A Prospective Randomized Trial of Corticosteroids for the Prevention of Restenosis after Intracoronary Stent Implantation

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관동맥내 스탠트 재협착에 대한 고용량 스테로이드 정주요법의 효과

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서 론 : 관동맥 질환의 중재적 치료 방법으로 스탠트 삽입술 시행이 증가하면서 스탠트내 재협착이 중요한 문제점으로 대두되었다. 신생내막증식에 의한 혈관 내강감소가 가장 중요한 기전으로 여겨지면서 이를 극복하기 위한 많은 시도들이 이루어지고 있다. 강력한 항염증 작용을 갖는 스테로이드가 신생내막의 증식을 억제한다는 동물실험 보고가 있었으나 스탠트 재협착과 관련된 임상연구는 보고된 바 없다.

방 법 : 관동맥 스탠트 시술을 받는 140명의 환자를 대상으로 스테로이드군과 대조군으로 각각 분류하여 전향적 연구를 시행하였다. 스테로이드 치료는 메틸프레드니솔론을 사용하였으며 스탠트 삽입 6-12 시간전에 1gm을 정주하였다. 삽입된 스탠트는 CrossFLEX(n=90, 15mm)와 9-cell NIR 스탠트(n=50, 16mm)였다.

결 과 : 1) 양 군 사이에 기저 임상상 및 혈관 조영술상의 차이점은 없었으며 스탠트 삽입은 모든 환자에서 성공적으로 시행되었다. 2) 평균 기준혈관의 내경은 스테로이드 군에서 3.45±0.37mm, 대조군에서 3.36±0.39mm였다. 스탠트 삽입직후 최소내경은 각각 3.34±
0.44mm와 3.30±0.44mm였다. 추적 관동맥조영술상 재협착율은 스테로이드군 17.5%, 대조군 18.8%로 양 군 사이에 유의한 차이는 없었다. 3) 추적 관찰기간 동안에 발생한 사망, 심근경색 및 표적 병변 재관류등은 양 군 사이에 차이가 없었다.

결 론 : 스탠트 삽입술 시행시 투여한 고용량 스테로이드 정주요법은 스탠트 재협착 감소에 효과가 없었으며 추적 기간동안의 임상 결과에서도 대조군과 차이점이 없었다.

중심 단어 : Intracoronary stent restenosis · Corticosteroid.

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In-stent restenosis(ISR) after stent implantation remains to be overcome, and becomes a growing clinical problem with increased use of coronary stents. Neointimal hyperplasia is the predominant mechanism of ISR rather than arterial remodeling[1-3]. Inflammatory responses have been implicated as one of the major contributors to neointimal hyperplasia after coronary stent placement[4-7]. Corticosteroids may play a role in reducing neointimal hyperplasia because of its potent antiinflammatory action, and was reported to attenuate neointima formation in experimental models[8,9]. However, the role of corticosteroids for the reduction of ISR has not been defined in humans. This study was performed to evaluate the effect of corticosteroids in preventing angiographic restenosis after successful coronary stent implantation.

Methods

One hundred and forty consecutive patients scheduled for elective coronary stent implantation were eligible for this study. Inclusion criteria included a focal, de novo lesion(lesion length <20mm) in a native coronary artery(reference artery diameter ≥3.0mm) in patients with symptomatic ischemic heart disease. The criteria for exclusion were contraindication to antiplatelet agents or corticosteroids, infarctrelated artery, left ventricular dysfunction(ejection fraction <40%) or inability to follow the protocol. Diagnostic coronary angiography was performed, and coronary stent was subsequently implanted 2 or 3 days later. Patients were randomly assigned to either a methylprednisolone or a placebo group according to the computer-generated randomization lists. Either 1000mg methylprednisolone in 100ml of 5% dextrose water or 100ml of 5% dextrose water alone was intravenously infused over 30 minutes, 6 - 12 hours before the elective stent implantation. All subjects provided informed consent for participation, and the study protocol was approved by our institutional review board. Two types of stent were consecutively used for this study : CrossFlex stent (n=90, 15mm, Johnson and Johnson Interventional Systems, Inc.) or nine-cell NIR stent(n=50, 16mm, Medinol, Inc.). The predilation was performed with undersized, conventional angioplasty balloons. Stent size was selected to achieve a final stent-to-artery ratio of 1.1 : 1. The stents were then deployed by inflating the stent delivery balloon at single high pressure(14 - 16 atm, Cross Flex stent) or at 2 to 4 atm above nominal inflation pressure(NIR stent), and, if necessary, adjunct high pressure balloon dilation was performed to achieve angiographic optimization. During the procedure, patients received 10,000 units bolus of heparin with a repeat bolus of 5,000 U to maintain the activated clotting time ≥250 seconds. We used aspirin and ticlopidine as antithrombotic regimen. Ticlopidine therapy(250mg twice a day) was started at least three days before the stenting procedure and continued for one month. All patients received aspirin(200mg a day) indefinitely. Two experienced angiographers blinded to the treatment regimen analyzed the angiographic results. Percent diameter stenosis, minimal lumen diameter(MLD), and reference diameter using an on-line quantitative angiographic analysis system(ANCOR V2.0, Siemens) were measured before predilation, after stenting procedure, and at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter for magnification calibration. Single matched views with the worst diameter stenosis were compared. Angiographic restenosis was defined as diameter stenosis of ≥50% at follow-up. All patients were requested to visit outpatient clinics at 1, 3 and 6 months and then every 4 months after stenting. Coronary angiographic follow-up was performed at 6 months or earlier if they had recurrent symptoms. The primary end point was angiographic restenosis. Secondary end points included the incidence of clinical events such as death, myocardial infarction, and target lesion revascularization. Data were expressed as mean±SD for

continuous variables, and frequencies for the categorical variables. Continuous variables were compared by unpaired Student t test, and categorical variables by chi-square test. Kaplan-Meier analysis using the log-rank test was performed to estimate the cumulative rates of clinical events. A two-sided value of $p<0.05$ was required for statistical significance.

Results

The baseline clinical and angiographic characteristics are summarized in Table 1 and 2. There were no significant differences between the two groups with respect to baseline characteristics. Stent implantation was successful in all patients, and in-hospital events including stent thrombosis, myocardial infarction, emergency bypass surgery or death did not occur(Table 3). The mean reference vessel diameter was also similar between the two groups. Before elective stenting, the dimater stenosis was 73.8±14.4%(MLD 0.89±0.50)

Table 1. Clinical characteristics

Characteristics	Steroid (n=70)	Placebo (n=70)
Age(years)	58.5± 7.8	57.5±9.7
Sex(male/female)	47/23	46/24
Risk factors		
Hypertension	25(35.7%)	23(32.9%)
Diabetes mellitus	19(27.1%)	17(24.3%)
Hypercholesterolemia (≥240 mg/dl)	9(12.9%)	7(10.0%)
Current smoker	28(40.0%)	33(47.1%)
Family history	5(7.1%)	7(10.0%)
Unstable angina	43(61.4%)	43(61.3%)
Previous myocardial infarction	6(8.6%)	7(10.0%)
LVEF	60.8±10.1	59.6±8.6
Diseased vessels, n		
1	27(38.6%)	25(35.7%)
2	30(42.9%)	36(51.4%)
3	13(18.5%)	9(12.9%)
Types of stent, n		
CrossFlex stent	45(64.3%)	45(64.3%)
NIR stent	25(35.7%)	25(35.7%)

LVEF : left ventricular ejection fraction

Table 2. Angiographic characteristics

Characteristics	Steroid (n=70)	Placebo (n=70)
Artery dilated		
LAD	32(45.7%)	33(47.1%)
LCX	13(18.6%)	9(12.9%)
RCA	25(35.7%)	28(40.0%)
Lesion morphology		
Type A	1(1.4)	2(2.9)
Type B1	42(60)	40(57.1)
Type B2	27(38.6)	28(40)
Proximal reference diameter(mm)	3.45±0.37	3.36±0.39
Balloon to artery ratio	1.07±0.07	1.08±0.02
Maximal balloon inflation pressure(atm)	15.0 ±2.9	15.2 ±2.4
Minimal lumen diameter(mm)		
Baseline	0.89±0.50	0.80±0.53
Final	3.34±0.44	3.30±0.44
Follow-up	2.15±0.77	2.13±0.79
Diamter stenosis(%)		
Baseline	73.8 ±14.4	75.8 ±15.4
Final	2.9 ± 9.1	1.8 ± 9.8
Follow-up	39.0 ±20.2	36.9 ±22.6
Acute gain(mm)	2.44±0.59	2.49±0.62
Late loss(mm)	1.27±0.65	1.20±0.73
Loss index	0.53±0.29	0.52±0.39
Angiographic restenosis	11/63(17.5%)	12/64(18.8%)

Atm=atmosphere
LAD=left anterior descending coronary artery
LCX=left circumflex artery
Loss index=late loss/acute gain
RCA=right coronary artery

Table 3. Clinical outcomes in the hospital and during follow-up

Clinical Events	Steroid (n=70)	Placebo (n=70)
In-hospital		
Procedure success	70(100%)	70(100%)
Death	0(0%)	0(0%)
Nonfatal myocardial infarction	0(0%)	0(0%)
Repeat revascularization	0(0%)	0(0%)
During follow-up(months)	10.3±2.3	10.3±2.8
Death	1(1.4%)	0(0%)
Nonfatal myocardial infarction	0(0%)	0(0%)
Repeat revascularization	4(5.7%)	5(7.1%)
Any events	5(7.1%)	5(7.1%)

for patients in steroid group, and 75.8±15.4%(MLD 0.80±0.53) for patients in placebo group(Table 2, p=NS). At follow-up, the diameter stenosis was 39.0±20.2%(MLD 2.15±0.77) in the steroid group, and 36.9±22.6%(MLD 2.13±0.79) in the placebo group (p=NS). Angiographic follow-up were obtained in 127 patients(91.4% of those eligible), including 63 patients(91.3%) in steroid group, and 64 patients (91.4%) in placebo group, and the rates of angiographic restenosis were 17.5% in steroid group, and 18.8% in placebo group(p=NS), with no differences between two types of stent. Relative gain, relative loss, and loss index were not different between the two groups(Table 2). Clinical follow-up was available in all patients at 10.3±2.5 months. One patient in steroid group died of stroke 4 months after stent placement, but no patient in placebo group. There were no differences in the incidence of clinical events including death, myocardial infartion, and target lesion revascularization during follow-up between the two groups (Table 3). Significant adverse reactions were not present in any patients receiving methylprednisolone pulse therapy.

Discussion

Coronary stent is increasingly used to improve the clinical outcome as the primary angioplasty strategy. However, ISR remains a major clinical problem despite improvements of stent designs and adjunctive pharmacologic therapies. ISR is primarily result from neointimal hyperplasia, which may be exaggerated by "foreign body" response to the metallic stents[1-3]. For these reasons, treatment strategies focused on limiting neointima formation ineffective in balloon angioplasty may be useful to reduce the rate of ISR after stent placement, and therefore need to be investigated after coronary stent placement. Coronary stent implantation leads to a complex inflammatory responses with a wound-healing process, which may be a major contributor to restenosis after stenting[4-7]. Therefore, inflammatory reaction has been regarded as novel target for pharmacologic intervention. Corticosteriods are a potent antiinflammatory agent, and were reported to attenuate neointima formation in experimental models[8,9]. Methylprednisolone pulse therapy has been widely used for potent suppression of inflammatory or immune reactions in various clinical settings. Previously, methylprednisolone was reported not to be impressive for reduction of the angiographic restenosis after conventional balloon angioplasty[10,11]. Despite these results, corticosteroids may be considered to reduce restenosis after coronary stenting because inflammatory reaction plays an important role in neointima formation, and therefore inflammatory responses are attractive target for prevention of ISR[6]. However, this study shows that methylprednisolone pulse therapy does not reduce the angiographic restenosis rate or the incidence of major clinical events after coronary stent implantation. From this observation, we can speculate that ISR may result from multifactorial process, and corticosteroid alone is not sufficient for suppression of neointimal hyperplasia. However, it does not mean that inflammatory responses do not play a role in the process of neointimal hyperplasia. In addition to inflammation, there may be more complex mechanisms responsible for ISR in humans. Several possible explanations may underlie the apparent negative results of this study. First, the dosage of corticosteroid in this study may be too low to fully suppress local inflammatory reactions despite its potent antiinflammatory effects[12]. In this study single pulse therapy was used because of safety concerns. Therefore, we think that local application of corticosteroids with larger dose may be preferable approach for prevention of ISR. Second, species differences in the biological responses to vascular injury may in part explain the different outcomes in this trial. Third, the relatively small number of patients eligible for analysis limit the statistical power. However, this study was prematurely terminated because the impact of corticosteroids on ISR was not prominent on interim analysis. Finally, the mechanisms responsible

for neointimal hyperplasia are not exactly understood, and therefore current strategies aimed at reducing neointimal hyperplasia may target the wrong mechanisms. Further studies may be needed to clarify the pathophysiologic mechanisms of neointimal hyperplasia, and to reduce ISR after coronary stent implantation.

In conclusion, this study shows that methylprednisolone pulse therapy is not effective for the prevention of angiographic restenosis rate or major clinical events after intracoronary stent implantation.

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