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Effect of Argatroban Injection on Clinical Efficacy in Patients with Acute Cerebral Infarction: Preliminary Findings

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Keywords
Argatroban injection · Acute cerebral infarction · [illegible] flow rheology · Safety

Abstract

Objective: The aim is to obse[illegible] t[illegible]ts of argatroban injection and butylphthali[illegible] inje[illegible]n [illegible]blood flow rheology, clinical efficacy, an[illegible]ety in[illegible]nts with acute cerebral infarction. ***Methods:*** [illegible] patients with acute cerebral infarction with[illegible]n afte[illegible]mission were divided into treatment grou[illegible]ontrol group, with 172 cases in each group. The[illegible]ol g[illegible]eceived routine treatment. The treatmen[illegible]ro[illegible]eceived argatroban injection 60 mg on the [illegible]is of [illegible]ntr[illegible]group, intravenously guttae (ivgtt) was d[illegible]or 2 [illegible] then changed to argatroban injection 10 m[illegible] bid for 5 days, and the total course of treatment [illegible] 7 d[illegible]. The neurological changes, activities of daily liv[illegible] and the rheology indicators (fibrinogen [Fib], platelet ag[illegible]gation rate [Pag], whole blood high shear viscosity [Whsv], hematocrit [Hct]) were compared between the 2 groups, clinical efficacy and adverse drug reactions. ***Results:*** [illegible]fter treatment, the total effective rates of the treatment group and the control group were 90.70% (156 /172 cases) and 74.41% (128 and 172 cases), respectively, and the difference was statistically significant ($p < 0.05$). After treatment, the National Institutes of Health Stroke Scale scores of the treatment group and the control group were (7.05 ± 1.97) and (8.30 ± 1.79), respectively, and the Barthel index was (68.02 ± 11.07) and (62.32 ± 11.46), respectively. The difference was statistically significant ($p < 0.05$). After treatment, the treatment group and the control group were (2.66 ± 0.22) g/L and (3.50 ± 0.22) g/L, respectively, and Pag were (0.68 ± 0.06)% and (0.81 ± 0.09)%, respectively, and Whsv was (6.44 ± 0.76) mPs/s and (6.87 ± 0.91) mPs/s, Hct were (8.19 ± 1.21)% and (10.44 ± 1.04)%, respectively, and the differences were statistically significant ($p < 0.05$). The incidence of adverse reactions in the treatment group and the control group was 6.97 and 5.81%, respectively, and the difference was not statistically significant ($p > 0.05$). ***Conclusion:*** Argatroban injection is effective in the treatment of acute cerebral infarction, which can significantly improve the hemorheology of patients with good safety.

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Introduction

Cerebral infarction that is commonly known as acute ischemic stroke (AIS) involves the ischemic necrosis or softening of brain tissue that occurs due to improper supply of blood so-called ischemia and hypoxia that mainly results in an exceptional increase in morbidity mortality as well rates disability. Besides, the disease is significantly harmful to human life since paralysis of lateral limbs or general paralysis, or even death is its very common consequence. Concerning age margins, cerebral infarction is generally observed in the older- or middle-aged population, but youngsters or even children have recently also been reported to be affected by this disease [1]. Currently, conventional therapy is usually used for the treatment of cerebral infarction. However, the prognosis of patients is relatively poor, and the disease relapse is commonly reported immediately after treatment [2]. Therefore, the development of proper treatment methods is still a great challenge for clinicians. Thus, there is a need to design such a treatment method that must be effective not only in terms of treatment of the disease but also should be supportive in the improvement of neurological function.

Thrombosis in patients with cerebral infarction is closely associated with the following 3 factors: damage the arterial wall; changes taking place in the composition of blood; and abnormality in blood rheology. There the improvement in abovementioned key factors with drugs is always understood as quite a better method for the improvement of neurological disorder and recovery of neurological function in patients suffering from a cerebral stroke. Argatroban injection causes inhibition of thrombin protein, thus showing significant antithrombotic activity through reversible binding at the active site of the protein. This study was primarily purposed at a detailed investigation of the effects of argatroban injection on hemorheology, its clinical efficacy, as well as exploring adverse reactions in patients with acute cerebral infarction in the sense of rationale for promotion and use of the clinical as well as optimization and treatment plans can be established.

Materials and Methods

Research Design

The protocol of the research was followed according to a well-established method involving a sequential approach of prospective, randomized, open, controlled, single-center clinical research steps.

Table 1. Comparison of clinical data between 2 groups of patients

Item	Treatment, $n = 172$	Control, $n = 172$
Sex (M/F)	100/72	108/64
Age, years	68.44±8.22	68.16±8.19
Course, h	9.04±2.19	8.97±2.
BMI, kg/m^2	22.53±1.78	22.44±2.1
Complication disease, *n* (%)		
Hypertension	24 (13.95)	28 (27)
Diabetes mellitus	16 (9.30)	3.1
Coronary disease	10 (5.81)	

Control group: basic treatment; Treatment group: Argatroban injection on the basis of control group

Materials

Primarily, cases of AIS patients admitted to the Department of Neuro Deyang People's Hospital from September 201 to July 2019 selected as the primary research objects. Th dy was appro by the Ethics Committee of the People's Hosp Deyang City Ethical Approval Number 2015-02-003. A med consent form was signed by all the patients or t famil

Criteria

The following were the inclusion criteria:

1. Patients who meet the diagnostic criteria for acute cerebral infarction according to the guidelines of diagnosis and treatment of AIS [3].
2. For patients whose cerebral infarction has been confirmed by transcranial CT or cranial MRI, 2 researchers confirmed that the pathogenesis was atherosclerotic thrombotic cerebral infarction.
3. Patients diagnosed with acute cerebral infarction within 48 h of onset.

Exclusion Criteria

The following were the exclusion criteria:

1. Patients who are allergic to or have allergies to the drugs used in this study.
2. Patients diagnosed with cerebral hemorrhage, aneurysms, cerebral arterial malformations, or brain tumors.
3. Patients suffering from severe heart, liver, and kidney dysfunction.
4. Patients with mental illness.

Drugs and Instruments

The folloiwng drugs and instruments were used:

- Argatroban injection (Dabei) (20 mL, 10 mg, 20141125; Tianjin Pharmaceutical Research Institute Pharmaceutical Co., Ltd.)
- AU480 full-automatic biochemical analyzer (Beckman Coulter Co., Ltd.)
- LBY-N6 full-automatic blood rheometer (Beijing Pulisheng Instrument Co., Ltd.)

Table 2. Comparison of NIHSS score and BI before and after treatment in 2 groups of patients (x ± s)

Item	Treatment, n = 172		Control, n = 172	
	B treatment	A treatment	B treatment	A treatment
NIHSS	11.48±1.89	7.05±1.97*	11.23±2.02	8.30±1.79*, #
BI	55.46±9.20	68.02±11.70*	55.69±8.35	62.32±11.46*, #

B treatment, before treatment; A treatment, after treatment; BI, Barthel inde[illegible] 0.05; compared with group at the same time. # $p < 0.05$.

Table 3. Comparison of blood flow rheological parameters before and after treatment in 2 groups of patients (x ± s)

Item	Treatment, n = 172)		Control, n = 172	
	B treatment	A treatment	B treatment	A treatment
Fib, g/L	4.51±0.23	2.66±0.22*	4.52±[illegible]	[illegible].50±0.22*, #
Pag, %	1.01±0.09	0.68±0.06*	[illegible]±0.1[illegible]	0.81±0.09*, #
Whsv, mPs/s	7.43±0.89	6.44±0.76*	[illegible].01	6.87±0.91*, #
Hct, %	12.11±1.98	8.19±1.21*	[illegible]	10.44±1.04*, #

B treatment, before treatment; A[illegible]tment[illegible]ter tr[illegible]nt; Hct, hematocrit; Fib, fibrinogen; Pag, platelet aggregation ra[illegible]hsv[illegible]ole blood high shear velocity. * $p < 0.05$; compared with group at the same time[illegible].05.

Grouping and Treatment Methods

A total of 344 patients with acute cerebral infarction were equally divided into the argatroban group and control group according to the random number table. The control group was tre[illegible]ed with antiplatelet aggregation and lipid-lowering drugs[illegible]e blood sugar level, blood pressure, and dehydrating agents [illegible] control group were kept normal by administrating [illegible]drug specific conditions. The treatment group was treate[illegible]argatr[illegible]ban injection (60 mg) for 2 days and then chang[illegible]rol[illegible]n injection (10 mg) for 5 days. Both groups wer[illegible]ated fo[illegible].

Observation Indicators

Assessment of Neurological Functi[illegible]and [illegible]ng Ability

The National Institutes of Heal[illegible]str[illegible](NIHSS score) was used to evaluate the changes in neurol[illegible]al f[illegible]tion in both groups of patients before and after t[illegible]ent [[illegible]el index (BI) was used to evaluate the daily living [illegible] of both groups of patients.

Hemorheology

Peripheral blo[illegible]collected before and after treatment to measure cha[illegible]in he[illegible]ogical indicators, including hematocrit (Ho[illegible]), fibrinogen (Fib), platelet aggregation rate (Pag), and whole blo[illegible]h shear viscosity (Whsv) [5].

Efficacy Evaluation

[illegible] evaluation was assessed by the decline rate of the [illegible] that was divided into a cure, significant effective, [illegible]tive, and ineffective categories. Where cure: NIHSS score [illegible]d by ≥90%; significant effective: NIHSS score lowered by 46–[illegible]%; effective: NIHSS score lowered by 18–45%; ineffective: NIHSS score lowered by ≤18% or no significant change in the patient's symptoms and signs.

[illegible]ug Reactions Observe

[illegible]o adv[illegible]ug reaction was observed during treatment in the 2[illegible]s o[illegible]atients.

Statistical Analysis

[illegible]atistical analysis was performed using SPSS17.0 software. [illegible]asurement data are expressed by x ± s, comparisons between groups are performed using paired t test, and comparisons within groups are performed using independent sample t test; count data are expressed by the rate (%), compared with χ^2 test, and rank data comparison is performed by rank-sum test (Wilcoxon 2 samples comparison method). Statistical significance was found at $p < 0.05$.

Results

General Characteristics of the Patients

All participants from MG group and control group completed the study and were included in the analysis. The demographic characteristics, comorbid diseases, and laboratory tests are shown in Table 1. All variables were not significantly different between the 2 groups ($p > 0.05$) Table 1.

Comparison of NIHSS Score and Barthel Index before and after Treatment in 2 Groups of Patients

Before and after treatment, there was a statistically significant difference in the NIHSS score and BI between the 2 groups of patients ($p < 0.05$), and there was a statisti-

Table 4. Comparison of clinical efficacy in 2 groups (*n*, %)

	Treatment, *n* = 172	Control, *n* = 172
Fully recovered, *n* (%)	0 (0.00)	0 (0.00)
Markedly effective, *n* (%)	116 (67.44)	48 (27.91)
Effective, *n* (%)	40 (23.26)	80 (46.51)
Ineffective, *n* (%)	16 (9.30)	44 (25.58)
Total efficiency, %	90.70	74.41*

Compared with treatment group. * $p < 0.05$.

cally significant difference in the above indicators between the treated and control groups after treatment ($p < 0.05$) Table 2.

Comparison of Blood Rheology Indexes before and after Treatment in 2 Groups of Patients

Before and after treatment, the differences in Fib, Pag, Whsv, and Hct between the 2 groups were statistically significant ($p < 0.05$), and the differences between the above indicators in the treatment group and the control group after treatment were statistically significant ($p < 0.05$) Table 3.

Comparison of Clinical Efficacy between 2 Groups of Patients

After treatment, the total effective rates of the treatment group and the control group were 90.7[illegible]6/172 cases) and 74.41% (128/172 cases), respectively, and the difference was statistically significant ([illegible]0.05) Table 4.

Safety Evaluation

In the treatment group, the [illegible]s of subcutaneous bleeding at the puncture site, [illegible] microscopic hematuria, 2 cases of hea[illegible], and [illegible]; the control group had 1 case of subcutaneous [illegible]eding at the acupuncture site, 2 cases of dizz[illegible] and 2 [illegible] of heat. The incidences of adverse reactions [illegible] 2 groups were 6.97 and 5.81%, respectively [illegible]o significant difference ($p > 0.05$).

Discussion

Studies show that stroke has become the third leading cause of death in China [6]. Among them, ischemic stroke is the most terrible because it has a high risk of death and disability which brings a serious burden to society [7, 8]. The TOAST etiological classification indicated that atherosclerotic cerebral infarction is caused by blood clotting in the major arteries [9]. Changes in the rheology of blood flow could promote the occurrence of atherosclerosis and increase the incidence of cerebral infarction [10].

Fib is a protein synthesized by the liver with coagulation function. It is a monomeric protein produced by the [illegible]moval of Fib A and B in Fib by thrombin. Fib pr[illegible]s smooth muscle and endothelial cell growth, proliferat[illegible] and contraction, increase blood viscosity and [illegible]l resistance, cause endothelial cell damage, pro[illegible]t[illegible]lla[illegible]en and deoxyribonucleic acid synthesis, chemo[illegible]io-nuclear or macrophage migration to[illegible]ma, and promote RBCs adhesion and thromb[illegible]11–[illegible]A change in these components or pathological [illegible]ge[illegible]n important cause of atherosclerosis. Se[illegible] studi[illegible]e reported that the Fib level is significan[illegible]n[illegible]d in [illegible]al infarction patients [14]. P[illegible] measu[illegible] of p[illegible]et function where the higher the P[illegible]alu[illegible]e gre[illegible]e possibility of thrombosis [15]. Stu[illegible] hav[illegible]own that Pag has a significant positive correlatio[illegible] the occurrence of cerebral infarction a[illegible]an be used [illegible] indicator of the prognosis and treatme[illegible]fect of cerebr[illegible] infarction Tong et al. [16].

[illegible] the resistance displayed by 2 adjacent parallel fl[illegible]laye[illegible]tive to each other during blood flow. Generally, Whs[illegible]fers to >100 mPa/s. Studies have shown that [illegible]er[illegible] resistance increases when whose increases lead to decreased cerebral perfusion and increased risk of cerebral infarction and form a vicious circle to further increase the risk of cerebral infarction [17]. Hematocrit (Hct), an important factor affecting blood viscosity, refers to the ratio of the volume occupied by RBC in the blood. When Hct is <45%, blood viscosity increases linearly with the increase of Hct, while when Hct is >45%, blood viscosity increases exponentially with Hct. Once Hct exceeds 45%, a slight change in Hct can cause a significant increase in blood viscosity, suggesting that Hct is also an important factor causing cerebral infarction. Studies have shown that when Hct is less than 30, 36–46, 46–50, and >50%, the probability of cerebral infarction is 6.6, 18.3, 43.6, and 63.6%, respectively [18].

The above content suggests that a change in hemorheology is an important cause of cerebral infarction. It will be an important method to prevent and treat cerebral infarction by improving the characteristics of hemorheology. Argatroban injection is a new type of thrombin inhibitor [19] that exerts an anticoagulant effect by inhibiting the reactions catalyzed or induced by thrombin where cofactor antithrombin III is not required such as the activation of factor V and protein C. Besides, it is highly selective for free thrombin and blood clot-associated thrombin suggesting a better safety [20].

At present, the main consumption of argatroban in mainland China is cerebral infarction anticoagulation and the curative effect is definite [21]. To explore the argatroban effect on the hemorheological characteristics of patients with cerebral infarction, this study found that Fib, Pag, Whsv, and Hct in the treatment group were significantly lower than those in the control group through randomized controlled trials. The argatroban can significantly improve the hemorheological characteristics of patients with cerebral infarction. The results exhibited that the decline of NIHSS score and an increase in the BI in the treatment group were better than those in the control group. These findings suggest that argatroban injection can significantly improve the neurological function defects of patients with acute cerebral infarction.

In summary, argatroban injection is safe and effective in the treatment of acute cerebral infarction. In addition to known anticoagulant pathways, it can also improve the prognosis of patients by improving the blood rheology of patients with acute cerebral infarction, which is worthy of clinical promotion in the future.

Statement of Ethics

This study was approved by the Ethics Committee of People's Hospital of Deyang City. The participants and their family members signed an informed consent form. The Ethical Approval Number is 2011-07-002.

Conflict of Interest Statement

The authors have no conflicts of interest to dec[illegible].

Funding Sources

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Author Contribution

Pan Huan[illegible]d to [illegible]ception of the study. Pan Huang and [illegible]u co[illegible]buted [illegible]ificantly to analysis and manuscript prepa[illegible] Huang and Min Xu performed the data analyses and wr[illegible] manuscript; Xiao-Ying Heb helped perfo[illegible]he analysis w[illegible]nstructive discussions.

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