Original Article
Efficacy of argatroban in the treatment of acute cerebral infarction

Xiuju Wang1*, Yulan Yan2*, Ying Song3, Chen Ma1

Departments of 1Cerebrovascular Disease Treatment Center, 2Oncology, 3Neurology, Tianjin No.5 Central Hospital, Tianjin City, China. *Equal contributors and co-first authors.

Received December 20, 2018; Accepted February 11, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: Objective: The goal of this study was to evaluate the therapeutic efficacy of argatroban for acute cerebral infarction. Methods: A total of 80 patients with acute cerebral sclerosis were enrolled in this study. Patients were randomly divided into two groups: the control group (n=40) and the argatroban group (n=40). Patients of the control group received routine treatment combined with aspirin, and patients of the argatroban group received routine treatment combined with argatroban treatment. The clinical efficacy, neurological function (National Institute of Health stroke scale (NIHSS)) score, daily life ability (Barthel) score, cerebral blood supply, and adverse reactions were evaluated and compared between the two groups. Results: The clinical efficacy of the argatroban group was significantly higher than that of the control group (87.5% vs. 67.5%, \(\chi^2=4.588\), \(P=0.032\)). After treatment, the neurological function of the two groups was both improved significantly, and the neurological function of the argatroban group was significantly better than that of the control group (NIHSS score: 5.10±2.09 vs. 8.12±2.31, \(t=3.811\), \(P=0.033\)). The ability of daily life in both groups was significantly improved after treatment, and the recovery of the ability of daily life in the argatroban group was significantly better than that of the control group (Barthel index score: 79.31±6.60 vs. 63.30±5.18, \(t=5.391\), \(P=0.039\)). After treatment, the blood supply of the argatroban group was significantly better than that of the control group (peak flow rate: 81.66±6.09 vs. 65.92±4.96, \(t=6.290\), \(P=0.016\); average flow rate: 46.80±3.08 vs. 38.61±3.09, \(t=5.390\), \(P=0.015\)). During treatment, no serious adverse reactions were found in the two groups. Conclusion: Argatroban is safe and effective in the treatment of acute cerebral infarction, which can promote the recovery of neurological function and the ability of daily life, and improve cerebral hemodynamics.

Keywords: Argatroban, acute cerebral infarction, clinical efficacy

Introduction

Acute cerebral infarction (ACI) is a common acute ischemic stroke disease with a high morbidity and mortality. If not treated in a timely manner, degeneration and necrosis of brain tissue will occur in a short period of time, and lead to a series of manifestations of neurological dysfunction, such as language loss, limb dysfunction, and even death [1, 2]. Early thrombolysis is an effective method in the treatment of acute cerebral infarction. Due to the limitation of time window, most patients have lost the opportunity of thrombolysis [3]. Statistically, only 0.5%-1.0% of acute cerebral infarction patients have the opportunity to receive thrombolytic therapy in China [4]. For ACI patients who have lost the chance of thrombolysis, the main treatment methods include active anti-thrombosis medication, improvement of microcirculation, and protection of nerve function [5]. The aim is to maximize clinical outcomes and reduce disability and mortality [6].

In the progression of acute cerebral infarction, coagulation and fibrinolysis function become imbalanced, which can lead to further expansion and aggravation of infarction area, upon hypoxia state is not corrected timely or the blood volume is not supplemented timely [7, 8]. Argatroban is a low-molecular weight L-arginine derivative and a highly selective thrombin inhibitor, which can reverse the binding of thrombin catalytic sites and exert competitive inhibition. It can inhibit fibrinogenesis and platelet focusing induced by thrombin, thereby reducing blood viscosity, improving hemodynamics and microcirculation, and promoting the recovery of
nerve function [7, 8]. Some previous study has shown that argatroban can effectively improve clinical symptoms and promote neurological recovery in the treatment of acute cerebral infarction [9, 10]. However, the underlying mechanism was not fully understood.

To further explore the therapeutic effect of argatroban in the treatment of acute cerebral infarction, in this study, the clinical efficacy was not only analyzed, but also adverse reactions, neuroprotective effects, and improvement of the ability of daily life, were also explored. The effect of argatroban on the blood supply was also examined. These endpoints increase our understanding on the mechanism of argatroban in the treatment of acute cerebral infarction.

Materials and methods

Patients enrolled

Inclusion criteria: Patients in accordance with the diagnostic criteria of acute cerebral infarction [11]; first onset patients; patients with neural function defect score (NIHSS) >5; patients with ADL score (Barhtel index) <80; patients with period from onset to admission >6 h, and <72 h. Exclusion criteria: Patients with liver and kidney dysfunction; patients with other bleeding disorders; patients with dysfunction al blood coagulation; patients with a history of trauma surgery or angina within half a year; tumor patients; patients with disturbed consciousness; patients allergic to the drugs used in this study.

A total of 80 ACI patients were enrolled in this study, who were treated from January 2017 to December 2017 at Tianjin No.5 Central Hospital. All the patients were randomly divided into two groups: the control group (n=40) and the argatroban group (n=40). As shown in Table 1, there was no significant difference in the general clinical data between the two groups (P>0.05). This study was approved by the Ethics Committee of Tianjin No.5 Central Hospital, and the signed informed consent was obtained from each patient before the trial started.

Treatment

The routine treatment: All the patients received routine treatment, including lipid lowering, blood pressure lowering and blood sugar lowering, water and electrolyte disturbance correction and acid-base balance maintenance.

The control group: On the basis of the routine treatment, patients were given aspirin (100 mg/tablet, Bayer Medical and Health Co., Ltd.) 100 mg/time orally. One time per day for a period of 15 days.

The argatroban group: On the basis of the routine treatment, patients were injected with argatroban injection intravenously (10 mg/branch, Tianjin Pharmaceutical Research Institute Flower Industry Co., Ltd.), 30 mg/time, 3 hours/time, twice a day for the first two days, then 10 mg/time, 3 hours/time, 2 times/day, for the following 13 days.

Outcome measures

Neurological function: NIHSS scale was used to assess the degree of the improvement of neurological function in patients. The total score was 34, and the lower the score, the better the neurological function of patients [12]. The NIHSS scores were evaluated before and after the treatment in both groups.

Clinical efficacy: The NIHSS scores before and after the treatment were compared, and the improvement of NIHSS score was used to evaluate the improvement of neurological function. Patients were divided into four levels: recovery, marked efficacy, improvement and ineffectiveness. Compared with that before the treatment, the improvement of NIHSS score was 91%-100% for recovery, 60%-90% for marked efficacy, 20%-59% for improvement, and failure to achieve the above was considered ineffectiveness [12].

Ability of daily life: Barhtel index scale was used to assess the improvement of the ability of daily life. The total score was 100. The higher the score, the stronger the patients ability of daily life [13]. The Barhtel index scales were evaluated before and after the treatment in both groups.

Cerebral blood supply: The peak flow velocity and mean flow velocity of the middle cerebral artery were measured using Color Doppler Ultrasound Examination before and after the treatment in both groups.
Argatroban in the treatment of acute cerebral infarction

Table 1. General clinical data

<table>
<thead>
<tr>
<th></th>
<th>Argatroban group (n=40)</th>
<th>Control group (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66.3±7.9</td>
<td>65.1±8.1</td>
<td>0.831</td>
</tr>
<tr>
<td>Gender (male/female, n)</td>
<td>23/17</td>
<td>28/12</td>
<td>0.245</td>
</tr>
<tr>
<td>Period from onset to admission (hour)</td>
<td>29.19±8.98</td>
<td>31.08±9.10</td>
<td>0.790</td>
</tr>
<tr>
<td>NIHSS (point)</td>
<td>11.10±5.09</td>
<td>10.99±5.18</td>
<td>0.310</td>
</tr>
<tr>
<td>Barhtel Index (point)</td>
<td>45.26±5.10</td>
<td>46.08±5.31</td>
<td>0.698</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>26.31±2.19</td>
<td>26.01±2.06</td>
<td>0.716</td>
</tr>
<tr>
<td>Concomitant diseases (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>21</td>
<td>0.653</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19</td>
<td>23</td>
<td>0.371</td>
</tr>
<tr>
<td>Hyperlipermia</td>
<td>26</td>
<td>23</td>
<td>0.491</td>
</tr>
</tbody>
</table>

Note: NIHSS, National Institute of Health stroke scale.

Table 2. Clinical efficacy of two the groups (n, %)

<table>
<thead>
<tr>
<th></th>
<th>Argatroban group (n=40)</th>
<th>Control group (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>12</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Marked effect</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Ineffectiveness</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>35 (87.5)</td>
<td>27 (67.5)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Adverse reactions: Adverse reactions during the treatment were recorded, including gastrointestinal reaction, gastrointestinal bleeding and urinary system bleeding.

Statistical analysis

SPSS18.0 package was used for statistical analysis, measurement data are expressed as (X ± sd). Independent t-test was used to analyze the difference between the two groups, and paired t-test was used to analyze intra-group before-after difference. Counting data was expressed as examples or percentage, χ² test or Fisher’s exact test was used to analyze the difference between the two groups. P<0.05 was considered statistically significant.

Results

Clinical efficacy of two the groups

As shown in Table 2, in the argatroban group, there were 12 cases with recovery, 10 cases with marked efficacy, 13 cases with improvement, and 5 cases with ineffectiveness. The clinical efficacy was 87.5%, which was higher than that of the control group (67.5%, χ²=4.588, P=0.032).

The improvement of neurological function in the two groups before and after treatment

As shown in Figure 1, before the treatment, there was no significant difference between the two groups with respect to NIHSS scores (11.66±4.31 vs. 12.06±4.39, t=0.879, P=0.310). After treatment, NIHSS scores of both groups decreased, compared with those before the treatment, and NIHSS score of the argatroban group was significantly lower than that of the control group (5.10±2.09 vs. 8.12±2.31, t=3.811, P=0.033).

Improvement of the ability of daily life in the two groups before and after treatment

As shown in Figure 2, before the treatment, there was no significant difference in Barhtel index scores between the two groups (43.98±4.31 vs. 46.98±4.90, t=0.980, P=0.698). After treatment, the Barhtel index scores of the two groups were significantly improved by comparison with those before treatment, and the Barhtel index score of the argatroban group was significantly higher than that of the control group (79.31±6.60 vs. 63.30±5.18, t=5.391, P=0.039).

Comparison of brain blood supply before and after treatment

As shown in Figure 3, there was no significant difference in the peak velocity of middle cerebral artery between the two groups before the treatment (56.09±3.61 vs. 55.60±3.21, t=2.310, P=0.510). After treatment, the peak flow velocity of middle cerebral artery in both groups was significantly improved compared with those before the treatment, and the blood supply of the argatroban group was significantly better than that of the control group (81.66±6.09 vs. 65.92±4.96, t=6.290, P=0.016).

As shown in Figure 4, before treatment, there was no significant difference in the mean flow
Argatroban in the treatment of acute cerebral infarction

Figure 1. Improvement of neurological function in two groups NIHSS, National Institute of Health stroke scale.

Figure 2. Improvement of daily life ability of two groups.

velocity of middle cerebral artery between the two groups (29.59±2.31 vs. 28.09±2.50, t=1.901, P=0.398). After treatment, the mean flow velocity of middle cerebral artery in both groups was significantly improved compared with those before the treatment, and the blood supply of the argatroban group was significantly better than that of the control group (46.80±3.08 vs. 38.61±3.09, t=5.390, P=0.015).

Adverse reactions

As shown in Table 3, during treatment, there were 2 patients with mild nausea in each group, who were relieved themselves. In addition, there was 1 case with gingival bleeding in the argatroban group and 1 case with urinary tract bleeding in the control group. There were no serious adverse reactions in other patients, such as liver and kidney damage. There was no significant difference between the two groups according to the adverse reactions (P>0.05).

Discussion

Acute cerebral infarction is a common acute and severe disease in clinic. Early thrombolysis, early recanalization, restoration of blood supply to brain tissue damage protection are the keys to the treatment [14, 15]. For the patients who lost the chance or were not suitable for thrombolysis, anticoagulation and antithrombotic therapy are feasible. Aspirin is a kind of non-steroidal anti-inflammatory drugs, which can effectively inhibit platelet aggregation, reduce thrombosis [16, 17]. Aspirin is the first choice for the treatment of cerebral infarction in clinic, but long-term use of aspirin can cause kidney damage, dysfunction of coagulation, and anemia [18].

Argatroban is a low molecular L-arginine derivative, which belongs to a synthetic preparation with short half-life. Therefore, it will not affect the liver and kidney function of patients in the process of liver metabolism [19]. In addition, the drug has a strong inhibitory effect on thrombin, which can effectively prolong PT and TT time, reduce blood flow viscosity, and improve the hemodynamics of patients [20, 21]. It has a strong inhibitory effect, when combined with thrombin. Furthermore, its molecular weight is small, so it can penetrate fibrinase directly into the lesion, thereby promoting thrombolysis, regulating endothelial cell function, inhibiting...
Argatroban in the treatment of acute cerebral infarction

The results in the current study showed that the clinical efficacy of the argatroban group was higher than that of the control group. Moreover, the NIHSS score of the argatroban group was significantly better than that of the control group. The Barthel index score of the argatroban group was improved than that of the control group. Argatroban can promote the recovery of neurological function and daily life ability of patients more effectively, when compared with aspirin. A previous study showed that the clinical efficacy of argatroban in the treatment of ACI was 93.3% [10]. After 2-week treatment, NIHSS score was significantly improved. The results of this study were in accordance with the previous report.

In addition, the effect of argatroban on cerebral blood flow was further analyzed in this study. The results showed that argatroban was more effective in improving cerebral blood supply. The peak and mean flow velocities of middle cerebral artery in the argatroban group were significantly improved by comparison with those before the treatment, and were significantly better than those in the control group. The above results suggest that argatroban therapy was more effective to improve hemodynamics, cerebral blood flow and neurological function of patients with cerebral infarction. In terms of safety, this study shows that argatroban treatment is safe, and causes no serious side effects during the treatment.

There are still some limitations in this study, such as a small number of cases included, a single-center study, no further follow-up data,
Argatroban in the treatment of acute cerebral infarction

and incomplete observation and evaluation indicators. All these may cause a statistical bias on the results. Our group will further improve the experimental design, further expand the number of cases, and carry out large-scale randomized case-controlled studies. In conclusion, argatroban is effective for treating acute cerebral infarction with high safety. It can promote recovery of neurological function and the ability of daily life, improve cerebral hemodynamics, and improve the quality of life in patients with acute cerebral infarction.

Disclosure of conflict of interest

None.

Address correspondence to: Ying Song, Department of Neurology, Tianjin No.5 Central Hospital, No.41, Zhejiang Road, Tanggu District, Tianjin City 300-450, China. Tel: +86-15620005918; E-mail: songying83jd@163.com

References

Argatroban in the treatment of acute cerebral infarction
