Comparison of Original and Generic Clopidogrel 600 mg Loading Dose in the Patients Who Planned Undergoing Coronary Angiography

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Objective: *To compare the efficacy and safety of original (Plavix®) and generic (Apolets®) clopidogrel 600 mg loading in patients planning to undergo coronary angiography.*
Material and Method: *This is an experimental design, parallel, randomized-controlled study. Coronary artery disease patients planned for cardiac catheterization were recruited. Patients were randomized to receive either original or generic clopidogrel 600 mg loading dose. Platelet aggregation induced by 5 µmol/L and 20 µmol/L adenosine diphosphate (ADP) was measured by light transmission aggregometry (LTA) at baseline and 6 hours after clopidogrel 600 mg administration.*
Results: *Forty-nine patients were enrolled, 24 patients received original clopidogrel, and 25 patients received generic clopidogrel. After six hours of loading, there was significantly reduction in platelet aggregation induced by adenosine 5 µmol/L from 41.08 ± 3.04% to 19.50 ± 1.68% ($p < 0.001$) in original group compared to 36.76 ± 2.66% to 21.32 ± 2.60% ($p < 0.001$) in generic group. When induced by 20 µmol/L, the platelet aggregation was reduced from 58.50 ± 2.09% to 32.25 ± 2.30% ($p < 0.001$) in original group and from 61.12 ± 2.54% to 30.04 ± 3.14% ($p < 0.001$) in generic group. There was no significant difference between original and generic clopidogrel in reducing platelet aggregation induced by both adenosine 5 and 20 µmol/L. Groin hematoma was found in one case (4.2%) in the original clopidogrel group.*
Conclusion: *Generic clopidogrel (Apolets®) 600 mg loading dose is as effective as original clopidogrel (Plavix®) in term of platelet aggregation inhibition.*

Keywords: *Original clopidogrel, Generic clopidogrel, Coronary artery disease, Platelet aggregation, Adenosine diphosphate, Light transmission aggregometry*

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Cardiovascular diseases are the number one cause of death globally[1]. Antiplatelet therapy is now a standard treatment of cardiovascular disease particular in acute coronary syndrome (ACS). In this situation, rapid inhibition of platelet aggregation for prevention of thrombus formation is needed. Aspirin plus 300 mg clopidogrel loading is recommended[2-5]. However, some interventionists prefer to use double loading dose of clopidogrel for the patients who undergoing percutaneous coronary intervention (PCI) in this setting to accelerate more rapid platelet inhibition[6-8].

With financial barrier to access the essential medicines, generic clopidogrel can increase the access with affordable prices. The objective of the present study was to compare the efficacy and safety of double loading dose of original (Plavix®) and generic (Apolets®) clopidogrel tablets in patients with suspected coronary artery disease who undergoing coronary angiography with or without adhoc PCI.

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Material and Method

This was an experimental design, parallel, randomized-controlled study. The primary objective

was to compare the changes in platelet aggregation induced by 5 µmol/L and 20 µmol/L adenosine diphosphate (ADP) between original (Plavix®) and generic (Apolets®) clopidogrel 600 mg loading dose. The secondary objective was to compare the post-catheterization complications and drug adverse events. Suspected coronary artery disease patients planned for cardiac catheterization were recruited from registered patients of Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University. The patients who had hypersensitivity to clopidogrel, bleeding disorder, history of gastrointestinal bleeding, thrombocytopenia, receiving treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) except low dose aspirin (equal or less than 81 mg), serum creatinine more than 2.5 mg/dl, pregnancy or lactation, ages less than 18 or more than 75 years, participation in any other clinical trials within 30 days were excluded.

The present study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. Signed informed consent was obtained from all participants. Physical examination including measurement of body weight, height, blood pressure, and pulse was performed at baseline. Patients were randomized (1:1 ratio) to receive either original or generic clopidogrel 600 mg loading dose one hour before cardiac catheterization. Random assignment followed simple randomization procedures (computerized random numbers) prepared by third party with no clinical involvement and the sequence was concealed from investigator in sequentially numbered and opaque-sealed packaging. Platelet aggregation was measured by light transmission aggregometry (LTA) at baseline and 6 hours after 600 mg of clopidogrel administration; platelet aggregation was induced by 5 µmol/L and 20 µmol/L adenosine diphosphate (ADP). The laboratory technicians did not know which types of clopidogrel the patients received. The sample size to achieve 95% confident interval and 80% power with 20% dropout rate was calculated based on equivalent hypothesis. An analysis of covariance (ANCOVA), t-test, Pearson Chi-square test, and analysis of variance (f-test) were used for comparing the various measurements including those of the primary and secondary objectives. A p-value less than 0.05 was considered statistically significant.

Results

Forty-nine patients were enrolled between July 2011 and March 2012, 24 patients received original clopidogrel, and 25 patients received generic clopidogrel. All per-protocol clinical activities were completed within a one-day visit by each patient for a planned cardiac catheterization. Baseline demographic and clinical characteristics of participants were shown in Table 1.

Measurements of 5 µmol/L and 20 µmol/L ADP induced-platelet aggregation by light transmission aggregometry at baseline and six hours after clopidogrel 600 mg administration were shown in Table 2 and Fig 1. For 5 µmol/L ADP induced-platelet aggregation, the aggregation was significantly reduced at 6 hours after clopidogrel 600 mg administration from baseline by 21.58% and 15.44% in original and generic group, respectively ($p < 0.001$) and for 20 µmol/L ADP induced-platelet aggregation, the aggregation was reduced at 6 hours after clopidogrel 600 mg administration from baseline by 26.25% and 31.08% in original and generic group, respectively ($p < 0.001$). There were no significant differences in platelet aggregation reduction between original and generic clopidogrel group ($p = ns$). In this study, only 2 patients (8%) in generic clopidogrel group had high on-treatment platelet reactivity when using 5 µmol/L ADP induced-platelet aggregation and no one had high on-treatment platelet reactivity when induced-platelet aggregation with 20 µmol/L ADP[9] (Table 2).

Bleeding at puncture site (groin hematoma) was found in one case (4.2%) of original clopidogrel group. No other adverse events were reported in the present study.

Discussion

Platelets aggregation plays the important role of thrombus formation after plaque rupture as occurs spontaneously in patients with an ACS or as the result of a PCI[10]. For patients with coronary artery disease (CAD), the potential utility of measuring platelet function includes monitoring antiplatelet therapy and predicting clinical outcomes[11]. Light transmittance aggregometry (LTA), the historical "gold standard" test for measuring of platelet function, which was used in the present study, is based on the stimulation of platelet-platelet aggregation in platelet-rich plasma after stimulation with ADP. Clopidogrel, the present study drug, is an antiplatelet agent that inhibits ADP receptor-mediated platelet activation[10].

The primary objective of this study was to compare the changes in platelet aggregation induced by 5 µmol/L and 20 µmol/L ADP at baseline and six hours after clopidogrel 600 mg administration. At

Table 1. Baseline demographics and clinical characteristics

	Original (n = 24) mean ± SD	Generic (n =25) mean ± SD	p-value
Age (years)	60.75 ± 9.47	63.52 ± 10.08	0.327
Male (n (%))	17 (70.8%)	14 (56.0%)	0.282
Body weight (kg)	67.53 ± 10.89	64.72 ± 13.39	0.425
Body mass index (kg/m^2)	25.67 ± 4.07	25.28 ± 4.53	0.755
> 25 kg/m^2 (n (%))	11 (45.8)	14 (56.0)	0.477
Systolic BP (mmHg)	138.25 ± 24.78	137.64 ± 29.49	0.938
Diastolic BP (mmHg)	75.33 ± 9.74	75.48 ± 13.91	0.966
Pulse (times/min)	70.67 ± 11.26	79.84 ± 15.12	0.020*
Renal function			
Blood urea nitrogen (BUN) (mg/dl)	16.92 ± 6.32	18.48 ± 9.97	0.517
Creatinine (mg/dl)	1.06 ± 0.37	1.00 ± 0.30	0.525
Risk factors/medical history (n (%))			
Hypertension	23 (95.8)	24 (96.0)	0.976
Dyslipidemia	22 (91.7)	19 (76.0)	0.138
Diabetes mellitus	9 (37.5)	11 (44.0)	0.644
CAD S/P PCI	0 (0.0)	5 (20.0)	0.021*
CAD S/P CABG	3 (12.5)	4 (16.0)	0.726
Cardiomyopathy	7 (29.2)	13 (52.0)	0.104
Chronic kidney disease	4 (16.7)	1 (4.0)	0.143
Atrial fibrillation	1 (4.2)	4 (16.0)	0.171
Habitual alcohol intake	0 (0.0)	1 (4.0)	0.322
Habitual caffeine intake	6 (25.0)	6 (24.0)	0.935
Habitual smoking	2 (8.3)	4 (16.0)	0.413
Medications (n (%))			
Aspirin	19 (79.2)	17 (68.0)	0.376
Angiotensin converting enzyme inhibitor	12 (50.0)	11 (44.0)	0.674
Angiotensin recepter blocker	3 (12.5)	9 (36.0)	0.056
Beta blocker	19 (79.2)	17 (68.0)	0.376
Calcium channel blocker	5 (20.8)	11 (44.0)	0.084
Statin	20 (83.3)	17 (68.0)	0.212
Nitrate	10 (41.7)	8 (32.0)	0.483
Proton pump	5 (20.8)	10 (40.0)	0.146
InhibitorIndications for cardiac catheterization (n (%))			
Chronic stable angina	14 (58.3)	9 (36.0)	0.117
NSTE-ACS	3 (12.5)	6 (24.0)	0.299
Cardiomyopathy	7 (29.2)	10 (40.0)	0.426

CAD = coronary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; NSTE = ACS non-ST-segment elevation acute coronary syndrome
* $p < 0.05$

six hours after clopidogrel 600 mg administration, platelet aggregation reduction from baseline was 21.58% and 15.44% through 5 µmol/L ADP induction and 26.25% and 31.08% through 20 µmol/L ADP-induction in original and generic group, respectively ($p < 0.001$). This showed that original (Plavix®) and generic (Apolets®) clopidogrel 600 mg loading dose achieved a significant antiplatelet activities at six hours after administration and supported the efficacy of clopidogrel 600 mg loading dose as found in previous studies[7,8]. There were no differences between original (Plavix®) and generic (Apolets®) clopidogrel 600 mg loading dose in the changes in platelet aggregation induced by 5 µmol/L and 20 µmol/L ADP. It is

Table 2. Measurements of platelet aggregation by light transmission aggregometry

	Original clopidogrel (n = 24) (mean ± SE)	Generic clopidogrel (n = 25) (mean ± SE)	p-value
5 µmol/L ADP-induced aggregation			
Baseline (%)	41.08 ± 3.04	36.76 ± 2.66	0.289
6 hours (%)	19.50 ± 1.68	21.32 ± 2.60	0.563
At 6 hrs > 42.9%* (n (%))	0 (0.0)	2 (8.0)	0.157
20 µmol/L ADP-induced aggregation			
Baseline (%)	58.50 ± 2.09	61.12 ± 2.54	0.433
6 hours (%)	32.25 ± 2.30	30.04 ± 3.14	0.575
At 6 hrs > 64.5%* (n (%))	0 (0.0)	0 (0.0)	-

ADP = adenosine diphosphate; SE = standard error
* Clopidogrel resistance level (high on-treatment platelet reactivity)[9]

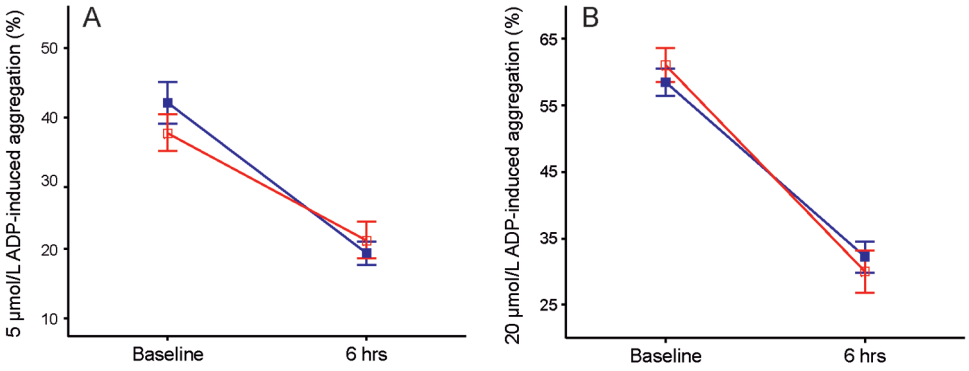

Fig. 1 5 µmol/L ADP-induced aggregation (A) and 20 µmol/L ADP-induced aggregation (B) at baseline and 6 hours after treatment with original (■) and generic (⊟) 600 mg clopidogrel loading dose (mean ± SE)

confirmed that the efficacy of original (Plavix®) and generic (Apolets®) clopidogrel were not different in term of platelet aggregation inhibition.

In conclusion, generic clopidogrel (Apolets®) 600 mg loading dose is as effective as original clopidogrel (Plavix®) and safe. In the patients who required rapid platelet inhibition such ACS or adhoc PCI patients, either original or generic clopidrogrel 600 mg can be used. The inhibition of platelet aggregation can achieve up to 80% at six hour after double loading dose.

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Potential conflicts of interest

None.

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การเปรียบเทียบประสิทธิภาพของยาโคลพิโดเกรลต้นแบบและสามัญขนาดยาเริ่มต้น 600 มก. ในผู้ป่วยที่ต้องได้รับการสวนหัวใจ

สุพจน์ ศรีมหาโชตะ, พลภัทร โรจน์นครินทร์, วสันต์ อุทัยเฉลิม, วศิน พุทธารี, จักรพันธ์ ชัยพรหมประสิทธิ์, วรฤทธิ์ เลิศสุวรรณเสรี, เบญจพร อัคควัฒน์, สมบูรณ์ จิรภัทรธำรง

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิภาพและความปลอดภัยในการยับยั้งการเกาะกลุ่มของเกล็ดเลือดของยาโคลพิโดเกรลต้นแบบและสามัญในขนาดยาเริ่มต้น 600 มก.

วัสดุและวิธีการ: การศึกษาเชิงทดลองแบบ randomized-controlled study ศึกษาในผู้ป่วยโรคหลอดเลือดโคโรนารีย์ที่ต้องได้รับการสวนหัวใจ ผู้ป่วยถูกสุ่มให้ได้รับยาโคลพิโดเกรล ต้นแบบ (Plavix®) หรือ สามัญ (Apolets®) ขนาดยาเริ่มต้น 600 มก. ทำการวัดการเกาะกลุ่มของเกล็ดเลือด กระตุ้นการเกาะกลุ่มของเกล็ดเลือดด้วย adenosine diphosphate (ADP) ที่ 5 และ 20 ไมโครโมล/ลิตร และทำการวัดโดย light transmission aggregometry (LTA) ก่อนและหลังรับประทานยาโคลพิโดเกรลครบ 6 ชั่วโมง

ผลการศึกษา: ผู้ป่วยเข้าร่วมการศึกษาจำนวน 49 ราย ได้รับยาโคลพิโดเกรลต้นแบบจำนวน 24 ราย และได้รับยาสามัญจำนวน 25 ราย การเกาะกลุ่มของเกล็ดเลือดลดลงอย่างมีนัยสำคัญทางสถิติหลังรับประทานยาครบ 6 ชั่วโมง โดยเมื่อกระตุ้นด้วย ADP ที่ 5 ไมโครโมล/ลิตร ลดลงจาก 41.08 ± 3.04% เป็น 19.50 ± 1.68% ($p < 0.001$) ในกลุ่มยาต้นแบบ และจาก 36.76 ± 2.66% เป็น 21.32 ± 2.60% ($p < 0.001$) ในกลุ่มยาสามัญ และเมื่อกระตุ้นด้วย ADP ที่ 20 ไมโครโมล/ลิตร การเกาะกลุ่มของเกล็ดเลือดลดลงจาก 58.50 ± 2.09% เป็น 32.25 ± 2.30% ($p < 0.001$) ในกลุ่มยาต้นแบบ และจาก 61.12 ± 2.54% เป็น 30.04 ± 3.14% ($p < 0.001$) ในกลุ่มยาสามัญ ไม่พบความแตกต่างทางสถิติระหว่างกลุ่มที่ได้รับยาโคลพิโดเกรลต้นแบบและสามัญในการยับยั้งการเกาะกลุ่มของเกล็ดเลือด พบเลือดออก (bleeding) บริเวณที่แทงสายสวนหัวใจจำนวน 1 ราย ในกลุ่มที่ได้รับยาโคลพิโดเกรลต้นแบบ

สรุป: ยาโคลพิโดเกรลต้นแบบ (Plavix®) และสามัญ (Apolets®) ขนาดยาเริ่มต้น 600 มก. มีประสิทธิภาพและความปลอดภัยไม่แตกต่างกัน