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Original Article

Impact of different dose and duration of clopidogrel on the postoperative efficacy of drug-eluting stent implantation in patients with coronary heart disease and diabetic mellitus

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Abstract: Objective: To study the effect of different dose and duration of clopidogrel on the efficacy of drug-eluting stent (DES) implantation in coronary heart disease patients complicated with diabetes mellitus. Methods: A total of 345 coronary heart disease patients admitted to our hospital from January 2014 to December 2016 were included in this study and randomly divided into the normal treatment group, double dose group and double courses group. Patients in the normal treatment group were given 300 mg clopidogrel 2 hours before operation and 75 mg per day postoperatively for 1 year; patients in the double dose group were given 600 mg clopidogrel 2 hours before operation and 150 mg per day postoperatively for 1 year; patients in the double courses group were given 300 mg clopidogrel for 2 hours before operation and 75 mg per day postoperatively for 2 years. The clinical data and 2-year major cardiac adverse events (MACEs), 1-year vascular restenosis rate and the rate of platelet aggregation inhibition and adverse effect after the surgery were compared and analyzed in patients of each group. Results: Compared with the normal treatment group, the double courses group and double dose group showed significantly reduction in the 2-year MACEs of the subjects after DES implantation (P=0.005, P=0.008). Besides, the double dose clopidogrel could obviously increase postoperative platelet aggregation inhibition rate (P=0.013) and decrease the 1-year postoperative vascular restenosis rate (P=0.007), which showed no apparent change when applied clopidogrel for two courses (P=0.524, P=0.479). There was no statistically significant difference in the incidence of 2-year MACEs between the two clopidogrel treatment groups (P=0.137), but the difference was statistically significant in the inhibition of platelet aggregation (P=0.015) and the 1-year vascular restenosis rate after operation (P=0.004). Meanwhile, the basic clinical data, the relevant characteristics of stent implantation and adverse effect between the three groups presented no statistically significant difference. Conclusion: The long-term use of clopidogrel after DES implantation is effective and safe. It can achieve a better long-term result by increasing the dosage and course appropriately.

Keywords: Clopidogrel, coronary heart disease combined with diabetes mellitus, drug-eluting stent, postoperative efficacy

Introduction

Percutaneous coronary intervention (PCI) is the first choice for the treatment of coronary heart disease [1]. Drug-eluting stent (DES) can significantly reduce the incidence of in-stent restenosis and target vessel revascularization [2, 3], but the risk of stent thrombosis after surgery limits its further application. Currently, clopidogrel and aspirin are commonly used anti-platelet drugs in clinical treatment, which are applied to prevent adverse reactions after DES implantation. Some studies have shown that clopidogrel withdrawal after DES implantation over 6 months significantly increased the risk of DES thrombosis [4, 5]. However, there has been controversy over the treatment duration and dose of clopidogrel following stent implantation.

Some research have suggested that diabetes, which may be a risk factor for coronary heart disease, can significantly increase the incidence of ischemic events and restenosis after the implantation of coronary stent [6], thereby

Table 1. Comparison of general information of patients in each group

Group	The normal treatment group	Double course group	Double dose group
Gender (male/female)	68/47	67/48	70/45
Age (years old)	52.55±3.28	53.09±2.54	51.26±2.35
BMI index (Kg/m^2)	25.25±2.65	24.76±5.11	25.52±3.36
Family history of coronary heart disease (n, %)	8 (6.96)	9 (7.83)	9 (7.83)
Smoke history (n, %)	18 (15.65)	20 (17.39)	17 (14.78)
Blood glucose (mmol/L)	10.2±1.23	9.8±0.93	10.6±1.37
Hyperlipidemia history (n, %)	22 (19.13)	21 (18.26)	20 (17.39)
Hypertension history (n, %)	37 (32.17)	40 (34.78)	39 (33.91)
LVEF (%)	56.4±9.3	57.2±8.7	56.9±8.1

for patients who have coronary heart disease with diabetes should pay more attention to prevention and treatment of the postoperative complications after stent implantation. At present, there are few reports about whether antiplatelet drugs can improve the long-term efficacy of stent implantation in patients with comorbidities of coronary heart disease and diabetes mellitus, and most of them are retrospective. In order to better confirm the safety and efficacy of clopidogrel in patients with coronary heart disease and diabetes after stent implantation, this study performed a randomized controlled trial to compare the clinical curative effects among normal treatment group, the clopidogrel double dose group and the double courses of clopidogrel treatment group.

Materials and methods

General information

A total of 345 patients with coronary heart disease and diabetes mellitus treated in our hospital from January 2014 to December 2016 were selected, including 205 males and 140 females with the average age of 52.3±2.48 years old and the average BMI index of 25.17±3.97 kg/m^2. Among them, 26 cases had the family history of coronary heart disease, 55 cases had smoking history, 63 cases had a history of hyperlipidemia, 116 cases had a history of hypertension, and the mean of left ventricular ejection fraction (LVEF) was (56.8±8.5)%. All the subjects were randomly divided into three groups: the normal treatment group, double dose group and double courses group with 115 cases for each. There were no significant differences in the general data between the groups, as shown in **Table 1**.

Inclusion criteria: patients whose symptoms conformed to the diagnostic criteria of coronary artery disease: coronary angiography (CAG) showed that at least 1 coronary stenosis degree was over 50%, meanwhile, these patients were also in line with the diagnostic criteria of diabetes [7]; patients with stable angina or unstable angina or acute myocardial infarction; patients who had no history of coronary stent implantation; patients who had operative indication for coronary artery stent implantation: CAG confirmed that at least one coronary artery vessel diameter appeared stenosis and the degree was greater than 70%. Exclusion criteria: patients who had antiplatelet drug tolerance or allergy; patients who could not reach the treatment effect of complete revascularization; patients who had severe liver, kidney and other organ diseases, or hemorrhagic stroke, intracranial hemorrhage, alimentary tract hemorrhage and active ulcer; patients who had ventricular dysfunction or whose echocardiography showed that LVEF was less than 30%. This study was approved by the Hospital Ethics Committee, all patients signed the informed consent.

Methods

DES implantation

All patients were managed with the method of DES implantation [8]. First, all patients underwent routine CAG and then, the release pressure of the rapamycin eluting stent was adjusted to 8-16 atm. Next, the length of the stent was adjusted according to the lesion of each patient so that the stent could adequately cover the lesion of the entire vessel and the balloon. Stent implantation success was defined as the residual stenosis of target vessel less than

Table 2. Comparison of the treatment condition among the 3 groups

Group	Vessel diameter (mm)	Number of stents	Stent length (mm)	Degrees of vascular stenosis before and after operation (%)
The normal treatment group	3.13±0.24	1.52±0.24	25.5±2.4	86.69±4.24/13.59±2.15
Double courses group	3.11±0.32	1.49±0.254	26.1±2.2	88.36±4.57/14.03±2.35
Double dose group	3.12±0.22	1.53±0.32	25.4±4.3	87.26±5.22/13.71±2.16

20%, no complication, TIMI grade 3 flow, complete revascularization, and no cardiac death, nonfatal myocardial infarction, or repeated revascularization while hospitalized.

Concomitant medications

All the enrolled patients were given normal medical therapy including aspirin, low molecular weight heparin, ester nitrate, statins and other drugs, additionally, calcium antagonists, beta-blockers, angiotensin converting enzyme inhibitors and etc. according to the condition of them. Meanwhile, the administration of drugs for diabetes treatment, such as Glucobay, metformin, diamicron or insulin, was performed to control the blood glucose in the normal level at 2 hours after a meal and the there was no significant differences in blood glucose levels among the three groups (P>0.05).

Two hours before the surgery, patients were given 300 mg of aspirin (J20080078, Bayer Health Care Ltd.), and 100 mg of it was administered daily after the surgery. Patients in different groups were treated with clopidogrel (J20130083, Sanofi-Aventis Pharmaceutical Co., Ltd.) in different ways: the normal treatment group received 300 mg clopidogrel 2 hours before surgery, and 75 mg per day for 1 year postoperatively; the double dose group received 600 mg clopidogrel 2 hours before surgery, and 150 mg per day for 1 year postoperatively; the double courses group received 300 mg clopidogrel 2 hours before surgery as well, and 75 mg per day for 2 years postoperatively.

Observation indexes

Clinical data such as the diameter of the vessel, the number and length of the stents, and the degree of stenosis before and after the operation were collected and recorded. After discharge, the patients were followed up once each month by outpatient appointment or phone call for 2 years. CAG was reviewed at 1 year after operation.

In the follow-up period, the occurrences of MACEs, in-stent restenosis and adverse reactions were diagnosed and recorded. The major adverse cardiac event was defined as the composite endpoint of noncardiogenic death, nonfatal myocardial infarction and re-target vascular intervention. In-stent restenosis was defined as CAG showed there were thrombosis and blockage in the site of stent implantation or on the edge of the stent. And the adverse reactions included gastrointestinal reaction, hemorrhagic events and rash reactions.

Vein blood samples were took 3 ml from the elbows of subjects in each group at 24 hours before the operation and 48 hours after the operation. The SC-2000 platelet aggregation instrument was applied to detect the inhibitory rate of blood platelet aggregation at different time points. Then, calculate and compare the inhibitory rate of blood platelet aggregation of the three groups. The inhibitory rate of blood platelet aggregation = the inhibitory rate before the treatment-the inhibitory rate after the treatment.

Statistical methods

Data were statistically analyzed using the SPSS 19.0 software. Enumeration data were shown as frequencies, and the comparison among groups used the chi-square test; measurement data were presented as mean ± standard deviation, and one-way analysis of variance (ANOVA) was used to analyze the differences among groups. P<0.05 was considered statistically significant.

Results

Comparison of stent implantation characteristics of patients in each group

All patients were given a 2-year follow-up visit and were successfully implanted with more

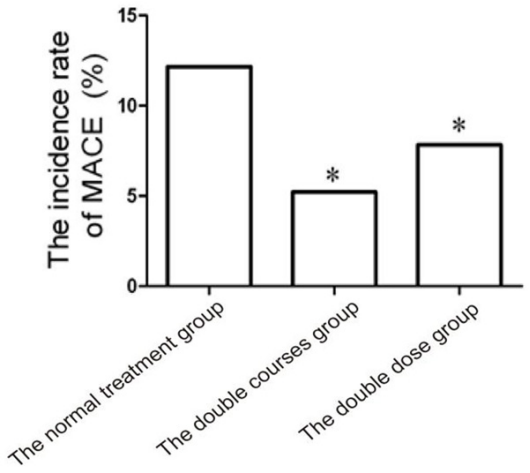

Figure 1. Comparison of the incidence of MACE in each group, compared with the normal treatment group, *P<0.05.

than one DES. There was no statistical difference among patients in the aspects of stents quantity, vessel diameter, stent length and degrees of vascular stenosis before and after the operation (P>0.05). As shown in **Table 2**.

Comparison of the incidence of MACEs of patients in each group

During the 2-year follow-up period, 14, 6 and 9 cases of MACEs were observed in the normal treatment group, double courses group and double dose group respectively. Compared with the normal treatment group (12.17%), the incidence of MACEs in double courses group (5.22%) and double dose group (7.83%) was significantly decreased (P=0.005, P=0.008), as shown in **Figure 1**.

Comparison of in-stent restenosis rate and platelet inhibition rate of patients in each group

One year after PCI, CAG was performed for reexamination of patients in each group. The results showed that the incidence of in-stent restenosis was significantly reduced in double dose group compared with the normal treatment group (P=0.007), but the comparison of in-stent restenosis between double courses group and the normal treatment group was not considered statistically different, as shown in **Figure 2A**.

Compared with the normal treatment group, the platelet inhibition rate was significantly higher than that in double dose group (P= 0.013). There was no statistical difference in the platelet inhibition rate between double courses group and the normal treatment group, as shown in **Figure 2B**.

Comparison of the adverse reactions of clopidogrel between each group

During the follow-up period, in the normal treatment group, 3 patients appeared hemorrhagic events, 2 patients were presented with gastrointestinal reactions and 2 patients with rash. In double dose group, 4 patients appeared hemorrhagic events, 2 patients were presented with gastrointestinal reactions and 2 patients with rash. In double courses group, 3 cases appeared hemorrhagic events, 3 patients were presented with gastrointestinal reactions and 3 patients with rash. There was no statistical difference in the incidence of adverse reactions among the groups (P=0.315), as shown in **Figure 3**.

Discussion

DES is a major clinical method for treating coronary heart disease and achieving coronary revascularization, of which principle is fully exerting the drug efficiency mainly via the stent carrying and releasing the drugs in local coronary and the stent has a supporting role, which can prevent from elastic recoil properties of the blood vessels at the end of the operation and vascular remodeling in the late stage, thus greatly reducing the occurrence of vascular restenosis after intracoronary stent implantation [9]. However, with the extensive use of DES in clinic, its in-stent thrombosis has been widely concerned by scholars. Study has shown that there were false understandings of the DES application, including underestimating the risk of its in-stent thrombosis and overestimating its role in reducing intravascular restenosis after PCI [10].

Clopidogrel is an antiplatelet drug commonly used after coronary stent implantation. Some studies have shown that early discontinuation of antiplatelet drugs or irregular application of antiplatelet agents will increase probability of stent thrombosis [11]. The main functional mechanism of clopidogrel is to bind to the ADP receptors on the surface of platelets to reduce its suppress effect on adenyl cyclase and there-

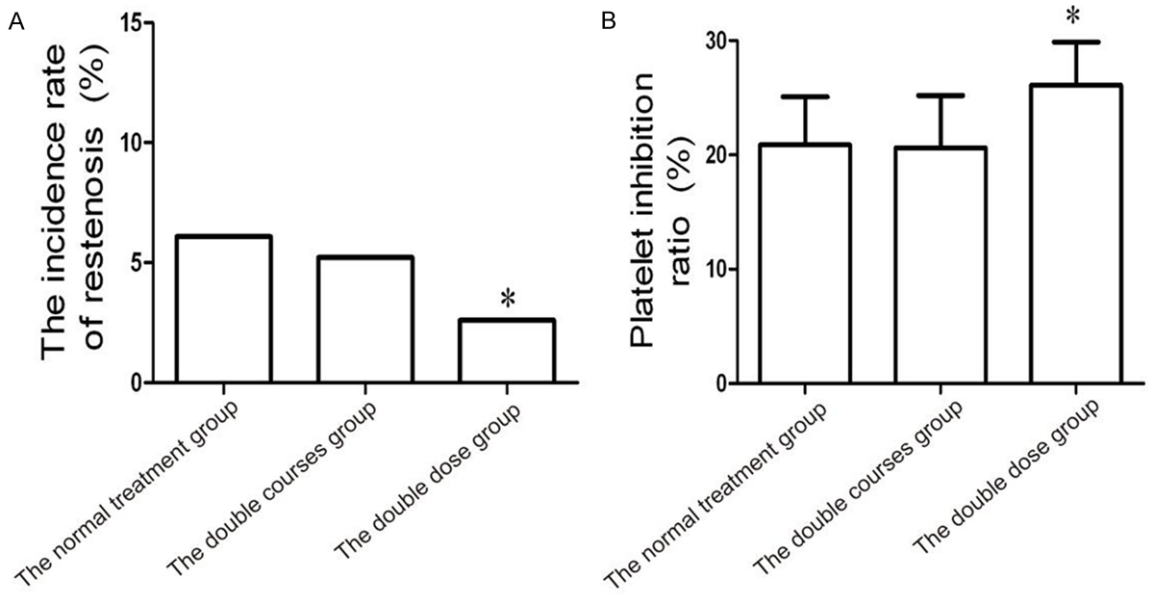

Figure 2. Comparison of in-stent restenosis rate and platelet inhibition rate in eachgroup, compared with the normal treatment group, *P<0.05.

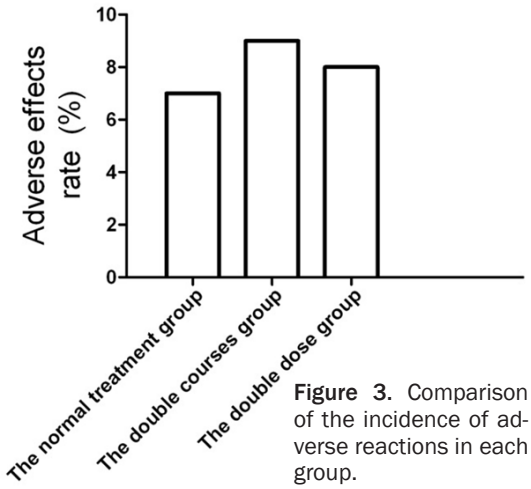

Figure 3. Comparison of the incidence of adverse reactions in each group.

by inhibit platelet aggregation [12, 13]. In addition, clopidogrel can reduce the expression of platelet selectin and affect the process of platelet activation. Moreover, study has shown that more than one year after implantation of DES, dual antiplatelet agents can effectively reduce the risk of late stent thrombosis [14]. But it is unclear whether the increase in dose of clopidogrel or the increase in the course of treatment can further reduce stent thrombosis or increase cardiovascular adverse events.

Another study has suggested that diabetes mellitus is one of the risk factors for coronary heart disease, and is a risk factor for coronary in-stent restenosis and thrombosis, because diabetics usually are associated with increased level of clotting factors and decreased activity of anticoagulant factors, which leads them more prone to suffer thrombosis [15]. Other studies have reported that diabetes mellitus can also cause the emergence of antiplatelet drug therapy resistance [16, 17]. Meanwhile, patients with coronary heart disease and diabetes mellitus may have an increase in vascular restenosis rate and revascularization rate after coronary stent implantation [18, 19]. Therefore, the improvement of the efficacy of DES after coronary stent implantation in these patients has become the focus and difficulty in the study and the study of antiplatelet therapy after DES implantation in patients with coronary heart disease and diabetes mellitus has a great significance [20].

The studies about the application of clopidogrel in patients with coronary heart disease and diabetes mellitus after DES surgery are mostly retrospective studies, and currently there are still lacks of randomized controlled trials. In this study, we performed a randomized controlled trial and found that compared with the the normal treatment group, the double dose clopidogrel significantly increased the inhibition rate of platelet aggregation, reduced the MACEs

within two years and the vascular restenosis rate within one year after drug-eluting stent implantation (DES) in subjects. Compared to the the normal treatment group, double courses clopidogrel could also reduce the MCAEs within two years after DES implantation in subjects, and these two kinds clopidogrel treatment groups did not show the rising risk of adverse reactions, indicating that theduration and dose of clopidogrel treatment could indeed affect the prognosis of patients. But judging from this study, the double dose clopidogrel has better efficacy, which might be due to high clopidogrel concentration that could raise the drug sensitivity in subjects, thus achieving the purpose of the improvement of efficacy.

In summary, for patients with coronary heart disease and diabetes mellitus, long-term use of clopidogrel is effective and safe after DES implantation, and the appropriate increase in drug dose and duration can get better long-term efficacy. However, there were some limitations in this study as well, such as the small sample size, single-center, and some interfering factors, which need to be further confirmed through a large, multicenter, randomized controlled study.

Disclosure of conflict of interest

None.

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