defined as glomerular filtration rate <60 mL/min), intracranial bleeding history or high bleeding risk, having more than one vessel intervention, left main coronary artery intervention, bifurcation lesions, multistent intervention, TIMI 0–1 flow after intervention, intervention to type C ACC/AHA lesion grade, and need of tirofiban and anticoagulant treatment.

All patients were loaded with 300-mg aspirin and P2Y12 inhibitors at our emergency department; hence, the timing was accurately documented. Patients loaded with clopidogrel upon admission were reloaded with 180-mg ticagrelor within the first hour of primary angioplasty in our coronary care unit; suitability of the patient for ticagrelor was at the discretion of the attending physician. Patients loaded with ticagrelor upon admission were followed up on their medication. In both arms, 90-mg ticagrelor BID was administered 12 h after the loading dose. Intravenous unfractionated heparin was administered at the start of the invasive procedure, and activated clotting time of 250–300 s was obtained. Primary angioplasty time was noted as the time from onset of pain to the restoration of blood flow by balloon. Stent implantation procedure was performed only by experienced operators, according to standard clinical practice. All patients had proximal segment total thrombotic lesions, either type B1 or B2, according to the ACC/AHA lesion classification.

After catheterization, patients were admitted to the coronary intensive care unit for follow-up. Blood was drawn routinely for troponin I upon admission to the emergency department and at

intervals of 6 h after admission. Admission and 6th-hour troponin I levels were analyzed, and absolute Δtroponin level (6th-hour troponin–admission troponin) was calculated to compare the level of myocardial cell loss between the two groups. Cardiac troponin I was measured using AccuTnI assay and UniCel DxI device (Beckman Coulter, CA, USA). The detection limit of the assay was 0.01 ng/mL, and the quantitation limit was 0.04 ng/mL with an imprecision of less than 10%.

MACE during the hospitalization period were evaluated and recorded, which was defined as in-hospital mortality, stroke, and recurrence of MI. Major bleeding events were recorded in hospital follow-up charts based on the Bleeding Academic Research Consortium (BARC), and BARC 3 or 5 bleeding events were considered major bleeding (11).

SPSS software package (version 20 for Windows, SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. The Kolmogorov–Smirnov test was used to determine the continuous data distribution normality. Discrete variables were expressed as numbers and percentages, whereas continuous variables were expressed as mean±standard deviation. Chi-squared analysis or Fisher's exact test for categorical variables and Student's t-test or the Mann–Whitney U test for continuous variables were performed to compare patients who were loaded with ticagrelor and those with clopidogrel and then shifted to ticagrelor. Longitudinal data (i.e., baseline and 6th-hour troponin levels) were analyzed by repeated measures of ANOVA to examine whether or not a group-by-time interaction effect was statistically significant. The mean difference in adjusted troponin levels between groups were also evaluated with analysis of covariance (ANCOVA) after adjustment for covariates (e.g., age and baseline troponin levels). Paired sample t-test was used to determine the difference between baseline and 6th-hour troponin levels within groups. P<0.05 was considered statistically significant.

Results

This study included 105 eligible STEMI patients; 52 patients were loaded with 180-mg ticagrelor, and 53 patients were loaded with 600-mg clopidogrel and then switched to 180-mg ticagrelor and reloaded in the first hour of angioplasty. The mean age of the patient population was 60±13 years old, and 11% of the entire population was female. Nine patients died (six due to pulmonary edema and cardiogenic shock, two due to intractable cardiac arrhythmia, and one due to sepsis after aspiration pneumonia), and two had recurrent MI during the mean 5±4 days of hospital stay; these events were considered as MACE. In-hospital MACE rates were not statistically different between the two groups. In terms of major in-hospital bleedings events, two were retroperitoneal (both in the ticagrelor-loaded group), and two were gastrointestinal in nature (one in the clopidogrel-loaded group and one in the ticagrelor-loaded group), and one patient who had massive hemoptysis was later diagnosed with pulmonary adenocarcino-

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ma (clopidogrel-loaded group). Statistical comparison in bleeding rates was not possible due to a small sample size. Table 1 presents the baseline characteristics of patients. There were significantly more complex lesions, defined as type B2 lesions, in the ticagrelor-loaded group (p=0.011). Δtroponin levels were significantly higher in the clopidogrel-loaded group compared with the ticagrelor-loaded group (53.23±34.01 vs. 37.95±27.28; p=0.013) (Fig. 1). We analyzed the difference between the groups using ANCOVA after adjustment for age. The statistical significance was still consistent after age adjustment (53.19±34.01 vs. 38.00±27.23; p=0.014). Repeated measures of ANOVA also yielded statistical significant results on the change of troponin levels in time between the groups (p=0.013).

Discussion

In this cohort of 105 patients who underwent primary percutaneous intervention for STEMI, we compared the absolute Δtroponin level (6th-hour troponin–admission troponin) between the groups according to the initially loaded drug, i.e., ticagrelor or clopidogrel. Δtroponin level, which represented myocardial injury in our study, was significantly higher in patients first loaded with clopidogrel, although they were switched and reloaded with ticagrelor in the first hour of angioplasty (p=0.013). To the best of our knowledge, this is the first study to compare the level of myocardial injury by using Δtroponin levels in patient groups initially loaded with and switched later to a novel P2Y12 inhibitor.

Table 1. Characteristics of patients first loaded with clopidogrel and then switched to ticagrelor and ticagrelor-loaded patients

	Clopidogrel loaded and then switched to ticagrelor (n=53)	Ticagrelor loaded (n=52)	*P* value
Age (years)	60.5±14.3	59.6±11.8	0.739
Women, n (%)	7 (13%)	5 (10%)	0.356
Family history of coronary artery disease, n (%)	21 (39%)	18 (35%)	0.595
Hypertension, n (%)	23 (43%)	17 (32%)	0.259
Hyperlipidemia, n (%)	29 (54%)	21 (40%)	0.141
Diabetes mellitus, n (%)	13 (24%)	11 (21%)	0.466
Current smokers, n (%)	20 (38%)	26 (50%)	0.205
Statin use, n (%)	16 (31%)	13 (26%)	0.620
Aspirin use, n (%)	10 (18%)	8 (15%)	0.899
GFR (mL/min/1.73 m^2), mean±SD	82.66±13.15	85.48±16.20	0.329
Basal troponin I (ng/mL) mean±SD	0.52±0.47	0.58±0.52	0.493
Troponin I 6th-hour, mean±SD	53.75±34.11	38.54±27.53	0.014
ΔTroponin (Trop6-Trop0) mean±SD	53.23±34.01	37.95±27.28	0.013
Primary angioplasty time* (hours), mean±SD	2.49±0.74	2.38±0.77	0.469
Door to balloon time (minutes), mean±SD	40.45±21.48	42.03±20.52	0.700
Radial vascular access, n (%)	33 (62%)	30 (58%)	0.282
Lesion site (all proximal segment)			
LAD, n (%)	12 (23%)	12 (23%)	0.958
CX, n (%)	17 (32%)	21 (40%)	0.376
RCA, n (%)	24 (45%)	19 (37%)	0.362
Lesion type			
B2 type lesion, n (%)	12 (23%)	24 (46%)	0.011
DES, n (%)	43 (81%)	43 (82%)	0.795
Stent length (mm), mean±SD	22.52±6.26	21.03±5.49	0.762
Stent diameter (mm), mean±SD	2.90±0.65	3.01±0,51	0.823
Inflation pressure (atm), mean±SD	14.26±0.96	15.34±1.41	0.765
Ejection fraction (%) in echocardiography, mean±SD	42.11±12.01	43.55±10.47	0.847
In-hospital MACE, n (%)	7 (13%)	4 (8%)	0.361

*Primary angioplasty time is the time from the onset of pain to balloon time.
GFR - glomerular filtration rate, LAD - left anterior descending artery, Cx - circumflex artery, RCA - right coronary artery, DES - drug-eluting stent, MACE - major adverse cardiac events
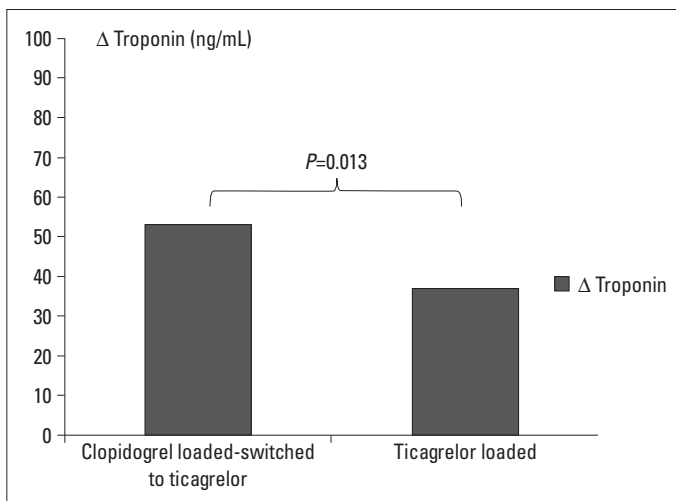
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Figure 1. Δtroponin levels (6th-hour troponin–admission troponin) were significantly higher in the clopidogrel-loaded group compared with the ticagrelor-loaded group

In daily clinical practice, in-hospital switching of antiplatelet drugs has emerged with the availability of more potent novel P2Y12 inhibitors, prasugrel and ticagrelor. In the PLATO trial, a significant portion of the patients (46%) randomized to ticagrelor received clopidogrel at first presentation, without any specific safety concerns (5). Ticagrelor is the recommended novel P2Y12 inhibitor, as class IB recommendation based on guidelines for loading in patients with acute coronary syndrome pretreated with clopidogrel and without contraindication (2). However, there are still hesitations due to safety concerns during routine application, and real-life data on switching is still scarce. Greek antiplatelet registry had investigated the prevalence, predictive factors, and short-term safety of in-hospital switching in 1794 patients with acute coronary syndrome (12). One-third of the patients were initially loaded with clopidogrel, and half of them were switched to a novel agent in the hospital. Switching was not accompanied by differences in MACE rate or bleeding events when compared with patients initially loaded with novel agents. Age of more than 75 years old emerged as the main factor against selecting a novel agent, despite the favorable data of ticagrelor at this group of patients (13).

No difference in the mean age of patient groups was observed in our trial. Our patients were loaded with P2Y12 inhibitors at our emergency department, and the drug type was chosen by the first-contact doctor. Although it is a PCI-capable hospital, doctors at the emergency department may still have safety concerns against novel agents. It may be due to unfamiliarity with the new drug, delay in guideline implementation, aim to load P2Y12 drug as fast as possible while remaining at the safe side, or lack of time or possibility to check the suitability of the patient to novel agents. In real-world practice, increasing age of patients with comorbidities, such as atrial fibrillation and chronic kidney disease, also keeps the doctors distant to first loading with novel agents. In a very recent meta-analysis of 22,500 acute coronary

syndrome patients, the use of clopidogrel as a first-line agent was still high (65%). The analysis revealed higher rate of short-term bleeding in switched patients and suggested that prescription of the most appropriate agent upon admission is of utmost importance for clinical benefit (14).

In the literature, the benefit of switching was shown on the basis of platelet reactivity. In addition, studies have shown a consistent enhancement of platelet inhibition when escalated from clopidogrel to ticagrelor, regardless of the clinical setting (15-17). Vilahur et al. (8) studied platelet activity, troponin, and infarct size progress in clopidogrel- and ticagrelor-loaded pigs. Ticagrelor reduced the infarct size to a significant extent compared with clopidogrel, and this effect was supported by troponin I assessment and histopathologic analysis. In conclusion, the authors suggested that ticagrelor exerts cardioprotective effects beyond its antiplatelet efficacy by reducing necrotic injury and edema formation via adenosine-dependent mechanisms. In a trial comparing the infarct size by cardiac magnetic resonance imaging in STEMI patients loaded with clopidogrel or ticagrelor, reduced myocardial infarct size and microvascular obstruction was demonstrated in the ticagrelor-loaded group (18). Platelet inhibition level was comparable between groups just before reperfusion; hence, the authors suggested a platelet-independent cardioprotective effect of ticagrelor. Alexopoulos et al. (9) studied platelet reactivity at 2 h of ticagrelor and clopidogrel loading, which showed lower reactivity in the ticagrelor-loaded patients. In addition, when clopidogrel-loaded patients were reloaded with ticagrelor, platelet reactivity became similar to patients first loaded with ticagrelor. Area under the curve analysis of cardiac enzymes in these two groups was shown to be similar (9). In our trial, when we consider the first contact time in the emergency department and reloading in the coronary care unit, there was approximately 2 h of delay at the ticagrelor onset of action between the two groups. We believe that this time delay should not have led to a difference in myocardial injury just because of more effective antiplatelet action or vessel patency success of ticagrelor. The two groups in our trial showed no difference at vessel patency or angiographic success rates; hence, other mechanisms at microvascular or cellular level may be playing a role at this difference of myocardial damage. Armstrong et al. (19) had compared the ST segment resolution of ticagrelor- and clopidogrel-loaded patients in the PLATO trial. The authors found that ticagrelor did not modify ST segment resolution at discharge; thus, they concluded that the short-term main effect of ticagrelor may not be related to rapidity or completeness of acute reperfusion and additional beneficial effects may be at play. They suggested that inhibition of adenosine uptake by red blood cells may favorably influence myocardial perfusion and that it may be one of the mechanisms.

Here, we aimed to work on a very specific group, i.e., only patients with proximal segment total thrombotic occlusion presenting in the first 3 h of chest pain onset. By using a wide range of exclusion criteria in these basally similar patient groups, we

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aimed to decrease the factors affecting troponin levels and solely examine the effect of P2Y12 inhibitors as much as possible. It was not possible to totally attribute the troponin difference between the groups to the initially loaded drug; however, we believe our results may give a clue of more advanced myocardial injury in clopidogrel-loaded patients, despite the switch to ticagrelor. An important detail we need to mention was that the ticagrelor-loaded group achieved this difference despite having more complex lesions upon coronary angiography compared with the clopidogrel-loaded group. Thus, we believe that patients who were first loaded with clopidogrel, though switched, may not be catching the same level of antiaggregant and the myocardial protective efficacy compared with patients first loaded with ticagrelor. We know that patients who switched to a novel agent have less ischemic events in the long-term follow-up compared with patients on clopidogrel. However, our results indicate that switching to ticagrelor may still be disadvantageous in the short term compared with those initially loaded with ticagrelor. The initial time period during PCI and reperfusion may be the key and critical period that the reloaded patients had missed. These results could be attributed to anti-inflammatory and protective effects of ticagrelor, aside from its potent antiaggregant action. Nonetheless, more studies with large patient size are definitely needed to discuss about this topic.

In our trial, we aimed to show the level of myocardial injury by the change in troponin levels, measured during admission and at specific intervals. Dynamic changes in concentration of troponin over a specified period, quantified as delta (Δ), have been used especially to differentiate various causes of myocardial injury (20). Absolute Δtroponin values, as used in our trial, were shown to be superior to relative (%) values (21, 22). Buber et al. (23) described the troponin release and elevation curve in STEMI patients who underwent primary PCI. Cardiac troponin I showed a single-peaked pattern with a median peaking time of 8 h, depending on the timing and success of PCI (23).

Two patient groups in our trial were similar with regard to their MACE rates; however, one cannot conclude any result due to a small number of events in the small patient population.

Study limitations

Our study has several limitations. It had a retrospective design that might lead to selection bias, and our patient number was limited due to the highly specific selection criteria. Limited sample size resulted in the inability to compare small-numbered data such as bleeding rates. We knew there were so many factors acting on troponin levels, and we tried to reduce the confounding factors as much as possible. We also knew that it is not totally possible due to the different types of culprit lesions at different vessels for different patients. To evaluate myocardial injury, we could not use a gold standard technique, such as magnetic resonance imaging. Additionally, troponin levels could give us the level of myocardial injury much less directly and specifically, which was the other limitation of our study.

Conclusion

In STEMI patients with two different P2Y12 inhibitor loadings, we showed that the degree of cell injury, measured by the change in troponin level, was more prominent in clopidogrel-loaded patients, despite switching to ticagrelor in the first hour of intervention. Although they had more complex lesions, the ticagrelor-loaded group had significantly less damage. We may conclude that clopidogrel is slow and modest and that variable platelet inhibition may continue to be a negative factor for protection from myocardial injury, even after switching to ticagrelor. Aside from that, the anti-inflammatory and protective effects of ticagrelor on the myocardium could be other contributing factors. Thus, we suggest that recent recommendations for dual antiplatelet loading in STEMI should be implemented into daily practice more effectively and that first loading with novel P2Y12 inhibitors, instead of needing to switch, should be carefully applied in all eligible patients.

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