New Drug-Eluting Stents to Prevent Stent Thrombosis and Restenosis for Acute Myocardial Infarction - From the Experience of Korean Acute Myocardial Infarction Registry

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ABSTRACT

Drug-eluting stents (DES) are superior to bare metal stents (BMS) in reducing restenosis rates across a wide range of patients and lesion subsets. This study presented the investigation of one-year clinical follow-up were registered in 52 primary percutaneous coronary intervention sites in Korea, and pre-clinical results of various drug-coated stent fabricating with many other coating approaches on physiological parameters, Based on our clinical study adverse cardiac events were 17.4 % after DES implantation, which was significantly lower compared with 24.9% of BMS implanted patients. As assumption above outcome, it well repays research and development in new DES. Our research group carefully chooses abciximab, alpha-lipoic acid, heparin / dopamine, inhibitors in cell signal cascade were employed as coating drug. These drug candidates were coated on BMS surface by various methods such as TiO2 film deposited by plasma enhanced chemical vapor deposition, ultrasonic sprayer / simple-dip coating, or bio-inspired natural binding technique. *In vitro* and *in vivo* results of these new DES fabricated by our research group have showed superior outcomes

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compare to BMS on physiological parameters such as inflammation score, re-endothelialization, preventing neointema or thrombosis etc. These results are promising safer and more effective to overcome the limitation of DES.

Keywords: Drug-eluting stent, acute myocardial infarction, Korean Acute Myocardial Infarction Registry, Abciximab, alpha lipoic acid, anti-oxidant agent, dual-coating, thrombosis, restenosis

1. INTRODUCTION

Incidence of acute myocardial infarction (AMI) has been increased in Korea and percutaneous coronary intervention using stent is a major therapeutic method in the management of AMI. Coronary arterial stenting with drug-eluting stent (DES) is a major therapy for the treatment of coronary arterial diseases in present interventional cardiology practice. Main characteristics of the culprit lesion in AMI are less plaque volume and more thrombus burden. Healing pattern of target lesion in AMI is different from stable angina. In contrast to stable angina, culprit lesion site is not covered by stent strut completely due to ruptured lesion. Delayed arterial healing and increased late stent thrombosis at culprit sites after DES placement for AMI patients were demonstrated on an autopsy study. DES in AMI may be feasible and safe [1]. However, there is a tendency to select a BMS rather than a DES in AMI patients. The possible reasons are long-term therapy of dual anti-platelets and insufficient long-term clinical outcomes about risk of late or very late stent thrombosis [2, 3]. Thus, we investigated twelve-month mortality in patients with AMI who underwent successful PCI using data from the Korean Acute Myocardial Infarction Registry (KAMIR). Moreover, in the present study, the reviews for *in vitro* and in *vivo* study of our own various self-fabricating drug-coated stent are represented.

2. METHODOLOGY

Animal study

The Ethics Committee of Chonnam National University Medical School and Chonnam National University Hospital approved the animal study for this research. BMS or various drug coating stent were implanted in two coronary arteries of pigs. Follow-up coronary angiogram and histopathologic assessment were performed at 4 weeks after stenting.

Study design and patient population

We have performed KAMIR for the commemoration of 50th anniversary of Korea Circulation Society. We have registered more than 38,000 patients so far. Between Nov 2005 and Jan 2008, 13,133 patients with one-year clinical follow-up were registered in 52 primary percutaneous coronary intervention sites in Korea.

Preparation of drug coating stent

The dual-coated stent was prepared by grafting abciximab and ALA to a bare metal stent (3.0×18 mm, MAC®stent, AMG, Munich, Germany) which had been coated with a polymer layer by plasma polymerization of 1,2-diaminocyclohexane (DACH) using the method of Song et al [4], or electrospray [5].

3. RESULTS

Clinical study

Based on our clinical study using intravascular ultrasound, we have found plaque prolapse developed frequently as 27 % of patients with AMI after stent implantation. Multiple plaque rupture and thrombus are frequently observed in diabetic AMI patients and dense calcium with large necrotic core were associated with no-reflow and stent thrombosis after stenting in AMI patients. Twelve month major adverse cardiac events, including cardiac death, non-cardiac death, myocardial infarction, repeated PCI, coronary artery bypass surgery, were 17.4 % after DES implantation, which was significantly lower compared with 24.9% of bare-metal stent (BMS) implanted patients [6].

Abciximab-coated stent

In animal study, abciximab-coated stent showed no platelet thrombi and small area of neointima formation. Inflammation score of abciximab-coated stent was lower than those of Cypher® and TAXUS® stent in a porcine model. In patients with abciximab-coated stents, late loss and neointimal area were significantly lower compared with BMS according to quantitative coronary angiographic and intravascular ultrasound (IVUS) findings. Late stent mal-apposition developed only in 4 % of abciximab coated stent by 6-9 month follow-up IVUS examination. We performed clinical

study in patients with AMI using abciximab-coated stent, no in-hospital MACE developed and no stent thrombosis was observed during two-year clinical follow-up [7, 8].

Anti-oxidants-coated stent

Anti-oxidants, carvedilol, probucol and alpha-lipoic acid (ALA), were used for stent coating. In a porcine model, carvedilol stent were more effective than probucol stent. No stent thrombosis was observed in clinical trial using carvedilol stent during two-year clinical follow up. Recently we have developed ALA coating stent, which inhibits neointimal cell proliferation by the inhibition of P-ERK and p-STAT3, and promotes endothelial coverage *in vitro* study. ALA stent inhibits Akt and VEGF expression in a porcine model [9]. ALA stent may be effective for AMI patients with diabetes mellitus.

Dual-coating stent

We have developed dual coating stents using nanotechnology and endothelial progenitor cell capturing stent to promote endothelialization. Dual coating stent using abciximab and ALA will be more effective in the prevention of stent thrombosis and restenosis, especially for the patients with AMI with large thrombus burden. Dual coating stent inhibits inflammation compared with BMS. Dual coating stent was prepared using TiO2 film deposited by plasma enhanced chemical vapor deposition. AFM image after TiO2 film coating demonstrated good attachment of abciximab and ALA, which were released over one month. This new technology will be effective in patients with AMI [10].

Polysaccharide, bio-inspired or gene coating stent

Currently we are developing new DES, Hepamine (dopamine+heparin) coating with natural binding technique [11], or Fucoidan, a powerful MAP kinase inhibitor, coating stents using bioabsorbable polymer, and gene-coated stent with drug on TiO2 film, and Akt1 siRNA-embedded coronary stent for the prevention of late stent thrombosis and restenosis [12].

4. DISCUSSION

According to the KAMIR data, DES penetration rate is more than 90%. As compared with BMS the event rates are lower after DES implantation in patients with AMI, indicating that DES can be used safely and effectively to treat AMI patients by reducting the need for repeat revascularizations and by not increasing the risks of mortality, MI, and stent thrombosis. According to our animal study, inflammation and delayed endothelialization were observed especially after overlapped DES implantation. Innovation should be needed to overcome late or very late stent thrombosis, inflammation, local hypersensitivity of drug, aneurysm, stent fracture and restenosis using different stent design, different coating, new polymers, bioabsorbable polymer-coated stents, polymer-free stents, new anti-platelet agents and more selective use of DES. We have developed many types of DES in our laboratories. Abciximab (Reopro®) is a potent anti-platelet agent. Systemic use of abciximab has significantly reduced thrombotic complications following complex angioplasty and stenting [13, 14]. ALA is a potent antioxidant and acts as a co-factor of key mitochondrial enzymes such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase [15]. ALA is beneficial for improving endothelial function and preventing atherosclerosis-related disease [16], and prevents insulin resistance, protects endothelial dysfunction and is effective in the diabetic neuropathy [9]. These two drugs were used for single or dual coating on BMS surface and they were showed better outcomes than comparison groups. Besides, our research group have been fabricated own DES such as hepamine stent by bio-inspired engineering using dopamine which is the composition of adhesive proteins in mussels, fucoidan stent using natural resource, or gene-coated stent were fabricated. These results provides basic information for developing new DES to overcome problems of existing DES, and further study are required for clinical application.

5. CONCLUSION

In conclusion, DES may be safe and effective in patients with AMI. However, problem of delayed endothelialization and late stent thrombosis should be solved. New DES, such as abciximab, anti-oxidants and dual coating stent using bio-absorbable or non-polymer techniques and gene delivery stent, will be safer and more effective in the prevention of late or very late stent thrombosis.

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