

Comparison of Short- and Long-Term Clinical Outcomes of Drug-Eluting Stent Implantation versus Coronary Artery Bypass Grafting in 121 Patients with Unprotected Left Main Coronary Artery Disease

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Abstract: Although previous studies have shown promising safety and feasibility outcomes for percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in patients with unprotected left main coronary artery (ULMCA) disease, limited data are available for comparison of DES implantation versus coronary artery bypass grafting (CABG) for ULMCA stenosis. A total of 121 symptomatic patients with >50% angiographic stenosis in the ULMCA underwent PCI with DES (PCI group, n=60) or CABG (CABG group, n=61). Cumulative incidence of major adverse cardiac events (MACE) including death, myocardial infarction and target-vessel revascularization were evaluated at follow-up. Baseline clinical characteristics were comparable in both groups except for a lower incidence of triple-vessel coronary disease in the PCI group compared to the CABG group (32% vs. 80%, $p < 0.01$). Stent implantation was successful in all lesions of the PCI group. The mean follow-up period was 20 ± 12 months in the CABG group and 17 ± 10 months in the PCI group. The incidence of MACE in the CABG group was significantly higher than that in the PCI group (9.8% vs. 0%, $p < 0.01$). And the total combined rate of MACE, heart dysfunction, cerebral infarction and re-hospitalization was also higher in the CABG group compared to the PCI group (32% vs. 0%, $p < 0.01$). This study indicates that PCI of ULMCA lesions with DES is safe and effective, and might be superior to CABG in some selective patients. In the PCI group, no serious procedure-related complication was observed, and the short- and long-term prognosis was better than that in the CABG group.

Keywords: ULMCA disease, drug-eluting stents, CABG, short- and long-term prognosis.

INTRODUCTION

Although percutaneous coronary intervention (PCI) of unprotected left main coronary artery (ULMCA) stenosis remains a challenging problem and coronary artery bypass grafting (CABG) has been considered as the sole or preferential choice to deal with the ULMCA lesions, PCI of ULMCA has achieved good efficacy with the emergence of stents and especially in recent years with the wide application of drug-eluting stents (DES), which can dramatically decrease restenosis rates. Interventional therapy of ULMCA lesions therefore has been increasing in frequency and a series of clinical trials have demonstrated the safety and feasibility of DES implantation in patients with ULMCA lesions [1-3]. Limited data are available for comparison of efficacy and prognosis between PCI and CABG, and there is no related report in China. This study compared the therapeutic effects and short- and long-term clinical prognoses of DES

implantation and CABG in 121 patients with ULMCA diseases.

METHODS

Study Population

Data were collected on a cohort of 60 consecutive patients (male 43, female 17) with ULMCA lesions who underwent selective PCI in several hospitals in Tianjin City from March 2003 to June 2007 and 61 patients (male 42, female 19) with ULMCA lesions who underwent selective CABG in Teda International Cardiovascular Hospital, College of Cardiovascular disease, Tianjin Medical University during the same time period. All patients had angiographic evidence of >50% diameter stenosis of the left main coronary artery and no previous history of CABG. In all patients, there was no good right-to-left collateral circulation in coronary angiography. Those patients undergoing intervention within 24 hours after acute myocardial infarction were excluded. The study protocol was approved by the institutional review board of hospitals. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written. All the centers included have completed PCI 200-1000 cases every

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year, and the physicians and teams have abundant experience.

Coronary Angiography and PCI

Coronary angiography was performed using the femoral approach and multi-angle projection according to current standard techniques. Stent implantation was performed in patients with >50% stenotic lesions in the left main coronary artery as measured by visual assessment and computer software. The types of implanted stents included sirolimus-eluting stents (Cypher, Cordis Corporation, USA; Firebird, Microport Corporation, China) and a paclitaxel-eluting stent (Taxus, Boston Scientific Corporation, USA). The selection of stenting technique, direct stenting or balloon pre-dilation followed by stenting, was dependent on the degree of stenosis. Every lesion at the ostium or shaft without involvement of the bifurcation was treated with a single stent. Bifurcation lesions were treated using one of the following strategies: single stenting, single stenting combined with kissing balloon, T-stenting, V-stenting and kissing stenting.

Anticoagulant and Antiplatelet Therapy after PCI

All patients were given: (1) a loading dose of aspirin 300mg and clopidogrel 300mg before the procedure; or (2) aspirin 300mg/day and clopidogrel 75 mg/day for at least 48 or 72 hours before the procedure; and (3) conventional-dose low molecular weight heparin (including Fraxiparine, Fragmin, and Clexane) for 3-5 days, and clopidogrel 75 mg/day (some patients were given 150 mg/day followed by 75 mg/day 2-3 months later) for 9-24 months, and lifelong aspirin at a dose of 75 mg to 150 mg after procedure if there was no complication or contraindication; and (4) a half- or 1/3-dose of GPIIb/IIIa receptor antagonist tirofiban hydrochloride in some patients during procedure and 2-3 days after procedure.

Coronary Artery Bypass Grafting

Under general anesthesia, a median sternotomy was performed. The vessels used as grafts included the left internal mammary artery (LIMA), the great saphenous vein (SV) and the radial artery (RA). Tubes were inserted into the ascending aorta and the right atrium to establish the cardiopulmonary bypass. Following the identification of the coronary lesions, the anastomosis site was decided. After aortic cross-clamping, cold oxygenated blood hyperkalemic cardioplegia was irrigated from the ascending aortic root. After completing distal anastomosis of bypass grafts under cardioplegia, the ascending aorta was opened and heart beating reestablished. Clamps were positioned on the ascending aorta wall for distal anastomosis of bypass grafts with the ascending aorta. All LIMAs, when used as bypass grafts, were anastomosed to the left anterior descending (LAD) artery. Only SVs were selected as bypass grafts in some patients because of senility, poor health or serious osteoporosis of sternum. Antiplatelet therapy with aspirin 100 mg/day was recommended to bypass surgery patients for a lifelong period.

Follow Up

Major adverse cardiac events during hospitalization and follow-up period included cardiac death, acute myocardial

infarction, any form of target-lesion revascularization (CABG or PCI) and re-hospitalization. All deaths were considered as cardiac deaths unless clinical diagnosis or autopsy had demonstrated a non-cardiac cause. Clinical follow-up was performed by re-admission history collection, telephone contact or out-patient visit throughout the entire follow-up period.

Statistical Analysis

Categorical data were presented as numbers and percentages and compared using the Chi-square or Fisher's tests. Continuous variables were presented as mean \pm standard deviation (SD) and compared with the paired *t* test. Single-variable tests of significance were performed on complications and prognoses by use of a set of candidate variables selected by literature review, including age, sex, LVEF, group (CABG or PCI), and history of hypertension, diabetes, hyperlipemia, and smoking. Logistic regression models were used to analyze complications and prognoses, respectively. Next, stepwise multiple regression analyses were performed with the use of those variables that were statistically significant in the single-variable analyses. All statistical tests were performed to reject the null hypothesis at a level of $\alpha=0.05$. Statistical analysis was automatically performed with the SPSS 11.0 software program.

RESULTS

Baseline Clinical Characteristics

A total of 121 patients were enrolled in this study; of them, 60 patients were treated with PCI (PCI group) and 61 patients with CABG (CABG group). Baseline clinical characteristics are shown in Table 1. Most baseline characteristics including sex, hypertension, diabetes, a history of smoking, left ventricular ejection fraction, left ventricular diastolic diameter, blood lipid and serum glucose levels were well matched between two groups. Compared with the CABG group, patients in the PCI group were younger (61 ± 9 vs. 65 ± 8 , $P = 0.012$) and had a lower proportion of hypertensive.

Baseline Angiographic Characteristics and Therapeutic Strategy

Coronary angiography showed there was no significant difference in degree and location of the ULMCA stenosis between two groups (Table 2). The percentage of patients with distal bifurcation lesions exceeded 50% in both groups. However, the incidence of patients with triple-vessel coronary diseases in CABG group was higher than that in the PCI group (80.3 vs. 31.7%, $P < 0.001$). The procedural success rate was 100% in both groups. The number of stents per patient was 1.4 ± 0.6 . The average length and diameter of stents were 19 ± 7 mm and 3.5 ± 0.3 mm, respectively. The average maximum dilated pressure of stents was 16.4 ± 3.4 atm. Single stenting was used as the main therapeutic strategy to treat the distal bifurcation lesions. A small proportion of patients with such lesions were treated with V-stenting. Most patients (82.6%) received final kissing balloon post-dilatation. In the CABG group, both the left internal mammary artery and the great saphenous veins were selected as grafts in most patients (91.8%), and only great saphenous veins were selected as grafts in others (8.2%).

Table 1. Comparison of Baseline Clinical Characteristics Between the Two Groups

	CABG Group (% , n=61)	PCI Group (% , n=60)	P Value
Male	42 (68.9)	44 (73.3)	0.754
Age	65±8	61±9	0.012
Previous MI	23 (37.7)	9 (23.1)	0.126
Hypertension	46 (75.4)	19 (48.7)	0.006
DM	16 (26.2)	9 (23.1)	0.723
Smoking	33 (54.1)	19 (48.7)	0.599
LVEF (%)	58.56±10	58.51±10	0.983
LVEDD (mm)	48.7±5.2	50.9±6.5	0.087
TC (mmol/L)	5.13±1.54	4.70±1.20	0.163
LDL (mmol/L)	3.02±1.18	2.71±0.74	0.206
Uric acid (mmol/L)	332.13±95.1	302.27±83.7	0.158
Creatinine (umol/L)	68.6±18.6	75.0±26.0	0.186

Table 2. Comparison of Baseline Angiographic Characteristics Between the Two Groups

	CABG Group (% , n=61)	PCI Group(% , n=60)	P Value
Degree of LM stenosis	72.2±16.4	75.2±15.6	0.356
Prevalence of different degree of stenosis(<75%)	29 (47.5)	25 (41.7)	0.536
Prevalence of different degree of stenosis(≥75%)	32 (52.5)	35 (58.3)	0.536
Lesion at ostial LM	6 (9.8)	7 (17.9)	0.239
Lesion at strunck of LM	18 (29.5)	11 (28.2)	0.889
Distal bifurcation lesion of LM	37 (60.6)	21 (53.9)	0.501
Involving ostial LAD	14 (23.0)	8 (20.5)	0.774
Involving ostial LCX	4 (6.5)	1 (2.6)	0.672
Involving both ostial LAD and ostial LCX	19 (31.1)	12 (30.8)	0.968
LM lesions combined with triple-vessel diseases	49 (80.3)	13 (33.3)	0.000

In-Hospital Outcomes and Clinical Follow-Up

The average follow-up period for the PCI group was 17±10 months. There was no MACE during the hospitalization and follow-up periods. The average follow-up period for the CABG group was 20±12 months. In the CABG group, two patients died during hospitalization (one of multiple organ failure 2 days after surgery; and the other of renal failure after remaining comatose for 19 days after surgery). One patient in the CABG group received inferior vena cava filter implantation because of deep vein thrombosis after lying in bed for a long time period. MACE occurred in 6 patients in the CABG group (9.8%). Three of them accepted revascularization, and another suffered from nonfatal myocardial infarction and also received revascularization. Although there was no significant differences in the rates of cardiac death, acute myocardial infarction, any form of the target-lesion revascularization (CABG or PCI) and re-hospitalization bet-

ween the two groups, the overall rate of MACE in the CABG group was significant higher than that in the PCI group (6 vs. 0, P = 0.047). Nine patients in the CABG group were re-admitted during the follow-up period. Apart from the six patients with MACE, three patients suffered from cerebral infarction and two from serious heart failure (Table 3). Therefore, a total of 14 cases (22.9%) suffered from other adverse events. If MACE was included, the rate of all adverse events achieved 32.8 percent in the CABG group while there was no adverse event in the PCI group. Multiple logistic regression analysis, MACE was significantly higher in patients who were old (72.00 vs. 63.33, P=0.036), and mortality, cerebral infarction, nonfatal myocardial infarction, re-hospitalization or revascularization was not significantly influenced by age, sex, LVEF, group (CABG or PCI), and history of hypertension, diabetes, hyperlipemia, and smoking.

Table 3. Comparison of MACE and Re-Hospitalization Between the Two Groups

	CABG Group (% , n=61)	PCI Group (% , n=60)	P Value
Re-hospitalization	9 (14.8)	0 (0.0)	0.009
Cerebral infarction	3 (4.9)	0 (0.0)	0.223
Cardiac dysfunction	2 (3.3)	0 (0.0)	0.370
Major adverse cardiovascular events	6 (9.8)	0 (0.0)	0.047
Non-fatal myocardial infarction	1 (1.6)	0 (0.0)	0.610
Revascularization	3 (4.9)	0 (0.0)	0.223
Death	2 (3.3)	0 (0.0)	0.370

DISCUSSION

The left main coronary artery is an extremely important inch-long body structure, providing 75% or more of the heart's blood supply. Previous studies have demonstrated that ULMCA lesions represent approximately 5% of all coronary lesions, and up to 50% of them are combined with triple-vessel coronary diseases. Outcomes of ULMCA diseases are always poor with a one-year mortality of up to 20% and a 7-10 year mortality of up to 50 per cent [4]. Surgical bypass grafting was the only strategy available to treat ULMCA diseases before the emergence of PTCA and PCI. However, CABG was associated with high morbidity and mortality and a high incidence of failure of great saphenous vein grafts. This retrospective analysis showed that DES implantation in ULMCA lesions is associated with a more favorable short- and long-term prognosis compared to CABG.

PTCA or PCI of left main coronary artery disease is very attractive to interventional doctors because of the short-length lesion, location near the proximal vascular and ease for crossing the guidewire and balloon. PTCA pioneer Dr. Grüntzig performed his fifth PTCA on a ULMCA lesion. However, a consensus recognized that PTCA and bare-metal stent (BMS) implantation for ULMCA have certain restrictions, such as an increase of in-hospital restenosis and mortality rates, a high incidences of long-term in-stent restenosis, revascularization and mortality. Previous studies showed that the effect of PTCA and BMS implantation on left main lesions is not long-lasting. PTCA of left main coronary artery was associated with a procedural mortality rate of 9.4% and a three-year mortality rate of 64% [5], and BMS implantation also with high rates of restenosis and mortality [6, 7]. After the application of DES, a number of clinical studies have demonstrated that DES implantation of left main dramatically reduced the MACE and target vascular restenosis compared to BMS implantation [7]. However, limited clinical data comparing bypass surgery and DES implantation are available in patients with ULMCA lesions. In a single-center non-randomized study enrolling a total of 173 patients with ULMCA lesions, 123 patients underwent bypass surgery and the remaining 50 patients accepted DES implantation [3]. The 30-day MACE rate of DES group was lower than that of the surgery group (2% vs. 17%, $P < 0.01$), but there was no significant difference in six-month outcome between the two groups. Up to now, no data from a randomized controlled

study has been reported. One small (105 patient) unpublished randomized trial of stenting (DES or BMS) versus CABG in patients with unprotected LMCA has showed that the PCI group was associated with an improved convalescent left ventricular function compared to the CABG group at 12 months. With follow-up completed at a mean duration of 40 months, the survival and angina status were similar in both groups, with no occurrences of stent thrombosis [4].

At present, despite the uncertain short- and long-term prognosis of drug-eluting stenting of ULMCA lesions, such strategy has been selected by more and more clinicians especially in some large- and medium-sized hospitals. Although there were some limitations in our study such as non-randomized design and difference of the triple-vessel rate and mean age between the two groups and use of different bifurcation techniques, differing APT regimens, the result showed that short- and long-term prognoses of the DES group were significantly better than those of the CABG group with ULMCA diseases. In a follow-up period of 8-15 months, the MACE rate for CABG group was 9.8%, the rate of re-hospitalization, cerebral infarction and cardiac dysfunction was 22.9%, and the rate of all adverse events was 32.8%, while there was no event at any time in PCI group. These results are very encouraging and indicate that DES treatment of ULMCA lesions is safe and feasible. However, we think that stenting cannot now replace CABG in the treatment of ULMCA diseases. CABG is still an indispensable method to deal with ULMCA lesions. As there are many uncertainties in drug-eluting stenting of ULMCA lesions, we should be cautious when selecting the cases and follow strict indications. We recommend that: (1) because left main coronary intervention is a high-risk procedure, it must be performed by experienced physicians and teams with abundant experience in hospitals with surgical back-up; (2) Stent implantation, pre-dilation and post-dilation should be performed rapidly and the balloon-dilation time should be shortened as much as possible (also, the ratio of contrast agent versus saline should be less than 1:1); (3) Try to perform coronary angiography again in all patients 6-12 months after PCI for early detection of problems, such as in-stent restenosis and some adverse factors such as vascular endothelial dysfunction, which might result in very late stent thrombosis; (4) Clopidogrel 150mg/day should be given for at least 2-3 months after the procedures in all patients. Stan-

standard dual anti-platelet medication with aspirin and clopidogrel should be given for 1-2 years and ideally up to a life-long period in the absence of contraindications or complications. According to above-mentioned principles, the results showed that the prognoses of the DES group were better than those of the CABG group; however, limited data and non-randomized design, no empirical evidence from appropriately designed and powered trials.

CONCLUSION

This study indicates that selective DES implantation in some ULMCA lesions is safe and feasible. Compared to CABG, PCI using DES is associated with more favorable short and long-term outcomes. However, which ULMCA treatment (PCI or CABG) is the optimal one remains unclear and large-scale randomized controlled clinical studies are required. All of the effective factors, including patient's status, technical proficiency of interventional doctors and surgical or general conditions of hospital, should be considered when performing PCI to treat patients with ULMCA diseases.

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