Can doubling the maintenance dose of clopidogrel prevent from early stent thrombosis after the primary percutaneous coronary intervention?

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Abstract

BACKGROUND: Treatment of significant coronary artery disease with primary percutaneous coronary intervention (PCI) seems better than angioplasty balloon; because the incidence of restenosis is lower in this method, however, a serious complication of PCI is stent thrombosis which would lead to repeated myocardial infarction (MI) and increase the mortality and morbidity. One of the frequent medications which is used to prevent from stent thrombosis is clopidogrel, but, stent thrombosis was seen in many of the patients despite given the conventional dosage of this drug. This study aimed to evaluate the effect of doubling the maintenance dose of clopidogrel to prevent from early stent thrombosis, MI and mortality rate.

METHODS: This was a clinical trial study which was done in Shahid Chamran Hospital in winter 2010 in Isfahan, Iran. A total of 400 patients with PCI were prospectively followed-up for 30 days. All the patients were randomly allocated into two groups. The control group received a maintenance dose of 75 mg clopidogrel while the case group received 150 mg clopidogrel after the initial dosage of 600 mg for 30 days after the PCI. The incidence of primary outcome such as total mortality was recorded during the study.

RESULTS: Early stent thrombosis was observed in 4 patients (1%) (One subject in the control group and 3 in the case group) during the first 30 days after PCI, but the difference was not significant between the two groups (P = 0.62). Mortality due to stent thrombosis occurred in 2 patients in the case group which showed no significant difference in this group (P = 0.5). In addition, MI occurred in 2 patients (1 in each group) which also showed no significant difference between the two groups (P = 1). Drug complication such as major bleeding had no significant difference between the two groups (P = 0.9).

CONCLUSION: The present study showed that doubling dose of clopidogrel could not reduce the incidence of early stent thrombosis, mortality and myocardial infarction in comparison with conventional dosage; therefore it is recommended that more studies be done in Iranian and Asian race for clinical decision-making to prevent form stent thrombosis using high dose of clopidogrel.

Keywords: Primary Coronary Intervention, Early Stent Thrombosis, Clopidogrel, Coronary Stenting.

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Introduction

Increasing incidence of cardiovascular disease particularly coronary artery diseases has enlarged the mortality rate due to prevalence of this group of disease all over the world, and it has reached the world's top 10 mortality causes.[1] On the other hand, high incidence of these diseases caused increasing progression and advancement of new techniques and methods to treat such diseases.[2] Naturally, invented techniques and tools to treat cardiovascular disease induce some complications for the patients. The tools which are highly applicable and effective for the patients with coronary artery stenosis and atherosclerosis are stents which are inserted for the patients in most of the medical and specialized cardiovascular centers. Despite its efficacy and high efficiency for saving the patients' life, stents have also a series of complication that sometimes lead to death.[3] According to the conducted studies, the prevalence of these complications in the patients

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undergoing stenting is 5-10 percent. The most important short-term complications in the studied patients are as the following:

1. Mortality: Death with all the cases

2. Myocardial Infarction: Increasing total CK ≥ 2 times the upper limit of normal or CK MB ≥ 20 (ng/ml) with or without the presence of new pathologic Q waves in at least two continuous leads.

3. Urgent Target Vessel Revascularization: Repeated PCI or surgery at the same treated vein.

4. Stroke

5. Acute thrombosis due to stent: As angiographic evidence of thrombus at the lesion site.

6. Angiographic complications: Including coronary dissection and coronary perforation.

One of the most serious stenting complications is the stent thrombosis which is considered as acute stent thrombosis (less than 24 hours), subacute stent thrombosis (24 to 30 days) and delayed stent thrombosis (30 days to 1 year).[4] Early stent thrombosis includes acute and subacute cases which are identified based on clinical, angiography and pathological criteria and usually are associated with serious and lethal complications, increase in mortality and morbidity and recurrent infarction. Furthermore, it can prolong the duration of hospitalization of the patients in the hospital and cause imposing exorbitant costs on them.

At the initial experiences of primary percutaneous coronary intervention, the incidence of early stent thrombosis was associated with more than 24% of the cases; however, following the use of antiplatelet aspirin and ticlopidine drugs and acquiring appropriate techniques of stenting, this figure declined to less than 2 percent.[1]

Clinical definition of the stent thrombosis includes each of the following items 30 days after the primary percutaneous coronary intervention.[1]

1. Observing stent occlusion based on angiographic criteria.

2. Sudden death without any clear reason when not sure about patency of the stent.

3. Myocardial infarction or need to emergency revascularization

In a study, the prevalence of mortality following the early stent thrombosis is reported 7-25 percent which the major prognostic factors included inadequate patency of the stents, residual tear and inadequate inhibition of the platelet aggregation.[5]

In order to prevent from dangerous and deadly complications, various factors have been studied; the most important of which are using platelet inhibitory drugs. Conventional and routine dose of these drugs are about 75-325 mg Aspirin and 300-600 mg Clopidogrel which the dosage would be different based on the type of the applied stents, the time of using and the dose of these two drugs. Using 150 mg Clopidogrel is recommended for the patients who have left main coronary artery involvement or if the only patent vessel of the patients had been PCI.[1]

It is recommended that combination of maintenance treatment be used for one year after the primary percutaneous coronary intervention and the combination of these two rugs also be used for at least 6 weeks.[6] One of the other causes of stent thrombosis is resistance to aspirin and Clopidogrel and/or inadequate dose these drugs in inhibiting the platelets. In a study, the comparison of Aspirin and Clopidogrel in inhibiting the platelets and resistance to them showed that stent thrombosis was more due to aspirin-resistance and increasing the dose of this drug had no effect on platelet inhibition.[4]

In a clinical trial study which was done by Steven in North America in 2011, 2116 patients who underwent PCI surgery were studied. In this study, 1053 patients (case group) received 300 mg Clopidogrel and the control group (1053 patients) received a daily placebo pill 3 to 24 hours before the surgery. Moreover, all the patients received 75 mg Clopidogrel for 28 days after the surgery and from the 29th day to the next 12 months after the surgery, the first group received 75 mg Clopidogrel while the control group received placebo. The results of the study after one year follow-up indicated that Clopidogrel could reduce the relative risk of mortality, myocardial infarction and stroke rate to 26.9%. In addition, taking Clopidogrel at least 6 hours before the surgery could reduce the relative risk of mortality rate to 38.6%. The mortality rate had no significant difference between the Clopidogrel group and placebo group since the 29th day to one year after the surgery[7] which was in accordance with the results of the present study.

In another study, 2954 patients underwent primary percutaneous coronary intervention; it was concluded that doubling the dose of Clopidogrel could reduce mortality, MI and stent thrombosis in the first 15 days after the PCI.[8]

Considering the different results of various studies, the fact is that there are still not adequate available documents for a decisive conclusion. Therefore, the present study aimed to evaluate the effect of doubling the maintenance dose of Clopidogrel on early stent thrombosist.

Materials and Methods

This clinical trial study was done in winter 2010 in Shahid Chamran Hospital in Isfahan. The study

population included all the patients with coronary stenosis who underwent stenting. Sampling method was done in simple consecutive sampling. The inclusion criteria included patients with marked coronary artery stenosis, candidates for stenting and desire to participate in the study. The exclusion criteria included stenosis in left main coronary artery and proximal part of LAD, allergy to Clopidogrel, implementing angioplasty, history of MI in the past month, symptoms toward congestive heart failure and stenting on the only patent vessel of the patient.

After selecting and obtaining the consent form, the patients were given the initial dose of 600 mg Clopidogrel one day before the PCI. The patients used two type of stents; Bare Metal Stent (BMS) and Drug Eluted Stent. The patients, who had PCI complications such as incomplete wall, dissection apposition or stent under expansion, were excluded from the study. Thereafter, the rest of the patients were divided into two groups with random allocation method. The first group was given 75 mg Clopidogrel once a day for 30 days. The second group also was given 75 mg Clopidogrel twice a day for 30 days. The mentioned patients were followed-up at the end of second and fourth weeks and the results were recorded in their files. Besides, the patients were recommended to contact the researcher if any problem such as bleeding or fever happened. The data was collected using a checklist which had been designed to do so through interviewing with the patients and their relatives, observing the patients' status and also results of the angiography and physical examination. Collection of the data was conducted by referring the researcher to the patients' beds and examination and also interviewing them to complete the checklist.

In order to review the drug complications such as bleeding, neutropenia (less than 1500 counts), thrombotic thrombocytopenia purpura (TTP) and also gastrointestinal symptoms, hive and purities one month later, the patients were contacted and additional test (complete blood count, …) was performed.

The data of the study, after collecting and revising were analyzed using Software $SPSS_{17}$. The statistical tests for analyzing the data used in this study included chi-square and if necessary, Fisher's exact test (to compare between the qualitative data) and logistic regression and student's T tests.

Results

In this study, 517 patients underwent stenting surgery out of which 117 cases were excluded from the study due to not using Plavix® and finally 400 patients entered the study. Among 400 patients, 195 of them took Plavix daily (control group), and 205 of them (as the case group) received doubled dose of Clopidogrel. Mean age of the total studied patients was 60.2 ± 11.5 years. Minimum and maximum age of them was 31 and 87 years, respectively. 128 patients in the control group and 136 patients in the case group were males (65.3% vs. 66.3%) and mean age of the males and females of the study was 59.3 ± 11.7 and 61.7 ± 10.9 years, respectively.

In this study, 184 of the patients (46%) had blood pressure (systolic BP equal/more than 140 or diastolic BP equal/more than 90), 62 of them (15.5%) had high blood fats (LDL ≥ 100; TG ≥ 250) 77 of them (19.3%) had diabetes HDS ≥ 45; FBS ≥ 126), 77 patients were smoker and 11 patients had mild to moderate renal failure (GFR < 60). The prevalence of these risk factors in the two groups is shown in Table 1.

In 95 patient in the control group and 92 patients in the case group, one stent had been inserted (48.7% vs. 44.9%). Furthermore, in 100 patients in the case group and 113 patients in the control group, two stents had been used (51.3% vs. 55.1%). Chi-square test also showed no significant difference between the two groups in terms of the number of the applied stents (P = 0.51).

Table 1. Frequency distribution of the cardiovascular risk factors in both groups

Risk factors	Control group		Case group		P
	Number	Percentage	Number	Percentage	
HTN	87	44.6	97	47.3	0.59
HLP	27	13.8	35	17.1	0.37
DM	40	20.5	37	18	0.53
Smoking	41	21	36	17.6	0.38
Renal Failure	6	0.03	5	0.02	0.9

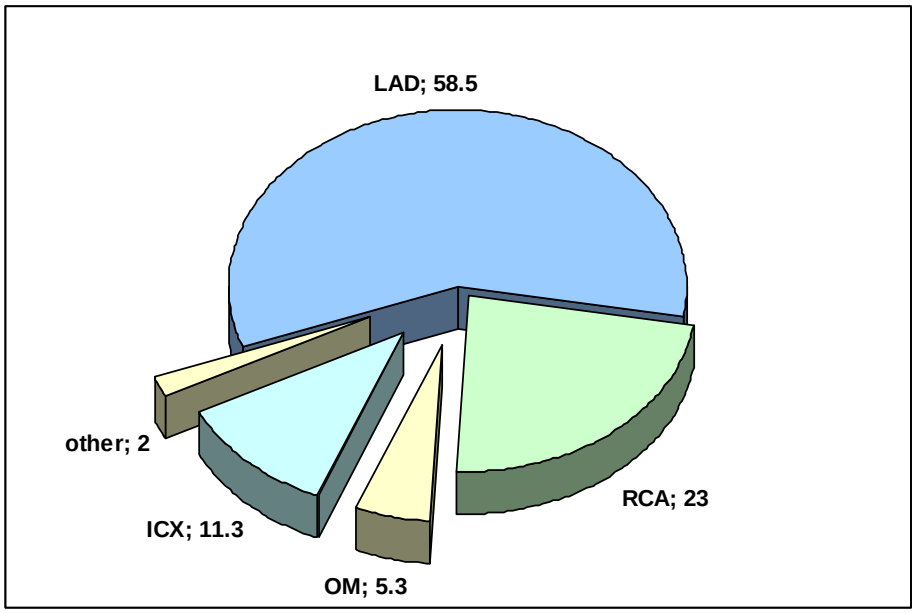

Chart 1. Frequency percentage of the artery stentingin the patients

Out of 321 applied stent in the control group, 254 of them were BMS (79%) and in the case group, out of 292 stents, 214 of them were BMS (73%) which the difference was not statistically significant (P = 0.7).

The frequency of artery stenting results is shown in chart 1. Moreover, in 8 patients (2%), more than one artery had been stenting such as using LAD and RCA which had been applied in 3 patients.

The average length of used stents in the study subjects was 21.7 ± 8.1 mm and according to student's T test, the difference in length of the stents in the two groups was not significant (P = 0.09).

According to the obtained results during the study, 4 cases of stent thrombosis occurred in the studied patients and cumulative incidence of stent thrombosis one month after the PCI surgery was 1%.

One case of thrombosis occurred in the control group (0.5%) and 3 cases in the case group (1.5%), however, Fisher's exact test showed that frequency distribution of stent thrombosis in the two groups had no significant difference (P = 0.62).

According to the results during the study, two deaths happened in all the patients. Hence, the incidence of mortality during one month after the primary percutaneous coronary intervention was equal to 0.5%. It should be noted that the both cases of mortality were related to the group consuming doubled dose of Plavix, but Fisher's exact test showed no significant correlation between mortality and dose of Plavix (P = 0.5). The both subjects passed away at the age of 55.

One month after the PCI surgery, two subjects suffered from recurrent myocardial infarction. Hence, the incident rate of recurrent MIin these patients was 0.5%. One of the subject with recurrent MIwas in the case group and the other was in the control group and according to Fisher's exact test, recurrent MIhad also no difference between the two groups (P = 1).

Life-threatening complications including excessive bleeding, neutropenia and thrombotic thrombocytopenia purpura (TTP) or gastrointestinal and cutaneous complications were not observed in none of the groups. However, nose bleeding was recorded in 3 cases in the case group and 2 cases in the control group which was not significant between the two groups (P = 0.9).

Discussion

The main objective of the present study was to evaluate the effect of doubling the maintenance dose of Clopidogrel to prevent from early stent thrombosis after stenting in the patients with coronary artery stenosis.

Mean age of the patients was 60.2 ± 11.5 years. The studied results showed that approximately 83 percent of those who die due to cardiovascular diseases are at the age of 65 and more. Hence, age is considered as one of the major risk factors for incidence of MI and with increase of age, the risk of cardiovascular diseases would be more.[9] In terms of gender distribution, 65.6% and 66.3% of the subjects of the control and case groups were males

respectively. Different studies around the world have shown that males suffer heart attack in lower ages compared to females.[10]

In this study, stent thrombosis was studied as the main dependent variable and at the end of the study; there was no significant difference between the case group that consumed doubled dose of Clopidogrel and the control group that consumed the conventional dose of this drug. In other words, increased dose of this drug had no effect on prevention from thrombosis in patients who underwent stenting.

In a prospective study which was done by Andrew in 2005, the patients were followed-up in terms of incidence of stent thrombosis one month after the PCI (for the early stent thrombosis) for the averagely 1.5 year after it.[11] The incidence rate of stent thrombosis was reported 0.5% which compared to the present study (1%) had a very minute difference that might be due to smaller sample size. But, in another study by Brendan Doyle et al, the cumulative incidence rate of stent thrombosis at the first 30 days after the surgery was 5% which was in accordance with the present study.[12] However, in another study it was concluded that doubling the Clopidogrel dose could reduce mortality, infarction and stent thrombosis at the first 15 days after the PCI.[8]

The study of Julie et al showed that increased maintenance dose of Clopidogrel for one month had not any additional effect on platelet activity among the patients which was in accordance with the present study.[13] But, in the study of Dominick et al they have came to realize that in high-risk groups, the patients with diabetes mellitus who had simultaneous coronary artery involvement, increased dose of this drug caused exacerbation of anti-platelet activity in the patients.[14] Moreover, the study of Gladding et al, showed that by giving 1200 mg initial dose and then repeating a 600 mg dose after two hours and continuing the treatment with maintenance dose of 150 mg daily could have a better effect on inhibiting the platelets activity in comparison with conventional dose (initial dose of 600 mg)[15] which indicated the necessity of more studies for administration of higher dosage for preventing stent thrombosis considering its potential complications.

In the study of Aleil et al, double initial and maintenance dose showed better effects in the laboratory tests in comparison with its conventional dose; however, it should be emphasized that clinical studies should confirm it.[16]

In the study of Tavassoli et al, it was indicated that double maintenance dosage of Clopidogrel caused lower rates of stent thrombosis and cardiovascular incidents compared to conventional dose (P = 0.002); however, the complications were similar for both groups.[17]

In the study of Palmerini et al, it was indicated that in patients with acute MI double dose could reduce stent thrombosis. But these patients, who were associated with high-risk of stent thrombosis, excluded from the present study.[18]

In the study of Gilles et al, the effect of high maintenance dose of Clopidogrel after 15 days in 2954 patients showed very little reduction in the stent thrombosis which was statistically significant.[19]

Nevertheless, as indicated, there were different results in various studies, but as it was mentioned in several recent studies, increased dosage could have beneficial effects which were *not* in accordance with the present study. However, the initial dose in the present study was 600 mg while it was 300 mg in other mentioned studies which might justify lack of difference between the two groups of the present study. Thereto, considering the very low incidence of stent thrombosis, further studies should be done with larger sample size. Certainly, it should not be ignored that genetic differences, as indicated in the mentioned studies, in European and American races could cause similarity of the results because pharmacokinetic and pharmacodynamics of the drugs are varied in different races. Besides, the above mentioned studies emphasized that the effect of increased dose might have different responses in low risk and high risk groups which may not specify this in general researches and requires to be conducted in the high risk groups separately.

At the end, it is recommended that future studies be done with larger sample size and higher dose and over a multi-level medical center particularly in Asian and Persian race and in a longer follow up time to review late stent thrombosis.

Conflict of Interests

Authors have no conflict of interests.

References

1. Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Single Volume (Heart Disease (Braunwald) (Single Vol)). 8th ed. Philadelphia: Saunders, 2007.
2. Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 2000; 102(25): 3137-47.

3. Humphrey LL, Fu R, Rogers K, Freeman M, Helfand M. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. Mayo Clin Proc 2008; 83(11): 1203-12.
4. Wenaweser P, Dorffler-Melly J, Imboden K, Windecker S, Togni M, Meier B, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. J Am Coll Cardiol 2005; 45(11): 1748-52.
5. Jey B. Doubling the maintenance dose of clopidogrel after percutaneose coronary intervention in low responders to therapy. J AM Coll Cardiol 2009; 98(2753): 2763
6. Steinhubl SR, Berger PB, Tift Mann J, Fry ETA, DeLago A, Wilmer Ch, et al. Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention. JAMA 2002; 288: 2411-2420 2002; 288(19): 2411-20.
7. Mario T, Meier A, Haeberli O, Otto M. Stent thrombosis with antiplatelet therapy. J AM Coll Cardiol 2005; 41(1348): 1352.
8. Lemesle G, Delhaye C, Sudre A, Broucqsault D, Rosey G, Bauters C, et al. Impact of high loading and maintenance dose of clopidogrel within the first 15 days after percutaneous coronary intervention on patient outcome. Am Heart J 2009; 157(2): 375-82.
9. Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease, and drug therapy. J Lab Clin Med 1989; 114(5): 473-501.
10. Ross AM, Coyne KS, Moreyra E, Reiner JS, Greenhouse SW, Walker PL, et al. Extended mortality benefit of early postinfarction reperfusion. GUSTO-I Angiographic Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. Circulation 1998; 97(16): 1549-56.
11. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005; 45(12): 2088-92.
12. Wiste HJ, Bell M, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. Circulation 2007; 116(21): 2391-8.
13. Oestreich JH, Holt J, Dunn SP, Smyth SS, Campbell CL, Charnigo R, et al. Considerable variability in platelet activity among patients with coronary artery disease in response to an increased maintenance dose of clopidogrel. Coron Artery Dis 2009; 20(3): 207-13.
14. Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. Circulation 2007; 115(6): 708-16.
15. Gladding P, Webster M, Zeng I, Farrell H, Stewart J, Ruygrok P, et al. The antiplatelet effect of higher loading and maintenance dose regimens of clopidogrel: the PRINC (Plavix Response in Coronary Intervention) trial. JACC Cardiovasc Interv 2008; 1(6): 612-9.
16. Aleil B, Jacquemin L, De Poli F, Zaehringer M, Collet JP, Montalescot G, et al. Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. JACC Cardiovasc Interv 2008; 1(6): 631-8.
17. Tavassoli N, Voisin S, Carrie D, Lapeyre-Mestre M, Galinier M, Montastruc JL, et al. High maintenance dosage of clopidogrel is associated with a reduced risk of stent thrombosis in clopidogrel-resistant patients. Am J Cardiovasc Drugs 2010; 10(1): 29-35.
18. Palmerini T, Barozzi C, Tomasi L, Sangiorgi D, Marzocchi A, De Servi S, et al. A randomised study comparing the antiplatelet and antiinflammatory effect of clopidogrel 150 mg/day versus 75 mg/day in patients with ST-segment elevation acute myocardial infarction and poor responsiveness to clopidogrel: results from the DOUBLE study. Thromb Res 2010; 125(4): 309-14.
19. Lemesle G, Delhaye C, Sudre A, Broucqsault D, Rosey G, Bauters C, et al. Impact of high loading and maintenance dose of clopidogrel within the first 15 days after percutaneous coronary intervention on patient outcome. Am Heart J 2009; 157(2): 375-82.