

관상동맥 스텐트 삽입술 후 항혈전요법으로서 Cilostazol-aspirin 병합요법과 Ticlopidine-aspirin 병합요법의 무작위 비교

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A Randomized Comparison of Cilostazol and Ticlopidine after Coronary-artery Stenting as Antithrombotic Regimen

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ABSTRACT

Background and Objectives : Combination of ticlopidine and aspirin has been accepted as a standard antiplatelet regimen after coronary stenting because it reduced the rate of cardiac events and hemorrhagic-vascular complications compared with intensive anticoagulation. Ticlopidine use, however, may accompany serious side effects such as neutropenia or liver dysfunction. Cilostazol, a c-AMP phosphodiesterase inhibitor, is a novel antiplatelet agent which is known to have less side effects. **Materials and Methods :** We compared the efficacy and safety of cilostazol plus aspirin (CA) with ticlopidine plus aspirin (TA) after elective coronary stenting. Patients were randomly assigned to receive either CA or TA two days before stenting. The primary end point was a composite of angiographic stent thrombosis, death, myocardial infarction (Q or Non-Q), repeat intervention or bypass surgery at 30 days. The secondary end points were hemorrhagic-vascular complications, or drug side effects such as neutropenia, thrombocytopenia, or any side effects requiring cessation of drugs at 30 days. **Results :** After randomization of 300 patients equally to each group, 4 patients were excluded from the analysis : 1 failure of stenting, 3 follow-up loss. The primary end point was reached in 2 patients (1.4%) in CA group and 3 patients (2.0%) in TA group ($p = 1.0$). The rate of hemorrhagic-vascular complications was not different between the groups (1.4% vs 2.0%, $p = 1.0$). The incidence of significant drug-related side effects was not statistically different between CA group and TA group (0.7% vs 2.7%, $p = 0.37$). However, serious side effect such as neutropenia was seen only in TA group. **Conclusion :** Compared with TA, CA has comparable effect for the prevention of stent thrombosis and major cardiac events with similar rate of hemorrhagic-complications and drug-related side effects after elective coronary-artery stenting. Thus CA regimen can be a safe alternative to TA in elective implantation of coronary artery stent. (Korean Circulation J 1999;29(7):688-696)

KEY WORDS : Cilostazol · Ticlopidine · Coronary artery · Stent.

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서론

1)2)

20%

3)

heparin, coumarin, dipyridamole, aspirin

4%

가

3% 13%

1)2)

(optimal)

ticlopidine aspirin

-

4 - 6)

ticlopidine - aspirin

1 2%

7 - 9)

ticlopidine - aspirin

10 - 13)

14)15)

16)17)

(thrombotic

thrombocytopenic purpura)¹⁸⁾¹⁹⁾

가

Cilostazol c - AMP phosphodiesterase

가

20 - 22)

Cilostazol ticlopidine

가

24)25)

cilostazol

가

26 - 29)

ticlopidine - aspirin(TA)

cilostazol - aspirin(CA) 30

CA TA
(major cardiac events)
가 ,
-
가
CA TA
.
대상 및 방법
선택 및 할당
CA TA
.
3 ,
 ,
가 (suboptimal)
2
6 5 1998 12 300
.
1 50%
.
(30%),
.
,
(< 150,000/mm³),
(< 3,000/mm³).
삽입술
.
, , ,
.
: Gianturco -
n II stent(Cook Cardiology, Bloomington, IN.),
GFX stent(Arterial Vascular Engineering,
Rosa, CA), JO stent(JOMED international
Helsingborg, Sweden), NIR stent(SciMed,
n Scientific, Maple Grove, MN), Palmaz -

Schatz stent(Johnson & Johnson Interventional Systems, Warren, NJ), Magic Wallstent(Schneider Europe, Bülach, Switzerland), Cordis CrossFlex stent(Cordis, a Johnson and Johnson Company, Warren, NJ), AVE Micro Stent II(Applied Vascular Engineering, Santa Clara, CA).
(P - S, NIR, JO)

(nominal pressure)
< 10%가 (12 atm)
(GR II, GFX, MicrolI, Cross - flex)
size
(nominal pressure)

. Magic Wallstent
10 12
10,000 unit
ACT 250
5,000 unit 가

항혈소판제 투여
CA cilostazol 100 mg 1 2
, TA ticlopidine 250 mg 1 2
2 30
, aspirin 100 mg
2

2 4 mg isosorbide dinitrate
2
digital caliper(Mitutoyo Corp, Tokyo, Japan)

digital caliper 가

computer
가³⁰⁾
,
shoulder to shoulder
가 (optimal result)
< 30% TIMI

추적검사
,
, creatinine phosphokinase(CK)
CK - MB 6 , 12 , 24
가
30

사건 및 종료점(End-points)
가 가
. 30 1

(), (Q Q),
()
가
. 2
(< 80,000/mm³), (< 1200/mm³),

24
TIMI 0 I 가
, 가
24
30
Q 가 2
CK 가 2 가
CK - MB 가 가
(target vessel revascularization)

가
(compression)
가
통계분석
±
two - tailed Student's t -
test
Fisher's exact test
p<0.05
결 과
대상 환자, 관상동맥 조영술 및 스텐트 시술상의 특성
CA 1 , 3
가 (CA
2 , TA 1) 가 296 (CA 147
, TA 149) 가
6 (2.7%) 8 :
CA 2 , 3 , TA 4 , 5 (p=0.64).

Table 1. Baseline characteristics of patients

| Characteristics | Cilostazol+ Aspirin n(%) (n = 147) | Ticlopidine+ Aspirin n(%) (n = 149) | p |
|-----------------------------|---------------------------------------|--|------|
| Age (yr) | 59 ± 10 | 58 ± 10 | 0.82 |
| Male | 108 (73.5) | 110 (73.8) | 0.94 |
| Risk factors | | | |
| Hypertension | 60 (40.8) | 62 (41.6) | 0.89 |
| Smoker | 85 (57.8) | 84 (56.4) | 0.80 |
| Diabetes mellitus | 28 (19.0) | 25 (16.8) | 0.61 |
| Hypercholesterolemia | 33 (22.4) | 35 (23.5) | 0.83 |
| Clinical diagnosis | | | |
| Acute myocardial infarction | 34 (23.1) | 31 (20.8) | 0.63 |
| Unstable angina | 71 (48.3) | 75 (50.3) | 0.73 |
| Previous CABS | 4 (2.7) | 5 (3.4) | 0.75 |
| Previous POBA | 20 (13.6) | 25 (16.8) | 0.45 |
| No of diseased vessel | | | 0.42 |
| 1 | 48 (32.7) | 53 (35.6) | |
| 2 | 52 (35.4) | 58 (38.9) | |
| 3 | 47 (32.0) | 38 (25.5) | |

CABS denotes coronary-artery bypass surgery, and POBA plain old balloon angioplasty.

(Table 1).

Table 2

Table 2. Angiographic characteristics of the patients

| Characteristics | Cilostazol+ Aspirin n(%) (n = 163 lesions) | Ticlopidine+ Aspirin n(%) (n = 167 lesions) | p |
|-----------------------------------|---|--|------|
| Lesions treated per patient | 1.1 | 1.1 | |
| Location | | | 0.65 |
| Left anterior descending | 77 (47.2) | 74 (44.3) | |
| Left circumflex | 28 (17.2) | 32 (19.2) | |
| Right coronary | 57 (35.0) | 59 (35.3) | |
| Saphenous vein graft | 1 (0.6) | 2 (1.2) | |
| AHA/ACC lesion type | | | 0.73 |
| Type A | 13 (8.0) | 10 (6.0) | |
| Type B1 | 36 (22.1) | 40 (24.0) | |
| Type B2 | 55 (33.7) | 63 (37.7) | |
| Type C | 59 (36.2) | 54 (32.3) | |
| Restenotic lesion | 11 (6.7) | 14 (8.4) | 0.54 |
| Thrombus | 30 (18.4) | 27 (16.2) | 0.64 |
| Moderate or severe calcifications | 27 (16.6) | 32 (19.2) | 0.49 |
| Ostial location | 12 (7.4) | 10 (6.0) | 0.65 |
| Bifurcation | 18 (11.0) | 15 (9.0) | 0.57 |
| Chronic total occlusion | 13 (8.8) | 17 (10.2) | 0.49 |

Table 3. Stent procedural characteristics

| Characteristics | Cilostazol+ Aspirin n(%) (n = 179) | Ticlopidine+ Aspirin n(%) (n = 184) | p |
|-------------------------|---------------------------------------|--|------|
| Stents per patient | 1.2 | 1.2 | |
| Stents per lesion | 1.1 | 1.1 | |
| Types of stent | | | 0.84 |
| GR11 | 39 (21.8%) | 45 (24.4%) | |
| GFX | 41 (22.9%) | 40 (21.7%) | |
| JO | 36 (20.1%) | 33 (17.9%) | |
| Nir | 29 (16.2%) | 26 (14.1%) | |
| PalmaZ-Schatz | 11 (6.1%) | 13 (7.1%) | |
| CrossFlex | 9 (5.0%) | 12 (6.5%) | |
| Microstent II | 7 (3.9%) | 8 (4.3%) | |
| Magic wallstent | 7 (3.9%) | 7 (3.8%) | |
| Reference diameter (mm) | 3.04 ± 0.44 | 3.06 ± 0.39 | 0.64 |
| Lesion length (mm) | 16.6 ± 7.1 | 16.3 ± 6.6 | 0.48 |
| Preprocedure MLD (mm) | 0.76 ± 0.35 | 0.74 ± 0.40 | 0.61 |
| Postprocedure MLD (mm) | 2.96 ± 0.45 | 2.98 ± 0.43 | 0.83 |
| Acute gain (mm) | 2.20 ± 0.38 | 2.24 ± 0.41 | 0.47 |

MLD : minimal luminal diameter

Table 4. Primary study end points

| Characteristics | Cilostazol+ Aspirin n(%) (n = 147) | Ticlopidine+ Aspirin n(%) (n = 149) | p |
|---------------------------------|---------------------------------------|--|-----|
| Angiographic events | | | |
| Acute stent occlusion | 0 | 0 | |
| Subacute stent thrombosis | 1 (0.7%) | 1 (0.7%) | |
| Major clinical events | | | |
| Myocardial infarction | 2 (1.4%) | 2 (1.3%) | |
| Q wave | 1 (0.7%) | 1 (0.7%) | |
| Non-Q-wave | 1 (0.7%) | 1 (0.7%) | |
| Target lesion revascularization | | | |
| Repeat intervention | 1 (0.7%) | 1 (0.7%) | |
| Emergency bypass | 0 | 0 | |
| Death | 0 | 1 (0.7%) | |
| Primary end point | 2 (1.4%) | 3 (2.0%) | 1.0 |

가 (p=0.54). , , ,
 , , ,
 ,
 가 (Table 3).

일차 종료점

30 Table
4 . 1 5
2(1.4%) CA , 3 (2.0%) TA
가 (p=1.0). 30
2
1 (0.7%) .
 ,
1 .
2 Q
가 .
 , TA 1 22
 . 5

이차 종료점

, 가 (1.4% vs 2.0%, p

Table 5. Secondary study endpoints

| Characteristics | Cilostazol+ Aspirin n(%) (n = 147) | Ticlopidine+ Aspirin n(%) (n = 149) | p |
|-------------------------------------|---------------------------------------|--|------|
| Bleeding and vascular complications | 2(1.4) | 3(2.0) | 1.0 |
| Major bleeding | 1 (0.7) | 1 (0.7) | |
| Local vascular complications | | | |
| False aneurysm | 1 (0.7) | 1 (0.7) | |
| Arteriovenous fistula | 0 | 0 | |
| Surgical repair | 0 | 1 (0.7) | |
| Side effects of drugs | 1 (0.7) | 4(2.7) | 0.37 |
| Neutropenia | 0 | 2(1.3) | |
| Thrombocytopenia | 0 | 0 | |
| Other side effects* | | | |
| Skin rash | 0 | 1 (0.7) | |
| Gastrointestinal disturbance | 1 (0.7) | 1 (0.7) | |

*Other side effects requiring cessation of the drugs

= 1.0). 2
CA 1 10
 , TA 1 .
 . CA TA
가 (0.7% vs 2.7%, p=0.37).
TA 2 (1.4%)
 ,
 . 3 TA 2
1 , 1
 , CA 1
 .

고찰

cilostazol

ticlopidine 가 -

가 .
ticlopidine .

density lipoprotein(HDL) - cholesterol, Apo - A1
가 , 가 ³⁶⁾

가 .
Aspirin prostaglandin G/H synthase , 가 (subop -
arachidonic acid가 thromboxaneA2 timal) (2.0%) .

가 . Ticlopidine ADP
, ADP
arachidonic acid . type B₂ C 70% ,
2 - methyl - ADP - binding 3 mm 42%
, glyco -
rotein b/ a fibrinogen .
가 2
^{31 - 33)} 12
Cilostazol cilostamide(2 - oxoquinolone) .
가 10.5 ± 4.4 ²⁰⁾²³⁾ 가 CA
TA
가 , (ISAR ⁷⁾ 1.6%, STARS
^{25 - 34)} Cilostazol , ⁸⁾ 0.6%, FANTASTIC ⁹⁾ 2.4%).
type phosphodiesterase CA TA
c - AMP 가 c - AMP ISAR STARS
가 ²⁰⁾²⁴⁾ 가 c - AMP
phospholipase cyclooxygenase th - FANTASTIC
romboxaneA2 2.4%. 0.4%
Cilostazol ADP, collagen, epinephrine, arachidonic 가 0% 가
acid 1 2 가
²⁰⁾²³⁾ cilostazol thromboxane 2
aspirin ticlopidine FANTASTIC
aspirin 10 30 ticlopidine . ticlopidine
가 ²³⁾ Aspirin cilostazol
prostaglandin 2 ^{31 - 32)} cilostazol
I₂(prostacyclin) 1 ²⁴⁾
prostaglandin I₂가 cilostazol cilostazol
²²⁾ cilostazol
type III phosphodiesterase 1% ^{26 - 29)}
c - AMP 가 2가 , CA
calcium ion
^{21 - 24)} TA
stent elastic recoil 가 , 가
cilostazol CA TA
³⁵⁾ high - 2

가

CA TA
(1.4% vs 2.0%).

ticlopidine
: ISAR , 1.2%, STARS , 2.2%,
FANTASTIC , 3.6%. cilostazol

Ticlopidine
($< 3000/\text{mm}^3$),
30
cilostazol

ticlopidine 2
($< 1200/\text{mm}^3$) 2.4%
가 2 3

ticlopidine 1
가
ticlopidine 15
가
ticlopidine
G - CSF
2 (1.3%)
TA 1
가 $92,000/\text{mm}^3$
($< 80,000/\text{mm}^3$)
ticlopidine
Ticlopidine

. Canadian American Ticlopidine Study
4.4% 2.3%
가
TA 82 , CA 78
alkaline
phosphatase, alanine aminotransferase, aspartate
aminotransferase 가
TA 3 (3.6%), CA
ticlopidine 가
CA
($< 3000/\text{mm}^3$),
30
cilostazol
CA
, 1 (0.7%)
가
CA
요 약
연구배경 :
ticlopidine aspirin
ticlopidine
aspirin
ticlopidine
Cilos -
c - AMP
dependent phosphodiesterase
cilostazol - aspirin(CA)

ticlopidine - aspirin(TA)

대상 및 방법 :

1996 5 1998 10
가 300
CA (n=150) TA (n=150)
2
가
(Q Q),
2 30
결 과 :
4 1
, 3 가
1 CA 1.4%(2/147), TA
2.0%(3/149) 가 (p
=1.0).
(1.4% vs 2.0%, p=1.0).
가 (0.7% vs 2.7%,
p=0.37).
ticlopidine
결 론 :
CA TA
30
가
TA CA
중심 단어 :

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