

Combination therapy with beraprost sodium and aspirin for acute ischemic stroke: a single-center retrospective study

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Abstract

Objectives: To evaluate the effectiveness and safety of the combination of beraprost sodium (BPS) and aspirin in patients with acute ischemic stroke (AIS).

Methods: There were 384 patients with AIS enrolled in this single-center, retrospective study. The BPS group comprised patients who received combination therapy with BPS and aspirin, and the control group comprised those who received only aspirin. Primary measurements were glomerular filtration rate (GFR), cystatin-c (Cys-C), National Institute of Health Stroke Scale (NIHSS) score, modified activities of daily living index (MBI), modified Rankin scale (mRS), and blood coagulation indexes. Recurrence and adverse events were recorded.

Results: There were no significant differences in patient characteristics at baseline between the two groups. GFR and Cys-C levels increased in the BPS group compared with the control group. After treatment, the NIHSS and mRS score were significantly lower in the BPS group compared with the control group, whereas the MBI scores were significantly higher in the BPS group compared with the control group. There was no significant difference in blood coagulation between the two groups. There were no serious adverse events in either group.

Conclusions: Combination therapy with BPS and aspirin may be a safe and effective treatment for AIS.

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Keywords

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Introduction

Stroke is the primary cause of acquired disability in adults and the second leading cause of death worldwide.^{1–3} Acute ischemic stroke (AIS) accounts for 60%–80% of stroke in patients, and it is associated with a high rate of morbidity, disability, and mortality.⁴ The annual incidence and overall prevalence of AIS continue to increase and it remains a leading cause of long-term disability. It is estimated that the incidence of AIS in China will increase at a rate of 8.7% per year over the next 30 years.⁵ Thus, timely and efficient treatment of AIS should be a priority for clinicians.

Intravenous thrombolysis of recombinant tissue plasminogen activator (rtPA) is currently the main treatment for AIS patients. The optimal time window for rtPA thrombolysis is within 3 to 4.5 h after AIS onset.⁶ If the optimal time for thrombolytic therapy is exceeded, or if patients also have thrombolytic contraindications, anticoagulant treatment can only be performed using aspirin or clopidogrel.⁷ However, anticoagulant treatment remains controversial. Currently, there is no consensus on the anticoagulant selection or strength, and on the route of administration or course of treatment in each country's national guidelines. Additionally, the most commonly used anticoagulant drugs, such as aspirin and clopidogrel, have only limited therapeutic efficacy and they are associated with a risk of intracranial hemorrhage.⁸ Thus, for many patients with AIS, adding an oral therapeutic agent that could further

decrease AIS symptoms and reduce adverse reactions is required.

Beraprost sodium (BPS) is a chemically stable and orally active prostaglandin I₂ (PGI₂) analogue.⁹ It has several biological activities, such as vasodilation effects, antiplatelet effects, and cytoprotective effects on endothelial cells.¹⁰ BPS has shown outstanding curative effects in pulmonary hypertension,⁹ intermittent claudication,¹¹ and lower extremity arterial occlusive disease.¹² Additionally, a previous study has demonstrated that BPS can protect against the development of stroke and renal damage in stroke-prone rats.¹³ Further clinical research by Nakayama et al.¹⁴ suggested that long-term administration of BPS reduces arterial stiffness and prevents the decline in arterial biomechanics in older adult patients with cerebral infarction. Based on the above description of BPS biological activities, we hypothesized that combination therapy with BPS and aspirin may exert a beneficial action for patients with AIS. To the best of our knowledge, few studies have investigated the effectiveness and safety of BPS in the treatment of AIS. In this study, we evaluated the effectiveness and safety of the combination of BPS and aspirin in patients with AIS.

Patients and methods

Patients

This single-center retrospective study enrolled 384 patients from the Neurology

Department in the First Affiliated Hospital of Shantou University Medical College. Patients were eligible for enrollment if they were 18 years of age or older and had a clinical diagnosis of AIS with an onset within the previous 72 hours. All patients were diagnosed with large-artery atherosclerosis (LA) and small artery occlusion lacunar (SA) based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and received antiplatelet therapy (BPS or aspirin treatment). The exclusion criteria were as follows: (1) coagulation disorder; (2) hemorrhage in the digestive tract or other parts of the body; (3) severe liver and renal insufficiency; (4) malignant tumor or trauma; or (5) history of surgery. The study was approved by the First Affiliated Hospital of Shantou University Medical College Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Treatment

Based on the treatment schedule, patients with AIS were divided into a BPS group ($n=200$) and a control group ($n=184$). Patients in the BPS group were treated with 40 μg BPS three times daily and 100 mg aspirin once daily for 18 months. Patients in the control group were treated with 100 mg of aspirin once daily for 18 months. All patients were administered aspirin within 72 hours after AIS onset. In addition to the antiplatelet treatment, conventional therapy was performed among patients in both groups based on the disease condition, including lipid regulation (40 mg of atorvastatin, once daily), free radical scavenging, blood pressure regulation with 0.15 g irbesartan once daily as appropriate, improvement of collateral circulation, and neurotrophic and brain protection treatment. The antiplatelet therapy lasted

6 months for each patient after hospital discharge.

Outcome and clinical assessment

For the effectiveness analysis, we included all patients with baseline data who had started any treatment and had undergone any post-treatment assessment (Table 1). The following data were collected for each patient: age, sex, and the levels of serum creatinine (Cr) and cystatin-c (Cys-C) measured at admission, 3 months, 6 months, and 1 year. Renal function was evaluated by the glomerular filtration rate (GFR) and Cys-C levels. The GFR was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation: $\text{GFR (mL/min/1.73 m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ female})$.

The levels of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fib), and the international normalized ratio (INR) were measured or calculated to evaluate blood coagulation. Neurological function was assessed based on the total National Institute of Health Stroke Scale (NIHSS) score. Additionally, the modified activities of daily living index (modified Barthel Index, MBI) and modified Rankin scale (mRS) were used to account for the functional abilities and disabilities in stroke patients. Adverse reactions and recurrence were also recorded. Patients were followed for 1 year after their anticoagulant treatment.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics 21.0 (SPSS Inc., IBM Corp, Armonk, NY, USA). Quantitative data are presented as the mean \pm standard deviation (SD). Qualitative data are described by a number or percentage. The quantitative data were tested using the

Table 1. Baseline Patient Characteristics.

Characteristic	BPS group (n = 200)	Control group (n = 184)	<i>p</i>
Age (years)	64.94 ± 10.18	63.08 ± 9.17	0.06
Gender (male/female)	127/73	113/71	0.68
TOAST classification (LA/SA)	163/37	154/30	0.59
History (NO)			
Hypertension	148	147	0.89
Diabetes	98	75	0.62
Heart disease	52	37	0.15
Blood lipids			
TC (mmol/L)	5.23 ± 1.35	5.43 ± 0.73	0.07
TG (mmol/L)	1.63 ± 1.15	1.84 ± 1.81	0.17
LDL (mmol/L)	3.17 ± 0.94	3.25 ± 0.94	0.41
HDL (mmol/L)	1.12 ± 0.27	1.15 ± 0.37	0.27
NIHSS score	5.11 ± 4.79	5.59 ± 4.31	0.30
ADL	61.30 ± 26.10	59.59 ± 27.29	0.53
mRS	3.14 ± 1.36	3.17 ± 1.36	0.779

LA, large-artery atherosclerosis; SA, small-artery occlusion lacunar; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NIHSS, National Institute of Health Stroke Scale; ADL, activities of daily living index; mRS, modified Rankin scale.

Kolmogorov–Smirnov test. Differences at baseline between groups were analyzed using the Pearson χ^2 test on categorical data and the independent sample student's *t*-test on continuous variables. Non-normally distributed variables were described by the mean and quartiles, and analyzed using the nonparametric Wilcoxon rank-sum test. Serial changes in quantitative variables were evaluated using a repeated-measures two-way analysis of variance (ANOVA), followed by a paired Student's *t*-test with the Bonferroni correction. A *p* value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

The baseline patient characteristics are presented in Table 1. Among the 384 patients with AIS who were enrolled in this study, 200 patients were treated with BPS and aspirin, and 184 patients were treated with

aspirin. The average age was 64.94 ± 10.18 years in the BPS group and 63.08 ± 9.17 years in the control group. No significant difference in age, sex, TOAST classification, AIS risk factors, NIHSS score, MBI score, or mRS score at admission was found between the two groups.

Renal function during follow-up

At baseline, no significant difference in the GFR and Cys-C was found between the two groups. During follow-up, the repeated-measures ANOVA showed a significant between-group difference in GFR, while there was a significant increase of the GFR levels in the BPS group over time (group: *p* < 0.001, time: *p* = 0.001, Figure 1a). However, the GFR level in the control group decreased significantly over time. Pairwise comparisons at each time point indicated a significantly higher GFR in the BPS group (*p* < 0.001). After treatment, the Cys-C level in the BPS group was significantly higher compared with the

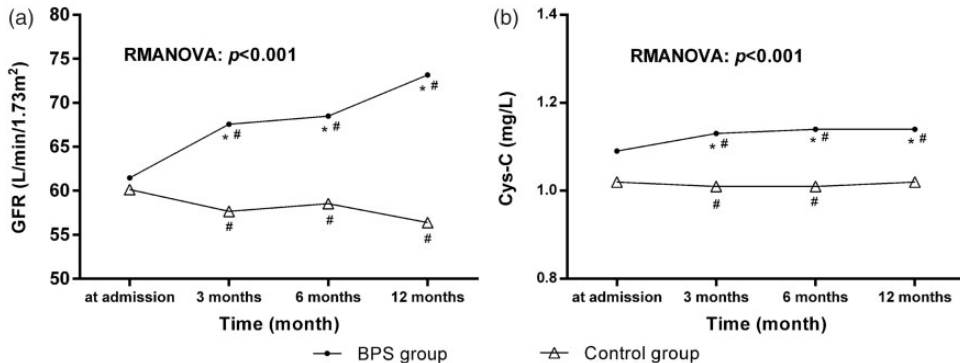


Figure 1. Renal function evaluated by the GFR and Cys-C levels. a) Changes in GFR levels during the follow-up period. b) Changes in Cys-C levels during the follow-up period. * $p < 0.05$ vs. control group; # $p < 0.05$ vs. at admission. GFR, glomerular filtration rate; Cys-C, cystatin-c; RMANOVA, repeated-measures analysis of variance.

control group ($p < 0.001$, Figure 1b), and the Cys-C level in the BPS group increased significantly compared with baseline ($p < 0.001$).

Neurological function, functional abilities, and prognosis during follow-up

For the NIHSS score, there was no significant difference between the two groups at baseline (BPS group, 5.11 ± 4.79 vs. control group, 5.59 ± 4.31). The repeated-measures ANOVA showed a significant between-group difference in the NIHSS score, while the NIHSS score in both groups decreased significantly over time during the study period (group: $p < 0.001$, time: $p = 0.001$, Figure 2a). Pairwise comparisons of the NIHSS score at each time point indicated a significantly larger reduction for the BPS group compared with the control group ($p < 0.001$). Additionally, distribution of the NIHSS scores was different at 6 months (Figure 2b). As shown in Figure 2b, 56.0% and 37.5% of the patients who had no stroke symptoms (NIHSS score < 1) were found in the BPS group and control group, respectively ($p < 0.001$). Only

0.5% of the patients had a severe stroke in the BPS group, which indicates a good outcome in the BPS group.

For the functional ability, there was no significant difference in MBI between the two groups at baseline (BPS group, 61.30 ± 26.10 vs. control group, 59.59 ± 27.29). After treatment, the MBI of the BPS group increased significantly compared with baseline (89.51 ± 18.02 , $p < 0.001$), while the MBI of the control group increased to 65.41 ± 30.82 ($p < 0.001$). A significant difference was detected between the two groups after treatment ($p < 0.001$). The distribution of the MBI was different at 6 months (Figure 3a). Figure 3a shows that 53.5% of patients in the BPS group showed complete recovery of the basic activities of daily living (MBI score of 100), while this number was 6.0% in the control group ($p < 0.001$).

For mRS, there was no significant difference between the two groups at baseline (BPS group, 4.00 [2.00–4.00] vs. control group, 4.00 [2.00–4.00]). After treatment, the mRS score in the BPS group decreased significantly at 6 months compared with baseline (1.00 [0.00–2.00], $p < 0.001$);

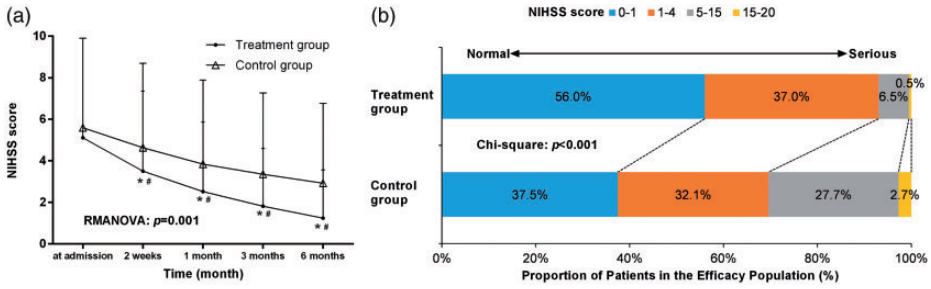


Figure 2. Neurological function evaluated by the NIHSS score. a) Changes in the NIHSS score during follow-up. b) Distribution of the NIHSS scores in the two groups at 6 months. * $p < 0.05$ vs. control group; # $p < 0.05$ vs. at admission. NIHSS, National Institute of Health Stroke Scale; RMANOVA, repeated-measures analysis of variance.

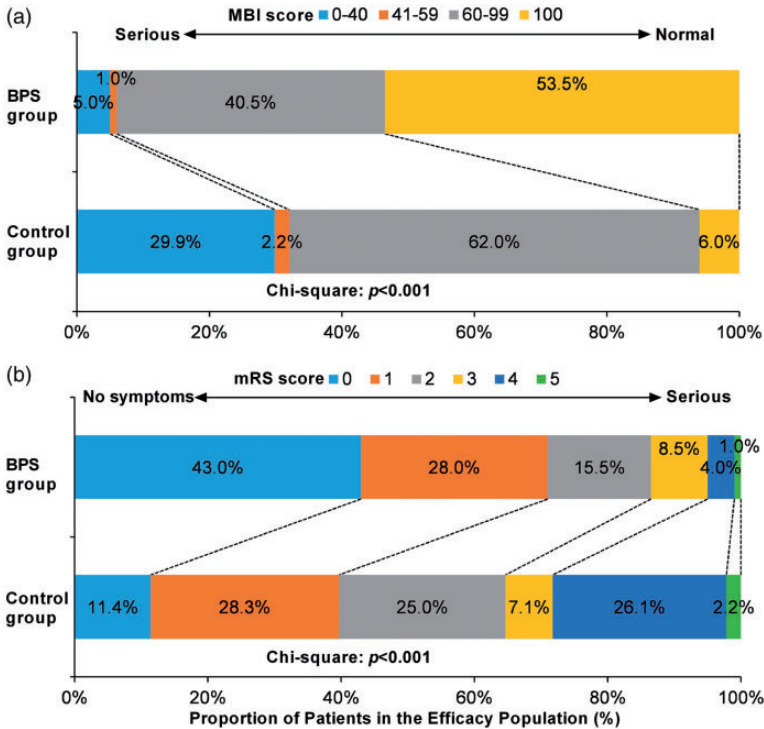


Figure 3. Functional abilities and prognosis during follow-up. a) Distribution of MBI in the two groups at 6 months. b) Distribution of the mRS scores in the two groups at 6 months. MBI, modified Barthel Index; mRS, modified Rankin scale.

similarly, it decreased significantly compared with baseline in the control group (2.00 [1.00–3.00], $p < 0.001$). There was a significant difference between the two groups

after treatment ($p < 0.001$). A favorable outcome (mRS score 0 or 1) was seen in 71% of patients in the BPS group and 39.7% in the control group ($p < 0.001$, Figure 3b).

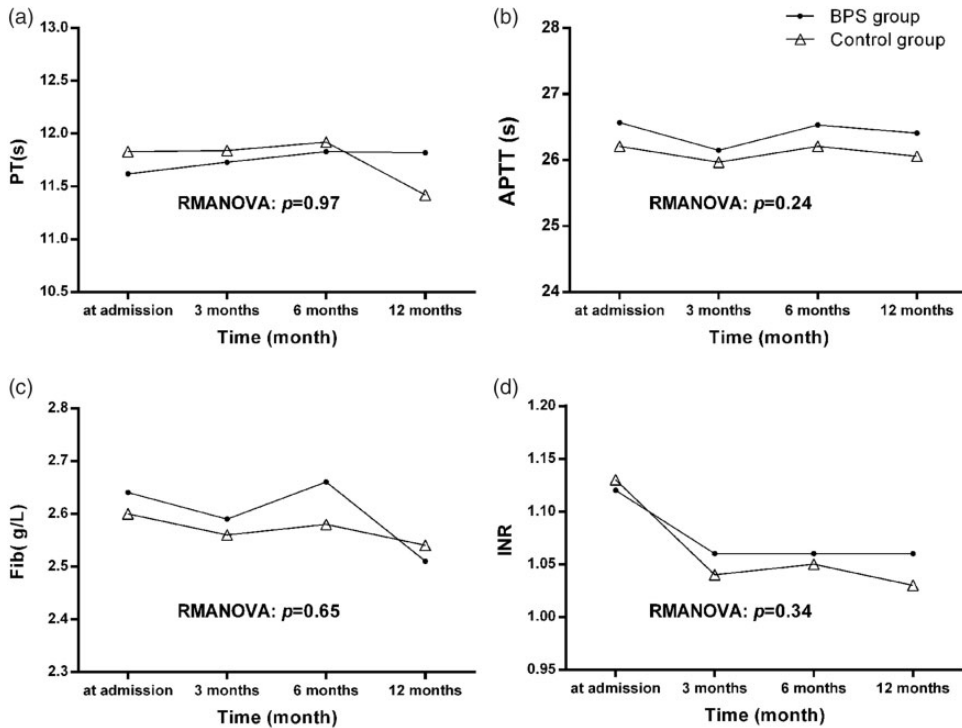


Figure 4. Function of the coagulation system assessed by PT, APTT, Fib, and INR. PT, prothrombin time; APTT, activated partial thromboplastin time; Fib, fibrinogen levels; INR, international normalized ratio; RMANOVA, repeated-measures analysis of variance

Blood coagulation during follow-up

During the follow-up period, the function of the coagulation system was assessed using the levels of PT, APTT, Fib, and INR. The result from the repeated-measures ANOVA showed no significant between-group difference in each index (PT, Figure 4a; APTT, Figure 4b; Fib, Figure 4c; INR, Figure 4d).

Recurrence and adverse events

During the 1-year follow-up period, there was no significant difference in the ischemic stroke recurrence between the two groups (BPS group, 16 [8%] patients vs. control group, 23 [12.5%] patients). No patient experienced serious adverse events in the two groups. There were four cases of mild

facial flushing and one case of mild gastrointestinal reaction in the BPS group, which all resolved soon by interrupting the medication and treating the symptoms. There were no adverse events in the control group.

Discussion

BPS, an orally active PGI₂ analogue with vasodilation and antiplatelet effects, has been confirmed to be beneficial in the treatment of cerebral infarction in older adult patients.¹⁴ Aspirin as an antiplatelet drug has also showed good outcomes in the treatment and secondary prevention of ischemic stroke.¹⁵ Although previous studies have verified that monotherapy with BPS or aspirin has a preventive effect on disease progression in patients with

AIS,^{1,15,16} the curative effect of combination therapy using BPS and aspirin has not been fully elucidated. Thus, for the first time, we evaluated the effectiveness and safety of this combination therapy with BPS and aspirin in patients with AIS. Our findings suggest that BPS can improve the neurological function and renal dysfunction caused by aspirin, and also improve the activities of daily living, while not negatively affecting coagulation disorders or causing serious adverse events.

Aspirin is a cyclooxygenase inhibitor, which can inhibit prostaglandin production in the kidney and reduce renal blood flow and GFR.^{17,18} Patients with long-term renal dysfunction are at a higher risk for adverse cardiovascular outcomes and they receive less aggressive treatment.^{19,20} Therefore, renal dysfunction caused by aspirin should be avoided as much as possible. Previous animal experiments have reported that BPS increased the serum creatinine level and prevented the reduction in the renal filtration rate, thereby ameliorating the decreased renal function.^{21,22} Thus, renal function was selected as a primary index of our study. GFR and Cys-C were measured to assess whether BPS improved renal function. Serum Cys-C, a simple, accurate, and rapid endogenous marker of GFR, is generally considered superior to serum creatinine as a marker of kidney function,²³ so it was also used as an evaluation index in our study. Our results showed that GFR and Cys-C levels in AIS patients after BPS treatment were significant higher compared with the control group, indicating that the combination therapy of BPS and aspirin could compensate for the aspirin-induced reduction of endogenous prostaglandin and alleviate renal dysfunction caused by aspirin. One possible explanation is that BPS suppresses serum uremic toxin accumulation and protects endothelial cells via the cyclic adenosine monophosphate mechanism, thereby

ameliorating the decreased renal function. This mechanism was shown in glomerulonephritis and chronic kidney disease (CKD) rats by Yamaguchi et al.²¹ Additionally, the renoprotective effect of BPS has also been shown in other animal models of CKD, which further explained the possible mechanism of BPS.^{22,24,25} BPS improved renal function by inhibiting inflammatory factor expression, apoptosis in renal microvascular endothelial and tubular epithelial cells, and tubulointerstitial fibrosis.^{26,27} Koyama et al.²⁸ also confirmed the clinical effect of BPS in preventing renal dysfunction in CKD patients in a randomized clinical trial. Thus, these findings further support the hypothesis that BPS might alleviate the decline in renal function caused by aspirin.

Our findings suggested that BPS can improve neurological function and the patient's quality of life. On the one hand, the beneficial effect of BPS on neurological function may be attributed to its antiplatelet and vasodilating effects. BPS was shown to have strong anti-platelet activity, including reduction in platelet aggregation and blockade of platelet adhesion.²⁹ Therefore, BPS was usually used to maintain vascular access patency and thus play a role in neural protection. On the other hand, BPS as a PGI₂ analogue may provide valuable protection for neurons by protecting the brain against neuronal damage produced by ischemia–reperfusion injury.^{30,31} High PGI₂ levels were reported to protect the brain from injury by regulating collateral blood flow through vascular endothelium G protein-coupled prostacyclin (IP) receptors.³² Thus, we speculate that exogenous BPS may be involved in adjusting the neurological function by increasing the level of endogenous substances such as PGI₂, or acting on other corresponding receptors. However, the exact mechanism is still unclear, and all these assumptions remain to be confirmed.

Although aspirin has been widely used to treat patients with ischemic stroke, it was reported to be associated with an increased risk of hemorrhagic stroke.¹⁶ To avoid the risk of hemorrhage caused by BPS, we evaluated blood coagulation after treatment. The results showed that BPS did not affect the coagulation function or increase the risk of bleeding, indicating that BPS will not cause additional risks and adverse effects in stroke patients. Similarly, previous animal experiments also confirmed that BPS prolonged bleeding time in mice, while not affecting the blood coagulation system.³³ This phenomenon might result from the favorable hemodynamic effects of BPS in patients. BPS is likely to promote self-adaptive adjustments in arterial vessels based on the hemodynamic conditions, and thus, favorable hemodynamic characteristics such as coagulation function were maintained. Additionally, among the 384 patients in our study, no patient experienced serious adverse events and only a few patients showed slight facial blushing or a mild gastrointestinal reaction. Moreover, these adverse events were controllable and tolerable, without influencing the treatment. Overall, BPS can be considered to be a safe therapeutic drug for patients with AIS.

Although there are important discoveries that were revealed by these studies, there are also limitations. First, our study has an inherent limitation because of its single-center, non-randomized, and retrospective design; therefore, further prospective clinical trials are required. Second, the short treatment time and small sample size may lead to bias in our results, such as the large standard deviations. Thus, further studies with a larger sample size and long-term follow-up are required to verify our findings.

Conclusion

Combination therapy with BPS and aspirin may be a safe and effective treatment for

patients with AIS because it can improve renal and neurological function while not increasing the risk of bleeding and adverse events after BPS treatment. However, further studies with a larger sample size and long-term follow up are required.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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