

정상인에서의 저용량의 Enteric-coated Aspirin 단독투여 및 Ticlopidine 병용 투여가 혈소판기능에 미치는 영향

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= Abstract =

Effect of Low Dose Enteric-coated Aspirin Alone or Combination with Ticlopidine on Platelet Aggregation in Normal Subjects

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Background : The role of platelet aggregation in the pathogenesis of acute coronary syndrome and cerebral thrombosis is well known and the platelet inhibitors are used widely for primary and secondary prevention of cardiovascular disease. Aspirin is the least expensive and most widely used antiplatelet agent and its effect is associated with its ability to inhibit platelet thromboxane A_2 synthesis. The effectiveness of aspirin is dependent on its ability to block the formation of thromboxane A_2 . Ticlopidine is another popular antiplatelet agent used today in the era of stent implantation for treating coronary artery obstructive disease(CAOD) with aspirin. The mechanism of action of ticlopidine is clearly different from that of aspirin. It is concluded recently that ticlopidine is an inhibitor of ADP binding to platelets. The inhibition of ADP binding to platelets by ticlopidine is very nicely correlated with its dose and the inhibition of platelet aggregation.

Therefore, in this study, antiplatelet effect of low dose enteric-coated aspirin in place of aspirin and combined therapy with low dose enteric-coated aspirin plus ticlopidine were evaluated in the normal subjects.

Methods : In twenty normal subjects, platelet aggregation tests with adenosine diphosphate (ADP) and collagen were performed baseline, after 1 week administration of enteric-coated aspirin,

and in randomly selected ten among twenty normal subjects, 1 week administration of enteric-coated aspirin and ticlopidine. The maximal aggregation rate was calculated by measuring the maximal change of light transmittance after addition of aggregating agents.

Results : Low dose enteric-coated aspirin inhibited platelet aggregation in response to collagen significantly. Less than 25% of antiaggregation effect was noted in about 50% of subjects with low dose enteric-coated aspirin when platelet aggregation was induced by ADP. Ticlopidine in combination with low dose enteric-coated aspirin potentiated the inhibitory effect significantly on platelet aggregation in response to ADP.

Conclusion : Effect of low dose enteric-coated aspirin alone on platelet aggregation in response to ADP stimulation was weak and showed variability, comparing to collagen stimulation. The combined treatment of ticlopidine plus aspirin was synergistically inhibited platelet aggregation responding to ADP stimulation. Therefore to achieve the synergistic inhibition of platelet aggregation to ADP and collagen stimulation, combination therapy might be a effective regimen.

KEY WORDS : Enteric coated aspirin · Ticlopidine · Platelet aggregation.

서 론

fibrinogen glycoprotein
IIb/IIIa(GPIIb/IIIa)
7), Savi 8)
가 ADP
ticlopidine
가 ticlopidine ADP
1). collagen . , ticlopidine ADP
, 가
ADP, serotonin, thrombin, thromboxane A₂ aspirin
2), enteric - coated aspirin ti -
clopidine 가
(platelet aggregat -
ion test)
stent가
가
가 3). Aspirin
cyclooxy - genase thro -
mboxane A₂
4), aspirin
prostacyclin
prostaglandin
aspirin
5,6). ticlopidine
, aspirin ADP

연구대상 및 방법

1. 연구대상
15
20 (10,
10, 30.2 ± 5.1)
7 100mg/d enteric - coated aspirin
random sampling 10 (6, 4,
32.3 + 4.8) enteric - coated aspirin
ticlopidine(500mg/d)

2. 연구방법

, PT, PTT, fibrinogen, SGOT, SGPT, creatinine

3.2% sodium citrate가

9 : 1

800rpm 5 platelet rich plasma

(PRP) 2800rpm 10

platelet poor plasma(PPP), PRP

450uL 5uM/L adenosine diphosphate

(ADP) 4ug/ml collagen 500uL가

platelet aggreg-

ometer(Chronolog Corp. USA) (light tran-

smittance percentage)

PRP 0%, PPP 100%

PRP

(

) /

) x 100% Collagen

latent period (Fig. 1).

GB-Stat 6.0 paired t-

test, ANOVA(repeated measurement), Chi

square test

결 과

1. 혈소판응집에 대한 저용량의 enteric-coated aspirin의 효과

20 enteric - coated aspirin

ADP 48.45 ±

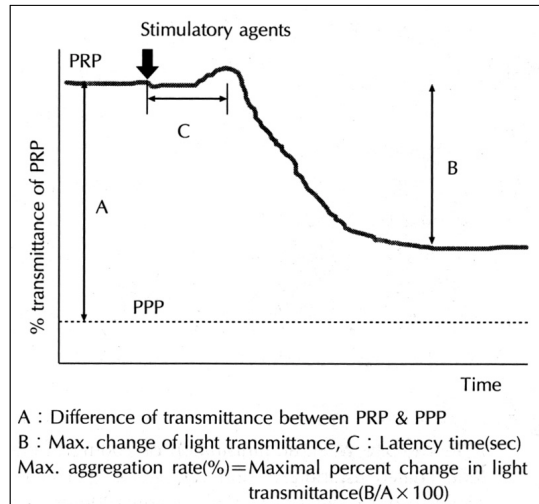


Fig. 1. Schematic presentation of platelet aggregation test.

19.75% 38.00 ± 10.58% (

21.21 ± 19.53%), collagen

63.65 ± 17.44% 13.83 ± 8.36%

(73.98 + 21.44%; p<0.05).

Collagen

latency time 53.37 ± 17.55sec

aspirin 77.95 + 19.91sec

가(53.3%) (p<0.05, Table 1).

2. 혈소판응집에 대한 저용량의 aspirin과 ticlopidine 병용투여 효과

10 7 enteric coated aspirin

, enteric - coated aspirin

ticlopidine 7

, ADP

18.07 ± 9.27% 50.87 ± 17.38%(

62.48 ± 20.07%, p<0.01), enteric - coated

aspirin 42.56 ± 11.63%

Table 1. Effects of enteric coated aspirin on platelet aggregation test(N = 20)

Stimulation agents	ADP		Collagen	
	Baseline	One week	Baseline	One week
Max. aggregation(%)	48.45 ± 19.75*	38.0 ± 10.58	63.65 ± 17.44*	13.83 ± 8.36
Inhibition rate(%)	21.21 ± 19.53		78.98 ± 21.44#	
Latency time(sec)	-		53.37 ± 17.55* 77.95 ± 19.91	

mean ± S.D., * : baseline vs one week administration of enteric coated aspirin, p<0.05 # : ADP induced platelet aggregation vs collagen induced platelet aggregation, P<0.05

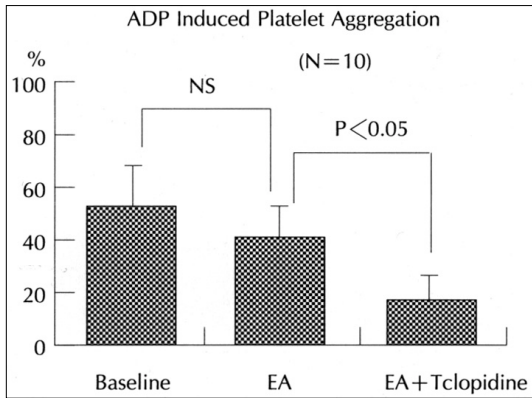


Fig. 2. Changes of ADP induced platelet aggregation from baseline, one week administration of 100mg of enteric coated aspirin(EA), and one week after combined use of enteric coated aspirin (100mg) and ticlopidine(500mg).

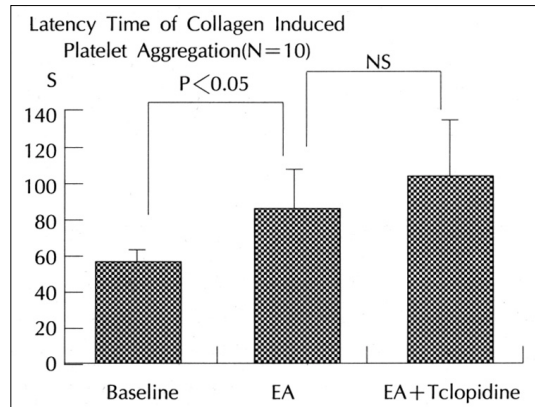


Fig. 4. Changes of latency time of collagen induced platelet aggregation from baseline, one week administration of 100mg of enteric coated aspirin (EA), and one week after combined use of entericoated aspirin(100mg) and ticlopidine (500mg).

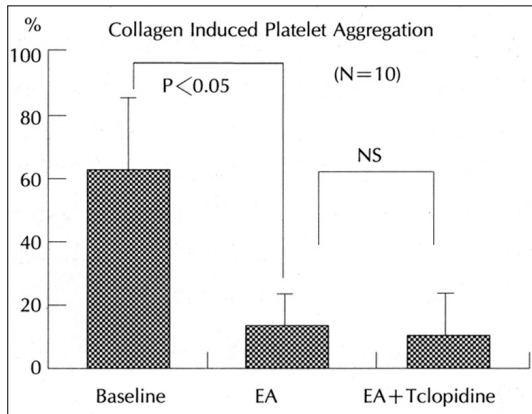


Fig. 3. Changes of collagen induced platelet aggregation from baseline, one week administration of 100mg of enteric coated aspirin(EA), and one week after combined use of entericoated aspirin (100mg) and ticlopidine(500mg).

Table 3. Comparison between enteric coated aspirin alone and combination with ticlopidine

	ADP		Collagen	
	R	NR	R	NR
EA	45%	55%	90%	10%
EA	90%	10%	100%	0%

EA : enteric coated aspirin, R : inhibition of platelet aggregation comparing to baseline <25%, NR : inhibition of platelet aggregation comparing to baseline <25%, * : P<0.05, NS : not significant

(p<0.05, Fig. 2, Table

2). Collagen 9.69 ± 14.59% 62.74 ± 22.45%

(79.22 ± 26.55), aspirin 13.82 ± 9.33%

가 (Fig. 3, Table 2). Collagen latency time ticlopidine 102.25 ± 34.98sec 54.10 ± 23.48sec 가 (p<0.05, Fig. 4, Table 2), aspirin 84.75 ± 24.69sec 가 .

3. 약물반응군의 비교

25% , ADP enteric - coated aspirin 45%

Table 2. Effects of enteric coated aspirin combined with ticlopidine on platelet aggregation test(N = 10)

Stimulation agents	ADP		Collagen	
	Baseline	One week	Baseline	One week
Max. aggregation(%)	50.87 ± 17.38*	18.07 ± 9.27	62.74 ± 22.45*	9.69 ± 14.59
Inhibition rate(%)	62.48 ± 20.07		79.22 ± 26.55	
Latency time(sec)	-		54.10 ± 23.48*	102.25 ± 34.98

mean ± S.D., * : baseline vs one week administration of enteric coated aspirin, P<0.05

Table 4. Changes of hematologic profiles in the normal subjects

	Baseline (n = 20)	EA (n = 20)	Baseline (n = 20)	EA + Ticlopidine (n = 10)
Hb(g/dl)	14.3 ± 1.3	14.2 ± 1.5	14.3 ± 1.6	14.1 ± 1.4
Platelet (× 10 ³ /ul)	227.8 ± 47.4	223.5 ± 49.8	215.5 ± 60.6	227.8 ± 53.2
SGOT(IU/L)	17.6 ± 4.4	19.4 ± 4.4*	18.3 ± 5.6	18.6 ± 4.3
SGPT(IU/L)	19.9 ± 15.7	23.0 ± 15.2*	20.2 ± 11.9	20.4 ± 12.5
Greatinine(mg/dl)	0.91 ± 0.11	0.89 ± 0.09	0.92 ± 0.09	0.90 ± 0.13
PT(INR)	1.05 ± 0.04	1.06 ± 0.05	1.06 ± 0.03	1.07 ± 0.05
PTT(sec)	36.5 ± 4.1	37.0 ± 0.1	35.7 ± 2.1	37.5 ± 3.2
Fibrinogen(mg/dl)	274.1 ± 66.0	230 ± 38.8*	270.5 ± 77.3	209.9 ± 41.5 *

mean ± S.D., * : baseline vs post-administration of drugs, P<0.05

ticlopidine 90%가 가 3,10,11).
 가 (p<0.05). Collagen enteric - coated aspirin aspirin enteric coated aspirin ticlopidine
 90%, 100%
 (Table 3).

4. 약물투여 전후의 혈청학적 검사결과

Low - dose aspirin ticlopidine in vitro 가
 creatinine
 , PT, PTT , SGOT,
 SGPT 가 aspirin 가
 (p<0.05) 가
 . Fibrinogen 가 aspirin aspirin 가
 , ticlopidine 10,12), 25%
 (p<0.05, Table 4). ent -

고 안

ericcoated aspirin 1 collagen
 95% 74%
 , ADP
 collagen fibronectin 45% 25%
 가 , 가
 가 ADP, 가
 serotonin, thromboxane A₂ 가 . Aspirin
 . ADP fibri - 가 가
 nogen von Willebrand factor(vWF) 가 가 12,13). Aspirin
 가 9).
 aspirin hydrolysis
 , 가 stent 14).
 가 1 100mg aspirin

, cyclo - oxygenase throm - opidine ticlopidine
 boxane A₂ 10 10 ADP
^{15,16} , aspirin 46.04 +
 ADP 18.65, 50.87 + 17.38, enteric coated aspirin
 . Enteric - coated aspirin gastroin - 33.44 + 12.48, 42.56 + 11.63
 testinal side effect aspirin ticlopidine enteric
 thromboxane A₂ coated aspirin ADP
 regular aspirin 가 ticlopidine 가
¹⁷ . 가
 Komiya ¹²) 81mg aspirin ADP
 collagen , shear stress가 19%, collagen
 ADP 63% 200mg ticlopidine
 low - 41%, 24%
 dose aspirin
 Ticlopidine 가 enteric coated aspirin(100mg) 21.21%,
 , 78.98% , ticlopidine 가
 가 ^{18,19} , enteric coated asp -
 가 irin(100mg) ticlopidine500mg)
⁸ . Tic - 62.48%, 79.22%
 lopidine ADP가 ADP receptor fibrinogen
 , gly - 가 enteric - coated aspirin
 coprotein IIb/IIIa fibrinogen vWF , ticlopidine
 , ticlopidine fi -
 ADP receptor glycoprotein ogen ²¹), aspirin
 lib/IIIa fibrinogen
^{7,20} . Ticlopidine ²² . aspirin
 ADP collagen SGOT, SGPT ,
¹² , ticlopidine 20 가
 , aspirin ,
 ADP 가
 가 ticlopidine ADP 요 약
 , aspirin
 collagen, ADP 연구배경 :
 , aspirin
 ticlopidine ADP
 62.48 + 20.07% . Aspirin ticlopidine 가
 20 ticl -

enteric - coated aspirin

ticlopidine

방 법 :

ADP, collagen

, collagen

latent time

결 과 :

enteric - coated aspirin ADP

collagen latent

time , ADP

가 50%

25% 가

. Ticlopidine ADP

가 enteric - coated aspirin

결 론 :

enteric - coated aspirin

collagen

, ADP 가

가 가 , aspirin

가

, ADP coll -

agen

ticlopidine

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