

돼지 관동맥 스텐트 재협착에 대한 Holmium-166 부착 풍선도자의 방사선 조사 효과

김 원¹ · 정명호³ · 이상록¹ · 박옥영¹ · 김정하¹ · 최명자¹ · 김인수¹
 정우곤¹ · 류제영¹ · 김주한¹ · 염주협¹ · 범희승² · 최선주⁴
 박경배⁴ · 안영근¹ · 박종태³ · 조정관³ · 박종춘³ · 강정채³

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

Weon Kim, MD¹, Myung Ho Jeong, MD³, Sang Rok Lee, MD¹, Ok Young Park, MD¹,
 Jeong Ha Kim, MS¹, Myung Ja Choi, RN¹, In Soo Kim, MS¹, Woo Kon Jeong, MD¹,
 Jay Young Rhew, MD¹, Ju Han Kim, MD¹, Ju Hyup Yum, MD¹, Hee Seung Bom, MD²,
 Sun Joo Choi, PhD⁴, Kyung Bae Park, PhD⁴, Young Keun Ahn, MD¹, Jong Tae Park, MD³,
 Jeong Gwan Cho, MD³, Jong Chun Park, MD³ and Jung Chae Kang, MD³

¹The Heart Center, ²Department of Nuclear Medicine, Chonnam National University Hospital, Chonnam,

³The Research Institute of Medical Sciences, Chonnam National University, Gwangju,

⁴Atomic Energy Research Institute, Daejeon, Korea

ABSTRACT

Background and Objectives : Brachytherapy is a promising method in the prevention and treatment of coronary stent restenosis. We sought to observe the therapeutic effects of a radioactive balloon loaded with Holmium-166 (¹⁶⁶Ho) in a porcine coronary stent restenosis model. **Materials and Methods :** A radioisotope of ¹⁶⁶Ho was coated on the balloon surface using a polyurethane coating (20 Gy in 0.5 mm depth). Stent overdilation injuries were performed in two coronary arteries in 8 pigs. Four weeks after the stent overdilation injury, radiation therapies were performed using a control balloon dilation in one coronary artery (Group I : n = 8) and a ¹⁶⁶Ho-coated balloon in the other coronary artery in each pig (Group II : n = 8). Follow-up coronary angiogram and histopathologic assessment were performed at 4 weeks after the therapy was administered. **Results :** Laboratory findings did not differ significantly between the pre-treatment baseline and the measurements taken after radiation. On quantitative coronary angiogram, the coronary artery diameters were not significantly different between the two groups before stenting or at 4 and 8 weeks after stenting. On histopathologic analysis, injury score, internal elastic lamina area and lumen area did not differ significantly between the two groups. The neointimal area was $1.78 \pm 0.11 \text{ mm}^2$ in group I and $1.36 \pm 0.12 \text{ mm}^2$ in group II ($p = 0.017$), and the histopathologic area of stenosis was $35.1 \pm 1.6\%$ in Group I, $27.6 \pm 1.9\%$ in Group II ($p = 0.005$). **Conclusion :** A

: 2002 2 15

: 2002 3 29

: , 501 - 757

1 8

: (062) 220 - 6243 · : (062) 228 - 7174 · E - mail : myungho@chollian.net

treatment of beta-radiation in a stented porcine coronary artery using radioactive Ho-166 coated balloon inhibits stent restenosis without any side effects. (**Korean Circulation J 2002;32(5):398-406**)

KEY WORDS : Coronary disease ; Coronary restenosis ; Stents ; Radioisotopes.

서 론

10

재료 및 방법

(Percutaneous coronary intervention : PCI)

재 료

, 30 40%

negative remodeling

,¹⁾ 10%

가

25 35 kg

3 5

,²⁾

가

가

, ticlopidine

(stent)

10 15% 1%

MAC

¹⁶⁾

4

8

,³⁾

(Arirang®, Korea Meditech)

(I, n=8)

8

¹⁶⁶Ho

(II, n=8).

20%

,³⁾⁴⁾

PCI

4

,⁵⁾⁶⁾

방 법

negative remodeling

,^{7 - 10)}

,^{11 - 14)}

holmium - 166

(¹⁶⁶Ho)

100 mg aspirin 250 mg ticlo-

pidine

ong Schwartz가

Je -

,^{17 - 19)}

Ketamine 12 mg/

kg Xylazine 8 mg/kg

2% lidocaine

,¹⁵⁾

8 Fr.

. Heparin sodium

¹⁶⁶Ho

10,000 U

7 F

8 F

방사선 풍선도자 제작방법 및 국소 방사선 조사 요법

midazolam ^{166}Ho

가 . , ^{166}Ho 13.04

가 , ^{166}Ho 2 3 20 Gy

1.3 : 1 standard mCi ^{166}Ho ^{165}Ho

indeflator 8 10 30 가 $(\text{NO}_3)_3$

(: $1.25 \times 10^{13} \text{ n/cm}^2 \cdot \text{sec}$, power : 20 MW) $^{166}\text{Ho}(\text{NO}_3)_3$ 10 mL vial

가 2.5 mm (100 mCi/mL) Infra - red lamp

Tetrahydrofuran : Dimethylformamide(THF : Car - DMF)(10 : 1) polyurethane 700 mg

dio 500(Kontron Inc.) 1 mL vial

2 3

4 0.35 mL pyrex ampoule

100 mg aspirin 250 mg

ticlopidine ^{166}Ho 15

4 THF가 ^{166}Ho

1 2 mm ,

8 (matrix) $^{165}\text{Ho}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ ^{166}Ho

(I ,

n=8), 8 Ho - 166 (dosimetry)

(II , n=8). 0.5 mm 23.05 cGy/s per GBq

1.1 : (0.853 cGy/s per mCi)

1 6 10 ,

0.5 mm 20 Gy 2 조직병리학적 평가

3 potassium chloride

4

100 mg aspirin 250 mg ticlopidine 10% (buffered formalin)

4 , 1 cm

4 , (methyl methacrylate : MMA)

가 He -

matoxylin - Eosin

8 Calibrated Mi -

croscope(Leitz CBA 8000)

calibrated digital microscopic planimetry, (neointima/media ratio=neointima area/media area), (Fig. 1).

가 Schneider²⁰⁾ (histologic injury score) 0

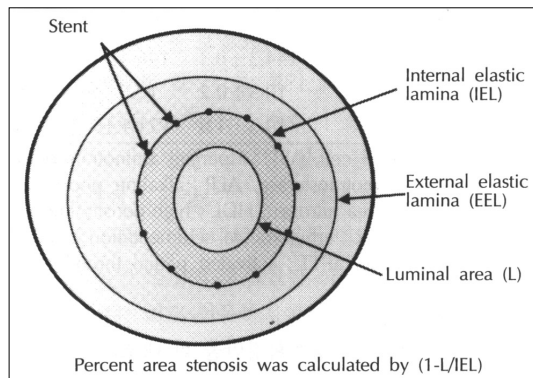


Fig. 1. Methods used to analyze the neointimal area and the area stenosis in porcine coronary stent restenosis model.

1, 2, 3 (internal elastic lamina area : IEL area) (lumen area) (histopathological area stenosis) $100(1 - \text{lumen area}/\text{IEL area})$

통계학적 분석

unpaired student 't'-test, p 0.05

결 과

정상적 관상동맥 조영술

I 2.81 ± 0.10 mm, 2.42 ± 0.10 mm, 2.67 ± 0.23 mm, II 3.09 ± 0.12 mm, 2.52 ± 0.25 mm, 2.84 ± 0.11 mm I $2.87 \pm$

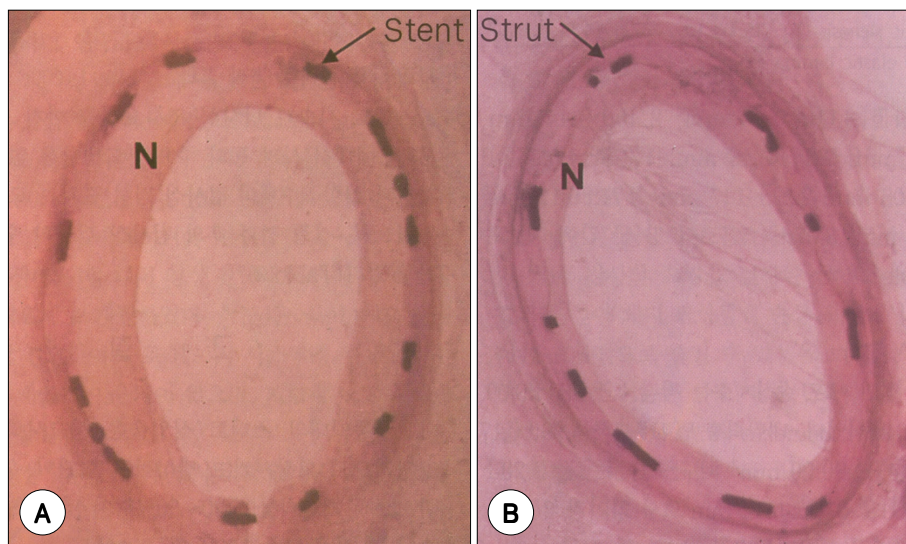


Fig. 2. Neointima area and histopathologic area stenosis were lower in locally radiated porcine coronary artery using ^{166}Ho -coated balloon (B) than in control artery (A).

Table 1. Quantitative coronary angiographic findings of porcine coronary arteries after control balloon (Group I) and radiation with ¹⁶⁶Ho-coated balloon (Group II)

	Group I	Group II	p
Baseline (mm)			
Proximal diameter	2.81 ± 0.10	3.09 ± 0.12	NS
Distal diameter	2.42 ± 0.10	2.52 ± 0.25	NS
Reference diameter	2.67 ± 0.23	2.84 ± 0.11	NS
Post-stenting diameter	2.87 ± 0.11	2.95 ± 0.13	NS
4 weeks after stenting (mm)			
Proximal diameter	2.93 ± 0.17	2.96 ± 0.25	NS
Distal diameter	2.49 ± 0.21	2.60 ± 0.18	NS
Target RD	2.71 ± 0.25	2.78 ± 0.19	NS
Minimal luminal diameter	2.52 ± 0.29	2.48 ± 0.18	NS
Diameter stenosis (%)	9.52 ± 3.33	9.18 ± 2.92	NS
4 weeks after ballooning (mm)			
Proximal diameter	3.00 ± 0.14	2.89 ± 0.08	NS
Distal diameter	2.45 ± 0.14	2.52 ± 0.17	NS
Target RD	2.73 ± 0.11	2.71 ± 0.12	NS
Minimal luminal diameter	2.35 ± 0.18	2.49 ± 0.12	NS
Diameter stenosis (%)	14.25 ± 4.02	8.07 ± 4.5	NS

RD : reference diameter, NS : not significant

Table 2. Histopathologic assessment of porcine coronary arteries after control balloon (Group I) and radiation with ¹⁶⁶Ho-coated balloon (Group II)

	Group I	Group II	p
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	0.005
Histopathologic stenosis (%)	35.1 ± 1.6	27.6 ± 1.9	0.017

IEL : internal elastic lamina

0.11 mm, II 2.95 ± 0.13 mm, 가 .
4
, , , , ,
I 2.93 ± 0.17 mm, 2.49 ± 0.21 mm, 2.71 ± 0.25 mm, 2.52 ± 0.29 mm, 9.52 ± 3.33%, II 2.96 ± 0.25 mm, 2.60 ± 0.18 mm, 2.78 ± 0.19 mm, 2.48 ± 0.18 mm, 9.18 ± 2.92%, , 8
, , , , ,
I 3.00 ± 0.14 mm, 2.45 ± 0.14 mm, 2.73 ± 0.11 mm, 2.35 ± 0.18 mm, 14.25 ± 4.02%, II 2.89 ± 0.08 mm, 2.52 ± 0.17 mm, 2.71 ± 0.12 mm, 2.49

Table 3. Laboratory results before and after radiation with ¹⁶⁶Ho-coated ballooning

	Baseline	¹⁶⁶ Ho-coated ballooning	p
WBC (/ μ L)	18.8 ± 1.2	20.3 ± 2.0	NS
Hemoglobin (g/dL)	10.2 ± 0.1	10.2 ± 0.4	NS
Platelet (K/ μ L)	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 (mg/dL)	41.4 ± 2.0	40.3 ± 4.4	NS
ESR (mm/hr)	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 (sec)	10.3 ± 0.2	10.5 ± 0.1	NS
aPTT (sec)	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 : high density lipoproteincholesterol, ESR : erythrocyte sedimentation rate, PT : prothrombin time, aPTT : activated partial thromboplastin time

± 0.12 mm, 8.07 ± 4.5%
(Table 1).

조직병리검사 결과

I 1.34 ± 0.09,
II 1.32 ± 0.10 . I 4.99 ± 0.17 mm², II 4.82 ± 0.20 mm², I 3.20 ± 0.10 mm², II 3.45 ± 0.14 mm² 가 .
I 1.78 ± 0.11 mm², II 1.36 ± 0.12 mm², I 35.1 ± 1.6%, II 27.6 ± 1.9%

(p=0.017, p=0.005,
Table 2, Fig. 2).

부작용 및 검사실 검사 결과

8

가
(Table 3).
mma - (5%)
ga - ^{166}Ho
 ^{166}Ho
고 찰
23)
 ^{166}Ho
가
20 30%
 ^{166}Ho
37
(1, 5, 1)
가
NaBH₄ Na₂CO₃
(radiation resistance test of balloon)
 ^{166}Ho 가
가 37
GBq(1 Ci) $^{166}\text{Ho}(\text{NO}_3)_3$
가 10 atm inflation
10 mm
beta - gamma -
gamma - 192 - Ir 252 vial
GAMMA - 1
EGS4 code system
21) beta Verin 22) 1.17 MGy
181
yttrium - 90
가
30
 ^{166}Ho
12.51 cGY/s per GBq(0.463
cGY/s per mCi) Ho - 166
 ^{166}Ho
가 26.8 beta -
(95%), 가 8.7 mm
90%가 X90 2.1 mm 4

15) ,
¹⁶⁶Ho
 vasomotor reactivity
 8
 late thrombo -
 sis
 24)
 Na₂CO₃
 20%
 , NaBH₄
 37
 1
 Ho(NO₃)₃가 Insoluble Ho
 가 (OH)₃
 0.5%
¹⁶⁶Ho
 ,
 ,
 ,
 ,
 4
 요 약

배경 및 목적 :
 ,
 가 가
 ,
 ,
 ,
¹⁶⁶Ho
 ,
¹⁶⁶Ho

20 Gy
¹⁶⁶Ho
 4
 4
¹⁶⁶Ho
 ,
 20 Gy
 4
 (I :)
 (II :)
 가 ,
 가

결 과 :
 endothelialization
 late throm -
 bosis가 가
 ,
 8
 . 4
 ,
 ,
 가

I 2.71 ± 0.25 mm, 2.52 ± 0.29 mm,
9.52 ± 3.33%, II 2.78 ± 0.19 mm, 2.48 ± 0.18 mm,
9.18 ± 2.92% , 8 ,
I 2.73 ± 0.11 mm, 2.35 ±
0.18 mm, 14.25 ± 4.02%, II 2.71 ± 0.12 mm, 2.49
± 0.12 mm, 8.07 ± 4.5%

I 1.34 ± 0.09, II 1.32 ± 0.10 .
가 .
I 1.78 ± 0.11 mm², II 1.36 ± 0.12 mm²,
I 35.1 ± 1.6%, II 27.6 ± 1.9%

(p=0.017, p=0.005).

가 .

결 론 :

¹⁶⁶Ho

중심 단어 : ; ; ;

2001

REFERENCES

- 1) Bittl JA. *Advances in coronary angioplasty*. *N Engl J Med* 1996;335:1290-302.
- 2) Lincoff AM, Popma JJ, Ellis SG, Hacker JA, Topol EJ. *Abrupt vessel closure complicating coronary angioplasty: clinical angiographic and therapeutic profile*. *J Am Coll Cardiol* 1992;19:926-35.
- 3) Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rut-
sch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand
V, Materne P. *A comparison of balloon-expandable stent
implantation with balloon angioplasty in patients with cor-
onary artery disease*. *N Engl J Med* 1994;331:489-95.
- 4) Fischman DL, Leon MB, Baim DS, Schatz RA, Savage
MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M. *A
randomized comparison of coronary stent placement and
balloon angioplasty in the treatment of coronary artery
disease*. *N Engl J Med* 1994;331:496-501.
- 5) Jeong MH, Ahn YK, Cho JG, Park JC, Kang JC. *Succe-
ssful coronary stent implantation using local NO donor
delivery*. *J Interv Cardiol* 2000;13:191-5.
- 6) Ahn YK, Jeong MH, Kim JW, Kim SH, Cho JH, Cho JG,
Park CS, Juhng SW, Park JC, Kang JC. *Preventive effects
of heparin-coated stent on restenosis in the porcine model*.
Catheter Cardiovasc Interv 1999;48:324-30.
- 7) Wiedermann JG, Marboe C, Amols H, Schwartz A, We-
inberger J. *Intracoronary irradiation markedly reduces
restenosis after balloon angioplasty in a porcine model*. *J
Am Coll Cardiol* 1994;23:1491-8.
- 8) Verin V, Popowski Y, Urban P, Belenger J, Redard M,
Costa M, Widmer MC, Rouzaud M, Nouet P, Grob E.
*Intraarterial beta irradiation prevents neointimal hyper-
plasia in a hypercholesterolemic rabbit restenosis model*.
Circulation 1995;92:2284-90.
- 9) Waksman R, Robinson KA, Crocker IR, Wang C, Grav-
anis MB, Cipolla GD, Hillstead RA, King SB 3rd. *Intra-
coronary low-dose beta-irradiation inhibits neointima for-
mation after coronary artery balloon injury in the swine
restenosis model*. *Circulation* 1995;92:3025-31.
- 10) Waksman R, Rodriguez JC, Robinson KA, Cipolla GD,
Crocker IR, Scott NA, King SB 3rd, Wilcox JN. *Effect
of intravascular irradiation on cell proliferation, apoptosis
and vascular remodeling after balloon overstretch injury of
porcine coronary arteries*. *Circulation* 1997;96:1944-52.
- 11) Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS,
Russo RJ, Schatz RA, Guarneri EM, Steurtamen S, Mor-
ris NB, Leon MB, Tripuraneni P. *Catheter-based radi-
otherapy to inhibit restenosis after coronary stenting*. *N
Engl J Med* 1997;336:1697-703.
- 12) Teirstein PS, Massullo V, Jani S, Russo RJ, Cloutier DA,
Schatz RA, Guarneri EM, Steurterman S, Sirkin K, Nor-
man S, Tripuraneni P. *Two-year follow-up after catheter-
based radiotherapy to inhibit coronary restenosis*. *Circul-
ation* 1999;99:243-7.
- 13) King SB 3rd, Williams DO, Chougule P, Klein JL, Wak-
sman R, Hilstead R, Macdonald J, Anderberg K, Crocker
IR. *Endovascular beta radiation to reduce restenosis after
coronary balloon angioplasty: results of the beta energy
restenosis trial (BERT)*. *Circulation* 1998;97:2025-30.
- 14) Meerkin D, Tardif JC, Crocker IR, Arsenault A, Joyal M,
Lucier G, King SB 3rd, Williams DO, Serruys P, Bonan
R. *Effects of intracoronary -radiation therapy after coro-
nary angioplasty: an intravascular ultrasound study*. *Cir-
culation* 1999;99:1660-5.
- 15) Lee SW, Jeong MH, Park HW, Cho CH, Kim NH, Kim
KH, Park JC, Ahn YK, Beom HS, Jeong HJ, Song HC,
Min JJ, Park KB, Kim YM, Park EW, Cho JK, Park JC,
Kang JC. *The Effects of local radiation using Ho-166
balloon on porcine coronary restenosis*. *Korean Circ J*
2000;30:1139-48.
- 16) Bae Y, Jeong MH, Chang YS, Cha KS, Park JC, Seo JP,
Ahn YG, Park JH, Cho JG, Park JC, Kang JC, Park OK.
*Comparison of porcine coronary stent restenosis between
MAC (maxi-mum arterial re-creation) stent and Palmaz-
Schatz stent*. *Korean Circ J* 1998;28:89-96.
- 17) Jeong MH, Schwartz RS. *Proliferation indices of coro-
nary neointima*. *J Invasive Cardiol* 1996;8:64.
- 18) Staab ME, Meeker DK, Edwards WD, Camrud AR, Jor-
genson MA, Camrud LJ. *Reliable model of severe coro-
nary stenosis in porcine coronary arteries*. *J Interv Cardiol*
1997;10:61-9.
- 19) Staab ME, Srivatsa SS, Lerman A, Sangiorgi G, Jeong
MH, Edwards WD, Holmes DR Jr, Schwartz RS. *Arterial*

- remodeling after experimental percutaneous injury is highly dependent on adventitial injury and histopathology. Int J Cardiol 1997;58:31-40.*
- 20) Schneider JE, Berk BC, Gravanis MB, Santoian EC, Cipolla GD, Tarazona N, Lassegue B, King SB 3rd. *Probucol decreases neointimal formation in a swine model of coronary balloon injury. Circulation 1993;88:628-37.*
 - 21) Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lanský AJ, Jani S, Wong SC, Fish D, Ellis S, Holmes DR, Kerieakes D, Kuntz RE. *Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001;344:250-6.*
 - 22) Verin V, Popowski Y, de Bruyne B, Baumgart D, Sauerwein W, Lins M, Kovacs G, Thomas M, Calman F, Disco C, Serruys PW, Wijns W. *Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. N Engl J Med 2001;344:243-9.*
 - 23) de Marchena EJ, Mallon SM, Knopf WD, Parr K, Moses JW, Murphy-Chutorian D, Myerburg RJ. *Effectiveness of holmium laser-assisted coronary angioplasty. Am J Cardiol 1994;73:117-21.*
 - 24) Rhew JY, Jeong MH, Kim W, Yem JH, Kim JH, Park OY, Lee SR, Ahn YG, Cho JG, Park JC, Kang GC. *The Effects of local radiation using Ho-166 balloon on endothelial function in a porcine coronary model. Korean Circ J 2002;32:118-24.*