Effectiveness of Clopidogrel and Aspirin *Versus* Ticlopidine and Aspirin After Coronary Stent Implantation: 1 and 6-month Follow-Up

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Abstract

Background : Clopidogrel is a new thienopyridine derivative and has less serious hematologic complications. We investigated the efficacy of clopidogrel plus aspirin (CA) in stent thrombosis prevention compared with ticlopidine plus aspirin (TA).

Method and Results : Sixty-eight patients who underwent coronary stenting were randomized into 2 groups: TA group, n = 31 and CA group, n = 37. At 1 month, there were 3 major bleeding complications, 2 in the CA group and 1 in the TA group. Neither stent thrombosis nor hematologic events were found in both groups. Two patients in the TA group died, 1 from sudden death and another from tracheal stenosis. At 6 months, five patients developed in-stent restenosis, 4 in the CA group and 1 in the TA group, p = NS. One patient in each group had acute coronary syndrome.

Conclusion : Clopidogrel plus aspirin is an effective coronary stenting regimen comparable to ticlopidine plus aspirin.

Key word : Clopidogrel, Coronary, Stent

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Coronary stent is widely used in the field of catheter-based coronary intervention and several studies have demonstrated the safety and efficacy of coronary stenting with appropriate technique and adequate antiplatelet therapy[1-4]. Ticlopidine has been used to reduce the incidence of stent thrombosis, but it can cause serious hematologic complications[4-6]. Clopidogrel, a new thienopyridine derivative, has been recently introduced and claimed to be more effective than aspirin in reducing cardiovascular events (ischemic stroke, myocardial infarction, or vascular death) in atherosclerosis patients without adverse hemotologic events[7] and a recent study also demonstrated that clopidogrel was effective in preventing stent thrombosis[8]. The purpose of this study was to evaluate the efficacy and safety of aspirin and clopidogrel in comparison to the combination of aspirin and ticlopidine for the prevention of stent thrombosis in patients undergoing coronary stent implantation.

METHOD

Study population

From June 1999 to December 2000, 68 patients underwent stent implantation for obstructive coronary artery disease. Inclusion criteria were symptomatic coronary artery disease or documented myocardial ischemia by treadmill exercise test or myocardial perfusion scan and coronary angiographic evidence of ≥ 70 per cent stenosis in diameter. Exclusion criteria were contraindication to antiplatelet agents, left main coronary artery disease, hemostatic disorder or systemic bleeding, history of thrombocytopenia or neutropenia, presence of abnormal white blood cell, differential or platelet count, requirement of long-term anticoagulant or nonsteroidal anti-inflammatory drugs, childbearing age women, and severe hepatic or renal dysfunction.

Randomization

All patients were randomly assigned to clopidogrel plus aspirin (CA) group and ticlopidine plus aspirin (TA) group by a research nurse. Ticlopidine was administered at 250 mg per oral twice a day 2 days prior to the stent implantation procedure and continued at the same dosage for 4 weeks. Clopidogrel was administered with a loading dose of 300 mg, 4 hours prior to the procedure, followed by 75 mg per oral once daily for 4 weeks. Aspirin was administered together with either ticlopidine or clopidogrel at 300 mg per oral twice a day in both groups. At 4-weeks follow-up, the dosage of aspirin was reduced to 300 mg once daily thereafter if there was no contraindication.

Stent implantation procedure

Predilation was performed before a stent was deployed in all patients. The stent was deployed by inflating the stent delivery balloon at nominal pressure. Adjunct high-pressure balloon dilation (12-14 ATM) was then performed to achieve angiographic optimization. Four types of stent were used during the study: NIR stent (Boston Scientific Corp. Boston, Massachusetts, USA, n = 41), ACS Multilink stent (Advance Cardiovascular Systems Inc., Santa Clara, CA, USA; n = 37), BX velocity stent (Cordis, Johnson & Johnson Corp., Miami, Florida, USA; n = 17), and GFX stent (Arterial Vascular Engineering Inc., Santa Rosa, California, USA; n = 6). Throughout the procedure, a 100 U/kg bolus dose of heparin was given initially, a repeated dose was given as needed to keep the activated clotting time ≥ a 250 seconds. The procedure was considered a success once the stent was placed at the desired position with ≤ 10 per cent residual stenosis.

Quantitative coronary angiography

An on-line quantitative angiographic analysis system (Toshiba, Japan) was used to analyze the coronary artery pre- and post-procedure.

Clinical follow-up and events

All patients were instructed to attend follow-up with their referring physicians at 4 weeks after the procedure for clinical assessment and complete blood count. Thereafter, clinical assessment was done every 8 weeks. Acute stent thrombosis was defined as thrombotic stent closure within 24 hours after the stent implantation. Subacute stent thrombosis was defined as thrombotic stent closure more than 24 hours after the stent implantation. Major cardiovascular events were defined as cardiovascular death, stroke, acute nonfatal myocardial infarction, and unstable angina. Acute myocardial infarction was diagnosed when there were two of the following; characteristic ischemic pain for ≥ 20 minutes, elevation of CK, CK-MB more than twice the upper limit, and new electrocardiographic changes. Major bleeding was defined as bleeding which required blood transfusion. Restenosis was defined as a diameter stenosis more than 50 per cent[9].

Statistics

Continuous normally distributed data were expressed as mean ± SD and were compared by Student's *t* test and Mann-Whitney test. Categorical variables were expressed as numbers and percentages and compared by the Fisher exact test. A 2-side p value < 0.05 was considered statistically significant.

RESULTS

Sixty-eight patients with 90 lesions were randomly assigned into the TA group (n = 31) and the CA group (n = 37). The success rate of the procedure was 100 per cent in both groups.

Patient characteristics and procedural data

Patient characteristics and angiographic measurement are shown in Tables 1, 2, and 3. After the procedure, the mean minimum lumen diameter in the TA group was smaller than the CA group (2.75 ± 0.33 *versus* 3.00 ± 0.52, p = 0.01). There was no difference in the percentage of residual stenosis (4 ± 4% *versus* 2 ± 3%, p = 0.20).

1-Month clinical outcome

There was no acute or subacute stent thrombosis and no major cardiovascular events in both groups. Three patients experienced major bleeding complication, 2 patients in the CA group and 1 patient in the TA group (2.45% *versus* 2.85%, p = 1.0, Table 4). There was 1 patient who developed skin rash in the TA group. There was no incidence of serious hematologic complications. Two patients died in the TA group. One patient died from tracheal stenosis. The other one died from sudden cardiac death.

6-Month clinical outcome

The clinical outcomes are shown in Table 4. One patient in each group had major cardiovascular events (non-Q myocardial infarction in the TA group and unstable angina in the CA group). There were 6 patients (1 patient in the TA group and 5 patients in the CA group) who had recurrent angina pectoris. Coronary angiography revealed in-stent restenosis in 4 patients (13.3%) in the CA group and 1 patient (3.6%) in the TA group at 6-month follow-up.

Discussion

Ticlopidine is a potent antiplatelet agent, but it has limitations due to serious adverse events, incidence of severe neutropenia occured in 1-2 per cent of patients but is almost always reversible[10]. Another serious adverse effect of ticlopidine is thrombotic thrombocytopenic purpura (TTP). A recent review documenting 60 cases of TTP resulted in 33 per cent mortality[6]. In addition; the drug could cause hepatic damage and gastrointestinal irritation.

Clopidogrel is a platelet adenosine diphosphate (ADP) receptor antagonist, acting by a direct inhibition of ADP binding to its receptor and also blocking ADP-induced fibrinogen binding to the glycoprotein IIb/IIIa complex[11,12]. The antiplatelet mechanism of action of ticlopidine and clopidogrel

Table 1. Patient baseline characteristics.

Patients	TA group (n = 31)	%	CA group (n = 37)	%
Age (yrs)	60 ± 9		61 ± 10	
Male, clinical diagnosis	26	84	27	73
Acute myocardial infarction	9	29	11	30
Unstable angina	10	32	10	27
Stable angina	12	39	16	43
Hypertension	15	48	14	38
Hypercholesterolemia	12	39	10	27
Smoking	14	45	10	27
Diabetes mellitus	9	29	14	38
Previous myocardial infarction	6	19	5	14
Previous revascularization	2	6	4	11

There was no difference between the 2 groups

Table 2. Angiographic characteristics.

Patients	TA group (n = 31)	CA group (n = 37)	p
Coronary artery			
Left anterior descending	20	21	NS
Left circumflex	11	4	0.03
Right	10	17	NS
Vein graft	0	1	NS
ACC/AHA Classification			
A	14	13	NS
B	21	26	NS
C	6	9	NS
Stent type			
NIR	21	20	NS
Multilink	13	24	0.002
BX velocity	11	6	NS
GFX	3	3	NS
Stent diameter, mm	2.86 ± 0.41	2.99 ± 0.43	NS
Stent length, mm	14.95 ± 4.67	14.98 ± 3.97	NS

NS, not significant

Table 3. Quantitative coronary angiographic results.

	TA (n = 31)	CA (n = 37)	p
Pre-procedure			
Reference diameter, mm	2.70 ± 0.54	2.99 ± 0.50	0.03
Minimum lumen diameter, mm	0.52 ± 0.31	0.48 ± 0.39	0.28
% stenosis	82 ± 10	84 ± 13	0.12
Post-procedure			
Reference diameter, mm	2.86 ± 0.34	3.08 ± 0.48	0.04
Minimum lumen diameter, mm	2.75 ± 0.33	3.00 ± 0.52	0.01
% stenosis	4 ± 4	2 ± 3	0.20

Table 4. Incidence of adverse events at 1 and 6-month follow-up.

Patients	TA group	%	CA group	%
1-month follow-up	31		37	
Death	2	6.5	0	0
Major bleeding	1	3.2	2	5.4
Minor bleeding	0	0	2	5.4
Drug side effects skin rash, n (%)	1	2.9	0	0
6-month follow-up	28		30	
Non-Q myocardial infarction	1	3.6	0	0
Angina pectoris	1	3.6	5	16.5
Unstable angina	0	0	1	3.3
Restenosis	1	3.6	4	13.3

There was no difference between the two groups.
All major bleeding was gastrointestinal bleeding.

is similar. Clopidogrel has been demonstrated to be as safe as aspirin, incidences of severe neutropenia, thrombocytopenia, and any other major bleeding complications (GI or intracranial) are similar regarding clopidogrel and aspirin (0.05% *versus* 0.04%, 0.26% *versus* 0.26%, and 1.4% *versus* 1.6%)[7]. A recent experimental study suggested that clopidogrel was more effective than either aspirin or ticlopidine in preventing high-shear-stress-dependent coronary stent thrombosis[13]. Clopidogrel has rapid onset in the inhibition of platelet aggregation, after administration of a 400 mg dose of clopidogrel, significant inhibition of platelet aggregation (47%-80%) appeared within 2 hours and remained at the same level for at least 48 hours[14,15]. From the above evidence of a good safety profile with clinical and experimental antiplatelet property, this would make clopidogrel a good alternative to ticlopidine after coronary stent implantation. Aspirin has been added to ticlopidine since the combination of both drugs work synergistically[5,16]. The regimen of ticlopidine plus aspirin reduced the incidence of stent thrombosis to < 1 per cent in most studies[5,16].

In this study, clopidogrel was administrated as a loading dose of 300 mg, followed by 75 mg once a day for 4 weeks. Aspirin was added to clopidogrel using the same regimen as ticlopidine. Our study showed clopidogrel plus aspirin was an effective poststenting antithrombotic regimen with comparable results to ticlopidine plus aspirin. At 1-month follow-up, there were neither stent thrombosis nor serious hematological complications in both groups. Similarly, there was no difference between the 2 groups in the incidence of major bleeding complication at 1-month follow-up (2.85% *versus* 2.45%, p = NS). Skin rash occurred only in the ticlopidine group. Two patients in the ticlopidine group died, one died from underlying disease and the other one died from sudden cardiac death. At 6-month follow-up, there was stent restenosis in 4 patients (13.3%) in the clopidogrel group and 1 patient (3.57%) in the ticlopidine group. This is not statistically significant, a larger number of patients may be needed for further study. There was no difference between both groups in the incidence of major cardiovascular events (3.3% *versus* 3.6%, p = NS).

SUMMARY

The authors suggest that clopidogrel plus aspirin is an effective medication in the coronary stent regimen comparable to ticlopidine plus aspirin. Clopidogrel may be of particular advantage in unplanned coronary stenting because of its rapid-onset of action.

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REFERENCES

1. Fischman DI, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angiograplasty in the treatment of coronary artery disease. N Engl J Med 1994; 331: 496-501.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489-95.
3. Colombo A, Hall P, Nakamura S, et al. Intracoronay stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995; 91: 1676-88.
4. Schömig A, Neumann FJ, Kastrati A, et al. A randomizied comparison of antiplatelet and anticoagulant therapy after the placement of coronart-artery stents. N Engl J Med 1996; 334: 1084-9.
5. Goods CM, al-Shabi KF, Liu MW, et al. Comparison of aspirin alone *versus* aspirin plus ticlopidine after coronary artery stenting. Am J Cardiol 1996; 78: 1042-4.
6. Bennett CL, Weinberg PD, Rosenber Ben-Dror K, Yarnold P, Kwaan H, Green D. Thrombotic thrombocytopenic purpura associated with ticlopidine. Ann Intern Med 1998; 128: 541-4.
7. CAPRIE Streering Committee. A randomized, blinded, trial of clopidogrel *versus* aspirin in patients at risk for ischemic events (CAPRIE). Lancet 1996; 348: 1329-39.
8. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin *versus* ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999; 99: 2364-6.
9. Roubin G, King SI, Douglas J, JR. Restenosis after percutaneous transluminal coronary angioplasty: Emory University experience. Am J Cardiol 1987; 60: 39B-43B.
10. Khurana S, Timmis G, Freed M. Adjunctive pharmacotherapy. In: Freed M, Grines C, Safian R. eds. The new Manual of Interventional Cardiology. Birmingham. Michigan: Physician's Press, 1996: 625-44.
11. Mills DCB, Puri R, Hu C-J, Minniti C, Freedman D. Clopidogrel inhibits the binding of ADP analogues to the receptor mediating inhibition of platelet adenylate cyclase. Arterioscler Thromb 1992; 12: 430-6.
12. Savi P, Heilmann E, Nurden P. Clopidogrel: An antithrombotic drug acting on the ADP-dependent activation pathway of human platelets. Clin Appl Thromb Hemost 1996; 2: 35-42.
13. Makker R, Eigler N, Kaul S, Zeng H, Herbert JM, Litvack F. Clopidogrel, a novel antiplatelet ADP receptor antagonist inhibits aspirin and ticlopidine resistant stent thrombosis. J Am Coll Cardiol 1997; 29 (Suppl A): 353A. abstract.
14. Herbert JM, Frehel D, Valle E. Clopidogrel, a novel antiplatelet and antithrombotic agent. Cardiovasc Drug Rev 1993; 11: 180-98.
15. Bachman F, Savcic M, Hauert J, Geudelin B, Kieffer G, Cariou R. Rapid onset of inhibition of ADP-induced platelet aggregation by a loading dose of clopidogrel. Eur Heart J 1996; 17: 263. Abstract.
16. Rupprecht HJ, Darius H, Borkowsky U, et al. Comparison of antiplatelet effects of aspirin, ticlopidine, or their combination after stent implantation. Circulation 1998; 97: 1046-52.

การศึกษาเปรียบเทียบประสิทธิภาพระหว่างยาต้านเกร็ดเลือด คลอพิโดเจลร่วมกับแอสไพริน กับ ไทคลอพีดีนร่วมกับแอสไพริน ในผู้ป่วยที่ได้รับการขยายหลอดเลือดแดงโคโรนารีร่วมกับการใส่ขดลวด, ที่ระยะเวลา 1 และ 6 เดือน

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การศึกษานี้เพื่อเปรียบเทียบประสิทธิภาพและความปลอดภัยของยาคลอพิโดเจลและแอสไพริน (CA) กับไทคลอพีดีนและแอสไพริน (TA) ในการป้องกันการเกิดการอุดตันของขดลวด หลังการรักษาโรคเส้นเลือดหัวใจตีบด้วยการใส่ขดลวด โดยสุ่มตัวอย่างเป็น 2 กลุ่ม ผู้ที่รับยา TA จำนวน 31 ราย และ ผู้ที่รับยา CA 37 ราย ในระยะ 1 เดือน, พบมีเลือดออกทางระบบทางเดินอาหารรุนแรง 2 ราย ในกลุ่ม CA และ 1 รายในกลุ่ม TA แต่ไม่พบผลแทรกซ้อน กลุ่ม TA มีผู้ป่วยเสียชีวิต 2 ราย ในระยะ 6 เดือน, พบว่ากลุ่ม CA มีผู้ป่วยเกิดการตีบตันในขดลวด 4 ราย, ในกลุ่ม TA เกิด 1 ราย และเกิดอาการหัวใจขาดเลือดเฉียบพลันกลุ่มละ 1 ราย การใช้ยาคลอพิโดเจลร่วมกับแอสไพริน มีประสิทธิภาพและปลอดภัยในการรักษาหลอดเลือดหัวใจตีบด้วยการใส่ขดลวดได้ผลเทียบเท่าการใช้ยาไทคลอพีดีนร่วมกับแอสไพริน

คำสำคัญ : คลอพิโดเจล, โคโรนารี่, สเต็น

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