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Effects of β-Radiation Using a Holmium-166 Coated Balloon on Neointimal Hyperplasia in a Porcine Coronary Stent Restenosis Model

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Brachytherapy is a promising method of preventing and treating coronary stent restenosis. The present study was designed to observe the therapeutic effects of a radioactive balloon loaded with Holmium-166 (^{166}Ho) in a porcine coronary stent restenosis model. A radioisotope of ^{166}Ho was coated onto the balloon surface using polyurethane (20 Gy at 0.5 mm depth). Stent overdilation injuries were induced in 2 coronary arteries in each pig (n=8). Four weeks after the injury, control balloon dilation was performed in one coronary artery (Group I) and radiation therapy using the ^{166}Ho coated balloon in the other coronary artery (Group II) in each pig. Follow-up coronary angiography and histopathologic assessment were performed at 4 weeks after the radiation therapy or the control balloon dilations. With regard to complete blood cell counts, liver function tests, lipid profiles and coagulation tests, there were no differences between the baseline and after radiation. On quantitative coronary angiographic analysis, reference and target artery diameter showed no differences between the 2 groups before, or 4 and 8 weeks after stenting. On histopathologic analysis of groups I and II, the injury score was 1.34±0.09 and 1.32±0.10, the area of internal elastic lamina was 4.99±0.17 mm^2 and 4.82±0.20 mm^2, and the luminal area was 3.20±0.10 mm^2 and 3.45±0.14 mm^2, respectively (p=NS). The neointimal area was 1.78±0.11 mm^2 in group I and 1.36±0.12 mm^2 in group II (p=0.017), and the histopathologic area of stenosis was 35.1±1.6% in group I and 27.6±1.9% in group II (p=0.005). In conclusion, β-radiation of the stented porcine coronary artery using a radioactive ^{166}Ho coated balloon inhibited stent restenosis without any side effects. (*Circ J* 2003; **67:** 625–629)

Key Words: Coronary artery diseases; Porcine model; Radiation; Restenosis; Stents

The incidence of coronary artery diseases, such as angina pectoris and myocardial infarction, has been increased rapidly over the past 10 years and it has become one of the major causes of death of adults in Korea. Percutaneous coronary intervention (PCI) is regarded as one of the effective therapeutic modalities for coronary artery disease, but the relatively high rate of restenosis (ie, 20–30%) after PCI remains a major clinical problem. Acute vessel closure because of intimal dissection and platelet thrombus, which occurs in 10% of cases after PCI, has been overcome by the recent advent of coronary stenting and antiplatelet agents. Thus, the major problem of PCI is stent restenosis[1,2] and the major mechanism of coronary stent restenosis after therapeutic injury of a coronary artery is neointimal formation.

Various materials and methods had been used to prevent the restenosis, including the drug-eluting stent, which recently showed powerful clinical results[3–5] Local delivery of new therapeutic agents and gene therapy, by catheter-based approach, have been performed to prevent the diffuse type of stent restenosis after PCI, but satisfactory results have not been achieved yet[6]

Local radiation therapy with beta or gamma radiation is known to control neointimal formation in animal experimental studies[7–10] Radiation therapy has been used to prevent restenosis in several clinical trials and its short-term effects have been reported[11–14]

We have previously reported that in an animal study, a balloon coated with a radioisotope Holmium-166 (^{166}Ho) had effectively reduced neointimal hyperplasia after balloon injury[13] In the present study, we investigated whether local radiation therapy with ^{166}Ho can prevent neointima formation in a porcine stent restenosis model.

Methods

All of the animal experiments were carried out under the auspices of the ethical committee of Chonnam National University Hospital. The 8 animals used in this study were 25–35 kg thoroughbred sows provided 3–5 days before the study and observed at the animal care house of the Research Institute of Medical Science of Chonnam National University with facilities for keeping constant temperature and humidity.

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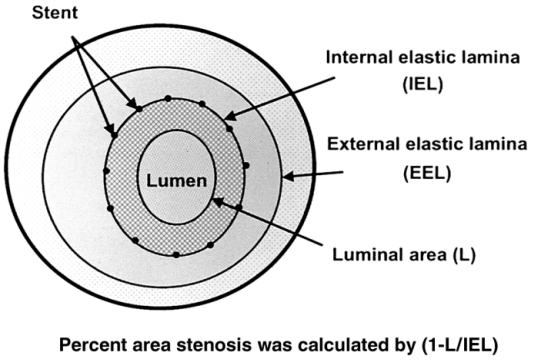

Fig 1. Methods used to analyze the neointimal area and the area stenosis in the porcine coronary stent restenosis model.

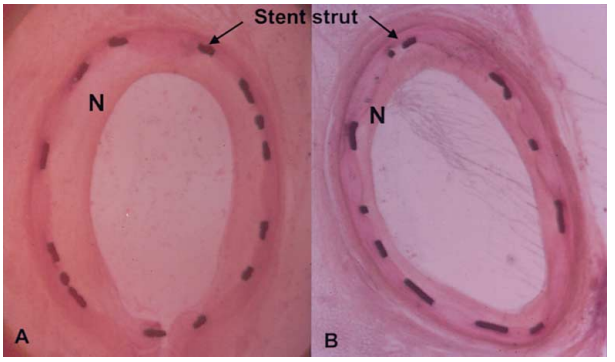

Fig 2. Neointimal area and histopathologic area of stenosis were greater in the control artery (A) than in the locally radiated porcine coronary artery (B), using the ^{166}Ho coated balloon. N, neointima.

Porcine Coronary Stent Restenosis Model and Experimental Method

Pigs were pre-treated with 100 mg aspirin and 250 mg ticlopidine per day and we used Dr Schwartz's coronary stent restenosis injury model. The pigs fasted overnight and general anesthesia was induced by intramuscular injection of ketamine (12 mg/kg) and xylazine (8 mg/kg). We inserted an 8Fr arterial sheath through the carotid artery after local anesthesia with 2% lidocaine and made a cut-down. We engaged the 7 or 8Fr coronary guiding catheter in the coronary ostium under fluoroscopic guidance using a Phillips C-arm system (BV-25 Gold). During the experiment, oxygen was supplied constantly by facial oxygen mask and saline solution was infused through an ear vein; anesthesia was maintained with additional injections of 5 mg midazolam.

We placed a coronary stent in the porcine coronary artery and subjected the vessel to overdilation injury for 30 s at 8–10 atm. Two stents were placed into 2 of 3 proximal coronary arteries that were bigger than 2.5 mm in diameter. The ratio of stent to artery diameter ratio was 1.3 : 1.0. The stent was 3.0 or 3.5 mm in size and 15 mm long. We recorded coronary angiograms before and after stenting and quantitative analysis was performed using a Phillips DCI program. After stenting, we ligated the carotid artery and returned the pig to animal cage. Each pig was observed for 4 weeks in the animal care unit, and 100 mg of aspirin and 250 mg of ticlopidine were administered daily. At 4 weeks after stenting, a follow-up coronary angiogram was performed through the other carotid artery. We dilated one stented coronary artery using a control Arirang balloon after confirmation of narrowing of the previously stented artery on the follow-up coronary angiogram (group I, n=8); the other coronary artery was dilated with the ^{166}Ho coated radioactive balloon (group II, n=8). The balloon was 3.0 or 3.5 mm in size and 20 mm long. For delivery of the optimal tissue radiation dosage (20 Gy at 0.5 mm depth), radioactive balloon dilation was done for 2–3 min at 6–10 atm. After dilation of the stented arteries using either the control or radioactive balloon, we sutured the skin and returned the pig to the animal cage again. A further 4 weeks after balloon dilation of the stented arteries (ie, 8 weeks after stenting) a histopathologic assessment was performed after a second follow-up coronary angiogram via femoral artery and subsequent killing of the pigs.

Routine complete blood cell count and chemistry were checked before stenting and 8 weeks later.

Radiation Balloon Procedure and Local Irradiation Therapy

The radiation dosage with the ^{166}Ho coated balloon was 20 Gy at 0.5 mm depth from the irradiated average of 482.48 MBq (13.04 mCi) for 2–3 min. The ^{166}Ho coated balloon was made as follows. A chemical change of ^{165}Ho $(NO_3)_3$ to radioactive ^{166}Ho$(NO_3)_3$ was performed in the Korea Atomic Hanaro Research Institute and ^{166}Ho in a 10-ml vial (3,700 MBq/ml) was dried by infra-red lamp. The extracted ^{166}Ho was melted into 700 mg of polyurethane, sealed in 1 ml of solution and injected into a dried vial. The ^{166}Ho containing polyurethane solution was melted for 2–3 h and taken into 0.35 ml solution in a pyrex ampoule, and put on the balloon surface by electromotive power. The final thickness of the ^{166}Ho coating was approximately 1 mm. The distribution of ^{166}Ho$(NO_3)_3$ $5H_2O$ was checked with an electric microscope and ^{166}Ho was confirmed to be evenly coated on the balloon surface. The dosimetry at the 0.5 mm radius revealed 23.05 cGy/s per GBq (0.853 cGy/s per mCi).

Histopathologic Assessment

Pigs were killed with potassium chloride injection after the second follow-up coronary angiogram. The extracted hearts were fixed in a perfusion chamber. The coronary artery from 1 cm proximal to the stented segment to 1 cm distal to the stented segment was removed and stained after infiltration, formatting and exfoliating of each section with hematoxylin-eosin. Histopathologic analysis was performed by a cardiac pathologists according to the established method with a computerized visual image analysis system (Visus 2000). Each cross-sectional area was measured with Visus 2000. Lumen and medial area, neointimal and medial thicknesses, and neointimal area were calculated (Fig 1).[17–19] The histopathologic injury score was measured according to Schneider's classification: 0 point for endothelial cell injury without injury of the internal elastic lamina (IEL) area, 1 point for injury to the IEL area with crushed media and 2 points for destruction of the media and external elastic lamina.[20] The neointimal area was calculated by subtracting luminal area from IEL area. Histopathological area of stenosis per vessel was calculated as $100 \times (1 - \text{lumen area/IEL area})$.[4]

Statistic Analysis

All data was designated as an average ± standard error and comparison between 2 groups was performed with the

Table 1 Quantitative Coronary Angiographic Findings of Porcine Coronary Arteries After Control Balloon Dilation (Group I) and Radiation With ^{166}Ho-Coated Balloon (Group II) Plus Dilation

	Group I	*Group II*	*p value*
Baseline (mm)			
Proximal diameter	*2.81±0.10*	*3.09±0.12*	*0.109*
Distal diameter	*2.42±0.10*	*2.52±0.25*	*0.484*
Reference diamter	*2.67±0.23*	*2.84±0.11*	*0.125*
Post-stenting diameter	*2.87±0.11*	*2.95±0.13*	*0.706*
4 weeks after stenting (mm)			
Proximal diameter	*2.93±0.17*	*2.96±0.25*	*0.796*
Distal diameter	*2.49±0.21*	*2.60±0.18*	*0.349*
Target RD	*2.71±0.25*	*2.78±0.19*	*0.743*
Minimal luminal diameter	*2.52±0.29*	*2.48±0.18*	*0.817*
Diameter stenosis (%)	*9.52±3.33*	*9.18±2.92*	*0.486*
4 weeks after ballooning (mm)			
Proximal diameter	*3.00±0.14*	*2.89±0.08*	*0.542*
Distal diameter	*2.45±0.14*	*2.52±0.17*	*0.715*
Target RD	*2.73±0.11*	*2.71±0.12*	*0.889*
Minimal luminal diameter	*2.35±0.18*	*2.49±0.12*	*0.292*
Diameter stenosis (%)	*14.25±4.02*	*8.07±4.5*	*0.056*

RD, reference diameter; NS, not significant.

Table 2 Histopathologic Assessment of Porcine Coronary Arteries After Control Balloon Dilatation (Group I) and Radiation With ^{166}Ho-Coated Balloon (Group II) Plus Dilatation

	Group I	*Group II*	*p value*
Injury score	*1.34±0.09*	*1.32±0.10*	*0.88*
IEL area (mm^2)	*4.99±0.17*	*4.82±0.20*	*0.53*
Lumen area (mm^2)	*3.20±0.10*	*3.45±0.14*	*0.17*
Neointima area (mm^2)	*1.78±0.11*	*1.36±0.12*	*0.017*
Histopathologic stenosis (%)	*35.1±1.6*	*27.6±1.9*	*0.005*

IEL, internal elastic lamina.

Table 3 Laboratory Results Before and After Radiation With ^{166}Ho-Coated Balloon

	Baseline	*^{166}Ho-coated ballooning*	*p value*
WBC (/ul)	*18.8±1.2*	*20.3±2.0*	*NS*
Hemoglobin (g/dl)	*10.2±0.1*	*10.2±0.4*	*NS*
Platelet (K/ul)	*237.4±22.6*	*260.5±23.7*	*NS*
AST (IU/L)	*42.8±4.7*	*37.2±4.6*	*NS*
ALT (IU/L)	*36.0±2.1*	*36.2±1.9*	*NS*
ALP (IU/L)	*160.6±13.8*	*132.2±7.5*	*NS*
BUN (mg/dl)	*13.8±0.9*	*17.2±1.8*	*NS*
Creatine (mg/dl)	*1.0±0.2*	*1.0±0.2*	*NS*
Total cholesterol (mg/dl)	*87.1±3.4*	*85.0±5.4*	*NS*
Triglyceride (mg/dl)	*36.4±5.2*	*24.2±4.6*	*NS*
HDL-C (mg/dL)	*41.4±2.0*	*40.3±4.4*	*NS*
ESR (mm/h)	*10.4±2.8*	*8.0±1.9*	*NS*
C-reactive protein	*0.31±0.10*	*0.36±0.08*	*NS*
Fibrinogen (mg/dl)	*144.3±8.3*	*146.4±11.8*	*NS*
PT (s)	*10.3±0.2*	*10.5±0.1*	*NS*
aPTT (s)	*19.3±1.6*	*21.1±1.2*	*NS*

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein- cholesterol; ESR, erythrocyte sedimentation rate; PT, prothrombin time; aPTT, activated partial thromboplastin time.

unpaired Student's t-test. A p value less than 0.05 was considered as significant.

Results

Quantitative Coronary Angiographic Analysis

On quantitative coronary angiographic analysis, the baseline proximal and distal vessel diameters, and the reference vessel diameter (RD) were, respectively, 2.81±0.10, 2.42±0.10, and 2.67±0.23 mm in group I and 3.09±0.12, 2.52±0.25, and 2.84±0.11 mm in group II. There were no differences between the groups.

On the first follow-up coronary angiogram at 4 weeks after stenting, the proximal RD, distal RD, RD, minimal luminal diameter (MLD), and diameter stenosis (DS) were, respectively, 2.93±0.17, 2.49±0.21, 2.71±0.25, 2.52±0.29 mm, and 9.52±3.33% in group I and 2.96±0.25, 2.60±0.18, 2.78±0.19, 2.48±0.18 mm, and 9.18±2.92% in group

II. On the second follow-up coronary angiogram at 8 weeks after stenting, the angiographic parameters were, respectively, 3.00±0.14, 2.45±0.14, 2.73±0.11, 2.35± 0.18 mm, and 14.25±4.02% in group I and 2.89±0.08, 2.52±0.17, 2.71± 0.12, 2.49±0.12 mm, and 8.07±4.5% in group II. There were no differences between the groups (Table 1).

Histopathologic Analysis

The injury score of the coronary artery was 1.34±0.09 in group I and 1.32±0.10 in group II. The IEL area was 4.99± 0.17 mm^2 in group I and 4.82±0.20 mm^2 in group II. Lumen area was 3.20±0.10 mm^2 in group I and 3.45±0.14 mm^2 in group II. There were no differences between the groups. The neointimal area was 1.78±0.11 mm^2 in group I and 1.36±0.12 mm^2 in group II, and the histopathological area of stenosis was 35.1±1.6% in group I and 27.6±1.9% in group II (p=0.017 and p=0.005 respectively, Fig 2,Table 2).

Safety and Side-Effects

The experimental pigs had no major events during the 8-week follow-up period. The radioactive ^{166}Ho coated balloon was compliant. The detectable leakage of radiation measured by a survey meter was absent after local ^{166}Ho delivery. The laboratory findings before and at 8 weeks after stenting demonstrated no differences (Table 3).

Discussion

Stenting the coronary artery effectively dilates the stenosis and reduces the restenosis rate by 20–30%. A stent prevents the elastic recoil after vessel dilation; however, stent restenosis is induced by neointimal hyperplasia and has become a major clinical problem associated with PCI. The exact mechanism of the neointimal hyperplasia has not been established and various approaches, such as gene therapy, radiation therapy and drug-coated or -eluting stents, have been tried to prevent it. Local vascular brachytherapy is an effective treatment![11–15]

Radiation therapy controls tissue hyperplasia by inhibiting cell division. Beta and gamma rays have been studied as sources for local radiation therapy, and animal and clinical studies have demonstrated good results. Gamma rays were successful in the GAMMA-1 study of 252 patients with stent restenosis after ^{192} Ir treatment;[21] and the β rays of yttrium-90 were effective in 181 patients after balloon dilation[22] The indication for radiation treatment of a coronary lesion is in-stent restenosis; however, the long-term effects of radiation therapy have not yet been clarified. Late thrombosis developed 30 days after brachytherapy because of delayed endotheliosis. According to our previous study, ^{166}Ho is a β-ray emitting radioisotope that effectively prevents restenosis without significant endothelial dysfunction.

The Korea Atomic Energy Research Institute developed ^{166}Ho as a therapeutic radioisotope with a half-life of 26.8 h and 95% release of β rays and 5% release of gamma rays. The maximum tissue penetration thickness is 8.7 mm and 90% of the dose distributing X90 is 2.1 mm. ^{166}Ho is not expensive and is easy to handle. ^{166}Ho is coated onto the balloon surface for simultaneous dilation and radiation. The radioisotope-coated balloon can be used for PCI.[23]

After ^{166}Ho-coated balloon dilatation, radiation dosimetry and radiation resistance testing were carried out to evaluate the safety and efficacy of the balloon. The amount of melted radioisotope dosage was measured in 37°C distilled water from the ^{166}Ho coated balloon surface. Approximately 20% of the aqueous solution had melted from the surface within 1 h. After treating the coated balloon with $NaBH_4$ and Na_2CO_3 aqueous solution, $Ho(NO_3)_3$ transformed to insoluble $Ho(OH)_3$, and the radiation leaking dose decreased to 0.5% of the first dose.

We inflated the balloon to 10 atm while it was immersed for 1 week in 37 GBq (1 Ci) $Ho(NO_3)_3$ to confirm explosion of the balloon and its material blazing by radiation until the radioactivity remained high. We used a 10 mm diameter vial to protect the radiation source of the coated balloon. The total absorption dose for 1 week estimated by EGS4 was 1.17 Mgy, and its safety was proved.

Local radiation therapy has been attempted via catheters or guide wires with a radioactive source within the coronary artery. We have developed a new, safe, convenient and cheap form of radiation therapy using a β-emitting radioisotope coated balloon. Another advantage of the coated balloon is less radiation than from a ^{166}Ho filled balloon, which has an estimated absorption radiation dose of 12.51 cGy/s per GBq (0.463 cGy/s per mCi) in the target area of the same location.

In our present results, there was the discrepancy between the 2 methods of evaluating the stenosis; that is, the histopathologic and angiographic analyses. In the clinical situation, much more severe stenoses are frequently demonstrated by intravascular ultrasound in angiographically milder coronary stenotic lesions. In addition, as Murata et al[24] show in their examples, the impact of the cross-sectional geometry of the stent overdilation injury in an animal experimental study must also be taken into consideration.

Local radiotherapy with ^{166}Ho coated balloon was effective in the prevention of neointimal hyperplasia after balloon overdilation injury in a porcine coronary artery injury model[15] We also reported that a ^{166}Ho coated balloon inhibited neointimal hyperplasia without significant endothelial dysfunction[25]

Previous studies have shown that cutting balloon angioplasty or the stent-in-stent method is effective in some cases of in-stent restenosis. The purpose of the present study was to investigate the effectiveness of a ^{166}Ho coated balloon on in-stent restenosis without any side-effects. At present, intracoronary brachytherapy is indicated in cases of diffuse in-stent restenosis. The difference between individual therapeutic modalities of in-stent restenosis was not assessed in this study.

We induced neointimal hyperplasia with a stent overdilatation injury, and after radiation therapy using a ^{166}Ho coated balloon the neointimal hyperplasia was successfully inhibited.

Study Limitations

A major limitation of this study is that intravascular ultrasonography was not performed for accurate measurement of the in-stent neointima. Long-term follow-up for more than 1 month is necessary to observe late stent thrombosis caused by delayed endothelization. In addition, the radiation dosage of the animal's blood was not measured. The concept of edge effect because of geographic miss is almost standard in radiation therapy in stent restenosis and using a 30-mm radioactive balloon is much better than a 20-mm balloon to treat a 15-mm in-stent restenosis. However, in this animal experiment a 20-mm balloon was chosen because the extent of the in-stent restenosis in this pig model is much less than in human beings. Thus we

could avoid the edge effect by using relatively short balloon. Using a long balloon is recommended for a future clinical trial.

Conclusion

Beta-radiation using a ^{166}Ho coated balloon effectively inhibited neointimal hyperplasia within the stented porcine coronary artery without systemic side effects. Therefore, the ^{166}Ho coated balloon should be assessed in a future clinical trial.

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