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Original Article

Efficacy and safety of Agatroban in improving the prognosis of ischemic stroke patients

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Abstract: Objective: To explore and analyze the efficacy and safety of combined treatment of Agatroban and Aspirin in improving short-term and long-term prognosis of ischemic stroke patients. Methods: In this retrospective study, the clinical data of patients with ischemic stroke admitted to the Department of Neurology, Songjiang Sijing Hospital from June 2021 to April 2023 were analyzed. A total of 108 patients were selected according to the inclusion and exclusion criteria, including 54 patients treated with Aspirin only, named the control group, and 54 patients treated with Agatroban plus Aspirin, named the study group. Results: Compared with the control group, the study group had a higher effective rate (P=0.047). There was no significant difference in MIESSS and daily living ability scores between the two groups before treatment (P>0.05). After treatment, compared with the control group, the study group had a lower MIESSS score and a higher daily living ability score (P=0.035; P=0.044). There was no significant difference in coagulation indicators between the two groups before treatment (P>0.05). After treatment, compared with the control group, the study group had lower platelet count, fibrinogen, and D-dimer levels (P=0.031; P=0.042; P=0.047). There was no significant difference in inflammatory cytokines between the two groups before treatment (P>0.05). After treatment, compared with the control group, the study group showed significantly decreased tumor necrosis factor (TNF)-α, interleukin-6 (IL-6) and interleukin-8 (IL-8) (P=0.041; P=0.038; P=0.046). Compared with the control group, the incidence of adverse reactions in the study group was lower (P=0.033), while the prognosis was better (P=0.029; P=0.033; P=0.048). Conclusion: Compared with Aspirin alone, Argatroban plus Aspirin can optimize coagulation parameters to a greater extent and reduce the level of cellular inflammatory factors, further improve the body's neurological functions, remarkably reduce the occurrence of adverse prognosis, and enhance the patient's ability of daily living, with remarkable therapeutic effect.

Keywords: Argatroban, Aspirin, ischemic stroke, short-term and long-term prognosis, safety

Introduction

Stroke, as a type of neurological disease, has multiple disease characteristics, with ischemic stroke as the typical disease type [1]. Ischemic stroke is primarily caused by local brain tissue hypoxia and ischemic necrosis, generally manifested as limb disorders, confusion and other clinical symptoms. If the disease is not effectively controlled, it can cause serious consequences and even death. At present, the basic treatment principles include early prevention and diagnosis, in-time treatment, and early rehabilitation; however, adverse prognosis with high disability rate and high mortality are still common, posing great mental and economic pressure on patients and their families [2]. Coagulation dysfunction directly impacts the formation and recurrence of ischemic stroke disease. Therefore, anticoagulant therapy is a main treatment mode in clinical practice [3].

Still, the effect of Aspirin produced for the correction of coagulopathy is unsatisfactory and cannot meet the clinical needs [4]. On this basis, Argatroban, as a new anticoagulant drug, can reduce the incidence of adverse reactions and decrease inflammatory factors [5]. Some studies have explored the impact of Argatroban on the prognosis of ischemic stroke patients. For example, a large-scale randomized controlled trial showed that additional Argatroban can reduce the risk of recurrence of ischemic stroke, with insignificant impact on mortality and disability rates [6]. In addition, some small sample, single-center studies have also shown

that Argatroban may help improve the prognosis of ischemic stroke patients. In this retrospective study, we studied the efficacy and safety of the Agatroban in improving the short-term and long-term prognosis of patients with ischemic stroke.

Materials and methods

General data

The Ethics Committee of Shanghai Songjiang Sijing Hospital had approved this study. In this retrospective study, the clinical data of patients with ischemic stroke admitted to the Department of Neurology, Songjiang Sijing Hospital from June 2021 to April 2023 were analyzed. According to the inclusion and exclusion criteria, 108 patients were selected, including 54 patients treated with Aspirin only, named the control group, and 54 patients treated with Agatroban plus Aspirin, named the study group. There were 29 males and 25 females in the control group, aged between 38 to 70, with an average age of (54.0±2.9) years old. Among them, 22 cases were complicated with hypertension, 20 cases with diabetes, and 12 cases with abnormal lipid metabolism. There were 30 males and 24 females in the study group, aged between 39 to 70, with an average age of (54.5±2.4) years old. Among them, 23 cases were complicated with hypertension, 19 with diabetes, and 12 with abnormal lipid metabolism.

Inclusion criteria: (1) The patients treated with Agatroban combined with Aspirin or Aspirin alone; (2) The patients with acute ischemic stroke that were confirmed by head MRI examination; (3) The patients who did not receive arterial or venous thrombolytic therapy or intravascular therapy within 48 hours of onset; (4) The patients with NIHSS score >15; (5) The patients without contraindications to antithrombotic therapy.

Exclusion criteria: (1) The patients who had received arterial and intravenous thrombolysis and intravascular therapy; (2) The patients with a history of atrial fibrillation and oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, before admission; (3) The patients with severe cardiac, renal, or liver dysfunction; (4) The patients with evidence of active bleeding; (5) The patients with incomplete clinical data.

Methods

According to whether the patients were treated with Agatroban or not, 108 enrolled patients were divided into a study group (54 cases, Agatroban + Aspirin) and control group (54 cases, Aspirin only). Patients who did not meet thrombololytic or intravascular therapy were treated with antiplatelet drugs (aspirin, hydroclopidogrel, aspirin combined with hydroclopidogrel) as soon as possible.

The treatment regimen in the control group: ① Aspirin enteric-coated tablet 100 mg orally, once a day (Shanghai Shangyao Xinyi Pharmaceutical Factory Co., LTD., SinopOD Approval H31022424); ② Hydroclopidogrel tablet 75 mg orally, once a day (Sanofi (Hangzhou) Pharmaceutical Co., LTD., Sinopol H20056410). The treatment regimen of study group: ① Agatroban was continuously pumped 60 mg daily for 2 days, and then 10 mg was continuously pumped each time for 5 days, twice a day (Nanjing Zhengda Tianqing Pharmaceutical Co., LTD., National drug approval number H20193333); meanwhile, aspirin enteric-coated tablets were orally administered 100 mg each time, once a day; ② Agatroban 60 mg a day for 2 days, oral hydroclopidogrel 75 g, once a day; ③ Agatroban 60 mg a day for 2 days, and aspirin enteric-coated tablets for 2 days; and 100 mg each time, once a day, oral hydroclopidogrel tablets, 75 mg each time, once a day.

Outcome measures

Primary outcome measures: the incidence of adverse reactions and the prognosis. Secondary outcome measures: daily living ability, blood clotting indicators and cytokines were collected before and 21 days after treatment.

Clinical therapeutic effect [7]: Remarkably effective: symptoms such as impaired consciousness and stress ulcer disappeared; coagulation indicators, inflammatory factors, activities of daily living returned to normal. Effective: symptoms such as impaired consciousness and stress ulcer were improved by more than 75%; coagulation indicators and others were improved by more than 70%. Ineffective: the above indicators did not change remarkably. Overall response rate = remarkable rate + effective rate.

Table 1. Comparison of baseline data between the two groups

Cluster	No.	Gender (male/female)	age	Comorbidities		
				Hypertension	Diabetes mellitus	Abnormal lipid metabolism
Control group	54	29/25	54.0±2.9	22	20	12
Study group	54	30/24	54.5±2.4	23	19	12
X^2/t	/	5.147	17.255	6.024	5.836	5.725
P	/	0.053	0.058	0.069	0.063	0.001

Table 2. Comparison of therapeutic effect between the two groups (case, %)

Cluster	No.	Markedly effective	Effective	Invalid	Effective rate
Control group	54	22	21	11	79.63%
Study group	54	35	15	4	92.59%
X^2	/	/	/	/	5.309
P	/	/	/	/	0.047

MIESSS score, ability of daily activities [8]: MIESSS was used to assess the impairment in brain function, with a total score of 45; and the higher the score, the more severe the impairment. The daily living ability was examined, and the higher the score, the higher the ability.

Coagulation indicators [9]: Platelet count, fibrinogen, D-dimer and other coagulation indexes were collected by blood test and compared between the two groups.

Cellular inflammatory factors [10]: The contents of TNF-α (Immuno Way, C66A631), IL-6 (Immuno Way, C41A631) and IL-8 (Immuno Way, C43A631) were determined by ELISA.

Adverse reactions [11]: The incidence of hematuria, decreased hemoglobin, nausea etc., were calculated and compared between the two groups.

Prognosis [12]: Prognostic outcomes such as unconsciousness and death were calculated and compared between the two groups.

Statistical methods

The data were processed using SPSS 25.0 software package. The measurement data were represented by ($\bar{x}$ ± s). Paired sample t-test was used for intra-group comparison before and after treatment, and independent sample t-test was used for inter-group comparisons. Counting data was represented by n (%) and compared using χ^2-test. P<0.05 indicated statistically significant differences. GraphPad Prism8 was used for figure rendering.

Results

Comparison of baseline data between two groups

The two groups were comparable in terms of age, sex, and comorbidities, including hypertension, diabetes and abnormal lipid metabolism (all P>0.05, **Table 1**).

Comparison of clinical therapeutic effects between two groups

Compared with the control group, the study group showed a significantly higher effective rate (79.63% vs. 92.59%; P=0.047) (**Table 2**).

Comparison of the scores of MIESSS and daily living ability

Before the treatment, there was no remarkable difference in MIESSS and activities of daily living between the two groups (all P>0.05). However, after the treatment, the MIESSS score of the study group was significantly decreased, and the score of the daily living ability of was significantly increased as compared with the control group (P=0.035; P= 0.044) (**Table 3**).

Coagulation indicators

Before the treatment, there were no remarkable differences in coagulation indicators between the two groups (all P>0.05). After the treatment, the platelet count, fibrinogen, and D-dimer level in the study group were obviously lower than those in the control group (P=0.031; P=0.042; P=0.047) (**Table 4**).

Table 3. Comparison of the scores of MIESSS and daily living ability (points, $\bar{x} \pm s$)

Cluster	No.	MIESSS score		Score of daily living ability	
		Before treatment	After treatment	Before treatment	After treatment
Control group	54	20.45±3.12	17.34±3.12	56.23±3.09	72.98±4.12
Study group	54	20.54±2.65	12.39±2.11	56.01±2.65	89.32±3.09
t	/	1.219	10.579	1.321	12.871
P	/	0.056	0.035	0.058	0.044

Table 4. Comparison of coagulation indicators between the two groups ($\bar{x} \pm s$)

Cluster	No.	Platelet count ($\times 10^9$/L)		Fibrinogen (g/L)		D-dimer (μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	54	346.23±7.89	305.67±5.98	7.02±1.12	5.32±1.14	742.89±4.98	570.54±4.12
Study group	54	345.98±8.91	217.23±4.76	7.00±1.07	2.98±1.02	741.55±5.12	339.20±5.98
t	/	1.761	18.234	1.023	10.312	1.332	20.786
P	/	0.056	0.031	0.062	0.042	0.059	0.047

Table 5. Comparison of inflammatory factors between the two groups (μg/L, $\bar{x} \pm s$)

Cluster	No.	TNF-α		IL-6		IL-8	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	54	125.76±8.13	111.34±9.67	150.23±7.23	136.20±6.10	86.12±7.12	106.67±8.91
Study group	54	125.21±4.23	102.67±6.12	149.65±6.12	113.23±7.56	86.00±5.45	130.22±5.98
T	/	1.609	10.987	1.786	12.248	1.113	13.760
P	/	0.068	0.041	0.053	0.038	0.044	0.046

Comparison of inflammatory factors between the two groups

No remarkable variance in cellular inflammatory factors between the two clusters before healing (P>0.05). After healing, contrasted with the control cluster, the levels of TNF-α, IL-6 and IL-8 within the study cluster were fewer (P=0.041; P=0.038; P=0.046) (**Table 5**).

Comparison of adverse reactions between the two groups

Compared with the control group, the incidence of adverse reactions, including hematuria, decreased hemoglobin and nausea, in the study group was significantly decreased (P=0.033) (**Table 6**).

Comparison of prognosis between the two groups

Compared with the control group, the study group had a better prognosis, indicated by higher cure rate, lower unconsciousness rate and death rate (P=0.029; P=0.033; P=0.048) (**Table 7**).

Discussion

Ischemic stroke is a cerebrovascular disease, and antiplatelet aggregation is generally the fundamental principle in clinical treatment, ensuring normal thrombin level in the body [13]. The application of Argatroban in addition to Aspirin can better stimulate the activity of thrombin, thereby controlling the catalysis of thrombin and the formation of related induction reactions to a greater extent, fully reflecting the value of anticoagulation. The major pharmacological characteristics of Argatroban: (1) Argatroban is highly selective, has high affinity for thrombin, and significantly inhibits the potency of other serine proteases [14]. (2) Argatroban, with small molecular weight, can penetrate the interior of the thrombus lesion from the thrombus barrier, which can completely inhibit throm-

Table 6. Comparison of adverse reactions between the two groups (case, %)

Cluster	No.	Hematuria	Hemoglobin decreased	Nausea	Occurrence
Control group	54	5	5	6	29.63%
Study group	54	2	2	2	11.11%
X^2	/	/	/	/	4.447
P	/	/	/	/	0.033

Table 7. Comparison of prognosis between the two groups (case, %)

Cluster	No.	Cure	Unconsciousness	Death
Control group	54	29 (53.70)	20 (37.04)	5 (9.26)
Study group	54	44 (81.48)	10 (18.52)	0 (0.00)
X^2	/	5.598	5.012	4.554
P	/	0.029	0.033	0.048

bin that has bound fibrin [15]. (3) Combined drug therapy has the advantages of rapid drug efficacy and enhanced body tolerance to dose, with a large range of adaptations. After discontinuation of drug, various coagulation indicators in the body generally reach the normal level after 2-4 h. At the same time, a reasonable dose can significantly enhance the treatment safety [16]. (4) The combination of Argatroban and Aspirin can coordinate endothelial cell function to meet body needs and substantially reduce cellular inflammatory factor levels. (5) The combination of Argatroban and Aspirin can effectively inhibit thrombin-mediated vasoconstriction and continuous enhancement of collateral circulation. Anticoagulant therapy has become the key to control ischemic stroke. Adding Argatroban based on Aspirin can greatly inhibit the binding of blood clots and dissolve thrombin to a greater extent. It has been widely used in the clinical treatment of ischemic stroke [17]. When Argatroban is added, it penetrates the blood-brain barrier by intravenous administration. The inhibition of thrombin and the enhancement of blood circulation can enhance the anticoagulant effect to a greater extent, thus effectively improving the cerebral blood flow and cerebral nerve function of the body [18].

Combined therapy can significantly and reversibly inhibit clots combined with thrombin, and then greatly hinder the occurrence of platelet aggregation by establishing a good collateral circulation system, which is conducive to the recovery of neurological function of patients [19]. The pathogenesis of ischemic stroke is very complex [20]. Data has shown that the appearance of microthrombi in the brain does not affect the physiological activity of thrombin. However, after the thrombus is dissolved, massive secretion of thrombin can promote the body to maintain a hypercoagulable state, and uncontrolled conditions will cause severe consequences of vascular occlusion, thus increasing the difficulty of clinical treatment to a greater extent [21]. The application of aspirin can effectively inhibit the synthesis of cyclooxygenase in the prostate, reduce the production of thromboxane A2, and achieve the purpose of antiplatelet to a greater extent. However, due to the problem of platelet aggregation in some parts after ischemic stroke, thrombosis will aggravate the coagulation disorders, leading to compromised treatment effect. Additional administration of Argatroban can significantly enhance the treatment safety, enhance the efficacy of the drug, and further shorten the treatment and rehabilitation time. At the same time, it can greatly alleviate the mental and economic pressure on patients and their families and promote clinical rehabilitation.

Combined administration of Argatroban and Aspirin accelerates the rate of binding thrombin and further inhibits the thrombin activity. However, in response to the decrease in thrombin concentration, some platelets can release many inducing factors after being fully activated, which in turn accelerates the rate of platelet aggregation [22]. Data have shown that a variety of factors can promote the occurrence of ischemic stroke, especially the inflammatory response, which aggravates ischemic infarc-

tion in brain tissues, severely damaging ischemia-reperfusion, and accelerating neuronal apoptosis to a greater extent. IL-6 can directly affect the level of cerebrovascular intimal cell adhesion molecules and further promote the apoptosis of vascular endothelial cells in a short time [23]. IL-8 can effectively induce the release of T lymphocytes in the body and can release massive interferon-gamma; neutrophils can form oxidative metabolites after massive accumulation and seriously damage the vascular endothelial cells [24]. The change of TNF-α level directly affects microvascular endothelial cells in patients with ischemic stroke and further affects tissue plasminogen activator which can regulate the synthesis and release of this substance, thereby enhancing the normal function of brain tissue and greatly improve vascular microcirculation. Blood circulation factors are critical in the progression of ischemic stroke. Microcirculation dysfunction can significantly promote the formation of thrombosis, produce severe damage to the vascular endothelium, and finally cause ischemic stroke. Therefore, the blood circulation of body directly affects the development and prognosis of ischemic stroke [25]. In addition, atherosclerosis, as a high-risk factor, has a direct impact on the occurrence of ischemic stroke. Combined treatment can effectively inhibit thrombin activity and ensure the treatment safety to meet the clinical needs [26].

Conclusion

Compared with Aspirin alone, combined treatment of Argatroban and Aspirin can optimize coagulation parameters, reduce the level of cellular inflammatory factors to a greater extent, promote the recovery of neurological function, remarkably reduce the occurrence of poor prognosis, and enhance the patient's ability of daily activities with remarkable therapeutic effect.

Disclosure of conflict of interest

None.

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