Efficacy of arsenic trioxide drug-eluting stents in the treatment of coronary heart disease

SHASHA ZHANG, YUPING ZHANG, SHICHUAN LI and ZHIFENG LI

Department of Cardiology, Yongchuan Hospital, Chongqing Medical University, Chongqing 402160, P.R. China

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Abstract. The aim of the current study was to evaluate the safety and clinical efficacy of arsenic trioxide drug-eluting (AVI) stents, manufactured in China, for the treatment of coronary heart disease (CHD). Between January and August 2014, 40 patients with CHD admitted to Yongchuan Hospital with implanted AVI stents alone were selected. A one-year clinical follow-up was completed and one year postoperative coronary angiography was reviewed. Major adverse cardiovascular events (MACE), recurrent angina, stent restenosis and stent thrombosis cases were detected. All 40 patients with CHD completed the one-year clinical follow-up, as well as the one-year postoperative coronary angiography. The follow-up results indicated that the MACE rate was 15.0% (6/40), the target lesion revascularization rate was 15.0% (6/40), the angina recurrence rate was 32.5% (13/40), the in-stent restenosis rate was 20.0% (8/40) and the stent thrombosis rate was zero. There were no cases of cardiac death or nonfatal myocardial infarction. The incidence of restenosis was higher following implantation of the AVI stent and the safety and clinical efficacy were worse than expected.

Introduction

Coronary heart disease (CHD) is a common disease and usually occurs following the build up of plaque inside the coronary arteries that supply oxygen-rich blood to the heart muscle. This build-up can induce angiostenosis or angiemphraxis of the coronary arteries, reducing the flow of oxygen-rich blood to the heart, which may result in myocardial necrosis (1). Percutaneous coronary intervention (PCI) is an important therapeutic method of treating CHD (2). The primary factor leading to restenosis after PCI is smooth muscle cell proliferation and intimal migration following local injury to the coronary artery (3,4). It has been demonstrated that stents coated with anticancer drugs may significantly inhibit the proliferation of smooth muscle cells following PCI and reduce the restenosis rate (5). A number of studies have demonstrated that, as an anti-cancer agent, arsenic trioxide (As_2O_3) is able to treat leukemia and other malignant tumors by inducing the apoptosis of tumor cells (6-12). The mechanism by which arsenic trioxide prevents restenosis is through attenuating smooth muscle cell proliferation by inhibiting the G1 and S phases of the cell cycle, as well as promoting apoptosis (13-15). Based on the aforementioned theory, novel domestically produced arsenic trioxide drug-eluting stents (AVI) have been developed, which have received a registration certificate issued by the State Food and Drug Administration (Beijing, China). Currently, AVI (Beijing Amsinomed Medical Device Co., Ltd., Beijing, China) is marketed for use in PCI, however, due to the lack of post-marketing clinical data, its safety and clinical efficacy are yet to be confirmed. The current study is a re-evaluation of prospective clinical studies with a monotherapy group on the basis of clinical registration, aimed at investigating the safety and clinical efficacy regarding the application of AVI stents in patients with coronary heart disease (CHD).

Patients and methods

Selection of cases. A total of 40 patients with CHD who underwent AVI implantation between January and August 2014 were selected from the cardiology department at Yongchuan Hospital of Chongqing Medical University (Chongqing, China). The present study consisted of 35 men and 5 women with a mean age of 63.4±11.6 years. Patients were included in the study if they were ≥18 years old, had symptomatic ischemic heart disease or presented with myocardial ischemia, in whom the stenosis diameter of at least one lesion was ≥70% and were suitable for implantation of AVI alone. Patients were excluded if they were pregnant, lactating or planning to become pregnant ≤1 year following PCI, had an unusual susceptibility of bleeding or were diagnosed with coagulation disorders, could not adhere to dual antiplatelet treatment, or were allergic to arsenic trioxide, stainless steel alloy, polylactic acid polymer or contrast agents. Patients with any of the following forms of CHD: severe tortuosity, calcified lesions, two or more chronic proximal total occlusions; or in which a double stenting style was required to be

Correspondence to: Dr Zhifeng Li, Department of Cardiology, Yongchuan Hospital, Chongqing Medical University, 439 Xuanhua Road, Yongchuan, Chongqing 402160, P.R. China
E-mail: zhifenglidoc@163.com

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performed for bifurcation lesions, were also excluded. The current study was completed in accordance with the Declaration of Helsinki and conducted with approval from the Ethics Committee of Chongqing Medical University. Each patient was informed of the nature of the study and had agreed to cooperate with postoperative follow-up and signed a form granting written informed consent.

Perioperative medication. Patients undergoing planned PCI were prescribed at least 100 mg aspirin (Bayer AG, Leverkusen, Germany) and 75 mg clopidogrel (Sanofi China, Hangzhou, China) orally each day for the three days prior to the procedure. Eight emergency patients who underwent PCI immediately chewed 300 mg aspirin and 300-600 mg clopidogrel. Unfractionated 100 U/kg heparin (Tianjin Biochemical Pharmaceutical Co., Ltd, Tianjin, China) was injected intravenously during surgery. If the surgery lasted >1 hr, an additional 1,000-2,000 U heparin was administered. For 5-7 days following surgery, 5,000 U/12 h low molecular weight heparin (Qilu Pharmaceuticals Co., Ltd, Jinan, China) was administered via subcutaneous injection. Aspirin was continued at 100 mg per day throughout the remainder of the patients' lifetimes. Clopidogrel, at 75 mg per day, was continued for ≥12 months. Comprehensive treatments including lipid adjustment, blood pressure and blood glucose management were administered according to the patient's condition.

Interventional treatment. The Seldinger technique (16) was used to perform femoral artery or radial artery puncture. Coronary angiography was performed using the Judkins method (17) and stenting surgery was performed once the presence of lesions suitable for PCI was confirmed by coronary angiography. When multiple stents were necessary in long lesions, an overlap of 2-3 mm was required between stents and high-pressure balloon dilation was performed to secure the overlapping. When the implanted stent length was ≥29 mm, high-pressure short balloon dilation to the same diameter as the diameter of the stent was performed once the stent was released. When residual stenosis of the lesion was >20%, a short balloon was used for dilation. The diameter ratio of the stent and the vasculature at the proximal and distal ends of the target lesion was 1:1.0-1.1, and the stents were placed to completely cover the lesion. Immediate success was indicated by a target lesion residual stenosis of <20% and forward flow of thrombolysis in myocardial infarction (TIMI) level three (18), without PCI complications. These included main branch occlusion or pressure, thrombosis, huge hematoma, severe dissection or shock.

Follow-up indicators. The occurrence of major adverse cardiovascular events (MACE), including cardiac death, target lesion revascularization and nonfatal myocardial infarction, during hospitalization was documented. Regular cardiology clinic review and telephone follow-up were completed following patient discharge, in which the patient's medication, MACE occurrence and angina recurrence were recorded. Coronary angiography review was performed one year later, through which stent restenosis and thrombosis were recorded.

Results

Patient clinical characteristics. The selected 40 patients included 22 patients with acute myocardial infarction, 16 patients with unstable angina, one patient with stable angina and one patient with old myocardial infarction. Diabetes, hypertension and hyperlipidemia prevalence rates were 15.0, 37.5 and 17.5%, respectively. The proportion of patients with a history of myocardial infarction, a family history of coronary heart disease or a history of smoking were 2.5, 10.0 and 80.0%, respectively. No patients had previously undergone PCI.

Coronary angiography and stenting. Coronary angiography indicated that there were 20 cases of simple anterior descending artery disease, six cases of right coronary artery disease, four cases of circumflex artery lesions, eight cases of double vessel disease and two cases of triple vessel lesions and no cases of left main artery disease. A total of 63 stents were implanted into 52 AVI target lesions. The stent length was 23.4±7.2 mm and its diameter was 3.02±0.24 mm. The immediate surgery success rate was 100%. No MACE occurred during hospitalization.

Follow-up. All 40 patients completed the one-year clinical follow-up, meaning that the total follow-up rate was 100%. During follow-up, one patient experienced gastrointestinal bleeding in the first two months following PCI, for which aspirin was discontinued and oral clopidogrel alone was administered for antiplatelet therapy; this patient experienced no recurrence of angina or MACE. The remaining 39 patients adhered to the aspirin and clopidogrel dual antiplatelet therapy for one year. The follow-up data concluded that the MACE rate was 15.0% (6/40) and the target lesion revascularization rate was 15.0% (6/40). Furthermore, no cardiac deaths or nonfatal myocardial infarctions occurred, the in-stent thrombosis rate was 0 and the angina recurrence rate was 32.5% (13/40). All patients agreed to undergo coronary arteriography review one year following surgery. Angiography revealed that the in-stent restenosis rate was 20.0% (8/40).

Discussion

The clinical application of drug-eluting stents (DES) is regarded as the third milestone in the development of PCI (19). Currently, the forms of DES that are widely used clinically include the sirolimus- and paclitaxel-eluting stents. As part of the Drug-eluting Stents project of Chinese Original products, the arsenic trioxide-eluting stent (AVI) has received eight utility model patents in China, the US, the EU, Japan and other countries, and was the first non-rapamycin/paclitaxel drug-eluting stent manufactured in China (20).

Although AVI has been used in the domestic market, only pre-marketing research data is currently available. Experimental results using New Zealand rabbits as animal models (11) indicated that no significant difference existed between 40 μg As_2O_3 DES and 180 μg paclitaxel DES in reducing intimal hyperplasia. Experimental results using pigs as an animal model (14) demonstrated that AVI can

reduce intimal proliferation following coronary artery damage without significantly delaying the vascular endothelial process at the stent implantation site and has a significant effect on restenosis rates. The results of this previous study demonstrated that after a 4-week follow-up period, the effect of As_2O_3 DES on restenosis rates was better than that of the stents without drug coating (14). Prior to the approval of AVI for use in PCI, randomized controlled trial data of AVI and sirolimus-eluting stents (20) demonstrated that out of 212 cases enrolled, who were randomly divided into groups receiving either arsenic trioxide (n=106) or rapamycin (n=106), the failure rate for the target vessels in the arsenic trioxide and rapamycin groups were 6.67 and 5.83% respectively (P=0.980) and the cardiac death or myocardial infarction event rate of the two groups were 0 and 3.88%, respectively (P=0.058) following the two-year follow-up period. Target lesion revascularization rates were 6.67 and 1.94% respectively (P=0.170) and the identified stent thrombosis rate were 0 and 0.97%, respectively (P=0.495). The angina recurrence rates of the two groups were 40.78 and 38.54%, respectively (P=0.747). The nine month follow-up coronary angiography demonstrated that the in-stent restenosis rates of the two groups were 7.92 and 1.61% respectively (P=0.155), and the late lumen loss of the two stent groups were 0.29-0.52 mm and 0.10-0.25 mm respectively (P=0.008), indicating that the late lumen loss of the arsenic trioxide group was greater than that of the SES group (20).

The current study is a prospective clinical study for a monotherapy group, following the clinical approval of AVI, aimed at investigating the post-marketing clinical efficacy of AVI. The 40 cases selected were followed up for one year. The results indicate that the MACE rate was 15.0% (6/40), the target lesion revascularization rate was 15.0% (6/40), no cardiac death or nonfatal myocardial infarction events occurred, the occurrence of stent thrombosis rate was 0 and the angina recurrence rate was 32.5% (13/40). The one-year postoperative review of coronary angiography indicated that the in-stent restenosis rate was 20.0% (8/40). Therefore, the restenosis rate of the implanted AVI was higher, and its safety and clinical efficacy were lower than expected. In the light of the small sample size in this study, the short follow-up time, and the fact that it is a single-center clinical study, further studies are required to confirm these conclusions.

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