Prospective Randomized Study of Sarpogrelate Versus Clopidogrel-based Dual Antiplatelet Therapies in Patients Undergoing Femoropopliteal Arterial Endovascular Interventions: Preliminary Results

Yue-Xin Chen[1], Wen-Da Wang[1], Xiao-Jun Song[1], Yong-Quan Gu[2], Hong-Yan Tian[3], He-Jie Hu[4], Ji-Chun Zhao[5], Xiao-Qiang Li[6], Chang-Wei Liu[1]

[1]Department of Vascular Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100068, China

[2]Department of Vascular Surgery, Peking XuanWu Hospital, Beijing 100053, China

[3]Department of Vascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China

[4]Department of Vascular Surgery, Anhui Provincial Hospital, Hefei, Anhui 230001, China

[5]Department of Vascular Surgery, West China Hospital, Chengdu, Sichuan 510100, China

[6]Department of Vascular Surgery, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, China

Abstract

Background: Sarpogrelate is a selective 5-hydroxytryptamine (5-HT) receptor subtype 2A antagonist which blocks 5-HT induced platelet aggregation and proliferation of vascular smooth muscle cells. We compared the efficacy of sarpogrelate-based dual antiplatelet therapies for the prevention of restenosis and target lesion revascularization (TLR) rates comparing with that of clopidogrel after percutaneous endovascular interventions (EVIs) of femoropopliteal (FP) arterial lesions.

Methods: This prospective, multicenter, randomized clinical trial recruited a total of 120 patients with successful EVI of FP lesions at seven centers across China between January 2011 and June 2012. Patients were randomized to receive either sarpogrelate (100 mg trice daily for 6 months, $n = 63$) or clopidogrel (75 mg once daily for 6 months, $n = 57$). All patients also received oral aspirin (100 mg once daily for 12 months). Clinical follow-up was conducted up to 12 months postprocedure.

Results: There was no significant difference between the two groups in basic demographic data. The restenosis rate was higher in the clopidogrel group (22.80%) than in sarpogrelate group (17.50%), but there was no significant difference between these two groups ($P = 0.465$). The TLR rate, ipsilateral amputation rate, mortality in all-cause and bleeding rate were also similar in the two groups ($P > 0.05$).

Conclusions: Aspirin plus sarpogrelate is a comparable antithrombotic regimen to aspirin plus clopidogrel after EVI of FP arterial lesions. Dual antiplatelet therapies might play an important role in preventing restenosis after successful EVI of FP lesions.

Key words: Clopidogrel; Femoropopliteal Artery; Percutaneous Endovascular Interventions; Restenosis; Sarpogrelate

Introduction

Percutaneous endovascular interventions (EVIs) are widely used to treat patients with femoropopliteal (FP) arterial stenosis or occlusions. Despite the recent development of endovascular therapy, a high incidence of late restenosis through intima hyperplasia remains as a major unsolved problem. The incidence of restenosis is still as high as 39.0%–74.3%.[1-3] For patients undergoing lower extremity balloon angioplasty with stenting, there is a general consensus for long-term use of aspirin (75–100 mg/d).[4] Still, in the absence of sufficient data, dual antiplatelet therapy is a common clinical practice for lower extremity balloon angioplasty and stenting.

Sarpogrelate is a newly developed selective 5-hydroxytryptamine receptor subtype 2A (5-HT_{2A}) antagonist. It blocks 5-HT induced platelet aggregation. Furthermore, sarpogrelate inhibits 5-HT-induced proliferation of smooth muscle cells in animal models.[5-7] This leads to the suggestion that sarpogrelate is a candidate for inhibiting 5-HT-induced neointimal hyperplasia (restenosis) after angioplasty.[8] Fujita *et al*.[9] reported that sarpogrelate reduces restenosis after coronary stenting. However, effects of sarpogrelate on restenosis have not been studied

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.158285

Address for correspondence: Prof. Chang-Wei Liu, Department of Vascular Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100068, China
E-Mail: liucw@vip.sina.com

in randomized controlled trials of EVIs in the peripheral circulation.

Based on these results, this prospective, randomized, open-label clinical trial is going to evaluate the effects of sarpogrelate versus clopidogrel based dual antiplatelet therapies in FP arterial EVIs.

Methods

Study design and patient selection

The study was a prospective, multicenter, randomized, open-label clinical trial. Its protocol was approved by the institutional review board of each center. All patients gave written informed consent.

A total of 120 patients at seven centers across China were recruited between January 2011 and June 2012 according to the inclusion criteria and exclusion criteria as bellows [Table 1].

Procedure and randomization

Prior to percutaneous EVI, all patients received oral aspirin (100 mg/d) for at least 1-week. When intervention, percutaneous transluminal angioplasty (PTA) for FP lesions was performed either by antegrade approach or crossover through the bifurcation approach. Unfractionated heparin (100 units/kg) was allowed to use during the procedure. The lesion was expanded using an optimal balloon for 60 s. Bare-metal self-expanding stents were implanted in accordance with the American College of Cardiology/American Heart Association guidelines in patients presenting with a residual pressure gradient >10 mmHg, residual stenosis >30%, or flow-limiting dissection after balloon dilatation.

Table 1: Inclusion criteria and exclusion criteria

Inclusion criteria
Patient inclusion criteria
Adult patients above 18 years old who underwent successful angioplasty (PTA) with or without stents for FP arterial lesions
Successful PTA was defined as diameter stenosis <30% with the relief of symptoms
Be able to be followed up for at least 6 months after surgery
Lesion inclusion criteria
Angiographically-confirmed significant FP artery stenosis or occlusions caused by the arteriosclerosis disease
At least 1 arterial runoff BTK, but stenosis lesions not limiting flow may be included
Without residual inflow problems in aortoiliac artery, but stenosis lesions not limiting flow may be included
Exclusion criteria
Patient exclusion criteria
Patients with or at risk of hemorrhagic complications or bleeding tendency
Patients with acute lower limb ischemia
Patients with thrombophilia
Patients with known contraindications for aspirin, clopidogrel, sarpogrelate or contrast agents
Allergic to aspirin, clopidogrel, sarpogrelate, contrast agents or other NSAID
Hemophilia
Thrombocytopenia
Severe hepatic dysfunction
Pregnancy or lactation
Severe renal dysfunction
Patients have to use warfarin
Previous bypass surgery or angioplasty for the FP lesions
Lesions exclusion criteria
Remnant inflow problems
No arterial runoff BTK

PTA: Percutaneous transluminal angioplasty; FP: Femoropopliteal; BTK: Below the knee; NSAID: Nonsteroidal anti-inflammatory drug.

After successful EVI, eligible patients were randomized to sarpogrelate group or clopidogrel group. Randomization was performed with the use of computer-generated random digits, and the assignments were placed in sealed envelopes. To ensure an equal distribution of treatment regimen in each center, block random design was applied. From surgery to postoperative 6 months, the patients in sarpogrelate group receive sarpogrelate (100 mg tid) plus aspirin (100 mg/day), and the patients in clopidogrel group receive clopidogrel (75 mg/day) plus aspirin (100 mg/day). Sarpogrelate or clopidogrel was started from successful surgery and continued until 6 months only if there are severe complications requiring discontinuance of these drugs. Aspirin overlapped the whole 12 months. Angiotensin converting enzyme inhibitor, b-blocker, statins, and calcium-channel blocker were allowed for patients when indicated. However, other antiplatelet agents were not allowed for study patients.

Follow-up

Telephone follow-ups were conducted at 1, 2, 4, 5 months after PTA. Telephone follow-ups included clinical symptoms according to Fontaine/Rutherford classification criteria. Visit follow-ups were conducted at 3, 6, 12 months after PTA in the outpatient clinic by the study investigator. Visit follow-up examinations included clinical symptoms according to Fontaine/Rutherford classification criteria, ankle brachial pressure index (ABI), and Doppler ultrasound scanning. Unscheduled follow-ups included clinical symptoms according to Fontaine/Rutherford classification criteria, ABI and other necessary examinations. If patients had worsened clinical symptoms, lowered ABI by 0.2 or abnormal Doppler ultrasound, arteriography had to be performed. If patients were not eventful, arteriography was required at 12 months follow-up. All causes of death, amputation, bleeding complication, and the need of target lesion revascularization (TLR) were recorded.

Other characters required included age, sex, pre-PTA Fontaine/Rutherford classifications, Transatlantic Inter-Society Consensus (TASC) classification for FP lesions by angiography, comorbidities (hypertension, hypercholesterolemia, diabetes mellitus, and current smoking), combined medicine therapy, types of stents used, complications and managements.

Endpoints

The primary endpoint of the trial was the restenosis and TLR up to 12 months after FP arterial EVI. Restenosis was defined

as angiographic luminal diameter stenosis >50%. TLR was defined as repeated PTA in patients who had a restenosis. The secondary endpoints were ipsilateral amputation due to lower extremity ischemia, mortality by all causes and bleeding complications.

Statistics analysis

All analyses were conducted by the SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard division (SD), and categorical variables were presented as counts and percentages. For the analysis of continuous data, unpaired Student's *t*-test and nonparametric analysis by the Mann–Whitney U-test were used to assess differences between the two treatment groups. As for categorical data, χ^2 test (Pearson Chi-square) and Fisher's exact test were used. The incidence of TLR per patient was analyzed by means of Kaplan–Meier survival curves with differences between the two treatment groups compared by Log–rank test. Differences were considered statistically significant at a value of $P < 0.05$.

Results

Patient characteristics

After successful EVI of femoropopliteal arterial lesions, a total of 120 patients were included according to the inclusion criteria and exclusion criteria and randomly assigned to either sarpogrelate group ($n = 63$) or clopidogrel group ($n = 57$) between January 2011 and June 2012. The general demographic data of these patients are listed in Table 2. There is no significant difference between the two groups, including age, sex, risk factors, blood tests before EVI, ABI before EVI, Rutherford, and TASC classification, etc. After successful EVI, the ABI was significantly improved ($P = 0.022$).

Clinical follow-up

Clinical follow-up was available in 100% of the patients. In the whole 120 cases, the 3 months, 6 months, and 12 months restenosis rates were 2.50%, 10.83%, and 20.00% individually. The primary and secondary endpoints are described in Table 3. The restenosis rate was higher in the clopidogrel group (22.80%) than in sarpogrelate group (17.50%), but there was no significant difference between these two groups ($P = 0.465$). Kaplan–Meier survival curves for patients with restenosis in both groups were shown in Figure 1, and Log–rank test indicated that the rates of target lesion restenosis had no statistical significant differences between the sarpogrelate group and clopidogrel group ($P = 0.507$).

In the sarpogrelate group, one patient discontinued the medication because of severe gastrointestinal discomfort. In clopidogrel group, three patients discontinued the medication because of gastrointestinal bleeding (1), skin rash (1) and liver dysfunction (1). The rate of study medication discontinuation because of side effects tended to be lower in the sarpogrelate group than in the clopidogrel group without significant difference (1.60% vs. 5.30%, $P = 0.345$). Bleeding rate was higher in the clopidogrel group than in sarpogrelate group, but there was no significant difference (5.30% vs. 0.00%, $P = 0.104$).

Table 2: Basic characteristics of patients

Characteristics	Treatment groups		*P*
	Sarpogrelate group ($n = 63$)	Clopidogrel group ($n = 57$)	
Male (*n*, %)	42 (66.67)	35 (61.40)	0.548
Age (mean ± SD)	68.84 ± 9.56	69.51 ± 9.66	0.705
Risk factors (*n*, %)			
Hypertension	51 (80.95)	40 (70.18)	0.168
Hyperlipidemia	22 (34.92)	16 (28.07)	0.420
Diabetes	37 (58.73)	36 (63.16)	0.483
Smoke	28 (44.44)	24 (42.11)	0.796
Blood tests (mean ± SD)			
PLT ($\times 10^9$/L)	193.18 ± 95.86	232.67 ± 105.74	0.052
Hgb (g/L)	125.81 ± 19.174	132.51 ± 40.69	0.264
ALT (U/L)	21.68 ± 10.37	26.91 ± 25.32	0.154
AST (U/L)	23.46 ± 13.53	23.90 ± 15.65	0.879
Cr (μmol/L)	82.24 ± 137.08	72.99 ± 25.91	0.643
Rutherford classification (mean rank)	60.96	54.88	0.311*
TASC classification (mean rank)	35.15	39.24	0.382*
ABI before EVI (mean ± SD)	0.43 ± 0.26	0.43 ± 0.19	0.978
ABI after EVI (mean ± SD)	0.78 ± 0.21	0.77 ± 0.23	0.864
Stent numbers (mean ± SD)	1.61 ± 093	1.52 ± 0.90	0.631

*Nonparametric' Mann–Whitney test for two independent samples. SD: Standard deviation; PLT: Platelet; Hgb: Hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TASC: Transatlantic Inter-Society Consensus; ABI: Ankle brachial pressure index; EVI: Endovascular intervention.

Table 3: Primary and secondary endpoints of patients

Endpoints	Treatment groups, *n* (%)			*P*
	Total ($n = 120$)	Sarpogrelate group ($n = 63$)	Clopidogrel group ($n = 57$)	
Primary endpoints	24 (20.00)	11 (17.50)	13 (22.80)	0.465
Restenosis	24 (20.00)	11 (17.50)	13 (22.80)	0.465
TLR	6 (5.00)	4 (6.30)	2 (3.50)	0.682*
Secondary endpoints	7 (5.80)	3 (4.80)	4 (7.0)	0.707*
Ipsilateral amputation	3 (2.5)	2 (3.20)	1 (1.80)	1.000*
Mortality in all cause	2 (1.7)	1 (1.60)	1 (1.80)	1.000*
Bleeding	3 (2.5)	0 (0.00)	3 (5.30)	0.104*

*Fisher's exact test. TLR: Target lesion revascularization.

Discussion

Our results demonstrate that there were no significant differences between sarpogrelate (plus aspirin) and clopidogrel (plus aspirin) with regard to effectiveness and safety after EVI of FP arterial lesions. However, comparing to the clopidogrel group, the sarpogrelate group has a

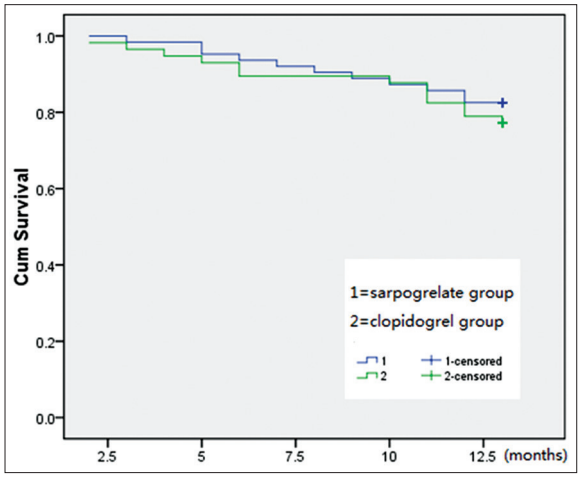

Figure 1: The Kaplan–Meier survival curves for patients with restenosis.

lower restenosis rate, bleeding rate, and study medication discontinuation rate because of side effects. These data are consistent with our previous study and other published studies[7,10] in animal models. Limited clinical studies[9,11] showed sarpogrelate treatment reduces restenosis after coronary stenting comparing with ticlopidine. Unfortunately, there is no study which compares sarpogrelate with clopidogrel. Our study was a meaningful attempt to testify the underrated effectiveness and safety of sarpogrelate in clinical EVI cases. Clopidogrel and sarpogrelate differ significantly in the mechanism by which they antagonize platelet aggregation. Clopidogrel acts as an adenosine diphosphate receptor antagonist, whereas sarpogrelate not only acts as a selective 5-HT_{2A} receptor antagonist but also inhibits smooth muscle proliferation.[12] The clinical benefits of sarpogrelate are possibly due to the inhibition of 5-HT-induced platelet aggregation and vascular smooth muscle cell proliferation which is thought to be the major mechanisms of intimal hyperplasia and the chronic restenosis.

In the whole 120 cases with dual antiplatelet therapies in our study, the restenosis rate of 20% at 12 months after EVI of FP lesions was much lower than other studies[13,14] of 41%–54% with single aspirin therapy. And the bleeding rate and side effects of dual antiplatelet therapies were also acceptable. Dual antiplatelet therapies (sarpogrelate plus aspirin/clopidogrel plus aspirin) might play an important role in preventing restenosis after EVI of FP lesions.

One limitation of our study was a possible bias from confounding factors such as the state of run-off and the length of lesions although the randomized design of this study makes no significant difference between the two groups in basic characteristics. The other limitation is the limited cases in this study which might weaken the statistical validity. These questions, therefore, remain to be answered by future studies.

In conclusion, the present prospective randomized multicenter study suggests that aspirin plus sarpogrelate is a comparable antithrombotic regimen to aspirin plus clopidogrel after successful EVI of FP arterial lesions.

References

1. Golledge J, Ferguson K, Ellis M, Sabharwal T, Davies AH, Greenhalgh RM, *et al.* Outcome of femoropopliteal angioplasty. Ann Surg 1999;229:146-53.
2. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, *et al.* Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006;354:1879-88.
3. Laird JR, Katzen BT, Scheinert D, Lammer J, Carpenter J, Buchbinder M, *et al.* Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: Twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv 2010;3:267-76.
4. Sobel M, Verhaeghe R, American College of Chest Physicians, American College of Chest Physicians. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:815S-43.
5. Sharma SK, Zahradka P, Chapman D, Kumamoto H, Takeda N, Dhalla NS. Inhibition of serotonin-induced vascular smooth muscle cell proliferation by sarpogrelate. J Pharmacol Exp Ther 1999;290:1475-81.
6. Watanabe T, Pakala R, Katagiri T, Benedict CR. Angiotensin II and serotonin potentiate endothelin-1-induced vascular smooth muscle cell proliferation. J Hypertens 2001;19:731-9.
7. Sharma SK, Del Rizzo DF, Zahradka P, Bhangu SK, Werner JP, Kumamoto H, *et al.* Sarpogrelate inhibits serotonin-induced proliferation of porcine coronary artery smooth muscle cells: Implications for long-term graft patency. Ann Thorac Surg 2001;71:1856-64.
8. Origuchi N, Shigematsu H, Muto T. Anplag, a selective 5-HT2 receptor antagonist, reduces stenosis induced by balloon injury in the hypercholesterolaemic rabbit. Int Angiol 1997;16:204-9.
9. Fujita M, Mizuno K, Ho M, Tsukahara R, Miyamoto A, Miki O, *et al.* Sarpogrelate treatment reduces restenosis after coronary stenting. Am Heart J 2003;145:E16.
10. Kodama A, Komori K, Hattori K, Yamanouchi D, Kajikuri J, Itoh T. Sarpogrelate hydrochloride reduced intimal hyperplasia in experimental rabbit vein graft. J Vasc Surg 2009;49:1272-81.
11. Tamura A, Watanabe T, Shinozaki K, Kotoku M, Yano S, Kadota J. Comparison of sarpogrelate and ticlopidine in bare metal coronary stent implantation. Int J Cardiol 2008;126:79-83.
12. Saini HK, Takeda N, Goyal RK, Kumamoto H, Arneja AS, Dhalla NS. Therapeutic potentials of sarpogrelate in cardiovascular disease. Cardiovasc Drug Rev 2004;22:27-54.
13. Salapura V, Blinc A, Kozak M, Jezovnik MK, Pohar Perme M, Berden P, *et al.* Infrapopliteal run-off and the outcome of femoropopliteal percutaneous transluminal angioplasty. Vasa 2010;39:159-68.
14. Shammas NW. An overview of optimal endovascular strategy in treating the femoropopliteal artery: Mechanical, biological, and procedural factors. Int J Angiol 2013;22:1-8.

Received: 09-09-2014 **Edited by:** Jian Gao
How to cite this article: Chen YX, Wang WD, Song XJ, Gu YQ, Tian HY, Hu HJ, Zhao JC, Li XQ, Liu CW. Prospective Randomized Study of Sarpogrelate Versus Clopidogrel-based Dual Antiplatelet Therapies in Patients Undergoing Femoropopliteal Arterial Endovascular Interventions: Preliminary Results. Chin Med J 2015;128:1563-6.

Source of Support: Nil. **Conflict of Interest:** None declared.