

항혈소판제와 병합요법에 따른 Probucol의 관상동맥 스텐트 시술 환자에서 임상적 효과

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The Effects of Probucol Combined with Antiplatelets on the Coronary Stented Patients

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ABSTRACT

Background : An antioxidant, probucol, prevents endothelial dysfunction and low density lipoprotein oxidation and also inhibits the secretion of interleukin-1 by macrophages. These effects of probucol may result in decreased production of matrix metalloproteinases by smooth muscle cells and thus modify remodeling of the extracellular matrix. **Methods and Materials :** We analyzed clinical events at 1 month and 6 months in 337 patients with 363 coronary arterial lesions after coronary stenting at Chonnam National University Hospital between January 1998 and May 1999. The patients were assigned to following four modalities : 500 mg of ticlopidine daily (Group 1), 200 mg of cilostazol daily (Group 2), 500 mg of probucol in addition to 500 mg of ticlopidine daily (Group 3), and 500 mg of probucol in addition to 200 mg of cilostazol daily (Group 4). All patients received aspirin. **Results :** Group 1 comprised of 149 (104 M, 45 F, 62 ± 10 years), Group 2 96 (73 M, 23 F, 60 ± 10 years), Group 3 50 (32 M, 18 F, 61 ± 10 years), and Group 4 42 (32 M, 10 F, 62 ± 10 years) patients. Clinical diagnosis was not different among four groups. Major adverse cardiac events, including myocardial infarction, cardiac death, and repeated intervention, at 1 month were 7 (4.7%) in Group 1, 2 (2.1%) in Group 2, 0 (0%) in Group 3, 2 patients (4.8%) in Group 4, and those at 6 months were 29 (19.5%) in Group 1, 17 (17.7%) in Group 2, 9 (18.0%) in Group 3, and 6 patients (14.3%) in Group 4. **Conclusions :** Probucol combined with aspirin and cilostazol has a tendency reducing the major cardiac events compared with aspirin and ticlopidine or cilostazol after stenting. (**Korean Circulation J 2000;30(7):811-818**)

KEY WORDS : Probucol · Major adverse cardiac events · Stent restenosis.

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서 론

1-3) , 20 30% 4)5) 가 6-8) , Probuco

interleukin - 1 metalloproteinase 9-11) Probuco

12)13) Probuco

bucol

관찰대상 및 방법

대상 환자 1998 1 1999 5 337 , 363 3 Asp - rin Ticlopidine Cilostazol , (Aspirin + Ticlopidine, 62 ± 10 , 104, 45), (Aspirin + Cilostazol, 60 ± 10 , 73, 23), (Aspirin + Ticlopidine + Probuco

32, 18), (Aspirin + Cilostazol + Prob

uol, 60 ± 8 , 32, 10) Aspirin(A) 100 mg/day, Cilostazol(C) 200 mg/day, Probuco(P) 500 mg/day 6 , Ticlopidine(T) 500 mg/day 1 .

Stent 시술 방법

, monorail Crossflex, GFX, MAC, Nir - Primo, Wiktor stent 11 , nitrate, 150U/kg, 10,000 Unit) . TIMI 가

추적 관찰

2, 4 1 , 6 (major adverse cardiac events : MACE) , (repeated intervention), 50% .

종료 시점

1 , 2 ,

통계처리

(continuous variables) St - udent's t - test , one - way ANOVA test . (categ - oric variables) 2 - test Fisher's exact test \pm p - value 0.05 가 .

결 과

(20.0%), 47 (29.6%), 30
(29.7%), 13 (24.5%), 12 (24.0%)

AHA

대상 환자의 임상적 특성

/ACC type B 94 (59.1%),
69 (68.3%), 36 (68.0%), 36
(52.2%) 가 , type C 62
(39.0%), 32 (31.7%), 17 (32.1%), 14
(28.0%)

Crossflex

MAC 44 (27.7%) 32 (20.1%),
80 (53.7%), 27 (26.7%) 18 (17.8%), 15
(28.3%) 20 (37.7%), 16 (32.0%)
(47.6%), 83 (55.7%), 71 (74.0%), 14 (28.0%) 가
30 (60.0%), 18 (42.9%), 41 29 (18.2%),
(27.5%), 43 (44.8%), 21 (42.0%), 13 (31.0%), 13 (12.9%), 11 (20.8%), 9
50 (33.6%), 28 (29.2%), 12 (24.0%), (18.0%),
12 (28.6%) 98 (61.7%), 73 (72.3%), 38 (71.7%),
53 ± 13%, 54 ± 12%, 58 33 (66.0%)
± 11%, 52 ± 14%
(Table 1).

혈청 지질의 변화

관상동맥 조영술 소견

가 130 mg/dl

91 (57.2%), HMG - CoA reductase inhibitor Pro -
57 (56.4%), 35 (66.0%), 28 bucol
(56.0%) 가 ,
21 (13.2%), 14 (13.9%), 5 (9.4%), 10 Total cholesterol, low density lipoprotein -
cholesterol(LDL - C), triglyceride

Table 1. Baseline clinical characteristics of four groups (A + T : aspirin + ticlopidine, A + C : aspirin + cilostazol, A + T + P : aspirin + ticlopidine + probucol, A + C + P : aspirin + cilostazol + probucol)

	A + T	A + C	A + T + P	A + C + P	P
Number, N (lesion)	149 (159)	96 (101)	50 (53)	42 (50)	
Age	62 ± 10	60 ± 10	61 ± 10	60 ± 8	NS
Sex (M/F)	104/45	73/23	32/18	32/10	NS
EF (%)	53 ± 13	54 ± 12	58 ± 11	52 ± 14	NS
Clinical diagnosis (n)					NS
Acute myocardial infarction	76 (51.0)	50 (52.1)	21 (40.2)	16 (38.1)	
Unstable angina	52 (34.9)	32 (33.3)	18 (36.0)	18 (42.9)	
Stable angina	14 (9.4)	10 (10.4)	7 (14.0)	3 (7.1)	
Old myocardial infarction	7 (4.7)	4 (4.2)	4 (8.0)	5 (11.9)	
Risk factors (n)					NS
Hypertension	80 (53.7)	36 (37.5)	22 (44.0)	20 (47.6)	
Diabetes	50 (33.6)	28 (29.2)	12 (24.0)	12 (28.6)	
Smoking	83 (55.7)	71 (74.0)	30 (60.0)	18 (42.9)	
Dyslipidemia	41 (27.5)	43 (44.8)	21 (42.0)	13 (31.0)	

Table 2. Angiographic characteristics of four groups (A + T : aspirin + ticlopidine, A + C : aspirin + cilostazol, A + T + P : aspirin + ticlopidine + probucol, A + C + P : aspirin + cilostazol + probucol)

	A + T (n = 159)	A + C (n = 101)	A + T + P (n = 53)	A + C + P (n = 50)	P
Target vessel (%)					NS
LAD	91 (57.2)	57 (56.4)	35 (66.0)	28 (56.0)	
LCX	21 (13.2)	14 (13.9)	5 (9.4)	10 (20.0)	
RCA	47 (29.6)	30 (29.7)	13 (24.5)	12 (24.0)	
ACC/AHA lesion classification (%)					NS
Type A	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Type B1	48 (30.2)	47 (46.5)	25 (47.2)	26 (32.0)	
Type B2	46 (28.9)	22 (21.8)	11 (20.8)	10 (20.0)	
Type C	62 (39.0)	32 (31.7)	17 (32.1)	14 (28.0)	
TIMI (%)					NS
0	32 (20.1)	11 (10.9)	5 (9.4)	5 (10.0)	
1	11 (6.9)	9 (8.9)	4 (7.5)	8 (16.0)	
2	79 (49.7)	58 (57.4)	28 (52.8)	23 (46.0)	
3	37 (23.3)	23 (22.8)	16 (30.2)	14 (28.0)	
Number of diseased vessel (%)					NS
1	99 (62.3)	60 (59.4)	31 (58.5)	31 (62.0)	
2	35 (22.0)	27 (26.7)	16 (30.2)	16 (32.0)	
3	25 (15.7)	14 (13.9)	6 (11.3)	3 (6.0)	
Types of stent (%)					NS
Crossflex	44 (27.7)	27 (26.7)	15 (28.3)	16 (32.0)	
GFX	11 (6.9)	7 (6.9)	4 (7.5)	7 (14.0)	
MAC	32 (20.1)	18 (17.8)	20 (37.7)	14 (28.0)	
NirPrimo	34 (21.4)	18 (17.8)	9 (17.0)	8 (16.0)	
Wiktor	26 (16.4)	19 (18.8)	4 (7.5)	3 (6.0)	
Others	12 (7.5)	12 (11.9)	1 (1.9)	2 (4.0)	
Indication for stenting (%)					NS
Bailout	29 (18.2)	13 (12.9)	11 (20.8)	9 (18.0)	
Suboptimal	98 (61.7)	73 (72.3)	38 (71.7)	33 (66.0)	
Restenosis	10 (6.3)	5 (5.0)	3 (5.7)	3 (6.0)	
Elective	22 (13.8)	10 (9.9)	1 (1.9)	5 (10.0)	

LAD ; left anterior descending artery, LCX ; left circumflex artery, RCA ; right coronary artery, ACC/AHA ; American College of Cardiology/American Heart Association, TIMI : thrombolysis in myocardial infarction

high density lipoprotein - cholest - . 6
erol(HDL - C) Probucol (5 , 1 , 1 , ,
,) (,) 19 , 15 , 9 ,
(Table 3). 4 , 5 , 1 ,
1 (Table 4).

임상적 추적 결과

1 4 , 추적 관상동맥 조영술 결과
1 142 (42.1%)
1 , 2 , 1 , 2 , 28.1%(18/64),

Table 3. Serum lipid levels of baseline and at 6 months after treatment in four groups (A + T : aspirin + ticlopidine, A + C : aspirin + cilostazol, A + T + P : aspirin + ticlopidine + probucol, A + C + P : aspirin + cilostazol + probucol)

	A + T	A + C	A + T + P	A + C + P	P
Total cholesterol (mg/dl)					NS
At base line	199 ± 38	200 ± 39	190 ± 32	197 ± 54	
At follow-up	188 ± 37	178 ± 31	182 ± 29	144 ± 24	
LDL cholesterol (mg/dl)					NS
At base line	131 ± 33	128 ± 36	123 ± 29	132 ± 38	
At follow-up	121 ± 40	110 ± 34	103 ± 25	96 ± 22	
HDL cholesterol (mg/dl)					NS
At base line	45 ± 10	45 ± 12	47 ± 11	40 ± 12	
At follow-up	47 ± 14	43 ± 12	48 ± 16	39 ± 18	
Triglyceride (mg/dl)					NS
At base line	113 ± 70	136 ± 67	94 ± 25	122 ± 45	
At follow-up	99 ± 37	101 ± 38	86 ± 62	112 ± 83	

LDL : low-density lipoprotein, HDL : high-density lipoprotein

Table 4. Major adverse cardiac events in four groups (A + T : aspirin + ticlopidine, A + C : aspirin + cilostazol, A + T + P : aspirin + ticlopidine + probucol, A + C + P : aspirin + cilostazol + probucol)

	A + T (N = 149)	A + C (n = 96)	A + T + P (N = 50)	A + C + P (N = 42)	P
MACE at one month (%)	7 (4.7)	2 (2.1)	0 (0.0)	2 (4.8)	NS
Myocardial infarction	4	0	0	1	
Repeated intervention	1	2	0	1	
Death	2	0	0	0	
MACE at six months (%)	29 (19.5)	17 (17.7)	9 (18.0)	6 (14.3)	NS
Myocardial infarction	5	1	0	1	
Repeated intervention	19	15	9	4	
Death	5	1	0	1	
Follow-up angiogram (%)	64 (43.0)	48 (50.0)	16 (32.0)	14 (33.3)	
Restenosis rate (%)	18 (28.1)	12 (25.0)	6 (37.5)	3 (21.4)	NS

MACE ; major adverse cardiac events

25.0%(12/48), 37.5%(6/16), 21.4%(3/14) . 가

합병증 1-3)

2 (1.3%), 2 (1.3%), 20 30%
1 (1.0%), 1 (1.0%), , 4)5)
1 (1.9%) . 6)7)

고 찰 가

가 가

14)

15 - 19)

가

, HDL - C Aspirin, Cilostazol, Probucol
 peroxidation 2.5%
 Aspirin, Ticlopidine, Probucol
 1
 6 MACE
 9 18% Aspirin Ticlopidine
 19.5%
 6
 27.5% Aspirin, Cilostazol,
 Probucol 21.4% Aspirin
 Ticlopidine 28.1%, Aspirin Cilost -
 azol 25%
 inrterleukin -
 metallopro -
 Aspirin, Cilostazol,
 9.5%
 Probucol
 21.4% 42.1%
 11)
 Probucol
 20 - 24)
 Tardif 20) Prob -
 ucol 30 Aspirin, Cilo -
 Probucol major cardiac event Aspirin Ticlopidine
 Cilostazol MACE
 Sekiya 21)
 5 Probucol 가
 Probucol 가
 Probucol Cilostazol 가
 APP - 4 가
 48 probucol
 LE trial²⁵⁾ 24 Probucol Lovastatin
 Probucol
 Probucol Probucol
 Probucol 가
 HDL - C 가 Probucol
 가 가
 가 130 mg/dl HMG - CoA
 reductase inhibitor (42.1%)
 Probucol 가

요약

연구배경 :
 Probucol

interleukin - 1
 metalloproteinase

대상 및 방법 :
 1998 1 1999 5
 337 363
 Aspirin(A) 100 mg, Ticlopidine(T)
 500 mg, Cilostazol(C) 200 mg, Probucol(P) 500 mg
 (A + T), (A + C), (A + T + P),
 (A + C + P) 1, 6

결 과 :
 1) 149 (104, 45, 62 ± 10),
 96 (73, 23, 60 ± 10), 50 (32,
 18, 61 ± 10), 42 (32, 10, 62 ± 10)
 337 363
 2) 76 (51.0%),
 52 (34.9%), 14 (9.4%),
 50 (52.1%), 32 (33.3%), 10 (10.4%),
 21 (40.2%), 18 (36.0%), 7 (14.0%), 16
 (38.1%), 18 (42.9%), 3 (7.1%)
 3) 1 MACE 7 (4.7%), 2
 (2.1%), 2 (4.8%)
 4) 6 MACE 29 (19.5%), 17
 (17.7%), 9 (18.0%), 6 (14.3%)
 5) 142 (42.1%)
 39 (27.5%),
 28.1%, 25.0%, 37.5%,
 21.4%
 6) 2 (1.3%), 2
 (1.3%), 1 (1.0%), 1
 (1.0%), 1 (1.9%)

결 론 :
 Aspirin, Cilostazol Pr -
 obucol Aspirin Ticlopidine Ci -
 lostazol major cardiac event
 가

중심 단어 : Probucol.

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