The Additional Effect of Cilostazol for the ADP-induced Platelet Aggregation and Soluble CD40L in Patients with Primary Percutaneous Coronary Intervention

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감사의 글

먼저 아무것도 모르는 저에게 생각을 주시고 논문이 무엇인지 알게 해 주신 이승환 교수님께 감사 드립니다. 교수님의 지도로 논문을 하나하나 완성해 가면서 제 자신이 커가는 것을 느꼈고, 교수님의 애정 어린 질책으로 인해 논문의 틀이 마련될 때마다 즐거움을 느꼈습니다.

그리고 실제적으로 샘플을 모으고 관리하는 기초적인 방법과 논문과 데이터를 관리하는 실제적인 모든 것을 가르쳐 주신 김장영 교수님, 항상 찾아 뵙지 못하였지만 애정을 가지고 논문 내용을 세심히 검토해 주신 어영 교수님 진심으로 감사 드립니다. 연구 과정에서 조언을 해주신 최경훈, 윤정한, 유병수 교수님께도 감사 드립니다. 또한 바쁜 일과에도 연구용 시료를 불평 없이 열심히 분리확인해준 진단검사의학과의 직원 분들께 감사 드립니다.

끝으로 첫째 아이를 키우며 둘째 아이를 가지면서도 힘들게 고생하는 나의 사랑하는 아내 김은진과 아직 철모르지만 아빠와 떨어져 지내면서도 항상 잘 웃어주는 첫째 아들 이준우 그리고 항상 마음속으로 격려해 주고 사랑해 주는 아버님, 어머님, 장모님과 기쁨을 함께하고 싶습니다.

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Abstracts

The Additional Effect of Cilostazol for the ADP-induced Platelet Aggregation and Soluble CD40L in Patients with Primary Percutaneous Coronary Intervention

Cilostazol increases in cyclic adenosine monophosphate levels in platelets and might ameliorate the antiplatelet activity of clopidogrel. This study investigated the additional effect of cilostazol for the platelet aggregation measured by a VerifyNow analyzer and soluble CD40 ligand (sCD40L) as a marker of the activated platelet in patients undergoing primary percutaneous coronary intervention (PCI). Sixty cases with primary PCI were randomly assigned to a dual (aspirin and clopidogrel) and triple (dual plus cilostazol) therapy. The antiplatelet effects of aspirin and clopidogrel were evaluated by VerifyNow™ tests. The plasma sCD40L levels at admission, 24 hours, and 21 days were measured by the ELISA method. The aspirin-induced platelet aggregation was similar in both groups. However, the triple group was significantly lower the P2Y12 reaction unit (dual; 208.8±69.0 vs. triple 168.2±79.2, p=0.041) and higher the % inhibition of P2Y12 receptor (dual 23.8±21.4 vs. triple 40.5±21.0 %, p=0.004). In multivariate analysis, cilostazol was the negative predictor for low responders to clopidogrel (95% confidence interval; 0.067-0.711). The plasma sCD40L levels were no significant differences between

the two groups at the same point of time. The addition of cilostazol to the combination of aspirin plus clopidogrel significantly increases in the inhibition of P2Y12-induced aggregation. However, there was no additive effect on aspirin-induced antiplatelet activity or lowering of sCD40L.

Key words: Cilostazol; Acute myocardial infarction; Platelets

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1. Introduction

Platelets play a central role in the pathogenesis of atherothrombosis.[1] Thus, achieving platelet inhibition is an important part of managing a patient with an atherothrombotic event. Dual antiplatelet therapy with clopidogrel plus aspirin has

been shown to reduce ischemic events in patients with unstable angina and myocardial infarction (MI), especially those undergoing percutaneous coronary intervention (PCI) and stenting.[2,3] Despite its proven benefit, there is a considerable heterogeneity in the responses of individual patients to each of aspirin and clopidogrel.[4-7] Emerging data show adequate antiplatelet effects are not achieved in 5 to 45% of patients taking aspirin and 4 to 30% of patients taking clopidogrel,[4-7] suggesting that many patients are resistant or only partially responsive to their antiplatelet effect. Some data suggest that these patients are at an increased risk of stent thrombosis and cardiovascular complications.[4,8-11]

Cilostazol is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase 3 and increases in cyclic adenosine monophosphate (cAMP) levels in platelets. The increase in the cAMP blocks all activating pathways in the platelets, inhibiting process such as adenosine diphosphate (ADP) induced platelet activation, arachidonic acid (AA) induced platelet activation, and cellular interaction among platelets, leukocytes, and vascular endothelial cells.[12-14]

Recent studies showed that adding cilostazol to an aspirin and clopidogrel regimen is associated with the additional suppression of P-selectin expression in vitro[15] and is more effective in preventing thrombotic complications after coronary stenting without an increased risk of side effects.[16] However, whether adding cilostazol has synergistic antiplatelet activities on the top of a standard dual antiplatelet regimen remains uncertain. Therefore, We hypothesized that adding cilostazol administration to the standard dual antiplatelet regimen might lead to additional suppression of platelet aggregation and soluble CD40 ligand (sCD40L, a marker of platelet activation) and ameliorate the aspirin and clopidogrel responsiveness in patients with primary PCI.

2. Methods and Materials

2.1 Study population

We enrolled 60 consecutive patients with ST elevation MI (STEMI) undergoing primary PCIs within 12 h of symptom onset. The patients were randomly assigned 1:1 to undergo either a standard dual regimen (aspirin and clopidogrel) or a triple regimen (aspirin, clopidogrel, and cilostazol). Exclusion criteria were any

contraindications for antiplatelet agents, severe left ventricular dysfunction (EF ≤ 30%), severe hepatic dysfunction (AST/ALT ≥ 3 times of upper normal limit), severe renal dysfunction (serum Cr ≥2), thrombocytopenia (<150×109/L), cardiogenic shock, infectious or neoplastic disease, and bleeding disorders (Fig. 1). This study was approved by the Investigational Review Board of the Wonju College of Medicine. All patients gave written informed consent.

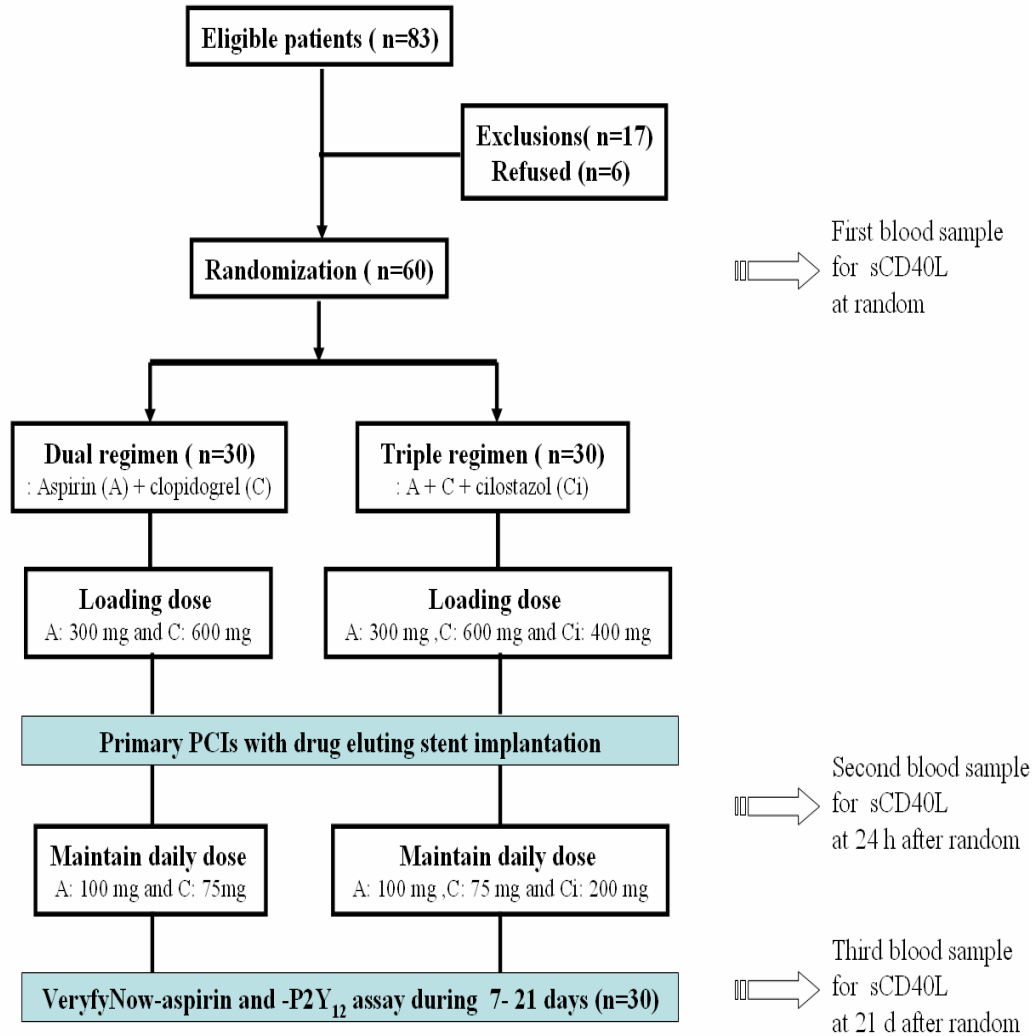

Fig.1. Flow chart of study design

sCD40L: soluble CD 40 ligand

2.2 Method

2.2.1. Study protocol

As soon as diagnosis of STEMI was confirmed at emergency department, we administered a loading dose of antiplatelet regimens and a bolus of unfractionated heparin (70U/kg) or enoxaparin (30mg) to the patients from before 30 to120 minutes before primary PCIs. Standard dual regimen groups received 600 mg clopidogrel and 300 mg oral aspirin in the emergency room, followed by 75 mg clopidogrel and 100 mg aspirin daily thereafter. In the triple regimen groups, patients received 600 mg clopidogrel, 300 mg oral aspirin and 400mg cilostazol as loading dosages, followed by 75 mg clopidogrel, 100 mg aspirin, and 200 mg cilostazol daily for 1 month.

After coronary angiography via transradial or transfemoral, primary PCIs were performed using standard technique for the infarct-related artery. Procedural success was defined as a residual diameter stenosis of < 30 % with TIMI grade 3 flows. Major adverse cardiac event (MACE) was defined as death, recurrent myocardial infarction and target vessel revascularization until 1 month. Major

bleeding was defined as a drop in hemoglobin of ≥ 5 g/dL, or significant hypotension with the need for inotropes, or requiring surgery (other than vascular site repair), or symptomatic intracranial hemorrhage (ICH), or requiring transfusion of four or more units of red blood cells.

2.2.2. VerifyNow-aspirin /P2Y12 assay and measurement of sCD40L

Blood samples for sCD40L were obtained at baseline, 24 hrs and 21 days in all participants. Concentrations of sCD40L in plasma were measured in duplicate with a standard enzyme-linked immunosorbent assay and a commercial kit (R&D Systems, Minneapolis, Minnesota) according to the manufacturer's instructions.

The samples for in vitro platelet function were obtained after 7th to 21st consecutive day in the study scheme when aspirin and clopidogrel were applied at a dosage of 100mg daily for aspirin and 75mg daily for clopidogrel. All specimens were obtained by venipuncture after a 5-ml whole blood sample drawn into two 1.8-ml blood collection tubes containing 3.2% citrate and were analyzed independently.

In vitro platelet function testing for aspirin and clopidogrel was performed with the

VerifyNow System (Accumetrics, San Diego, California), which is similar to the principle of light transmission aggregometry.

The VerifyNow-aspirin system measures the change in optical signal caused by aggregation using cartridges containing fibrinogen coated beads and platelet agonists (cationic propyl gallate which activate the cyclooxygenase-1 pathway). The results were expressed in the Aspirin Reaction Units (ARUs) based on the extent of platelet aggregation. An ARU of ≥550 indicates the absence of aspirin-induced platelet dysfunction and was defined as aspirin resistance.[17,18]

TheVerifyNow-P2Y12 system measures the change in optical signal caused by aggregation using cartridges containing fibrinogen coated beads and platelet agonist ADP. Prostaglandin E1 is added to this channel to reduce the nonspecific contribution of the P2Y1 receptor. The results were expressed in P2Y12 reaction units (PRU) based on the ADP-mediated aggregation and percentage inhibition of P2Y12 receptor (% inhibition) was calculated as follows: 1- (PRU after clopidogrel/PRU at baseline) X 100. The PRU at baseline defines the platelet aggregation in the thrombin receptor activating peptide (TRAP) channel and serves

as an estimate of the baseline platelet function independent of P2Y12 inhibition.

A lower responder to clopidogrel was defined as those patients with % inhibition of P2Y12 receptor less than 20.

2.2.3. Statistical analysis

Continuous variables (presented as mean ± SD) were compared by Student's t-test for normally distributed variables and by the Wilcoxon test for non-normally distributed variables. Categorical variables were expressed as the number of subjects and percentages and were analyzed by the chi-square or Fisher's exact tests, as appropriate. Serial measurements for sCD40L between two groups were compared using repeated measures of AVOVA, and Scheffe's multiple comparison tests was used to compare the mean different intervals. Multivariate stepwise logistic regression analyses were performed to identify independent predictors for low responders to clopidogrel as the dichotomous dependant variable. Statistical analysis was performed with the SPSS software package for Windows 12.0 (SPSS Inc., Chicago, Illinois). P values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics and clinical outcomes

Baseline clinical, angiographic, and procedural characteristics were similar between the dual and triple regimens shown in Table 1. Procedural success was achieved in 100% in both groups. A complete 30-day follow-up was available for all eligible patients. MACE was 3.3% in dual regimen group (one case of recurrent Non-Q wave MI) and 6.7% in triple regimen group (two cases of recurrent Non-Q wave MI) ($p = 0.554$). There was no major bleeding in both groups and no discontinuation of cilostazol due to adverse drug reactions.

Table 1. Clinical Characteristics of Study Patients

	Dual (n = 30)	Triple (n = 30)	*p*
Age, year	63.9±9.0	62.3±11.1	0.571
Male (%)	21 (70)	21 (70)	1.000
Total cholesterol(mg/dL)	167.1±47.8	181.8±47.2	0.237
Hypertension (%)	14 (47)	17 (59)	0.571
Diabetes (%)	8 (27)	9 (31)	0.633
Hypercholesterolemia (%)	4 (13)	6 (20)	0.406
Smoking (%)	18 (60)	18 (60)	0.221
β-blocker (%)	19(63)	23 (77)	0.266
ACE inhibitor (%)	10 (33)	12 (40)	0.691
ARB (%)	8 (27)	11 (37)	0.485
Statin (%)	22(73)	20 (67)	0.485
Diuretics (%)	10 (33)	13 (43)	0.493
LV ejection fraction (%)	46.3±8.1	46.2±12.6	0.702
Killips class , %			0.215
I/ II/ III	80.8 /11.5/7.7	92.0 /0 /8.0	
Access site, %			0.166
Radial artery/ femoral artery	90.0/10.0	76.7/23.3	
Lesion Type (A/B/C), %	15.4 /53.8 /30.8	12.0 /40.0 /48.0	0.648
Stent type(SES/PES/others), %	79.2/16.7/4.2	84.0/8.0/8.0	0.290
Infarct-related artery, %			0.203
LAD/LCX/RCA	53.3 /20.0 /26.7	41.4 /10.3 /48.3	
1 month MACE	3.3%	6.7%	0.554

ARB: Angiotensin II Receptor Blocker, ACE: Angiotensin Converting Enzyme, MACE: Major Adverse Cardiac Event, SES : Sirolimus-eluting stent, PES : Paclitaxel-eluting stent, LAD : Left anterior descending artery, LCX : Left circumflex artery, RCA : Right coronary artery

3.2. *In vitro* Platelet function test by VerifyNow on aspirin and clopidogrel response

The mean ARUs for the dual and triple regimen were similar between the two groups. (dual: 421.1±49.6, vs. triple; 426.4±62.1, p = 0.717). Aspirin resistance (ARU ≥ 550) rate was also identical in both groups (3.4 vs. 3.6%, p=0.960). However, the VerifyNow P2Y12 assay showed a significantly lower degree of PRU in the triple regimen (168.2±79.2) than in the dual regimen group (208.8±69.0, p=0.041). The % inhibition of P2Y12 receptor was significantly higher in the triple than the dual regimens (dual: 23.8±21.4, vs. triple; 40.5±21.1, p =0.004)(Fig. 2). The rate of lower responder to clopidogrel was significantly lower in the triple regimen group than in the dual regimen (dual; 46.4, vs. triple; 15.4 %, p=0.014).

In multivariate logistic regression analysis using age, sex, risk factors and medications as independent variables and lower responder to clopidogrel as a dependent variable, additional cilostazol (triple regiment) was the only independent negative risk factor for a lower responder to clopidogrel. (odds ratio=0.219, 95% confidence interval 0.067 – 0.711: Table 2.).

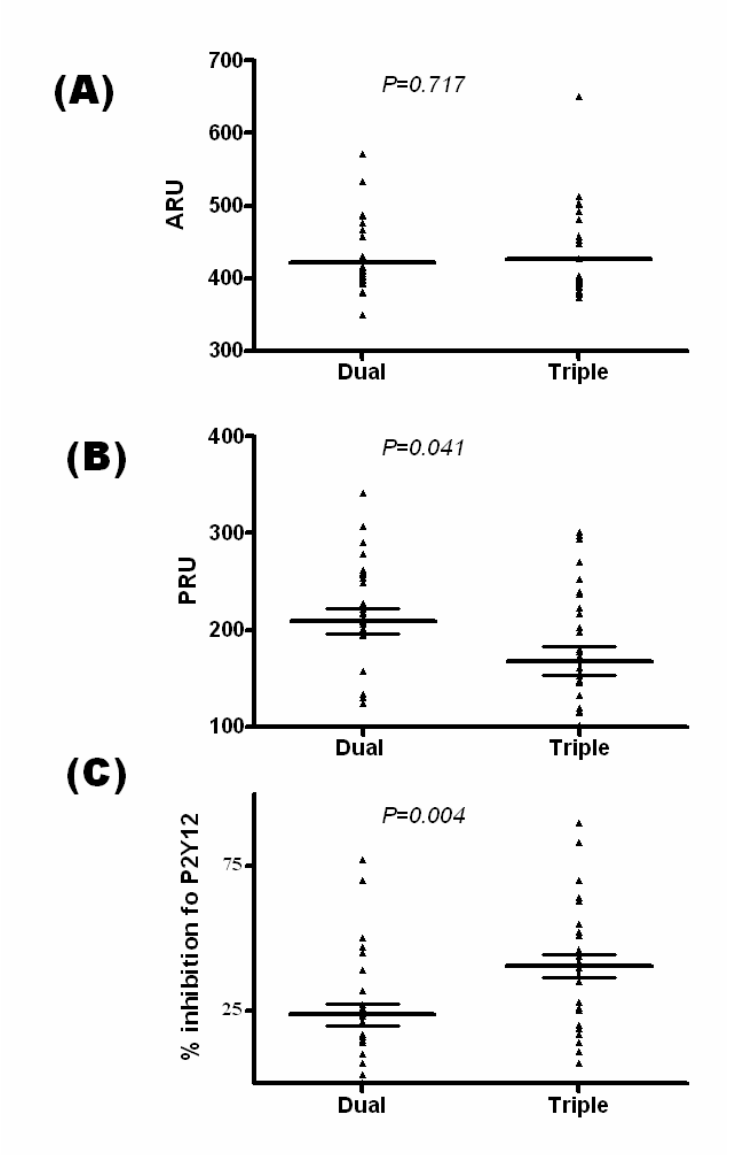

Fig.2. The ARU (A), PRU (B), and % inhibition (C) of P2Y12 receptor between dual and triple regimen group using VerifyNow assay

ARU: aspirin reaction unit, PRU: P2Y12 reaction unit

Table 2. Multivariate logistic regression analysis for independent variables for low responder to clopidogrel

	Adjusted OR	95% CI	*p* value
Cilostazol medication	0.219	0.067 – 0.711	0.011
Blocker medication	1.095	0.314 – 3.815	0.886
ARB medication	0.678	0.185 – 2.481	0.557
ACEI medication	1.602	0.475 – 5.408	0.448
Statin medication	2.317	0.594 – 9.046	0.226
Hypertension	0.745	0.248 – 2.243	0.601
DM	1.369	0.396 – 4.736	0.620
Smoking	2.046	0.100 – 6.719	0.354

OR: odds ration, CI: confidence interval, ARB: Angiotensin II Receptor Blocker, ACEI : Angiotensin Converting Enzyme inhibitor, DM : Diabetes Mellitus

3.3. Serial changes in sCD40L

The mean plasma sCD40L concentration between the dual and triple regimen group did not differ at admission (dual: 395.8±622.5, vs. triple; 346.6±489.5 pg/mL, p = NS). The level of sCD40L in plasma decreased in both groups at 24 hour compare to the baseline values, but, the Δ change of sCD40L was not statistically significant between both groups (dual: 131.8±219.1 vs. triple; 110.9±186.5 pg/mL, p = NS). The plasma sCD40L further decreased in both groups at 21 days compare to at 24 hour, but, the Δ change of sCD40L was also insignificant between both groups (dual: 166.9±150.1 vs. triple; 148.0±157.6 pg/mL, p = NS) (Fig. 3).

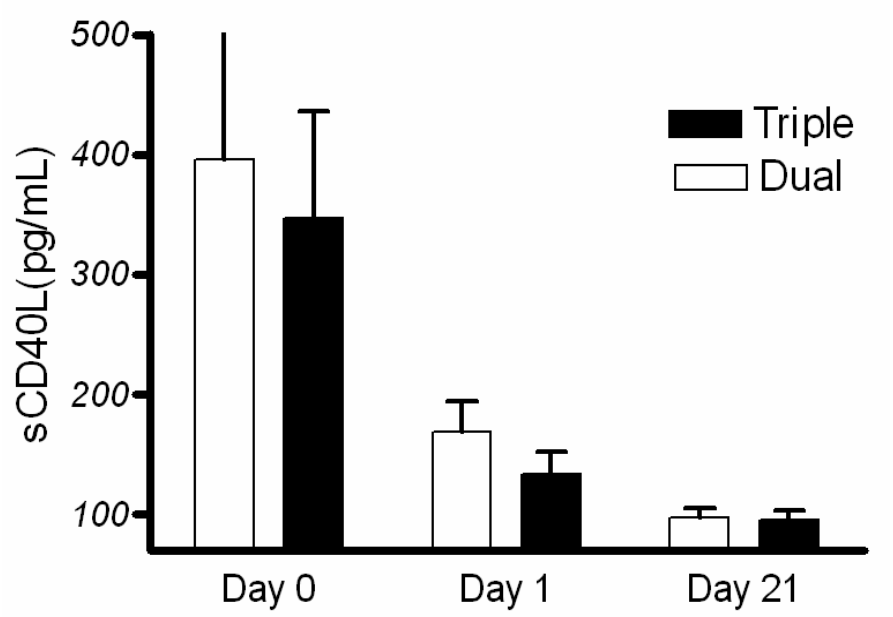

Fig.3. Serial changes in plasma concentrations of sCD40L (pg/mL) between dual and triple regimen group

sCD40L: soluble CD 40 ligand

4. Discussion

The main finding of the present study was that adding cilostazol to an aspirin and clopidogrel regimen significantly increases the inhibition of P2Y12-induced platelet aggregation compared with aspirin plus clopidogrel regimen in patients undergoing primary PCIs. However, there was no additive or synergistic effect on aspirin-induced antiplatelet activity or lowering of sCD40L.

Cilostazol is a 2-oxo-guinoline derivative with antithrombotic, vasodilator, and antimigrogenic properties. This compound is a potent inhibitor of phosphodiesterase (PDE) 3A, leading to increase intracellular cAMP of platelets by inhibiting the degradation to AMP (Fig. 4). Although, the detailed signal transduction pathways remain unclear, increased cAMP can activate cAMP-dependent protein kinase (PKA) in human platelets .[15,19] The PKA activation induce the phosphorylation of vasodilator-stimulated phosphoprotein (VASP) which is closely correlated with the inhibition of fibrinogen binding to integrin αIIbβ3 and the inhibition of platelet aggregation and adhesion.[20]

In randomized clinical trials, cilostazol was as effective as ticlopidine[21] or

clopidogrel[22] in preventing stent thrombosis after coronary stenting, and triple antiplatelet therapy with aspirin, cilostazol plus clopidogrel or ticlopidine was more effective in preventing stent thrombosis than aspirin plus clopidogrel or ticlopidine.[16] Based on the different mechanisms compared to the clopidogrel and clinical data of cilostazol, we hypothesized that a triple regimen might result in additional suppression of platelet aggregation and sCD40L, and ameliorate the aspirin and clopidogrel responsiveness in high risk of atherothrombotic patients. Our date clearly showed that adding cilostazol administration to the standard regimen additionally suppressed P2Y12-induced platelet aggregation and significantly decreased the clopidogrel resistance.

Although the exact mechanism of the beneficial effects of adding cilostazol was unclear, our results suggested that cilostazol has a different mode of action (increased the cAMP mediated by PDE 3) from that of the P2Y12 receptor inhibition of clopidogrel and the additional inhibition of ADP induced platelet aggregation. Supporting results in previous studies showed that the addition of cilostazol to an aspirin and clopidogrel regimen resulted in additional suppression

of platelet P-selectin expression.15 Indeed, there was 23 to 35% increase in inhibition of ADP-induced ex vivo platelet aggregation and no additive or synergistic effect on arachidonic acid-induced platelet aggregation by cilostazol plus aspirin when compared with aspirin alone.[23] Inhibitory effects of PDE3A activity correlated with their inhibition of platelet aggregation induced by thrombin, collagen, or ADP.[24] Taken together of previous studies and our results, one another logical approach to overcome clopidogrel resistance might be adding cilostazol to the standard dual antiplatelet regimen. Despite the additional antiplatelet effects, cilostazol did not additionally inhibit the release of sCD40L, which is a prothrombotic and proinflammatory biomarker mainly derived from activated platelets in acute coronary syndrome.[25,26] Thus, further studies should clarify the role of cilostazol in patients with clopidogrel resistance in primary PCI settings and with a high risk for stent thrombosis.

There were some limitations in our study. First, the sample size was relatively small, but we found the significant difference in PRU value and % inhibition of P2Y12 receptor between the dual and triple regimen. We also verified the

additional benefit of cilostazol for clopidogrel resistance by multivariate regression models. Second, we evaluated ex vivo platelet responsiveness to P2Y12 receptor inhibition based on VerifyNow P2Y12 test. Ideally, responses are monitored by light transmission aggregometry using 5 or 20 μM ADP based on measuring the change in aggregation at baseline and post-drug.[27] However, ADP-induced LTA is impractical to test in primary PCI settings. VerifyNow P2Y12 test is also a reliable and sensitive measure for monitering clopidogrel therapy in a recent validation study.[28]

5. Conclusions

This study was a randomized and controlled study to compare adding cilostazol administration to the standard dual antiplatelet regimen versus the standard dual antiplatelet regimen in patients with primary PCI. The aim of the study was to evaluate the effect and the aspirin and clopidogrel responsiveness of triple antiplatelet regimen. The important findings are as below.

1. The VerifyNow P2Y12 assay showed a significantly lower degree of PRU in the triple regimen (168.2±79.2) than in the dual regimen group (208.8±69.0,

p=0.041). The % inhibition of P2Y12 receptor was significantly higher in the triple than the dual regimens (dual: 23.8±21.4, vs. triple; 40.5±21.1, p =0.004)(Fig. 2). The rate of lower responder to clopidogrel was significantly lower in the triple regimen group than in the dual regimen (dual; 46.4, vs. triple; 15.4 %, p=0.014).

2. The level of sCD40L in plasma decreased in both groups at 24 hour compare to the baseline values, but, the Δ change of sCD40L was not statistically significant between both groups (dual: 131.8±219.1 vs. triple; 110.9±186.5 pg/mL, p = NS). The plasma sCD40L further decreased in both groups at 21 days compare to at 24 hour, but, the Δ change of sCD40L was also insignificant between both groups (dual: 166.9±150.1 vs. triple; 148.0±157.6 pg/mL, p = NS).

3. There was no major bleeding in both groups and no discontinuation of cilostazol due to adverse drug reactions.

In conclusion, cilostazol in addition to an aspirin plus clopidogrel regimen led to additional inhibition of P2Y12-induced platelet activation in primary PCI settings. These results suggested that cilostazol can improve clopidogrel resistance in patients with acute myocardial infarction with stenting.

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국문 요약

일차적 관동맥 중재술을 받은 환자에서 ADP유발 혈소판 응집과 soluble CD40L에 대한 실로스타졸 추가투여의 효과

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이 경 훈

아스피린과 클로피도그렐의 2제요법은 관동맥중재술과 스텐트시술을 받은 환자에서 표준요법으로 사용되고 있다. 하지만 클로피도그렐을 투여받는 환자의 4-30%가 적절한 항혈소판효과가 얻어지지 못하고 있다. 실로스타졸은 혈소판에서 cAMP 농도를 증가시키는 경구용 항혈소판제재로 클로피도그렐의 항혈소판작용을 개선시킬수 있는것으로 알려져 있다. 본 연구는 일차적 관동맥중재술을 시행받은 급성 심근경색증 환자에서 VerifyNow분석기에 의해 측정되는 혈소판 응집과 활성화된 혈소판의 표지자인 sCD40L에 대해 실로스타졸의 부가적인

투여가 미치는 영향을 보고자 하였다.

일차적 관동맥 중재술을 시행받는 연속적인 60명을 대상으로 전향적, 이중맹검, 무작위 배정을 통하여 2제요법 (아스피린과 클로피도그렐)군과 3제요법 (아스피린, 클로피도그렐과 실로스타졸)군으로 나누어 비교하였다. VerifyNow분석기로 아스피린과 클로피도그렐의 항혈소판 효과를 측정하였고, ELISA 방법으로 입원시, 입원후 24시간후, 21일후의 혈장내 sCD40L를 측정하여 다음과 같은 결과를 얻었다.

1. VerifyNow 분석 결과 PRU (P2Y12 reaction unit) 정도가 2제요법군 (208.8±69.0)보다 3제요법군 (168.2±79.2)에서 의미있게 낮았다. (p=0.041) P2Y12 수용체억제율의 변화는 2제요법군 (23.8±21.4 %) 보다 3제요법군 (40.5±21.1 %)에서 의미있게 높았다. (p=0.004) 클로피도그렐의 반응성이 낮은 환자의 비율이 제요법군 (46.4%) 보다 3제요법군 (15.4%)에서 의미있게 낮았다. (p=0.014)
2. 혈장내 sCD40L 입원시에 비해 입원 24시간후의 농도가 양군

모두 낮았으나 sCD40L의 변화량은 양군간에 통계적으로 의미있는 차이는 없었다. (2제요법군: 131.8±219.1 3제요법군 : 110.9±186.5 pg/mL, p = NS) 혈장내 sCD40L는 입원 24시간후에 비해 입원 21일후의 농도가 양군 모두 낮았으나 sCD40L의 변화량은 양군간에 차이는 통계적으로 의미가 없었다. (2제요법군: 166.9±150.1 3제요법군 : 148.0±157.6 pg/mL, p = NS)

3. 양군 모두 심각한 출혈은 없었고, 이상약물반응 때문에 실로스타졸을 중지한 경우도 없었다.

이상의 결과로 아스피린과 클로피도그렐의 2제요법에 실로스타졸의 부가적인 투여가 P2Y12 유발 혈소판응집억제를 증가시켰다. 하지만 sCD40L를 낮추거나 아스피린유발 항혈소판 작용에는 부가적인 효과가 없었다.

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핵심 되는 말: 실로스타졸, 급성심근경색증, 혈소판