Overcoming Aspirin Resistance with Loading Clopidogrel Earlier in Elective Percutaneous Coronary Intervention

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Abstract

We aimed to analyze the clinical effect of clopidogrel loading time on adverse cardiovascular events among patients with aspirin resistance. Recurrent adverse events may still occur despite dual antiplatelet therapy after coronary stenting. Aspirin resistance is one of the possible reasons of this trouble. Optimal antiplatelet strategy for coronary stenting is unknown among patients with aspirin resistance. A total of 980 patients scheduled for elective coronary stenting were enrolled and allocated into two groups according to the loading time of clopidogrel more or less than 6 hours before coronary intervention (early- or late-loaded groups, respectively). Aspirin resistance was determined according to the urinary levels of 11-dehydrothromboxane B2. Overall 240 patients who were allocated to early- and late-loaded groups were identified as aspirin resistant according to the urinary levels of 11-dehydrothromboxane B2. After a follow-up period of 12 months major adverse cardiac events were observed among 16 patients (13.9%) in the early-loaded group and 30 patients (25.8%) in the late-loaded group ($p = 0.02$). Early loading of clopidogrel was an independent predictor of lower rate of cardiac events (hazard ratio = 0.46 [0.32–0.76, 95% confidence interval], $p = 0.001$). The rates of bleeding events and periprocedural myocardial infarction were similar in early- and late-loaded groups. The current study demonstrated that loading of clopidogrel earlier than 6 hours before elective coronary stenting among aspirin-resistant patients was associated with increased benefits for ischemic events with similar bleeding rates.

Keywords

- antiplatelet drugs
- chronic stable angina
- coronary artery disease
- stents

Intracoronary stenting is widely used during elective angioplasty to reduce the rate of restenosis. Effective platelet inhibition after stenting is needed to decrease the risk of unfavorable cardiovascular events. Dual antiplatelet therapy combining aspirin and a thienopyridine is the standard of care for stable coronary artery disease patients who have undergone elective percutaneous coronary intervention (PCI).¹ Clopidogrel pretreatment followed by maintenance therapy effectively reduced the occurrence of major cardiovascular events in patients undergoing PCI.²

Aspirin has been shown to reduce the rate of serious vascular events especially among high-risk patients although considerable number of patients still continues to suffer from adverse cardiovascular events while under aspirin therapy.³

Lack of antiplatelet effects of aspirin has been defined as “aspirin resistance.” This condition may be observed clinically or biochemically as elevated urinary levels of 11-dehydrothromboxane B2 (11-dTxB2), which has been known to be a stable metabolite of thromboxane A2.⁴ Despite adequate pretreatment with clopidogrel, patients with aspirin resistance have an increased risk following nonurgent PCI.⁵

Pretreatment of clopidogrel earlier than 6 hours before PCI is tended to enhance the beneficial effects of the drug, but giving the loading dose later did not reduce adverse events.⁶ Earlier and stronger antiplatelet effects have been demonstrated after loading with 600 mg of clopidogrel in patients undergoing PCI.^{7,8} Conversely, the rates of adverse

Fig. 1 Flow diagram of early-loaded versus late-loaded group. The diagram includes detailed information on the excluded patients.

cardiovascular events were similar when a loading dose of 600 mg of clopidogrel was used compared with the conventional dose of 300 mg in stable patients undergoing elective PCI.⁹ Optimum loading time for clopidogrel before elective PCI in patients who do not respond adequately to antiplatelet therapy with aspirin has not been fully determined yet. We hypothesized that administering a loading dose of 600 mg clopidogrel earlier than 6 hours before PCI would reduce the cardiac events among patients with known aspirin resistance with stable coronary artery disease. The current prospective cohort study was therefore set up to test this hypothesis. We also aimed to test the safety of this antiplatelet strategy.

Methods

This prospective cohort study was set to evaluate the efficacy and safety of two antiplatelet strategies. This report complies with Consolidated Standards of Reporting Trial (CONSORT) statement.¹⁰

Study Population and Ethics

All patients scheduled for elective PCI were screened for eligibility. Patients with acute coronary syndrome, known aspirin intolerance, contraindications to antithrombotic or antiplatelet therapy, renal failure (creatinine > 2 mg/dL), under therapy of

glycoprotein IIb/IIIa inhibitors or chronic oral anticoagulation were excluded. The study protocol was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki, as revised in 2000. All the patients gave written informed consent before their inclusion into the study. Eligible patients were assigned alternately into two groups according to the loading time of clopidogrel more or less than 6 hours before elective coronary intervention (early- and late-loaded groups, respectively). After PCI patients were tested for aspirin resistance and divided into quartiles according to the urinary levels of 11-dTxB2. The patients in the highest quartile were identified as aspirin-resistant patients and followed up for further analysis. The detailed flow diagram of participants is shown in ►Fig. 1. Sample size was calculated with assumed event rates 24 and 10%, respectively, in aspirin-resistant and aspirin-sensitive groups, which is in agreement with a previous prospective study.³ A sample size of 224 was necessary for a two-sided test with 0.80 statistical power and an α -level of 0.05.

Coronary Angiography and Stenting

Enrolled patients received 300 mg of aspirin and 600 mg of clopidogrel before entering the catheterization laboratory. The right femoral approach was the preferred method, and the radial approach was utilized in selected patients without

femoral access. During the intervention an intravenous bolus of weight-adjusted unfractionated heparin with a targeted activated clotting time (ACT) of 250 to 300 seconds was administered. Extra pre- or postdilatation with a balloon, or intracoronary nitrate administration for maximal epicardial vasodilation were left at the discretion of the operator. As the final step, stenting was performed. The arterial sheaths were removed by manual compression, once the ACT was ≤ 160 seconds or 5 hours after the anticoagulation was discontinued. On days 2 through 365 all the patients received 100 mg of aspirin and 75 mg of clopidogrel once a day. Locally approved preparations of aspirin and clopidogrel were used. Either enteric-coated or nonenteric-coated aspirin preparations were allowed. Beta blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were given unless contraindicated. To exclude the effect of different stents with regard to the risk of stent thrombosis only one type of stent was implanted (Gazelle coronary stent system, Biosensors International, Morges, Switzerland).

Urinary Analysis

Aspirin resistance was determined according to the urinary levels of 11-dTxB2. The first morning urine samples were collected and levels of 11-dTxB2 were determined by means of commercially available enzyme immunoassay (11-dehydrothromboxane B2 EIA Kit, Cayman Chemical, Ann Arbor, MI) following the manufacturer's instructions with laboratory personnel blinded to clinical status of patients. Urine samples were first purified as recommended by immunoassay kit using a solid phase extraction cartridge (Cayman Chemical). All urine samples were assayed in duplicate, and the mean intra-assay coefficient of variation (CV) was 7.2%. The interassay CV from three samples assayed in duplicate was 9.4%. Patients were divided into quartiles according to the urinary levels of 11-dTxB2.

Follow-Up Outcomes

Follow-up visits were scheduled at 1st and 2nd months after discharge and thereafter patients were followed bimonthly up to 12th month. Drug compliance was checked, efficacy and safety outcomes were recorded at follow-up visits. Assessment of outcomes was performed by two physicians blinded to the study groups.

The predefined efficacy outcome was the composite rate of cardiovascular death, myocardial infarction, definite/probable stent thrombosis and stroke at 1 year. Myocardial infarction was diagnosed as occurrence of ischemic symptoms and

elevation of troponin greater than the upper limit of normal. Safety outcomes were defined as major and minor bleedings. Major bleeding was defined as fatal bleeding, intracranial hemorrhage, and bleeding that necessitated red blood cell transfusion ≥ 2 units. Bleeding events other than major bleedings were defined as minor bleedings.

Statistical Analysis

Baseline demographics and clinical properties were expressed as mean or proportion. Student *t* and Mann–Whitney *U* tests were used for comparing groups according to the distribution of data. Fisher exact chi-square and Pearson chi-square tests were used for analyzing the categorical variables. Kaplan–Meier curve and log rank tests were used for evaluating clinical events. Relation of clinical outcomes and different variety of clinical and demographic characteristics were evaluated by multivariate Cox proportional hazards regression models. All the statistical analyses were performed using the SPSS software package (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY) version 20 and a *p* value < 0.05 was considered statistically significant. The confidence intervals were calculated at the 95% level.

Results

Highest quartile of 960 patients according to the urinary levels of 11-dTxB2 who were allocated to early- and late-loaded groups were identified as aspirin resistant (**►Table 1**). **►Table 2** outlines the number of participants in each group and comparison of baseline clinical and demographic characteristics. There was no significant difference between the two groups regarding the age, sex, risk factors, previous myocardial infarction, coronary artery bypass grafting or PCI and medical therapy. Bare metal stents were implanted to all patients and the numbers of stents implanted were also similar between the groups. Mean loading time of clopidogrel before PCI was 479.6 ± 140.0 minutes in the early-loaded group and 153.7 ± 114.2 minutes in the late-loaded group ($p < 0.001$). Five patients in the early-loaded group and four patients in the late-loaded group were lost to follow-up; thus data from 231 patients were available for analysis. No patient was considered protocol violator. After follow-up period of 12 months cardiovascular outcomes were observed among 16 patients (13.9%) in the early-loaded group and 30 patients (25.8%) in the late-loaded group ($p = 0.02$) (**►Fig. 2**). Predictors of cardiac events in multivariate Cox regression model and Kaplan–Meier curve of early- and late-loaded groups were demonstrated in **►Table 3** and **►Fig. 3**,

Table 1 Quartiles according to the urinary levels of 11-dehydrothromboxane B2 (11-dTxB2)

Quartile	Early-loaded group	Late-loaded group
	Urinary 11-dTxB2 level (ng/mmol creatinine)	Urinary 11-dTxB2 level (ng/mmol creatinine)
I	< 24.2 ($n = 120$)	< 25.1 ($n = 120$)
II	$24.2\text{--}37.8$ ($n = 120$)	$25.1\text{--}38.6$ ($n = 120$)
III	$37.9\text{--}54.7$ ($n = 120$)	$38.7\text{--}56.6$ ($n = 120$)
IV	> 54.7 ($n = 120$)	> 56.6 ($n = 120$)

Table 2 Baseline characteristics of study participants in early- and late-loaded groups

Characteristic	Early-loaded group (n = 120)	Late-loaded group (n = 120)	p-Value
Age (y)	62 ± 10	61 ± 11	0.71
Sex (male)	80 (67)	79 (66)	0.91
Smoking	50 (42)	59 (49)	0.35
Hypertension	69 (58)	74 (62)	0.58
DM	33 (28)	28 (23)	0.39
Previous MI	32 (27)	35 (29)	0.75
Previous CABG	22 (18)	13 (11)	0.11
Previous PCI	51 (43)	36 (30)	0.08
Number of stent per patient	1.4	1.38	0.82
ACE-I/ARB tx	100 (83)	104 (87)	0.45
Beta blocker tx	78(65)	83(75)	0.14
Statin tx	111 (93)	115 (96)	0.67
PPI tx	30 (25)	22 (18)	0.29
Calcium channel blocker	4 (3)	5 (4)	0.71
Time of loading clopidogrel (min)	479.6 ± 140.0	153.7 ± 114.2	< 0.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; tx, therapy.
Note: Values are presented as mean ± SD or n (%).

Fig. 2 Cardiovascular event rate according to the loading groups of clopidogrel.

Fig. 3 Kaplan–Meier curve of early- and late-loaded groups.

Table 3 Predictors of cardiac events in multivariate Cox regression model

Characteristics	HR	95% CI	p-Value
Age	0.98	0.96–1.03	0.92
Female sex	1.24	0.56–2.58	0.26
Diabetes mellitus	1.14	0.56–2.29	0.71
Previous MI	1.42	1.10–2.68	0.02
Beta blocker	0.61	0.36–1.05	0.077
Early loading of clopidogrel	0.46	0.32–0.76	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Table 4 Comparing periprocedural event rates (%) in early- and late-loaded groups

Complication	Early-loaded group	Late-loaded group	HR	p-Value
Major bleeding rate (%)	2.5	1.7	1.21 (0.63–2.26)	0.71
Minor bleeding rate (%)	6.7	5.0	1.55 (0.76–2.03)	0.52
Periprocedural myocardial infarction (%)	3.3	4.2	0.71 (0.26–1.92)	0.62

Abbreviation: HR, hazard ratio.

respectively. Periprocedural efficacy and safety outcomes were similar between groups (→ **Table 4**).

Discussion

The current study demonstrated that loading 600 mg of clopidogrel earlier than 6 hours before elective coronary stenting lessened the detrimental effects of aspirin resistance and early loading of clopidogrel was an independent predictor of lower cardiac event rate (hazard ratio = 0.46, [0.32–0.76, 95% confidence interval], $p = 0.001$). This finding is in agreement with the pharmacokinetic profile of the prodrug clopidogrel that requires metabolization into an active molecule.

In suspicion of aspirin resistance, clinicians should follow other antiplatelet strategies. Potent inhibition of adenosine diphosphate-mediated platelet reactivity may be more beneficial to reduce clinical events in aspirin-resistant patients. New P2Y₁₂ antagonists, prasugrel and ticagrelor achieve greater platelet inhibition, compared with clopidogrel;^{11,12} however, no clinical studies have evaluated the benefit of these drugs in stable coronary artery disease patients. So an effective clopidogrel therapy should be implemented to aspirin-resistant patients. To our best knowledge, this is the first study to examine the long-term effect of the timing of clopidogrel loading in patients with aspirin resistance.

The complete antiplatelet effect occurs at 6 to 8 hours after loading 600 mg of clopidogrel and at 18 to 24 hours after loading with 300 mg.^{13,14} A loading dose more than 300 mg was known to provide faster onset of action and greater reduction in platelet activation during the first 24 hours.¹⁵ On the other hand, individual variations of antiplatelet response after clopidogrel loading have been demonstrated in many studies.^{16–18} A recent meta-analysis showed that clopidogrel pretreatment in stable patients undergoing elective PCI is not associated with lower rate of mortality or cardiac adverse events, as compared with clopidogrel administration in the catheterization laboratory.¹⁹ So, clopidogrel treatment is recommended after the coronary anatomy is known. Our data are discordant with this meta-analysis among aspirin-resistant patients.

Resistance to clopidogrel may coexist with aspirin and may be prevalent up to 50% of patients with aspirin resistance. The routine testing for clopidogrel resistance is not recommended.^{20,21} In this trial, the ischemic benefit of an early increased dose of clopidogrel before coronary stenting was demonstrated among aspirin-resistant patients without considering clopidogrel resistance in the study population.

In general, ischemic benefits of an antithrombotic strategy are counterbalanced by increased bleeding rates. However, early loading of clopidogrel among aspirin-resistant patients was associated with increased benefits for ischemic events with similar bleeding rates in this trial. This observation may be due to ineffectiveness of aspirin. All together, these findings suggest that loading high dose of clopidogrel earlier than 6 hours before PCI may counteract the negative effects of aspirin resistance. Certainly testing for aspirin resistance cannot be recommended on the basis of these data, but at least additional information for clinical practice may be added to patients with known or suggested aspirin resistance.

Conclusions

Preliminary results from this trial demonstrated that loading 600 mg of clopidogrel earlier than 6 hours before elective coronary stenting may lessen the detrimental effects of aspirin resistance without increasing the risk of bleeding. This strategy may be useful antiplatelet therapy in patients with known aspirin resistance before elective coronary stenting, and may help to modify the clinical outcomes in aspirin-resistant patients. Early administration of clopidogrel strategy may also be an option when not using new P2Y₁₂ antagonists, such as prasugrel, ticagrelor, or cangrelor.

Conflict of Interest

The authors report no financial relationships or conflicts of interest regarding the content herein.

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