นิพนธ์ต้นฉบับ • Original Article

รายงานเบื้องต้นกรณีความชุกของภาวะดื้อยาโคลพิโดเกรล (Clopidogrel) ในผู้ป่วยโรคกล้ามเนื้อหัวใจขาดเลือดซ้ำจากการศึกษาในสถาบันเดียว

บูรพา ปุสธรรม, ทรงศักดิ์ เกียรติชูสกุล, ไชยสิทธิ์ วงศ์วิภาพร
ศูนย์หัวใจสิริกิติ์ภาคตะวันออกเฉียงเหนือและโรงพยาบาลศรีนครินทร์ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

The Prevalence of Clopidogrel Resistance in Reinfarction and Recurrent Myocardial Infarction; a Single-Center Preliminary Report

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หลักการและวัตถุประสงค์: ความผิดปกติทางพันธุกรรมที่ทำให้เกิดภาวะดื้อยาโคลพิโดเกรลพบได้บ่อยในประชากรภาคตะวันออกเฉียงเหนือของประเทศไทย แต่ยังไม่เคยมีการศึกษาถึงผลกระทบของปัญหาดังกล่าวทางคลินิก

วิธีการศึกษา: ทำการศึกษาแบบพรรณนาในผู้ป่วยโรคกล้ามเนื้อหัวใจขาดเลือดซ้ำจำนวน 56 ราย โดยตรวจหาภาวะดื้อยาโคลพิโดเกรลโดยการตรวจ VerifyNow©P2Y12 (Accumetrics, San Diego, CA, USA) ซึ่งใช้ค่า P2Y12 reactivity unit (PRU) ≥ 240 เป็นเกณฑ์วินิจฉัย

ผลการศึกษา: ผู้ป่วยทั้งหมดมีอายุเฉลี่ย 64 ปี เป็นเพศชายร้อยละ 64 ค่า PRU เฉลี่ย 227 และพบความชุกของภาวะดื้อยาโคลพิโดเกรลร้อยละ 50 แบ่งเป็นผู้ป่วย reinfarction จำนวน 24 รายและผู้ป่วย recurrent myocardial infarction (MI) จำนวน 32 ราย โดยร้อยละ 62.5 ของผู้ป่วย reinfarction และร้อยละ 40.6 ของผู้ป่วย recurrent MI มีภาวะดื้อยาโคลพิโดเกรล (p = 0.25) และพบ stent thrombosis (ST) หรือ in-stent restenosis (ISR) จำนวน 35 รายและไม่พบ ST หรือ ISR จำนวน 21 รายโดยร้อยละ 57 และร้อยละ 38 ของผู้ป่วยที่พบและไม่พบภาวะดังกล่าวตามลำดับมีภาวะดื้อยาโคลพิโดเกรล (p = 0.36)

สรุป: ภาวะดื้อยาโคลพิโดเกรลพบได้บ่อยในผู้ป่วยโรคกล้ามเนื้อหัวใจขาดเลือดซ้ำในภาคตะวันออกเฉียงเหนือของประเทศไทย การตรวจหาภาวะดังกล่าวจึงอาจจำเป็นเพื่อการปรับยาต้านเกร็ดเลือดที่เหมาะสม

คำสำคัญ: ภาวะดื้อยาโคลพิโดเกรล กล้ามเนื้อหัวใจขาดเลือดซ้ำ VerifyNow P2Y12 assay

Background and objective: Genetic polymorphisms leading to clopidogrel resistance was highly prevalent among the Northeastern population of Thailand; however, the magnitude of problem had never been evaluated clinically.

Methods: A preliminary analysis of a descriptive study was done among 56 patients who presented by reinfarction or recurrent myocardial infarction (MI) during clopidogrel therapy. Baseline clinical, laboratories, and procedural data were collected. Clopidogrel activity was assessed by a VerifyNow© P2Y12 assay (Accumetrics, San Diego, CA, USA) with a cut-off value of ≥ 240 P2Y12 reactivity unit (PRU) used as a criteria for clopidogrel resistance.

Results: Across overall patients, mean age was 64 years, 64% of patients were males, mean PRU was 227, and the prevalence of clopidogrel resistance was 50%. Twenty-four patients presented by reinfarction with mean PRU of 232, and 32 patients presented by recurrent MI with mean PRU of 224, and 62.5% of the former and 40.6% of the latter group had clopidogrel resistance (p = 0.25). Thirty-five patients had stent thrombosis (ST) or in-stent restenosis (ISR) with mean PRU of 231, and 21 patients had neither ST nor ISR with mean PRU of 221, and 57% of the former and 38% of the later group had clopidogrel resistance (p = 0.36).

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Conclusion: Clopidogrel resistance is highly prevalent among patients with reinfarction and recurrent MI in the Northeastern of Thailand. Platelet function testing should be performed in such patients to further guide the P2Y12 inhibitor regimen.

Key words: Clopidogrel resistance, VerifyNow P2Y12 assay, reinfarction, recurrent myocardial infarction

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Introduction

Cardiovascular diseases (CVD) are the currently leading cause of death in the world. In Thailand, about 30% of death resulted from CVD and diabetes,[1] and from the estimation in 2005, 7.3% of male, and 8.6% of female died from ischemic heart disease (IHD).[2] Acute coronary syndrome (ACS) comprises of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) is one of IHD spectrum,[3] and also lead to high rate of hospital admission and mortality among Thai patients in the recent years.[4]

Treatment of ACS requires prompt coronary revascularization and optimization of antithrombotic therapies.[5-8] Combination of aspirin (ASA) and P2Y12-inhibitor orally is the main recommended regimen of antithrombotic therapies both in the acute and maintenance phase of ACS treatment. Currently, there are three oral P2Y12-inhibitors available worldwide, *i.e.,* clopidogrel, prasugrel, and ticagrelor. Among those, clopidogrel is the most widely used agent in Thailand due to health care coverage scheme's regulation and its most affordability and availability.

Clopidogrel resistance or hyporesponsiveness (the persistent activity of clopidogrel target despite an adequate antiplatelet regimen),[9] resulting primarily from genetic polymorphisms leading to heterogeneity of its pharmacokinetics[10], however, is an issue of concern. It was shown from many studies that patients with clopidogrel resistance had increased occurrence of short-and long-term ischemic events.[11,12]

Genetic polymorphisms of CYP2C19, including CYP2C19*2, *3, and *4, reduced function of CYP2C19 enzyme resulting to lower level of clopidogrel active metabolite and clopidogrel resistance.[13-17] Unfortunately, the Asian population had a high prevalence of genetic polymorphisms.[18] There was a report showing that 52.3% of healthy Northeastern populations of Thailand had CYP2C19*2 or *3 allele.[19] We therefore evaluated the prevalence and characters of clopidogrel resistance in reinfarction and recurrent myocardial infarction (MI) among patients with high prevalence of genetic polymorphisms.

Materials and methods

Study design and patients

A single center, descriptive study was performed at Queen Sirikit Heart Center of the Northeast and Srinagarind hospital, Khon Kaen University, Khon Kaen, Thailand, since December, 2012 and still ongoing. We planned to enroll 200 patients, or until target of 100 patients with clopidogrel resistance was met. Male or female consecutive patients ≥ 30 years of age, with history of ACS underwent percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery, or medical therapy alone whom clopidogrel was taken during the occurrence of reinfarction or recurrent MI were included. The patients who omitted any dose of clopidogrel within 1 week prior to occurrence of reinfarction or recurrent MI and who denied to participate were excluded. All patients were provided written informed consent. The study had already approved by the Khon Kaen University Ethics Committee in human research.

Procedures

All eligible patients who was admitted due to

reinfarction or recurrent MI would underwent clopidogrel activity assessment using the VerifyNow© P2Y12 assay (Accumetrics, San Diego, CA, USA). Clopidogrel had to be taken for at least 7 days in all patients before the event and might be additional loaded with a dose of 300 or 600 mg before the coronary angiogram. A washout period of 24 hours and 10 days was required before VerifyNow© P2Y12 testing if eptifibatide or tirofiban, and abciximab were used during the PCI, respectively. Research coordinator performed the VerifyNow© P2Y12 testing and immediately informed the result to the investigators. All baseline characteristics and clinical data were reviewed and collected by researcher (BP). Additional investigation for genetic polymorphisms was also performed in all patients, however, the results will not be reported in this preliminary analysis.

Definitions

MI was defined as the definition from the universal definition of myocardial infarction,[20] and by using the high-sensitivity cardiac troponin T assay (hs-cTnT) as a primary biomarker for myocardial injury. Reinfarction was defined as MI that occurs within 28 days of an incident or a recurrent MI, recurrent MI as MI occurs after 28 days of an incident event, while incident MI as the person's first MI ever.[21] Clopidogrel resistance was originally defined by the VerifyNow© P2Y12 assay $p \geq$ 240 P2Y12 reactivity unit (PRU).[22] Which there were evidences showed the relationship between VerifyNow© P2Y12 assay-diagnosed clopidogrel resistance and adverse clinical outcomes after PCI.[23,24] We also used the newer cut-off criteria of clopidogrel resistance, using VerifyNow© P2Y12 assay > 208 PRU to analyze the magnitude of its effect.[12] Definite stent thrombosis (ST) was defined as angiographic findings according to the Academic Research Consortium (ARD) definition.[25] And in-stent restenosis (ISR) was angiographically defined as the presence of > 50% diameter stenosis in the stented segment.[26]

Statistical analysis

As the aim of prevalence determination, we used a formula of estimating a population proportion with specified absolute precision ($n = [Z^2_{1-\alpha/2}P(1-P)]/d^2$), in which confidence level ($1-\alpha$) = 95%, anticipated population proportion p = 0.44[17], and absolute precision required (d) = 0.1, then the total calculated study population was 95 patients.

The continuous variables were presented by mean, range, and standard deviation (SD).The Shapiro-Wilk test of normality was used to assess the data distribution, in which variables with normal distribution were compared by Student's *t* test, while variables with abnormal distribution were compared by Wilcoxon test. Categorical variables were presented by number and percentage. The comparison was performed by Chi-square test with continuity correction if the expected cell count was less than 5 in less than 20% of cases, and otherwise was compared by Fisher's Exact test if the expected cell count was less than 5 in more than 20% of cases. A difference with $p < 0.05$ was considered statistically significant. The analysis was run by SPSS version 19.0.

Results

Fifty six patients were enrolled into the preliminary analysis. Across overall populations, the mean age was 64 years, 64.3% of patients were male, 89.3% of patients underwent PCI with stenting, 3.6% of patients underwent CABG, and 7.1% of patients stayed only on medical therapy without revascularization. According to the cardiovascular risk factors; diabetes, hypertension, CVA (cerebrovascular accident, and current smoking were presented in 58.9%, 55.4%, 5.4%, and 1.8% of patients, respectively. Heart failure was presented in 13 (23.2%) patients, and the mean left ventricular ejection fraction (LVEF) was 47%. At initial physical examination, the mean heart rate was 81 beat per minute and mean systolic/diastolic blood pressure was 130/76 mmHg. The mean fasting blood sugar (FBS) and Hemoglobin A1C (HbA1C) was 175 mg/dl and 7.1, respectively. The mean estimated glomerular filtration rate (eGFR) was 70 ml/min/1.73m^2. The mean low-density lipoprotein (LDL) was 100 mg/dl, however, there was a statistical significant difference of mean LDL between patients with reinfarction and recurrent MI. The mean LDL was 113 mg/dl in the former and 89 mg/dl in the later (p = 0.008).

The mean PRU was 227, 232, and 224 among overall populations, patients with reinfarction, and patients with recurrent MI, respectively. The most form of clopidogrel used was Apolets (54.7%), while the original Plavix was used in 26.4%, and non-original Clopidogrel GPO was used in 17.0% of patients. 76.8% of index event diagnosis across overall populations was NSTEMI, however, 58.3% of patients with reinfarction but 90.6% of patients recurrent MI presented by NSTEMI, and this difference was statistically significant (p = 0.01). STEMI was more frequent among patients with reinfarction (37.5%) comparing with patients with recurrent MI (9.4%), however, without statistical significant (p = 0.36). Definite ST was more prevalent among patients with reinfarction (73.9%) than in patients with recurrent MI (16.1%), this differ was statistically significant (p = 0.02).

According to the concomitant medications; aspirin, beta-blocker, statins, and nitrate were prescribed in most of the patients, of 96.4%, 80.4%, 89.3%, and 66.1%, respectively. Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) was prescribe in almost half of the patients (41.1%), while diuretics and calcium channel blocker (CCB) were used in less proportion (21.4% and 8.9%, consecutively). The proton pump inhibitor (PPI) was used in over half of patients (56.4%), which the most-used agent was omeprazole (90.6%). The baseline characteristics and investigational details were presented as Table 1.

The prevalence of clopidogrel resistance among overall patients, as the classic criteria of PRU $\geq$ 240, was 50% (95% confidence interval (CI) 36.50-63.50). Nevertheless, if the newer criterion of PRU > 208 was applied, then the prevalence of clopidogrel resistance was increased to 62.5%. Prevalence of clopidogrel resistance among patients with reinfarction and recurrent MI was 62.5% (95% CI 40.76-80.45) and 40.6% (95% CI 24.20-59.19), respectively, (p = 0.25). In the stratification according to the presence of ST or ISR, the mean PRU among patients with ST/ISR and without ST/ISR were 231 and 221, respectively, p = 0.1. There was a higher proportion of clopidogrel resistance among patients with ST/ISR comparing with patients without ST/ISR, however, without statistical significant, 57.1% vs 38.1% (p = 0.36) as PRU $\geq$ 240, and 71.4% vs 47.6% (p = 0.20) as PRU > 208. (Table 2)

Discussion

This single-center study, conducted at a high prevalence area of CYP2C19 genetic polymorphisms, evaluated the magnitude of clopidogrel resistance in regional clinical practice and its effect to clinical outcomes. A preliminary analysis of 56 patients who presented with reinfarction or recurrent MI while clopidogrel was taken, whether in original or non-original form, disclosed a high prevalence of clopidogrel resistance (50%) judging by the VerifyNow© P2Y12 assay cut point $\geq$ 240 PRU. Our finding gave the same conclusion along with other studies from many regions of the world[23,24, 27,28] and also strongly confirms the importance of clopidogrel resistance to clinical adverse outcomes among a selected population of Thailand.

Regarding the stratification with ST/ISR, the prevalence of clopidogrel resistance among patients with ST/ISR was quite high at 57.1%, while it was lower among patients without ST/ISR at 38.1%. Although it was a non-statistical significant difference (p = 0.36), however, this trend should be viewed cautiously as clopidogrel resistance was not only a risk for reinfaction or recurrent MI, but also a specific risk for ST or ISR like it had been shown from many case reports and clinical trial.[12, 29-31]

The international standard practice guideline recommends against routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI (recommendation class III).[32] However, in the special circumstances with high prevalence of genetics polymorphisms and high prevalence of clopidogrel resistance among patients with reinfarction or recurrent MI, especially in patients with ST or ISR, as in our area of coverage, this should be viewed in a different way. The routine platelet function testing for clopidogrel after PCI might be warranted and changing to a more potent agent; such as ticagrelor or prazugrel might be needed, even though there is currently no definite evidence confirms the clinical benefits of this treatment strategy and the practice guideline permits just only a class IIb recommendation due to its lack of evidence.[32]

Table 1 Baseline characteristics and investigational details*

Characteristic	Overall patients (N = 56)	Reinfarction (N =24)	Recurrent MI (N =32)	p- value
Age – year	64 ± 11	63 ± 11	65 ± 10	0.48
Male sex – no. (%)	36 (64.3)	19 (79.2)	17 (53.1)	0.08
CV risk – no. (%)				
Diabetes	33 (58.9)	12 (50.0)	21 (65.6)	0.37
Hypertension	31 (55.4)	13 (54.2)	18 (56.3)	0.10
CVA	3 (5.4)	2 (8.3)	1 (3.1)	0.57
Current smoker	1 (1.8)	0 (0.0)	1 (3.1)	1.0
Previous treatment –no. (%)				
PCI	50 (89.3)	23 (95.8)	27 (84.4)	0.22
CABG	2 (3.6)	0	2 (6.3)	0.50
Medication only	4 (7.1)	1 (4.2)	3 (9.3)	-
Heart failure – no. (%)	13 (23.2)	4 (16.7)	9 (28.1)	0.49
BMI – kg/m^2	24 ± 4	24 ± 5	25 ± 3	0.25
Heart rate – bpm	81 ± 17	82 ± 18	81 ± 16	0.81
SBP/DBP – mmHg	130/76 ± 26/16	125/75 ± 22/13	134/78 ± 28/18	0.25/0.97
LVEF – %	47 ± 16	48 ± 17	46 ± 15	0.64
Fasting plasma glucose –mg/dl	175 ± 85	177 ± 91	174 ± 80	0.78
Hemoglobin A1C	7.1 ± 1.8	6.9 ± 1.9	7.3 ± 1.8	0.48
Low-density lipoprotein –mg/dl	100 ± 33	113 ± 37	89 ± 25	0.008
eGFR** – $ml/min/1.73m^2$	70 ± 37	75 ± 39	66 ± 35	0.39
VerifyNow P2Y12 assay – PRU	227 ± 69	232 ± 61	224 ± 76	0.69
With > 240 PRU – no. (%, 95% CI)	28 (50, 36.50-63.50)	15 (62.5, 40.76-80.45)	13 (40.6, 24.20-59.19)	0.25
Type of clopidogrel* – no. (%)**				
Plavix®	14 (26.4)	9 (39.1)	5 (16.7)	0.38
Apolets®	29 (54.7)	13 (56.5)	16 (53.3)	0.86
Clopidogrel-GPO®	9 (17.0)	1 (4.3)	8 (26.7)	-
Time to index event –days	173 ± 352	8 ± 6	297 ± 428	0.005
Index event diagnosis – no. (%)				
NSTEMI	43 (76.8)	14 (58.3)	29 (90.6)	0.01
STEMI	12 (21.4)	9 (37.5)	3 (9.4)	0.36
Angiographic findings of index event –no. (%) (N =)				
Definite stent thrombosis	22 (40.7)	17 (73.9)	5 (16.1)	0.02
In-stent restenosis	13 (24.1)	1 (4.3)	12 (38.7)	-
Others	21 (37.5)	6 (25.0)	12 (38.7)	0.50
Previous medications – no. (%)				
Aspirin	54 (96.4)	24 (100.0)	30 (93.8)	0.50
Beta-blocker	45 (80.4)	16 (66.7)	29 (90.6)	0.04
ACEI/ARB	23 (41.1)	6 (25.0)	17 (53.1)	0.06
Statins	50 (89.3)	2 (8.3)	28 (87.5)	0.69
CCB	5 (8.9)	3 (12.5)	2 (6.3)	0.08
Nitrates	37 (66.1)	13 (54.2)	24 (75.0)	0.12
Diuretics	12 (21.4)	2 (8.3)	10 (31.3)	0.51
PPI use – no. (%)	32 (56.4)	14 (58.3)	17 (54.8)	0.79
Omeprazole	29 (90.6)	13 (86.7)	16 (94.1)	0.49
Lanzoprazole	1 (3.1)	1 (6.7)	0 (0.0)	-
Esomeprazole	2 (6.3)	1 (6.7)	1 (5.9)	-

ACEI denotes Angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, BMI body mass index, CABG coronary artery bypass graft, CCB calcium channel blocker, CI confidence interval, CV cardiovascular disease, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, LDL low-density lipoprotein, LVEF left ventricular systolic function, MI myocardial infarction, NSTEMI non-ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, PPI

proton pump inhibitor, PRU P2Y12 reactivity unit, SBP systolic blood pressure, STEMI ST-segment elevation myocardial infarction.
*Plus-minus values are mean ± SD.
**By Modified of Diet in Renal Disease (MDRD) formula
***There were 3 types of clopidogrel available in Thailand and its use primarily depended on the health care coverage of each individual patient. Plavix® is original clopidogrel and was able to use for patients who covered by Civil Servant Medical Benefit Scheme (CSMBS) or paid by themselves, Apolets® and Clopidogrel-GPO® are non-original clopidogrel and were able to use for patients who covered by Social Security Scheme (SSS) or Universal Coverage Scheme (UCS).

Table 2 Relationship between platelet reactivity and stent thrombosis/in-stent restenosis*

	Either ST or ISR (N=35)	Neither ST nor ISR (N=21)	p-value
VerifyNow P2Y12 testing – PRU ± Range	231 ± 71 8-368	221 ± 68 126-357	0.61
With > 240 PRU – no. (%)	20 (57.1)	8 (38.1)	0.36
With > 208 PRU** – no. (%)	25 (71.4)	10 (47.6)	0.20

ISR denotes in-stent restenosis, PRU P2Y12 reactivity unit, ST stent thrombosis.
*Plus-minus values are mean ± SD.
**A newer and lower cut-off value of clopidogrel resistance was analyzed additionally

There were many of known causes of clopidogrel resistance; such as genetic polymorphisms, non-compliance, concomitant medication, comorbidity, and smoking.[33] The genetic polymorphisms, anyhow, are still currently unable to analyze. Non-compliance should not be mentioned as a cause of clopidogrel resistance among our study populations due to all eligible patients had to take clopidogrel in everyday within 1 week before an index event. Concomitant medication, especially PPI, had been previously viewed as a potent cause of clopidogrel resistance. There were evidences demonstrated that concurrent treatment with PPI, especially omeprazole, could reduced clopidogrel activity and increased platelet activity.[34,35] Our study, however, had a small number of population, hence the correlation between each risk factor and clopidogrel resistance was unable to demonstrate due to the high chance of unreliability.

Although there were 3 types of clopidogrel using in real clinical practice, *i.e.,* plavix, apolets, and clopidogrel-GPO, and the pharmacologic efficacy of non-original clopidogrel (apolets and clopidogrel-GPO) might be doubted. However, two clinical studies conducted in Thai patients showed the equality of efficacy between each type of clopidogrel,[36,37] therefore, the non-originality of clopidogrel should not be viewed as a potential cause of its resistance.

There are limitations to our study. First, since it was a preliminary analysis, hence it was inevitably underpowered due to its small population compare to the total planned-number; however, due to the low incidence of reinfarction and recurrent MI, then the recruitment was slow and the preliminary analysis might be necessary and give some insight into a full study. Second, a nature of single-center study could lead to bias in clinical practice or management strategy; however, as the tertiary cardiac center in the region, we kept practice according to the recommendation from international practice guideline tightly, or as much as possible. Another limitation was lack of genetic polymorphisms data, in which interpretation of both platelet function testing and genetic polymorphisms should give some interesting viewpoints.

Nevertheless, this is the first study ever demonstrated the high prevalence of clopidogrel resistance in real clinical practice among the Northeastern populations of Thailand. Further analysis of genetic polymorphisms is awaiting, and further study of treatment strategy with routine platelet function testing for patients born from region with high prevalence of genetics polymorphisms treated with clopidogrel is suggested.

Conclusion

Clopidogrel resistance is highly prevalent among reinfarction and recurrent MI patients in the Norhteastern of Thailand. The platelet function testing might be performed in patients whom reinfarction or recurrent MI developed while clopidogrel was taken to guide the adjustment of P2Y12 inhibitor. Further study for routine platelet function testing in patients of the Northeastern of Thailand who had undergone PCI is suggested.

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Disclosures

The Authors declare that there is no conflict of interest.

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