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Original Paper

Open-Label Phase I Clinical Study to Assess the Safety and Efficacy of Cilostazol in Patients Undergoing Internal Carotid Artery Stent Placement

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Keywords

Aspirin · Carotid stenosis · Cerebral infarction · Cilostazol · Clopidogrel · Internal carotid stent placement · Transient ischemic attack

Abstract

Background: One-month dual antiplatelet treatment, with aspirin and clopidogrel, following internal carotid artery stent placement is the current standard of care to prevent in-stent thrombosis. Cilostazol, an antiplatelet drug, has been demonstrated to have a safety profile comparable to aspirin and clopidogrel. **Objective:** To evaluate the safety and clinical efficacy of cilostazol and aspirin therapy following internal carotid artery stent placement up to 1 month postprocedure. **Methods:** A phase I open-label, nonrandomized two-center prospective study was conducted. All subjects received aspirin (325 mg/day) and cilostazol (200 mg/day) 3 days before extracranial stent placement. Two antiplatelet agents were continued for 1 month postprocedure followed by aspirin daily monotherapy. The primary efficacy end point was the 30-day composite occurrence of death, cerebral infarction, transient ischemic attack, and in-stent thrombosis. The primary safety end point was bleeding. **Results:** Twelve subjects (mean age ± SD, 66 ± 12 years; 9 males) were enrolled and underwent internal carotid artery angioplasty and stent placement. None of the subjects who successfully followed the study protocol experienced any complications at the 1- and 3-month follow-ups. One patient had a protocol deviation due to concurrent use of enoxaparin (1 mg/kg twice daily) in addition to aspirin and cilostazol, resulting in a fatal symptomatic intracerebral hemorrhage

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following successful stent placement on postprocedure day 1. One patient discontinued cilostazol after the first dose secondary to dizziness. **Conclusion:** The use of cilostazol and aspirin for internal carotid artery stent placement appears to be safe, but protocol compliance needs to be emphasized.

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Introduction

Cilostazol, an antiplatelet medication different from aspirin and clopidogrel, selectively inhibits phosphodiesterase III, increases intraplatelet intracellular cyclic 3'-5'-adenosine monophosphate levels, activates protein kinase A, and decreases intracellular calcium levels [1, 2]. The antiplatelet effect of cilostazol, a prodrug, begins after it is hepatically metabolized. It has been demonstrated to have pleiotropic effects, reducing smooth muscle proliferation and intimal hyperplasia and causing vasodilation [3–5]. Cilostazol, also known as Pletal, has been approved in the United States since 1999 for the treatment of symptomatic peripheral arterial disease [6]. The Cilostazol Stroke Prevention Study (CSP 2) demonstrated that cilostazol (200 mg/day) was associated with fewer incidence of hemorrhagic events compared to aspirin (81 mg/day) for the prevention of stroke after an initial ischemic stroke (1.2 vs. 0.036%) with similar risk reduction for ischemic events [7].

The 2011 multispecialty Guidelines on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease: Executive Summary recommended dual antiplatelet therapy with aspirin (81–325 mg daily) plus clopidogrel (75 mg daily) prior to and for a minimum of 30 days after carotid artery stent placement; for patients intolerant of clopidogrel, ticlopidine (250 mg twice daily) may be substituted based on C level evidence [8]. The current guidelines on carotid artery stent placement do not mention cilostazol as an alternative to clopidogrel [9]. In the coronary circulation, cilostazol reduced the incidence of restenosis after balloon angioplasty and bare metal stent placement compared with aspirin and clopidogrel or ticlopidine [10–12]. Similarly, the combination of cilostazol and aspirin had lower rates of restenosis following carotid artery stent placement compared with aspirin and clopidogrel or ticlopidine in an observational study [13]. We performed a phase I open-label, nonrandomized two-center prospective study, to determine the safety of 1-month treatment with aspirin (325 mg/day) and cilostazol (200 mg/day) following extracranial stent placement.

Methods

We conducted a phase I open-label, nonrandomized two-center (Hennepin County Medical Center, Minneapolis, MN and University of Minnesota Medical Center, Minneapolis, MN) prospective study with the approval of the institutional review board of both hospitals. All subjects signed an informed consent prior to participating in the study. Each patient received aspirin (325 mg/day) and cilostazol (200 mg/day) for 3 days before extracranial stent placement. The two antiplatelet agents were continued for 1 month postprocedure and then aspirin (325 mg) daily monotherapy was continued thereafter. Study subjects were 18 years of age or older, with a baseline modified Rankin score of 0–2, who were scheduled to undergo extracranial internal carotid artery stent placement with or without balloon angioplasty for symptomatic or asymptomatic carotid artery stenosis. A distal embolic protection device was used with every stent placed. The internal carotid stenosis had to be greater than 50% and less than or equal to 99% as measured by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [14]. Subjects who received a carotid stent had high surgical risk features such as clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery or radiation therapy to the neck, recurrent stenosis after endarterectomy, and age greater than or equal to 80 years [15]. Also, stenting was preferred when there was a high carotid artery bifurcation, at the level of the C2 vertebra and above.

Subjects were excluded from participating in the study if they had a history of bleeding diathesis, including disorders treated by warfarin therapy (however, those who had received warfarin but had stopped taking the medication 3 days before the procedure and had an international normalized ratio less than 1.2 were eligible for inclusion). Similarly, subjects were excluded if they had severe hypertension (defined as systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 100 mm Hg, despite therapy), had a major surgery within the previous 6 weeks, or had a previous history of a hemorrhagic stroke. Pregnant patients or women who were breast-feeding were excluded from the study. Subjects were also excluded if they had gastrointestinal or genitourinary bleeding within the previous 30 days of treatment, had platelets less than 30,000, and/or had congestive heart failure.

The primary efficacy end point was the 30-day composite occurrence of death, cerebral infarction, transient ischemic attack, and in-stent thrombosis requiring unplanned endovascular revascularization procedure. The primary safety end point was bleeding. Bleeding complications were classified as major, moderate, or minor according to criteria used by the Thrombolysis in Myocardial Infarction trial group [16]. Major bleeding was defined as any intracranial hemorrhage or a decrease in hemoglobin level of less than 5 g/dL that resulted in hemodynamic compromise requiring treatment. Moderate bleeding was defined by the need for transfusion. Minor bleeding was defined as any decrease in hemoglobin level of 3 to 5 g/dL, not requiring transfusion or causing hemodynamic compromise. The age of the subjects, gender, medical comorbidities, length of intensive care stay (days), length of hospital stay (days), clinical indication for treatment, clinical presentation, and location of carotid stenosis were abstracted from the electronic medical record. The intraprocedural details regarding the stent deployed, whether pre- or post-balloon angioplasty was utilized as well as the balloon type, the posttreatment stenosis, and complications were abstracted from the medical record. Similarly, the follow-up complications and 1-month modified Rankin scale scores were also documented for each patient.

Statistical Analysis

The data is presented in a descriptive presentation. The mean value with standard deviation (SD) was presented for continuous variables including age and pre-stent and post-stent stenosis with or without angioplasty. The total number of immediate procedure-related and postprocedure follow-up complications were documented and counted. Postprocedure follow-up complications were defined as any complication that occurred after the immediate procedure and within the follow-up time period.

Results

Twelve subjects (mean age \pm SD, 66 ± 12 years; 9 men) were enrolled using the study protocol and underwent internal carotid artery stent placement with or without angioplasty with a distal embolic protection device. All the patients who received a carotid artery stent had stenosis secondary to extracranial atherosclerotic disease; there were no carotid stents placed for an arterial dissection. The procedure was performed in the right and left extracranial internal carotid arteries in 7 (58%) and 5 (42%) subjects, respectively. All the subjects were treated using the Nitinol PRECISE[®] PRO RX[®] Stent system (Johnson and Johnson; New Jersey) except for one patient who was treated with an Xpert stent (Abbott; Illinois, USA). The decision to use the 4-mm Xpert stent (Abbott) was based on the size of the internal carotid artery. The pre-stent percent stenosis and post-stent percent stenosis represented as mean \pm SD were $79 \pm 10\%$ and $9 \pm 10\%$, respectively. Pre-stent angioplasty was used in 5 subjects. Post-stent angioplasty was used in 5 subjects. There was one patient who received pre-angioplasty dilation of the stenotic lesion followed by post-stent angioplasty for further lesion dilation. One patient had stent placement alone, without pre- or post-angioplasty (see Table 2). Patients 3 and 6 represent the same patient but the extracranial carotid arteries were treated at separate time points, respectively, and were treated as two subjects (see Table 1). Other comorbidities among study subjects included: hypertension in 10 (83%), hyperlipidemia in 9 (75%), atrial fibrillation in 2 (17%), diabetes mellitus in 5 (42%), history of recent ischemic stroke and/or TIA in 7 (58%), congestive heart failure in 3 (25%), and tobacco dependence in 4 (33%) subjects.

Table 1. Baseline and angiographic characteristics of the study subjects recruited in the phase I trial

Patient	Age, years/ sex	Clinical presentation	Cardiovascular risk factors	Lesion site	Pre-treatment stenosis, %
1	63/M	1 month prior to stenting had multiple MRI-proven subacute and acute infarcts in right cerebral hemisphere; refused CEA	DM type II, hypertension	Right ICA	90
2	60/M	Multiple spells of amaurosis fugax of right eye	Occluded left ICA, HTN, HPLD, severe COPD	Right ICA	75
3	56/M	Acute ischemic stroke with right-side hemiparesis and dysarthria	Nine years prior had neck radiation for Hodgkin's lymphoma; HTN; tobacco dependent	Left ICA	85
4	75/F	TIA: sensory alteration of the right side of the body	HTN, A. Fib., CHF, DM type II, HLPD	Left ICA	80
5	50/M	Acute ischemic stroke with left sided hemiparesis	HTN, HLPD	Right ICA	70
6	56/M	Asymptomatic	Acute ischemic stroke secondary to a severe left ICA 85% stenosis 2 months prior to stenting; 9 years prior had neck radiation for Hodgkin's lymphoma; HTN; tobacco dependent	Right ICA	85
7**	63/F	TIA: left hand weakness a week prior to stenting	A. Fib., HTN, CHF, DM type II	Right ICA	80
8**	72/M	Amaurosis fugax of the left eye	HTN, HLPD, coronary artery disease, DM type II	Left ICA	60
9	91/F	TIA: intermittent word finding difficulties	HTN, DM type II, ischemic stroke (2004); coronary artery disease with CABG	Left ICA	75
10	57/M	Right corona radiata ischemic stroke with left hemiparesis	HTN, DM type II	Left ICA	99
11	71/M	Asymptomatic	HTN, HPLD, right ICA stenosis treated with carotid stent previously, CHF	Right ICA	80
12	81/M	Acute ischemic stroke with left arm and leg hemiparesis	Had poor medical follow-up. Did not have any prior medical history	Right ICA	70

Patients No. 3 and 6 represent the same patient treated at different time points. The 2 subjects with asterisks were not included in the study analysis because they did not complete the study. A. Fib., atrial fibrillation; CABG, coronary artery bypass graft; CEA, carotid endarterectomy; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; F, female; HLPD, hyperlipidemia; HTN, hypertension; ICA, internal carotid artery; M, male; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

All of the study subjects who successfully followed the study protocol completed the study without any change in their pre- and posttreatment modified Rankin score and did not experience any intracerebral hemorrhage, systemic bleeding complications, ischemic stroke, transient ischemic attack, or in-stent thrombosis at the 1-month and 3-month follow-up. Prior to stent placement, one patient discontinued cilostazol after the first dose secondary to nonspecific dizziness. There was a protocol deviation in one patient due to concurrent use of enoxaparin (1 mg/kg twice daily) in addition to aspirin and cilostazol. The patient suffered a fatal symptomatic intracerebral hemorrhage following successful stent placement on postprocedure day 1. A third patient was successfully enrolled in the study but the cilostazol was discontinued by her cardiologist 5 days after the successful and uncomplicated stent placement.

Table 2. Procedural information and clinical outcomes in study subjects

Patient	Angioplasty performed	Stent (type, size)	Post-treatment stenosis, %	Intra-procedural complication	Post procedure death	Bleeding complications, stroke, TIA, stroke or in-stent thrombosis/occlusion at 1 month posttreatment	ICU/total hospital stay, days	1 month modified Rankin scale score
1	Maverick ^a , 3 mm × 20 mm	Precise, 7 mm × 40 mm	20	0	0	0	1/1	0
2	Aviator ^a , 4 mm × 20 mm; Aviator ^b , 5 mm × 20 mm	Precise, 8 mm × 30 mm	10	0	0	0	1/1	0
3	Viatrac ^b , 4 mm × 20 mm	Precise, 7 mm × 30 mm	10	0	0	0	2/9	0
4	Aviator ^a , 4.0 mm × 30 mm	Precise, 7 mm × 30 mm	25	0	0	0	1/1	0
5	Viatrac ^b , 4.5 mm × 20 mm	Precise, 8 mm × 30 mm	0	0	0	0	1/3	2 (baseline)
6	Viatrac ^b , 4 mm × 20 mm	Precise, 7 mm × 40 mm	20	0	0	0	1/1	0
7**	Viatrac ^a , 4 mm × 30 mm	Precise, 7 mm × 30 mm	0	0	1	–	1/2	6
8**	None	Xpert, 4 mm × 20 mm	0	0	0	0	1/1	0
9	Aviator ^a , 4.5 mm × 15 mm	Precise, 7 mm × 40 mm	20	0	0	0	1/1	0
10	Maverick ^a , 3 mm × 20 mm	Precise, 7 mm × 30 mm	0	0	0	0	1/2	0
11	Aviator ^b , 5 mm × 30 mm	Precise, 6 mm × 40 mm	0	0	0	0	1/1	0
12	Viatrac ^b , 5 mm × 30 mm	Precise, 7 mm × 40 mm	0	0	0	0	1/7	1

The 2 subjects with asterisks were not included in the study analysis because they did not complete the study.

^aPre-stent balloon. ^bPost-stent balloon.

Discussion

Ischemic stroke can occur during or after extracranial internal carotid artery stent placement in rates varying from 4 to 10% depending on patient characteristics due to thromboembolic complications [17]. Clopidogrel and aspirin are the most commonly utilized antiplatelet medications prescribed prior to and following extracranial internal carotid artery stent placement to prevent in-stent thrombosis. This is the first phase I study in the United States that demonstrated the feasibility of using cilostazol and aspirin dual antiplatelet therapy to prevent in-stent thrombosis following internal carotid artery stenting. When adhering to the treatment regimen, cilostazol and aspirin appeared to be a safe treatment alternative to aspirin and clopidogrel, but such an observation requires further prospective studies to demonstrate efficacy in prevention of ischemic events. There are few reports that have examined the efficacy of dual antiplatelet treatment with aspirin and cilostazol specifically following carotid stent placement, with the majority of studies focusing on patients with coronary artery disease who have coronary stents placed [18].

Aspirin and clopidogrel have been demonstrated to be safe in the setting of extracranial carotid artery stenting. The IDEALCAST (Investigation on Devices and Antiplatelet Therapy for Carotid Artery Stenting) investigators conducted a multicenter prospective observational study on the onset of vascular events after carotid artery stenting in an effort to find out the efficacy and safety of carotid artery stenting in Japan and to investigate the effects of antiplatelet drugs administered before and after carotid artery stenting on efficacy and safety of carotid artery stenting. A total of 949 patients with extracranial carotid artery stenosis were enrolled and 934 had carotid artery stents placed with antiplatelet drugs and were followed for 1 year. The primary end point (incidence of the first event of death, ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, or serious hemorrhage within 1 year after enrollment) was observed in 69 patients (7.4%) within 30 days of enrollment and in 40 patients (4.3%) between 31 days and 1 year after enrollment. The choice of antiplatelet agents in the periprocedural period was up to the investigators. The incidence of the first event for aspirin and cilostazol was significantly lower than that for aspirin and clopidogrel ($p = 0.01$), aspirin and clopidogrel and cilostazol ($p = 0.01$), and antiplatelet monotherapy ($p < 0.01$) [9].

One of the limitations of bare metal stent implantation is the restenosis secondary to intimal hyperplasia within or adjacent to the stent [19, 20]. Cilostazol has been found to reduce neointimal formation in balloon-injured rat carotid arteries and inhibits restenosis after percutaneous transluminal coronary angioplasty [21, 22]. Takayama et al. [13] performed a retrospective, multicenter trial of 62 carotid artery lesions in 60 patients, studying the restenosis rate following carotid artery stenting with the carotid wall stent. There was a cilostazol (aspirin, 100 mg, and cilostazol, 200 mg; $n = 30$) and non-cilostazol group (aspirin, 100 mg, and clopidogrel, 75 mg [$n = 29$], or ticlopidine, 100 mg [$n = 2$] or 200 mg [$n = 1$]). The two antiplatelet medications were given 1 week preoperatively and continued for at least 3 months postoperatively. The patients were followed at 3 and 6 months postoperatively with an angiographic study. Takayama et al. [13] found that there were 5 cases of asymptomatic restenosis (8.3%) (4 were from the aspirin and clopidogrel group, and 1 was from the ticlopidine group) but none in the cilostazol treatment group, and the difference was statistically significant ($p = 0.0239$).

This study was intended to demonstrate the safety and feasibility of the addition of cilostazol to aspirin prior to and following extracranial carotid artery stenting, but there are limitations. One limitation of the study is the small sample size and its open-label design. The subjects were not randomized with a comparator group, and the results may not be representative of patients with characteristics different from the inclusion and exclusion criteria used.

Conclusion

The use of cilostazol and aspirin for internal carotid artery stent placement appears to be safe, but protocol compliance needs to be emphasized. Further studies are required to analyze the effectiveness and role of cilostazol in neurointerventional procedures.

Statement of Ethics

All the research meets the ethical guidelines, including adherence to the legal requirements of the study country.

Disclosure Statement

None of the authors involved in the study had any conflict of interest.

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