Article

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Efficacy and Prognosis of Adjuvant Argatroban Treatment in Acute Ischemic Stroke Patients with Early Neurological Deterioration

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Background: The therapeutic outcomes for acute ischemic stroke (AIS) with early neurological deterioration (END) are adverse. Argatroban is a novel direct thrombin inhibitor, which is safe in the treatment of AIS, but its efficacy is controversial. This study sought to assess the therapeutic effect of argatroban as an adjunct to aspirin in the treatment of AIS patients with END. Patients' prognosis for the presence of END was also evaluated.

Methods: Overall, 166 AIS patients with END were included in the study from June 2018 to June 2021 in The Affiliated Zhangjiagang Hospital of Soochow University. Patients were divided in the control group (aspirin alone) and the study group (aspirin combined with argatroban). General data of the patients were collected. Clinical indexes such as the modified Edinburgh-Scandinavian stroke scale (MESSS), and the serum fibrinogen (FIB) and neuropeptide Y (NPY) levels before and after treatment were also collected. Correlations between prognosis and general data, and FIB and NPY levels in AIS patients with END were analyzed by multivariate logistic regression. The performance of FIB and NPY levels in predicting patients' prognosis was further analyzed using receiver operating characteristic (ROC) curves.

Results: There was no significant difference in the general data, such as sex, age, course of disease and basic diseases between the 2 groups. After treatment, the MESSS score (13.08 $\pm$ 3.24 vs. 16.48 $\pm$ 3.32, $p < 0.001$), serum FIB level (2.72 $\pm$ 0.81 vs. 3.52 $\pm$ 0.71, $p < 0.001$), and NPY level (121.28 $\pm$ 17.34 vs. 152.09 $\pm$ 18.25, $p < 0.001$) of the study group was significantly lower than that of the control group. A further analysis revealed that the serum FIB (OR, odds ratio = 2.296, 95% confidence interval, CI: 1.437–3.669, $p = 0.001$) and NPY (OR = 1.020, 95% CI: 1.002–1.039, $p = 0.031$) levels were independent risk factors of patients' prognosis for the presence of END.

Conclusions: Aspirin combined with argatroban significantly improved neurological impairment of AIS patients with END, which is worthy of clinical application.

Keywords: acute ischemic stroke (AIS); argatroban; aspirin; early neurological deterioration; prognosis

Introduction

Stroke, also known as a "cerebrovascular accident", is an acute cerebrovascular disease. Stroke is a consequence abnormal blood flow to the brain caused by the rupture or obstruction of brain blood vessels, which induces a series of brain tissue damage [1]. This disease is a major contributor to global mortality and disability [1]. In 2010, there were 11.6 million patients with ischemic stroke (IS) worldwide [2]. In 2017, 9.5 million new IS cases and 2.7 million IS-related deaths were reported [2]. Acute IS (AIS) is the most common manifestation of IS, and accounts for 70–80% of IS cases. AIS significantly increases the risk of death and permanent disability. Early neurological deterioration (END) is a frequent IS symptom [3]. However, therapeutic outcomes for AIS are not satisfactory.

Currently, AIS treatment focus on the following 3 aspects: (I) Dredging the occluded blood vessels and reperfusion of ischemic tissues in a timely manner, (II) optimizing collateral blood flow of the occluded vessels, and (III) avoiding secondary brain injury. Re-dredging and reperfusion are the primary AIS treatment strategies, they can effectively reduce the infarction size and reverse the neurological deficit [4]. Recombinant tissue plasminogen activator (also known as alteplase) and mechanical thrombectomy with retrievable stents are 2 evidence-based strategies for dredging occluded blood vessels [5]. All the existing treatments have been shown to have some therapeutic effects, but they may cause brain injury reperfusion and are not applicable to all patients. Thus, the treatment strategies for AIS need to be further optimized to reduce the risks.

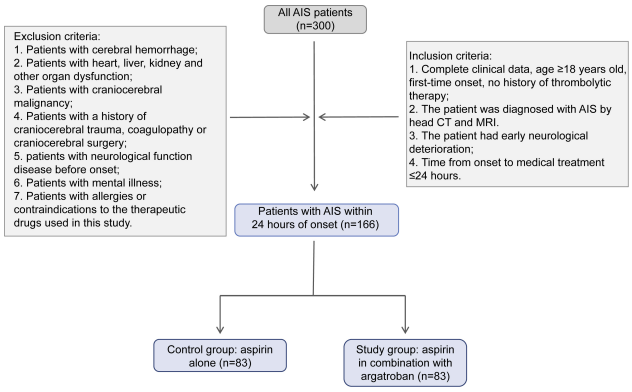

Fig. 1. Screening process for the included patients. AIS, acute ischemic stroke.

The use of antiplatelet therapy has been well documented in the treatment of stroke and secondary stroke prevention [6]. Clinically, aspirin is often used as an antiplatelet drug during the acute phase of stroke. Aspirin is used to prevent acute noncardioembolic IS or transient ischemic attack, for the long-term treatment of noncardioembolic cerebrovascular diseases, or for AIS patients who are not suitable for or do not need intravenous thrombolysis and mechanical thrombectomy. However, aspirin increases bleeding risk in patients and its efficacy is limited [7]. For this reason, most studies on ischemic diseases have focused on observing aspirin clinical efficacy and safety in combination with other drugs and have achieved some progress. Wang *et al.* (2013) [8] found that the therapeutic effect of clopidogrel combined with aspirin was better than that of aspirin alone to treat acute minor stroke or transient ischemic attack. The combination of both effectively reduced the risk of stroke within the first 90 days after stroke diagnosis without an increased bleeding risk [8]. Johnston *et al.* (2020) [9] observed that compared to aspirin alone, aspirin combined with ticagrelor significantly reduced the risk of the composite of stroke or death within 30 days for patients with acute noncardioembolic IS. Collectively, the combined use of aspirin and other drugs is an effective strategy for improving the therapeutic outcomes of AIS patients.

Argatroban is a selective thrombin inhibitor that effectively slows blood coagulation. It is mainly used to treat neurological symptoms, such as daily activity disorders, caused by ischemic cerebral infarction [10]. It can effectively bind to thrombin active site, thereby inhibiting fibrin formation, and protein C and coagulation factors V, VIII, and XIII activation. As argatroban does not induce antiplatelet antibodies production [11], it is often used to treat heparin-induced thrombocytopenia with or without thrombosis. A clinical study showed that argatroban significantly reduces the incidence and mortality with heparin-induced thrombocytopenia with or without thrombosis. Moreover, it is well tolerated by patients, and does not increase bleeding risk [12]. Besides, a few studies focusing on argatroban efficacy in the treatment of stroke have now been conducted. Liu *et al.* (2020) [13] found that when treating acute paraventricular IS patients based following American Heart Association guidelines, the conventional treatment combined use of argatroban significantly increased the basal vein Rosenthal drainage rate and improved patients' outcome after stroke. A meta-analysis reported that argatroban was not more effective than the conventional AIS treatment, but it did not increase bleeding risk [14]. Argatroban combined with dual antiplatelet therapy have a better therapeutic effect and higher safety than argatroban or dual antiplatelet therapy alone when treating AIS [15]. Chen *et al.* (2018) [16] reported that the combination of argatroban and aspirin significantly reduced the National Institutes of Health Stroke Scale scores of AIS patients, indicating the potential benefit of adjuvant argatroban in treating AIS. However, previous studies have not fully demonstrated argatroban effect on patients with AIS, argatroban efficacy is controversial.

We hypothesize that argatroban as adjuvant treatment compared with aspirin alone is more efficient in the treatment of AIS. Thus, a case control study was conducted to assess the effect of the combined use of argatroban and aspirin on the modified Edinburgh-Scandinavian stroke scale (MESSS) scores, and fibrinogen (FIB) and neuropeptide Y (NPY) levels of patients with AIS.

Methods

Study Subjects

The data of 300 AIS patients admitted at The Affiliated Zhangjiagang Hospital of Soochow University within 24 h of AIS onset from June 2018 to June 2021 were included in this study. Patients who were treated with aspirin combined with argatroban were included in the study group, while patients who were treated with aspirin alone were included in the control group. Patients' screening process flowchart is shown in Fig. 1. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) Have a complete clinical data, be aged $\geq$18 years, be suffering from the first AIS episode, and have no previous history of thrombolytic therapy and are not suitable for or do not need intravenous thrombolysis and mechanical thrombectomy, (II) have an AIS diagnosis confirmed by brain computed tomography (CT) and magnetic resonance imaging (MRI) (Figs. 2,3 list the MRI imaging of typical sequences of AIS caused by basilar artery stenosis and anterior circulation stenosis, respectively), (III) have END, (IV) have a time from onset to medical treatment that was $\leq$24 h. Patients were excluded from the study if they met any of the following exclusion criteria: (I) Had a cerebral hemorrhage confirmed by brain CT scan and MRI , (II) had heart, liver, kidney, or other organ dysfunction, (III) had a brain malignant tumor, (IV) had craniocerebral trauma and coagulation dysfunction, or had a history of craniocerebral

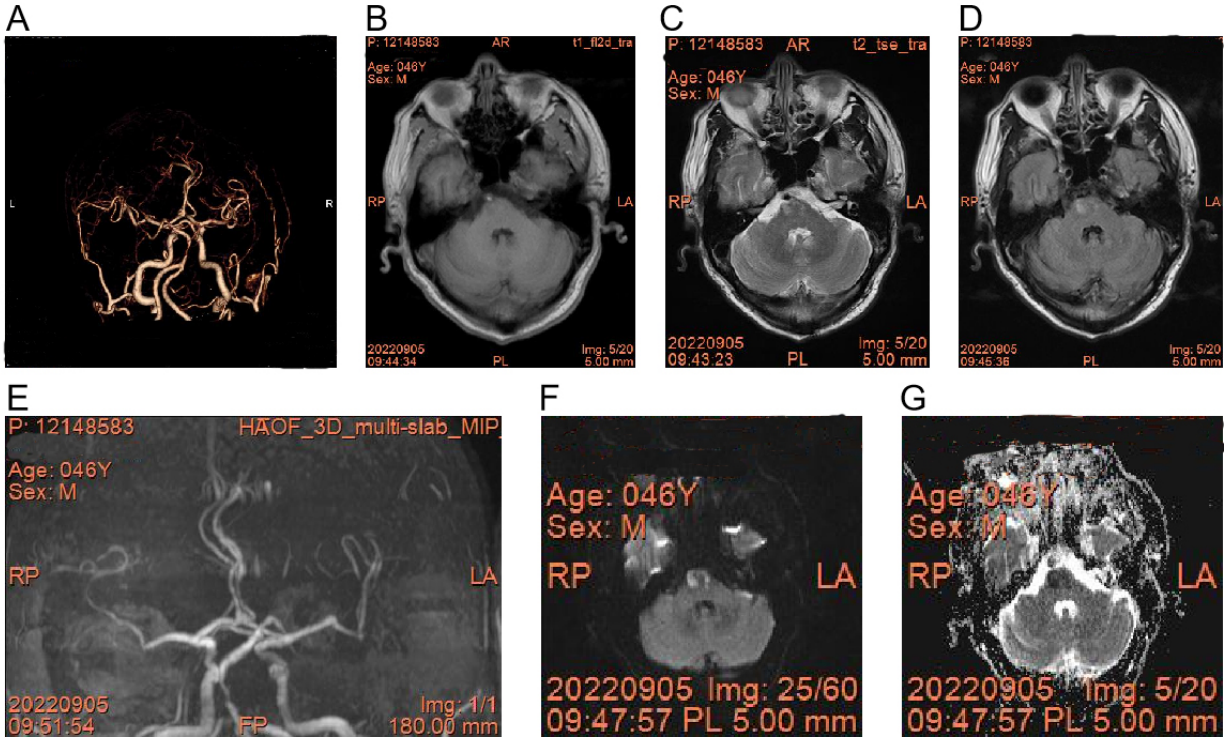

Fig. 2. MRI imaging of typical AIS sequences caused by basilar artery stenosis. (A) CTA diagram of basilar artery stenosis. (B) T1WI sequence of right brainstem infarction. (C) T2WI sequence of right brainstem infarction. (D) FLAIR sequence of right brainstem infarction. (E) TOF sequence of basilar artery stenosis. (F) DWI sequence of right brainstem infarction. (G) ADC sequence of right brainstem infarction. MRI, magnetic resonance imaging; AIS, acute ischemic stroke; CTA, computed tomography angiography; T1WI, T1 weighted image; T2WI, T2 weighted image; FLAIR, fluid attenuated inversion recovery; TOF, Time of Flight; DWI, diffusionweighted imaging; ADC, Apparent Diffusion Coefficient.

surgery, (V) had a neurological disorder before AIS onset, (VI) had a mental illness, and/or (VII) had an allergy to or contraindication to the therapeutic drugs used during study.

Intervention Measures

The treatment of the included patients was based on Chinese guidelines on the treatment for AIS. Patients in the control group were treated only with 100 mg aspirin (bj59012, Yonghe Pharmaceutical Co., Ltd., Zhengzhou, China) once per day. Patients in the study group were treated with 100 mg aspirin once daily + 60 mg of argatroban (2010091, Pharmaceutical Research Institute Pharmaceutical Co., Ltd., Tianjin, China) once daily for first 2 days followed by 10 mg of argatroban once daily [17]. Patients of both groups were treated on the day of admission and continued treatment for 2 weeks.

Data Collection

Patients' general data included sex, age, course of disease (in hours), and body mass index. Details of whether diabetes, hypertension, or coronary heart diseases complications, and the presence or absence of a large area of infarction were recorded. The infarction location (anterior circulation or posterior circulation) was also recorded.

MESSS Score

Patients' cerebral neurological deficit degree was evaluated by the MESSS score before and after treatment. MESSS items included consciousness, horizontal gaze, facial palsy, speech, upper limb muscle strength, hand muscle strength, lower limb muscle strength, and walking ability. The highest possible score was 45 points. A score of 0–15 points indicated minor neurological deficit, a score of 16–30 points indicated moderate neurological deficit, and a score of 31–45 points indicated severe neurological deficit.

FIB and NPY Levels in Serum

Before and after treatment, 5 mL of peripheral venous blood was drawn from patients after fasting 8 h. Blood was collected in coagulation promoting tubes for 20 min. After centrifugation (20 min, 4 °C, 2000 rpm), upper serum was taken and placed into new centrifuge tubes and stored at –80 °C. Serum FIB (SPS-17183) and NPY (SPS-14593) levels were determined using the enzyme-linked immunosorbent assay kit (SAIPEISEN biology, Shanghai, China) following manufacturer's instructions. Next, 10 μL of serum was taken and incubated in an enzyme plate for 30 min, and then, the corresponding horseradish peroxidase was added. Chemiluminescence reagent was added, and ab-

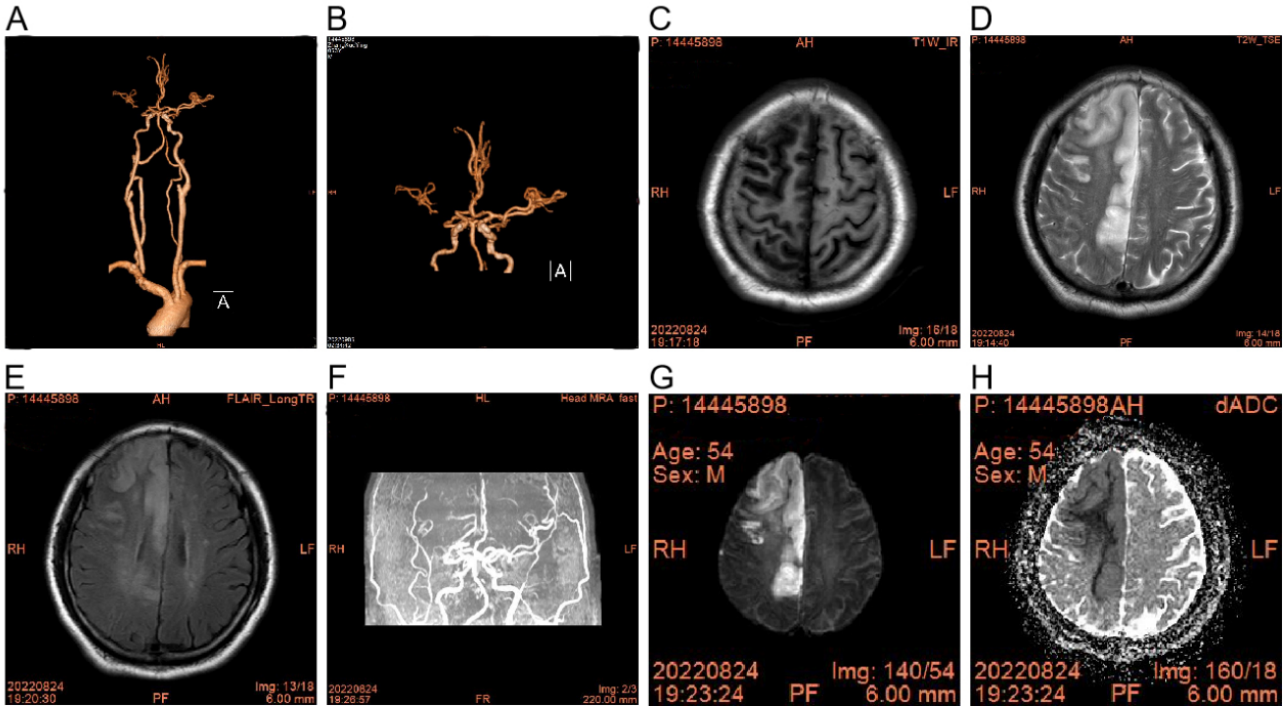

Fig. 3. MRI of typical AIS sequences caused by anterior circulation stenosis. (A) CTA of head and neck with stenosis of anterior circulation vessels. (B) CTA of right middle cerebral artery stenosis. (C) T1WI sequence of right cerebral hemisphere infarction. (D) T2WI sequence of right cerebral hemisphere infarction. (E) FLAIR sequence of right cerebral hemisphere infarction. (F) TOF sequence of right middle cerebral artery occlusion. (G) DWI sequence of right cerebral hemisphere infarction. (H) ADC sequence of right cerebral hemisphere infarction. MRI, magnetic resonance imaging; AIS, acute ischemic stroke; CTA, computed tomography angiography; T1WI, T1 weighted image; T2WI, T2 weighted image; FLAIR, fluid attenuated inversion recovery; TOF, Time of Flight; DWI, diffusion-weighted imaging; ADC, Apparent Diffusion Coefficient.

sorbance was tested at 450 nm, and the levels of FIB and NPY were calculated.

Statistical Analysis

All the data of this study were analyzed using Statistical Product and Service Solutions (SPSS) version 26.0 software (IBM Corp, Armonk, NY, USA). Enumeration data are expressed as the number (percentage), and chi-square test was used to test differences between the 2 groups in this type of data. Measurement data are expressed as mean $\pm$ standard deviation, and *t*-test was used to test differences between the 2 groups in this type of data. A multivariate logistic regression was used to determine the risk factors affecting the prognosis of AIS patients with END. The receiver operating characteristic (ROC) curve was used to evaluate the prognostic predictive value of FIB and NPY levels. $p < 0.05$ was considered statistically significant.

Results

Comparison of the General Data between the 2 Groups

A total of 166 patients (83 in the study group and 83 in the control group) were ultimately included in this study (Fig. 1). No hemorrhage adverse events were observed in the treated patients. All these patients were followed up during the treatment. In the study group, there were 46 (55.4%) male patients and 37 (44.6%) female patients, with an age range of 43–64 years and an average age of age of 56.24 ± 4.12 years. The course of disease in the study group was 6–9 h with an average of 7.02 ± 0.87 h. In the control group, there were 39 (47.0%) male patients and 44 (53.0%) female patients, with an age range of 46–66 years and an average age of 55.83 ± 3.94 years. The course of disease in the control group was 5–8 h with an average of 7.08 ± 0.72 h. There were no significant differences in terms of the sex, age, and course of disease between the 2 groups ($p > 0.05$). In addition, there were no significant differences in the 2 groups in terms of body mass index, complicated diabetes, complicated hypertension, complicated coronary heart disease, infarction location (anterior circulation or posterior circulation), and large infarction area (all yes or no except body mass index) (all $p > 0.05$, Table 1). In short, there was no difference in the general data between the 2 groups, and thus subsequent comparisons of the 2 groups could be conducted.

Table 1. Comparison of the general data between the 2 groups.

Details	Control group (n = 83)	Study group (n = 83)	χ^2/t	p
Sex (%)			1.181	0.277
Male	39 (47.0)	46 (55.4)		
Female	44 (53.0)	37 (44.6)		
Age (years)	55.83 ± 3.94	56.24 ± 4.12	0.655	0.514
Course of disease (h)	7.08 ± 0.72	7.02 ± 0.87	–0.486	0.627
Body mass index (kg/m^2)	23.56 ± 2.25	23.67± 1.92	0.341	0.734
Complicated diabetes (%)			0.869	0.351
No	62 (74.7)	67 (80.7)		
Yes	21 (25.3)	16 (19.3)		
Complicated hypertension (%)			1.186	0.276
No	66 (79.5)	60 (72.3)		
Yes	17 (20.5)	23 (27.7)		
Complicated coronary heart disease (%)			2.604	0.107
No	72 (86.7)	64 (77.1)		
Yes	11 (13.3)	19 (22.9)		
Infarction location (%)			1.226	0.268
Anterior circulation	46 (55.4)	53 (63.9)		
Posterior circulation	37 (44.6)	30 (36.1)		
Large area infarction (%)			0.481	0.488
No	62 (74.7)	58 (69.9)		
Yes	21 (25.3)	25 (30.1)		

Data is presented as count (percentage) or mean ± SD.

Table 2. Changes in the MESSS scores, and FIB and NPY levels before and after treatment in the 2 groups.

Details	Group	Case (n)	MESSS	FIB	NPY
Before treatment	Control group	83	18.60 ± 3.58	4.75 ± 1.11	196.93 ± 24.94
	Study group	83	18.29 ± 3.41	4.69 ± 1.05	198.44 ± 21.28
	t		–0.577	–0.387	0.419
	p		0.564	0.699	0.676
After treatment	Control group	83	16.48 ± 3.32*	3.52 ± 0.71*	152.09 ± 18.25*
	Study group	83	13.08 ± 3.24*	2.72 ± 0.81*	121.28 ± 17.34*
	t		–6.675	–6.803	–11.152
	p		<0.001	<0.001	<0.001

Data is presented as mean ± SD. *Denotes $p < 0.05$ vs. before treatment. MESSS, modified Edinburgh-Scandinavian stroke scale; FIB, fibrinogen; NPY, neuropeptide Y.

Changes in MESSS Scores and FIB and NPY Levels before and after Treatment in the 2 Groups

As Table 2 shows, there was no significant difference in MESSS scores (18.29 ± 3.41 vs. 18.60 ± 3.58) between the 2 groups before treatment ($p > 0.05$) (Table 2). However, after treatment, MESSS scores of both groups were lower than those before treatment ($p < 0.05$). Further, MESSS score of the study group after treatment were significantly lower than those of the control group (13.08 ± 3.24 vs. 16.48 ± 3.32) ($p < 0.05$). Similarly, before treatment, FIB (4.69 ± 1.05 vs. 4.75 ± 1.11) and NPY (198.44 ± 21.28 vs. 196.93 ± 24.94) levels were similar between groups ($p > 0.05$). However, after treatment, FIB and NPY levels of both groups decreased significantly ($p < 0.05$). FIB (2.72 ± 0.81 vs. 3.52 ± 0.71) and NPY (121.28 ± 17.34 vs. 152.09 ± 18.25) levels of the study group were significantly lower than those of the control group ($p < 0.05$).

Multivariate Logistic Regression Analysis of the Risk Factors Affecting the Prognosis of AIS Patients with the Presence of END

To examine the risk factors affecting the prognosis of AIS patients with the presence of END, a multivariate logistic regression analysis was conducted with general characteristics, or the serum FIB and NPY levels as dependent variables (Table 3). Univariate analysis showed that FIB levels [odds ratio (OR) = 2.946, 95% confidence interval (CI): 1.890–4.593, $p < 0.001$] and NPY levels (OR = 1.034, 95% CI: 1.018–1.051, $p < 0.001$) were associated with END in AIS patients. Multivariate analysis showed that FIB (OR = 2.296, 95% CI: 1.437–3.669, $p = 0.001$) and

Table 3. Univariate analysis of risk factors affecting patients' prognosis.

Details	*B*	*S.E*	*Wald*	OR (95% CI)	*p*
Sex	0.383	0.319	1.445	1.467 (0.785–2.739)	0.229
Age	0.018	0.040	0.211	1.018 (0.942–1.101)	0.646
Course of disease	0.298	0.203	2.169	1.348 (0.906–2.005)	0.141
Body mass index	0.140	0.076	0.032	1.014 (0.873–1.177)	0.858
Complicated diabetes	0.185	0.378	0.241	1.204 (0.574–2.525)	0.623
Complicated hypertension	0.285	0.367	0.602	1.330 (0.648–2.729)	0.438
Complicated coronary heart disease	0.102	0.412	0.001	1.012 (0.452–2.269)	0.976
Infarction location	–0.172	0.325	0.280	0.842 (0.446–1.591)	0.596
Large area of infarction	0.089	0.353	0.063	1.093 (0.547–2.183)	0.801
FIB	1.081	0.227	22.757	2.946 (1.890–4.593)	<0.001
NPY	0.034	1.162	19.260	1.034 (1.018–1.051)	<0.001

FIB, fibrinogen; NPY, neuropeptide Y; OR, odds ratio; CI, confidence interval.

Table 4. Multivariate analysis of risk factors affecting patients' prognosis.

Details	*B*	*S.E*	*Wald*	OR (95% CI)	*p*
FIB	0.841	0.239	12.389	2.296 (1.437–3.669)	0.001
NPY	0.022	0.009	6.097	1.020 (1.002–1.039)	0.031

FIB, fibrinogen; NPY, neuropeptide Y; OR, odds ratio; CI, confidence interval.

Table 5. Evaluation of FIB and NPY predictive value.

Details	AUC	95% CI	*p*	Sensitivity (%)	Specificity (%)
FIB	0.731	0.651–0.812	<0.001	74.2	70.0
NPY	0.710	0.630–0.789	<0.001	78.8	64.0

FIB, fibrinogen; NPY, neuropeptide Y; AUC, area under the curve; CI, confidence interval.

NPY levels (OR = 1.020, 95% CI: 1.002–1.039, $p = 0.031$) were independent risk factors for neurological deficit in patients with AIS (Table 4).

Value of Serum FIB and NPY Levels to Predict END in Patients with AIS

The performance of the serum FIB and NPY levels in predicting END risk in patients with AIS was analyzed using ROC curves. The area under curve (AUC) of serum FIB (AUC = 0.731) and NPY (AUC = 0.710) levels to predict END in patients with AIS were >0.700 (Fig. 4), indicating that the FIB and NPY levels had moderate predictive value. The AUC of the serum FIB level for predicting the risk of END was 0.731 (95% CI: 0.651–0.812) with a sensitivity of 74.2% and a specificity of 70.0%, while the AUC of the serum NPY level for predicting the risk of END was 0.710 (95% CI: 0.630–0.789) with a sensitivity of 78.8% and a specificity of 64.0%, which indicated that the predictive performance of the serum FIB levels was superior to that of the NPY levels (Table 5).

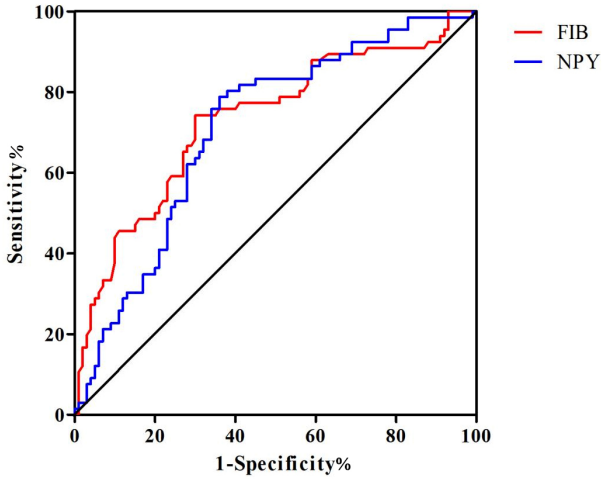

Fig. 4. ROC curve analysis of the FIB and NPY levels predicting the risk of neurological deficit aggravation in patients with AIS. FIB, fibrinogen; NPY, neuropeptide Y; ROC, receiver operating characteristic curve.

Discussion

Those patients who received the combined treatment of argatroban, and aspirin had lower MESSS scores, serum FIB and NPY levels compared to those patients that were treated with aspirin only. In China, MESSS is the most commonly used criteria for scoring neurological deficit degree in stroke patients [18]. The higher the MESSS score, the more severe the injury. The results of this study indicate that argatroban combined with aspirin protective effect on the neurological function of AIS patients was better than that of aspirin alone. These results may provide the basis for the clinical use of argatroban-assisted aspirin to treat AIS.

FIB is a major factor determining blood viscosity and platelet activity. It is involved in the pathophysiology of platelet aggregation, blood coagulation, and inflammation [19]. You *et al.* (2017) [20] showed that FIB levels increased gradually in the first 24 h after AIS onset. A high

level of FIB is associated with poor patient outcomes [20]. NPY is a 36 amino acid peptide neurotransmitter, which is abundantly produced and expressed in the mammalian nervous system [21]. Recent studies have indicated that serum NPY level is associated with the risk of cognitive impairment and epilepsy after IS [22,23]. In this study we found that after treatments, serum FIB and NPY levels of both groups decreased, but this effect was significantly enhanced in the study group compared to the control group. No previous study has shown the relationship between AIS prognosis and FIB and NPY levels after the combined treatment of argatroban and aspirin. The logistic regression analysis also showed that FIB and NPY levels were independent risk factors for neurological impairment. Further, the ROC curve analysis demonstrated that serum FIB and NPY levels have potential as prognostic predictors. FIB levels showed better predictive efficacy than NPY levels.

Previous studies on the use of argatroban in AIS used National Institutes of Health Stroke Scale (NIHSS) score [16,24]. To our knowledge, no correlation study has used MESSS score to evaluate the effect of argatroban in the treatment of AIS. As MESSS score is also an important index to evaluate the neurological deficit degree of stroke patients, our study overcame the limitations associated to the use of NIHSS score. Argatroban has been already proved safe in the treatment of AIS in line to the safety analysis provided in this study. However, the effect of adjuvant argatroban has been controversial. Chen *et al*. (2018) [16] demonstrated that argatroban has no additional benefit on short-term outcomes compared to high-dose aspirin alone. A recent study reported that argatroban is safe but does not improve functional outcome at 90 days in Chinese patients with AIS treated with recombinant tissue-type plasminogen activator (r-tPA) [24]. A meta-analysis concluded that patients with AIS might not benefit from the combined therapy with argatroban [14]. In contrast, our study showed an opposite result. Adjuvant argatroban achieved a better therapeutic effect than aspirin alone in AIS patients with END.

Our study had a number of limitations. First, the sample size of this study was small, thus a study with a large sample size needs to be conducted to obtain more reliable results. Second, there were few observation indicators, a comprehensive assessment of the factors affecting AIS prognosis could not be conducted. Finally, we only evaluated the prognosis of AIS patients during hospitalization. Thus, a prospective, large sample size study with sufficient observation indicators, and a long-term follow-up period needs to be conducted in future.

Conclusions

The combined use of aspirin and argatroban achieved a better therapeutic effect than aspirin alone. Moreover, adjuvant argatroban treatment had a significant modulation effect on serum FIB and NPY levels in AIS patients with END. Our study could be used as the basis for clinical adjuvant argatroban treatment. However, given the limited samples size of this study, more studies with larger sample sizes need to be conducted to confirm the above conclusions.

Author Contributions

SX and TW—made substantial contributions to conception and design and been involved in drafting the manuscript and revising it critically for important intellectual content; WZ, YZ and ZX—acquisition of data, and analysis and interpretation of data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in compliance with the *Helsinki Declaration (as revised in 2013)* and were approved by the Ethics Committee of The Affiliated Zhangjiagang Hospital of Soochow University (No. 20180603). Since this study is retrospective, informed consent is not required.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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