Beneficial Effect of Beraprost Sodium Plus Aspirin in the Treatment of Acute Ischemic Stroke

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Background: To investigate the combination of beraprost sodium (BPS) and aspirin in the treatment of acute ischemic stroke (AIS).

Material/Methods: 308 patients with acute cerebral infarction were randomly divided into two groups: experimental group (n=154), treated with BPS (40 μg, tid) and aspirin (100 mg, qd); control group (n=154), treated with 100 mg of aspirin, qd). The antiplatelet therapy remained unchangeable until six months after hospital discharge.

Results: Initially, no significant differences were found between the two groups. After six months, the relapse-free survival rate was similar between the treatment group (98.1%) and the control group (97.4%). One patient died from AIS in the control group. However, glomerular filtration rate was significantly higher; neurological function and functional ability of patients were better in patients treated with BPS plus aspirin (experimental group) than that in aspirin alone group. No significant difference was found in the function of the coagulation system, suggesting that BPS plus aspirin treatment did not increase the risk of bleeding. Serious adverse events did not occur in both groups. Facial flushing (one case) and mild gastrointestinal reaction (one case) were found in the treatment group without influencing treatment.

Conclusions: In our trial involving patients with acute cerebral infarction, BPS plus aspirin was not found to be superior to aspirin in reducing the recurrence of cerebral infarction or death. However, BPS plus aspirin treatment could improve renal function and neurological function without increasing the risk of bleeding.
Background

Acute ischemic stroke (AIS) causes high morbidity and mortality, and also has a high recurrence rate. Secondary prevention in patients with first onset ischemic stroke is extremely important. The initiation of antiplatelet therapy immediately after AIS is widely applied to prevent the recurrence and progression of the disease and also reduce the incidence of other vascular events [1]. Besides the hemorrhagic complications associated with antiplatelet therapy, aspirin monotherapy dose not significantly reduce stroke progression [2]. Even though the combination antiplatelet therapy might reduce the recurrence and stroke progression in large artery disease [3,4], increased bleeding complications minimize the benefit from antithrombotic therapy and poses a great challenge. The pathophysiology of AIS is very complex, and patients with AIS often suffer from other vascular diseases such as renal diseases and myocardial disease. Thus, it is especially important to develop new treatment combinations which can also improve neurological function and protect other organic functions, beyond preventing ischemic stroke recurrence.

Beraprost sodium (BPS), a stable synthetic and orally active prostacyclin (PGI2) analogue, can inhibit platelet aggregation mediated by cAMP, and can also inhibit vasoconstriction and leukocyte chemotaxis [5,6]. BPS has been reported to prevent microcirculatory derangement in the acute stage of ischemic stroke in rat [7], and also has renal and neurological protective roles [8–10]. Considering the comprehensive role of BPS in inhibition of platelet aggregation and protective roles in renal and neurological function, we hypothesized that the combination of BPS with aspirin may exert potent anti-platelet effects and improve renal and neurological function in patients with acute ischemic stroke.

In the present study, we recruited 308 patients with acute ischemic stroke; these patients were randomly treated with BPS plus aspirin or aspirin alone. The therapeutic efficacy, adverse effects, and renal and neurological outcomes were reported.

Material and Methods

Patients

In all, 308 patients with acute ischemic stroke were recruited for a double-blind trial of antiplatelet therapy using combination of beraprost sodium (BPS) and aspirin versus aspirin alone. Patients were included based on the following criteria: 1) patients suffered from large-artery atherosclerosis (LA) and small-artery occlusion lacunar (SA) according to the TOAST classification for ischemic stroke; 2) first onset of stroke and admitted to our hospital; and 3) treated within 72 hours after the onset of cerebral infarction. We excluded patients with coagulation disorder, patients with hemorrhage in digestive tract or other parts of the body, patients with severe liver and renal insufficiency, and patients with malignant tumor, trauma, or surgery. The inclusion and exclusion criteria are listed in Table 1. The study was approved by the Institutional Ethics Committee, and informed consent was obtained from all patients.

Treatment

The 308 patients with acute cerebral infarction were randomly divided into two groups: the experimental group (n=154), treated with BPS (40 μg, tid) and aspirin (100 mg, qd); and the control group (n=154), treated with 100 mg of aspirin, qd). All patients were treated with aspirin within 72 hours after the onset of cerebral infarction. The antiplatelet therapy remained unchanged till six months after hospital discharge. Besides the antiplatelet treatment, patients received regular treatments such as lipid regulation, free radical scavenging (30 mg of edaravone, intravenously, bid) and regulation of blood pressure and blood glucose. The average hospitalization days for each group were 14.2±3.5 days.

Study design and biochemical analysis

The levels of serum creatinine (Cr), prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (Fib) were measured at admission, and at two weeks, one month, and six months of treatment. The National Institute of Health Stroke Scale (NIHSS) was used to evaluate neurological function after anterior circulation infarction (ACI). Functional abilities of stroke patients were recorded using the Barthel index (BI) at admission and during follow-up. The adverse effects were also recorded. Glomerular filtration rate was calculated using the simplified MDRD equation:

\[ \text{GFR (mL/min/1.73m}^2) = 186 \times (\text{Scr}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ female})] \]

Statistical analysis

Statistical analysis is processed by SPSS 18.0, and quantitative data are presented by mean ± standard deviation (mean ±SD). Repeated measures analysis of variance was used to compare the differences between the two groups. Relapse-free survival rate was compared by Kaplan-Meier test. Probability value of \( p<0.05 \) was considered to be significantly different.

Results

Initial patient characteristics

At onset of the study, no significant difference existed in patient characteristics such as age, gender distribution, and...
body mass index (BMI) as shown in Table 1. The treatment group includes 154 patients (male, 94), with the average age of 66.6±12.1 years (range: 40–80 years). The control group also contains 154 patients (male, 90), with the average age of 66.6±11.5 years (range: 40–85 years). The distribution of patients with hypertension, diabetes, and coronary disease was similar when comparing the two groups (Table 1). Moreover, the neurological function and functional abilities were without significant differences according to NIHSS and Barthel index (BI) at admission.

Recurrence and death

After six-month follow-up, cerebral infarction recurrence was reported in three cases in the treatment group and four cases recurrence in the control group. No significant difference was found in the relapse-free survival rate between the treatment group (98.1%) and the control group (97.4%) (Table 2, Figure 1). One patient died from AIS in the control group.

Renal function, neurological function, and functional abilities during follow-up

Glomerular filtration rate was calculated using the simplified MDRD equation, and was used to evaluate renal function. In our study, we found that the GFR in the BPS-aspirin group was significantly higher than the aspirin group (p<0.05) (Table 3, Figure 2). Neurological function was evaluated by NIHSS. As shown in Table 4 and Figure 3, NIHSS score was significantly reduced after BPS-aspirin treatment compared with aspirin alone (p<0.001). Moreover, we used the Barthel index (BI) to measure the functional abilities of stroke patients. Our results showed that after the six-month treatment, the Barthel index was significantly elevated in the treatment group using

| Parameter | Treatment group (n=154) | Control group (n=154) | t/χ² | p Value |
|-----------|------------------------|-----------------------|------|---------|
| Age (years) | 66.6±12.1 | 67.1±11.5 | 0.37 | 0.71 |
| Gender | | | | |
| Male | 94 | 90 | 0.12 | 0.73 |
| Female | 60 | 64 | | |
| BMI | 22.5±3.86 | 22.46±3.92 | 0.16 | 0.87 |
| Hypertension | 115 | 105 | 1.29 | 0.26 |
| Diabetes | 55 | 46 | 0.94 | 0.33 |
| Blood lipids | | | | |
| TC | 5.15±1.41 | 5.41±1.35 | 1.65 | 0.09 |
| LDL | 3.37±0.90 | 3.63±1.25 | 1.48 | 0.23 |
| HDL | 1.23±0.29 | 1.12±0.41 | 2.40 | 0.13 |
| Smoking | 40 | 36 | 0.16 | 0.69 |
| Alcohol use | 19 | 21 | 0.029 | 0.87 |
| Coronary disease | 15 | 12 | 0.16 | 0.69 |
| TOAST classification | | | | |
| LA | 72 | 65 | 0.47 | 0.49 |
| SA | 82 | 89 | | |
| Embolic stroke | 35 | 28 | | |
| Thrombotic stroke | 119 | 126 | | |
| NIHSS score | 4.66±3.58 | 4.99±3.47 | 0.82 | 0.41 |
| BI | 82.0±16.72 | 80.39±16.76 | 0.243 | 0.62 |

LA – large-artery atherosclerosis; SA – small-artery occlusion lacunar.
BPS plus aspirin, compared with the control group treated with aspirin ($p<0.001$) (Table 5, Figure 4).

**Blood coagulation and adverse events**

After six-months of treatment, the function of the coagulation system was assessed using aPTT (activated partial thromboplastin time), PT (prothrombin time, also used to determine INR) and fibrinogen testing. Our results showed that no significant difference was found in patients treated with BPS plus aspirin compared with aspirin alone in the function of the coagulation system (Table 6), suggesting that BPS plus aspirin treatment did not increase the risk of bleeding. Serious adverse events did not occur in either group. Facial flushing (one case) and mild gastrointestinal reaction (one case) were found in the treatment group without influencing treatment.

**Discussion**

In the present study, patients with ischemic stroke who underwent randomization within 48 hours after symptom onset were treated with either a combination of beraprost sodium (BPS) and aspirin or aspirin alone during the hospitalized period and the six-month follow-up. We found that the combination of BPS and aspirin was not superior to aspirin alone in reducing the recurrence of cerebral infarction or death. However, BPS plus aspirin treatment could improve renal and
neurological function without increasing the risk of bleeding and other adverse events.

Prostacyclin (PGI2), released from vascular endothelial cells, could inhibit platelet aggregation, vasoconstriction, and smooth muscle cell proliferation. BPS is a stable and orally available PGI2 analogue. Tanaka et al. reported that BPS could prevent microcirculatory derangement in cerebral ischemia in rats [7]. BPS has been reported to prevent the development of arterial stiffness in elderly patients with cerebral infarction [11]. However, the role of BPS in the anti-platelet therapy in acute ischemic stroke (AIS) has been less reported. Considering the anti-aggregating effects of aspirin are relatively weak, the effect of the combination of BPS and aspirin was evaluated in this study. This combination is considered to be relatively safe because BPS and aspirin do not cause synergistic reactions. In this study, although BPS plus aspirin did not significantly reduce the recurrence of cerebral infarction or death compared with aspirin alone, the incidence of patients with hemorrhagic complications was similar in both groups. This result suggests that the combination of BPS and aspirin did not increase the risk of bleeding.

In our study, we found that the GFR after BPS plus aspirin treatment was significantly higher than the GFR after treatment with aspirin alone. It is an important consideration that patients with AIS often suffer from hypertension and diabetes, conditions which increase the risk of cerebrovascular disease. Moreover, hypertension and diabetes also increase the risk of secondary renal function damage. It has reported that PGI2 could improve renal function through antiplatelet and blood vessel dilation to

Table 4. NIHSS score for treatment group (BPS-aspirin) and control group (aspirin).

| NIHSS score | Treatment group | Control group | F     | p    |
|-------------|---------------|---------------|-------|------|
| At admission| 4.97±3.55     | 4.66±3.58     |       |      |
| 2 weeks     | 2.97±2.51*    | 3.64±2.27     |       |      |
| 1 month     | 1.55±1.87***  | 3.12±1.83     |       |      |
| 6 months    | 1.05±1.52***  | 2.79±1.76     | 25.828| <0.001|

* p<0.05, *** p<0.001 vs. control group

Figure 3. NIHSS score for treatment group (beraprost sodium (BPS) plus aspirin) and control group (aspirin).

Table 5. BI for treatment group (BPS-aspirin) and control group (aspirin).

| BI | Treatment group | Control group | F     | p    |
|----|----------------|---------------|-------|------|
| At admission| 82.05±16.68  | 98.08±5.34    |       |      |
| 6 months | 80.45±16.61*** | 90.26±8.83  | 18.581| <0.001|

*** p<0.001 vs. control group.
increase the blood perfusion of renal tubular capillary. This could alleviate tubule interstitial hypoxia-ischemia and improve renal function [12,13]. However, aspirin could cause a reduction of prostaglandin, which may then reduce glomerular filtration. Therefore, the combination of BPS and aspirin could compensate for the aspirin-induced reduction of endogenous PGI and alleviate the adverse effects of aspirin in renal function.

The neuro protective role of BPS has been mainly reported in animal studies; the underlining mechanisms include BPS-induced dilation of blood vessels, anti-platelet aggregation, reduction of oxidative stress injury, and protection of reperfusion injury [10,14]. A double-blind, randomized clinical trial carried out by Rasmussen et al. in 2015 aimed to investigate whether prostacyclin could prevent cerebral vasospasm [15], but no positive results have been obtained yet. In our study, we found that the NIHSS score was reduced after treatment in both groups. The combination of BPS and aspirin significantly improved the neurological function compared to aspirin alone. Moreover, the functional abilities of stroke patients in daily life were significantly improved by BPS plus aspirin compared with aspirin alone after six-months of treatment. This may be related to the promotion of neural functional recovery by BPS. However, we found no significant difference in the recurrence rate of ischemic stroke between the two groups, which may be associated with the relative short follow-up period or the relative small number of patients involved. Thus, this study cannot provide valid evidence for whether BPS can be used for secondary prevention of ischemic cerebrovascular diseases. Further study with more participants and longer follow-up is needed to validate the role of BPS in the prevention of secondary ischemic stroke.

In our study, among the 154 patients in the BPS plus aspirin group, only one patient had slight facial blushing, and one patient had mild gastrointestinal reaction. These side effects did not influence treatment. Bleeding and other severe adverse effects were not found in any patients during the six-month follow up period, and no significant difference was observed in the coagulation function between the two groups. These results further suggest that the use of BPS in acute phase and convalescence does not increase the risk of bleeding. The safety of long-term use of BPS needs further long-term follow-up study.

Conclusions

In our trial involving patients with acute cerebral infarction, BPS plus aspirin was not found to be superior to aspirin in reducing the recurrence of cerebral infarction or death. However, BPS plus aspirin treatment could improve renal function and neurological function without increasing the risk of bleeding.

Conflict of interest

None.

Table 6. Function of the coagulation system.

|                | Treatment group | Control group | F    | p     |
|----------------|----------------|---------------|------|-------|
| PT (s)         |                |               | 2.001| 0.114 |
| At admission   | 11.1±1.0       | 11.2±1.0      |      |       |
| 2 weeks        | 11.4±1.3       | 11.1±1.0      |      |       |
| 1 month        | 11.2±1.3       | 11.3±1.0      |      |       |
| 6 months       | 11.2±1.3       | 11.3±1.0      |      |       |
| APTT (s)       |                | 0.492         | 0.688|       |
| At admission   | 28.8±4.3       | 28.7±4.2      |      |       |
| 2 weeks        | 28.5±3.3       | 28.9±3.0      |      |       |
| 1 month        | 28.5±3.2       | 28.7±3.8      |      |       |
| 6 months       | 28.4±3.2       | 28.6±3.7      |      |       |
| Fbi (g/L)      |                | 0.902         | 0.441|       |
| At admission   | 3.3±0.9        | 3.2±1.0       |      |       |
| 2 weeks        | 3.3±1.0        | 3.6±2.8       |      |       |
| 1 month        | 3.2±0.9        | 3.2±0.9       |      |       |
| 6 months       | 3.3±0.9        | 3.2±0.9       |      |       |

APT T – activated partial thromboplastin time; PT – prothrombin time; Fbi – fibrinogen.

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DRUG CONTROLLED STUDIES
References:

1. Gentile NT, Vaidyula VR, Kanamalla U et al: Factor VIIa and tissue factor procoagulant activity in diabetes mellitus after acute ischemic stroke: Impact of hyperglycemia. Thromb Haemost, 2007; 98: 1007–13

2. Markus HS, Droste DW, Kaps M et al: Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation, 2005; 111: 2233–40

3. Wong KS, Chen C, Fu J et al: Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): A randomised, open-label, blinded-endpoint trial. Lancet Neurol, 2010; 9: 489–97

4. Diener HC, Bogousslavsky J, Brass LM et al: Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomised, double-blind, placebo-controlled trial. Lancet, 2004; 364: 331–37

5. Umetsu T, Murata T, Nishio S: Studies on the antiplatelet effect of the stable epoprostenol analogue beraprost sodium and its mechanism of action in rats. Arzneimittel-Forschung, 1989; 39: 68–73

6. Kainoh M, Imai R, Umetsu T et al: Prostacyclin and beraprost sodium as suppressors of activated rat polymorphonuclear leukocytes. Biochem Pharmacol, 1990; 39: 477–84

7. Tanaka K, Gotoh F, Fukuuchi Y et al: Stable prostacyclin analogue preventing microcirculatory derangement in experimental cerebral ischemia in cats. Stroke, 1988; 19: 1267–74

8. Peng L, Li J, Xu Y et al: The Protective effect of beraprost sodium on diabetic nephropathy by inhibiting inflammation and p38 MAPK signaling pathway in high-fat diet/streptozotocin-induced diabetic rats. Int J Endocrinol, 2016; 2016: 1690474

9. Shima A, Miyamoto M, Kubota Y et al: Beraprost sodium protects against diabetic nephropathy in patients with arteriosclerosis obliterans: A prospective, randomized, open-label study. J Nippon Med Sch, 2015; 82: 84–91

10. Pan Y, Yu L, Lei W et al: Beraprost sodium protects against chronic brain injury in aluminum-overload rats. Behav Brain Funct, 2015; 11: 6

11. Nakayama T, Hironaga T, Ishima H: The prostacyclin analogue beraprost sodium prevents development of arterial stiffness in elderly patients with cerebral infarction. Prostaglandins Leukot Essent Fatty Acids, 2004; 70(6): 491–94

12. Yamaguchi S, Inada C, Tamura M et al: Beraprost sodium improves survival rates in anti-glomerular basement membrane glomerulonephritis and 5/6 nephrectomized chronic kidney disease rats. Eur J Pharmacol, 2013; 714: 325–31

13. Jenkins A, Wang-Smith L, Marbury T, Laliberte K: Pharmacokinetics of treprostinil diolamine in subjects with end-stage renal disease on or off dialysis. J Cardiovasc Pharmacol, 2013; 61: 272–76

14. Yu L, Yang B, Wang J et al: Time course change of COX2-PGI2/TXA2 following global cerebral ischemia reperfusion injury in rat hippocampus. Behav Brain Funct, 2014; 10: 42

15. Rasmussen R, Wetterslev J, Staunsgaard T et al: Effects of prostacyclin on cerebral blood flow and vasospasm after subarachnoid hemorrhage: Randomized, pilot trial. Stroke, 2015; 46: 37–41