Original Article

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

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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-HT₂A) 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 yet.

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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.

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

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, 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.
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, χ² 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 | Clopidogrel group |
| (n = 63)                             | (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 (×10^10/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 ± 0.93      | 1.52 ± 0.90 | 0.631 |

Table 3: Primary and secondary endpoints of patients

| Endpoints                      | Treatment groups, n (%) | P    |
|--------------------------------|-------------------------|------|
| (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 |
| Ipsiateral 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
Sarpogrelate inhibits serotonin-induced infrapopliteal run-off and the outcome of multicenter study suggests that aspirin plus sarpogrelate (aspirin/clopidogrel plus aspirin) might play an important role in preventing restenosis after EVI of FP lesions.

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.

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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 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.

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