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Original Article

The clinical efficacy of compound Danshen injection on acute cerebral infarction and on the changes in the CRP, D-dimer, and IL-6 levels

Fengming Bian[1], Shijin Kang[2], Honghai Cui[3], Fang Wang[1], Tianwei Luan[1]

[1]Department of Neurology, The Fifth Hospital in Harbin, Harbin, Heilongjiang Province, China; [2]Department of Neurology, Mishan People's Hospital, Mishan, Heilongjiang Province, China; [3]The Second Ward, Department of General Internal Medicine, Daoli District People's Hospital, Harbin, Heilongjiang Province, China

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Abstract: Objective: To study the clinical curative effect of compound Danshen injection on acute cerebral infarction (ACI) patients and its impact on the CRP, D-dimer, and IL-6 levels. Methods: 116 patients with ACI admitted to our hospital were randomly placed in an observation group (n=58) or a control group (n=58). The control group received rosuvastatin tablets (10 mg/time, qd) in addition to the standard treatment. The observation group received compound Danshen injection in addition to the standard treatment. The treatment continued for 21 days. The clinical treatment efficacy, the CRP, D-dimer, and IL-6 levels, the NIHSS scores (to evaluate the degree of neurological impairment), the Fugl-Meyer scores (to access patients' motor function), the ADL scores, the sleep quality (the PSQI and AIS scores), and the complication incidence rates were compared between the two groups. Results: After the treatment, the effective rate in the observation group (89.66%) was significantly higher than it was in the control group (74.14%) (P<0.05). After the treatment, the serum CRP, D-dimer, and IL-6 levels in the two groups were lower than they were before the treatment, and the levels were lower in the observation group than they were in the control group (all P<0.05). After the treatment, the NIHSS scores in the observation group were lower than they were in the control group, and the Fugl-Meyer and ADL scores were higher than they were in the control group (all P<0.05). Compared with the control group, the PSQI and AIS scores in the observation group were lower than they were in the control group after the treatment (P<0.05). The severe diarrhea, bedsore, urinary tract infection, liver and kidney function injury, skin allergic reactions and other total adverse reaction incidence rates in the observation group were lower than they were in the control group. Conclusion: Rosuvastatin combined with compound Danshen injection is effective in ACI treatment. It is able to effectively improve the clinical symptoms, reduce the incidence of complications, improve the recovery of the IL-6, CRP, and D-dimer levels and enhance patients' sleep quality.

Keywords: Compound Danshen injection, acute cerebral infarction, clinical efficacy, CRP, D-dimer, IL-6

Introduction

Acute cerebral infarction (ACI) is the most common type of cerebrovascular disease, and it refers to the stenosis and blockage of the cerebral arteries caused by abnormal blood vessels, blood, and hemodynamics, resulting in brain tissue necrosis after a sudden interruption of the brain. Its etiology is complex and closely related to factors such as hypertension, coronary heart disease, diabetes, hyperlipidemia, smoking, alcohol consumption, and obesity [1-3]. Studies have reported that the incidence of ACI is 109.7/100,000-217/100,000, and the mortality rate is 116/100,000-141.8/100,000, mostly in middle-aged and elderly patients. With the increase in age, the incidence and mortality rates show a significant increase after age 45, and while the mortality rate of the disease is low, the disability rate is high [4, 5]. The disease has a sudden onset and often develops at rest or during sleep, and patients are generally conscious at the initial stage. Disturbances of consciousness, coma, quadriplegia, and stress ulcers occur at the middle stage. When it progresses to the late stage and has cerebral hernia complications, it is often life-threatening, leading to

Table 1. Comparison of the general baseline data between the two groups (n, $\bar{x}\pm sd$)

Indicators	Observation group (n=58)	Control group (n=58)	χ^2/t	P
Age (years old)	45.4±4.1	44.6±5.8	0.858	0.393
Sex (n)			0.032	0.852
Male	32	31		
Female	26	27		
Body mass index (Kg/m^2)	22.75±2.05	22.50±3.00	0.524	0.601
Concomitant disease (n)				
Hypertension (n)	15	13	0.191	0.664
Coronary heart disease (n)	10	8	0.262	0.608
Diabetes (n)	6	5	0.102	0.751
Smoking history (n)	9	7	0.291	0.590
Alcohol history (n)	5	4	0.128	0.728
Primary infarct location (n)			0.212	0.994
Basal ganglia	22	24		
Frontal lobe	9	8		
Parietal lobe	8	7		
Temporal lobe	7	7		
Occipital lobe	12	12		
Infarct size (cm^2)	3.80±1.01	3.54±1.05	1.359	0.177
Motor involvement (n)			0.339	0.560
Yes	22	19		
No	36	39		

brain death and is therefore a serious threat to human health [6, 7]. Surgery, traditional Chinese medicine therapy, interventional therapy, and drug therapy are the main methods for the treatment of ACI [8, 9]. For drug therapy, there is no specific drug for the treatment of cerebral infarction in clinical practice, and symptomatic and supportive drugs, such as those that protect the nerves and improve the cerebrovascular microcirculation, are routinely used in clinical practice [10]. Studies have indicated that rosuvastatin is effective in ACI treatment, and it has been widely used in clinical treatment [11]. It has also been shown that compound Danshen injection is effective in patients with ischemic brain disease [12]. At present, although there are studies published at home and abroad on the application of compound Danshen injection combined with rosuvastatin in the treatment of patients with ACI, no studies have focused on its effect on patients' sleep quality [13]. Therefore, this study mainly focuses on the clinical curative effect of compound Danshen injection combined with rosuvastatin in ACI, and focuses on an analysis of the efficacy of this combination on the NIHSS, Fugl-Meyer, ADL, sleep quality, CRP, D-dimer, and IL-6 levels and on the incidence of complications in patients, in order to offer theoretical guidance for clinical treatment. The study is reported as follows.

Materials and methods

General data

A prospective study was conducted. 116 patients with ACI admitted to our hospital from December 6, 2018 to February 18, 2020 were randomly placed into one of two groups, with 58 patients in the observation group, and 58 patients in the control group. The two groups' general clinical data are shown in **Table 1**. The medical ethics committee of our hospital approved this study.

Inclusion criteria: (1) Patients with ACI, brain infarction [14]. (2) Patients whose head CT showed no large area infarction (>1/3 d middle cerebral artery blood supply area). (3) Patients who missed their thrombolysis and intervention window times (6 hours), onset to treatment time within 24 hours. (4) Patients experiencing their first episode. (5) Patients 18 years old or older. (6) Patients who were able to understand

the purpose of this study and who signed the informed consent form.

Exclusion criteria: (1) Patients with severe mental illness. (2) Patients with severe heart, liver, or kidney function damage. (3) Patients with cognitive dysfunction. (4) Patients whose speech was not affected.

Methods

The patients in the two groups were both given fundamental treatment such as oxygen inhalation and respiratory support, body temperature control, intracranial pressure control, blood glucose and blood lipid regulation, nutritional support, improvement of their cerebral circulation, anti-platelet aggregation, and neuroprotection.

The control group was treated with rosuvastatin tablets (AstraZeneca Pharmaceutical Co., Ltd., China), 10 mg each time, qd, orally.

The observation group was given rosuvastatin tablets and compound Danshen injection (Sichuan Sanjing Shenghe Pharmaceutical Co., Ltd., China). 16 mL of compound Danshen injection was added to 150 mL of 5% glucose solution, intravenous drip, bid. During the course of treatment, if the patient did not tolerate the treatment or experienced serious adverse effects, the drug was immediately discontinued.

The patients in two groups started treatment immediately after their diagnoses upon admission, and the treatment lasted for 21 days. At the late stage of the treatment, they all underwent rehabilitation training to restore some body functions, such as standing, squatting, leg raising, and so on.

Outcome measures

Primary outcome measures: (1) After 21 days of treatment, the clinical curative effects of the two groups were compared, according to the clinical curative effect assessment criteria established by the 4th National Academic Conference on Cerebrovascular Disease [14]. Basically cured: the neurological deficit score decreased by 90%-100%. Significant improvement: the neurological deficit score decreased by 45%-90%. Improved: the neurological deficit score decreased by 18%-45%. No change: the neurological deficit score decreased by less than 18%. Deterioration: the neurological deficit score increased by more than 18%. Overall effective rate = (basically cured cases + significantly improved cases + improved cases)/total cases * 100%.

(2) After 21 days of treatment, the CRP, D-dimer, and IL-6 levels were compared between the two groups. 5 mL of venous blood (3 tubes) were drawn from all the study subjects upon enrollment (before they received any treatment), of which two tubes were centrifuged at 3,000 r/min for 5 min. The separated serum was used to measure their IL-6 and CRP levels using enzyme-linked immunosorbent assays (Spectra-MaxParadigm multifunctional microplate reader, Molecular Devices, USA), and the kits were purchased from Shanghai Future Industrial Co., Ltd. The other tube was centrifuged, and the plasma was drawn for future use to measure the plasma D-dimer levels using enzyme-linked immunosorbent assays, and the kit were purchased from the Shanghai Enzyme-linked Biotechnology Co., Ltd.

(3) After 3 months, the NIHSS, Fugl-Meyer, and ADL scores were compared between the two groups [15-17]. The NIHSS score scale was used to assess the degree of neurological deficits in the patients, with the total possible score ranging from 0-42, and the lower the score, the less the neurological deficit. The Fugl-Meyer scale was used to assess each patient's functional capacity, with a total possible score of 0-100, and the higher the score the better the motor function. The ADL scale was used to assess each patient's daily living activities, with the total possible score ranging from 0-100 points, and the score was directly proportional to the patient's self-care abilities.

(4) After 21 days of treatment, the two groups' sleep quality was compared. The Pittsburgh Sleep Quality Index (PSQI) and the Athens Insomnia Scale (AIS) were used to assess the sleep quality. The worse the PSQI score, the more severe the AIS score, and the more severe the sleep disorder [18].

Secondary outcome measures: During the treatment, the skin allergic reaction, shock, acute laryngeal edema, severe diarrhea, neurotoxicity, liver and kidney damage, asthma, sinus

Table 2. Comparison of the treatment efficacy between the two groups (n, %)

Group	Control group (n=58)	Observation group (n=58)	χ^2	P
Deterioration	0 (0.00)	0 (0.00)	7.100	0.068
No change	15 (25.86)	6 (10.34)		
Improvement	14 (24.13)	10 (17.24)		
Significant improvement	14 (24.14)	18 (31.03)		
Basically cured	15 (25.86)	24 (41.38)		
Overall effective rate	43 (74.14)	52 (89.66)	4.710	0.030

Table 3. Comparison of the CRP, D-dimer, and IL-6 levels between the two groups ($\bar{x}$±sd)

Indicators	Control group (n=58)	Observation group (n=58)	t	P
CRP (mg/mL)				
Before treatment	15.60±4.08	15.11±4.42	0.685	0.487
After treatment	7.10±3.59***	4.16±3.98***	4.307	0.000
D-Dimer (mg/mL)				
Before treatment	3.30±0.48	3.47±0.56	0.843	0.400
After treatment	2.85±0.47***	2.46±0.19***	5.713	0.000
IL-6 (ng/mL)				
Before treatment	58.97±13.39	58.15±14.51	0.349	0.730
After treatment	34.10±11.86***	25.14±12.29***	3.982	0.000

Note: Compared with before the treatment, ***P<0.001.

tachycardia, bradycardia, bedsore, urinary tract infection, and other adverse reaction incidence rates were compared between the two groups. If the same patient had multiple complications, the multiple complications were calculated when the total incidence rate was calculated, that is, total incidence rate = complications/total cases × 100%.

Statistical analysis

SPSS 20.0 was used for the data analysis. The enumeration data were represented as n/%, χ^2 tests were used for the comparisons. The measurement data conforming to a normal distribution were represented as the mean ± standard deviation ($\bar{x}$±sd). Independent t tests were used for the inter-group comparisons, and the intra-group comparisons were done using paired t tests. P<0.05 was considered statistically significant.

Results

In this study, 116 patients were included, and during the treatment, no intolerance to the treatment or serious adverse reactions occurred.

Comparison of general baseline data between the two groups

There were no significant differences in terms of age, gender, body mass index, infarct location, area, speech, or motor involvement between the two groups (P>0.05). See **Table 1**.

Comparison of the clinical curative effects between the two groups

The effective rate in the observation group (89.66%) was significantly higher than the effective rate in the control group (74.14%, P<0.05). See **Table 2**.

Comparison of the CRP, D-dimer, and IL-6 levels between the two groups

The serum CRP, D-dimer, and IL-6 levels in the two groups after the treatment were significantly lower than they were before the treatment, and the observation group's levels were lower than the control group's levels (all P<0.001). See **Table 3**.

Table 4. Comparison of the NIHSS, Fugl-Meyer, and ADL scores between the two groups ($\bar{x}$±sd)

Indicators	Control group (n=58)	Observation group (n=58)	t	P
NIHSS (points)				
Before treatment	11.38±1.02	12.08±1.33	2.494	0.015
After treatment	9.02±1.07***	7.05±1.08***	10.117	0.000
Fugl-Meyer (points)				
Before treatment	41.10±4.02	40.70±3.45	0.555	0.586
After treatment	69.16±3.88***	81.38±4.13***	16.920	0.000
ADL (points)				
Before treatment	39.12±6.32	40.33±5.64	1.222	0.218
After treatment	67.55±4.04***	80.85±5.78***	14.254	0.000

Note: Compared with before the treatment, ***P<0.001.

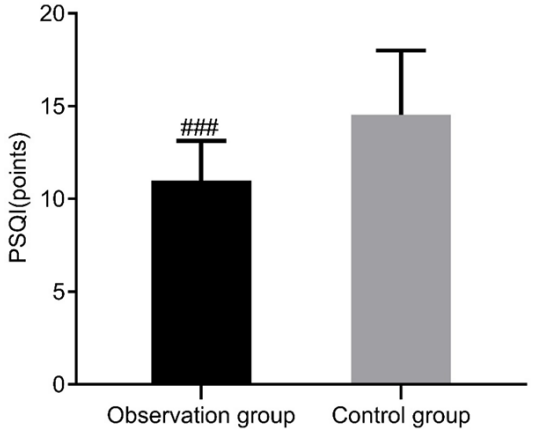

Figure 1. Comparison of the PSQI scores between the two groups. Compared with the control group, ###P<0.001. PSQI: Pittsburgh Sleep Quality Index.

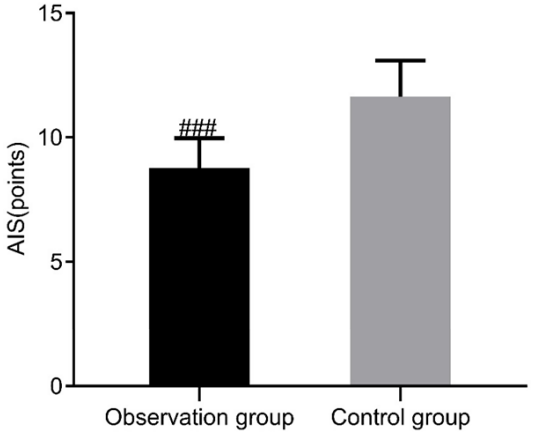

Figure 2. Comparison of the AIS scores between the two groups. Compared with the control group, ###P<0.001. AIS: Athens Insomnia Scale.

Comparison of the NIHSS, Fugl-Meyer, and ADL scores between the two groups

After the treatment, the NIHSS scores in the observation group were significantly lower than they were in the control group, and the Fugl-Meyer and ADL scores were significantly higher than they were in the control group (all P<0.001). See **Table 4**.

Comparison of the post-treatment PSQI scores in the two groups

Compared with the control group, the PSQI scores in the observation group were significantly lower than they were in the control group (10.98±2.15 vs. 14.54±3.46, t=7.592, P< 0.001). See **Figure 1**.

Comparison of the post-treatment AIS scores in the two groups

Compared with the control group, the AIS scores in observation group were significantly lower than they were in the control group (8.78±1.19 vs. 11.64±1.45, t=11.612, P<0.001). See **Figure 2**.

The incidences of adverse reactions in the two groups

The total adverse reaction incidence rates, including incidents such as severe diarrhea, bedsores, urinary tract infections, liver and kidney function injuries, and skin allergic reactions in the observation group were significantly less than they were in the control group (P<0.05).

Table 5. The incidence of adverse reactions in the two groups (n, %)

Group	Control group (n=58)	Observation group (n=58)	χ^2	P
Severe diarrhea	2 (3.45)	1 (1.72)	0.342	0.558
Bedsore	6 (10.34)	1 (1.72)	3.800	0.051
Urinary tract infection	6 (10.34)	1 (1.72)	1.214	0.213
Hepatic and renal impairment	1 (1.72)	1 (1.72)	0.000	1.000
Allergic skin reaction	0 (0.00)	1 (1.72)	1.008	0.315
Total adverse reactions	15 (25.86)	5 (8.62)	6.041	0.014

Other adverse reactions were not observed in the two groups. See **Table 5**.

Discussion

Rosuvastatin, a statin drug, is an important drug in ischemic cerebral infarction treatment [19]. Compound Danshen injection is a pure Chinese herbal preparation, and its main components are two Chinese herbs, Danshen and *Dalbergia odorifera*. Danshen contains tanshinone, which can improve blood circulation and remove blood stasis, nourish the blood and regulate menstruation, and tranquilize the mind and relieve pain. *Dalbergia odorifera* is warm in nature and enters the liver meridian, and it can play a role in regulating qi and relieving pain, and perform blood stasis and hemostasis, so it has the curative effects of dilating the blood vessels, preventing myocardial ischemia and hypoxia, and scavenging free radicals [20]. Liu et al. took 67 elderly patients with ACI as their study cohort, and the control group used rosuvastatin alone, and the observation group used basic compound Danshen injection. The study concluded that the clinical therapeutic effect of the combination of the two in the treatment of elderly patients with ACI was significant [13]. In this study, rosuvastatin combined with compound Danshen Injection was used to cure patients with ACI. The results indicated that the overall effective rate in the observation group was more than it was in the control group, indicating that the efficacy of the combination is significant and that the cerebrovascular blood supply and circulation can be improved, which is consistent with the above study results.

CRP is a classical acute phase protein. Studies have shown that CRP can lead to inflammatory cascades in the ischemic area and aggravate brain edema, and neuronal and brain tissue injuries. It has also been shown that the CRP expression levels are associated with the prognoses of ACI patients [21, 22]. IL-6 is a type of interleukin, and it plays a role as a pro-inflammatory cytokine and anti-inflammatory myosin. Studies suggested that IL-6 is involved in the occurrence and development of ischemic cerebrovascular disease and is involved in the process of ACI injury or repair [23]. D-dimer is derived from a plasmin-solubilized cross-linked fibrin clot as a marker of thrombin activity and thrombosis or lysis [24]. Studies have found that there is a close relationship between the D-dimer levels and the severity and prognosis of cerebral infarction [25]. Ma et al. analyzed the IL-6, CRP, and D-dimer expressions in 300 patients with ACI and suggested that the IL-6, CRP, and D-dimer levels can be used as important indicators for efficacy evaluation [26]. Other studies have found that the inflammatory factor levels are related to the NIHSS scores and the sleep quality [27, 28]. The results of this study revealed that the CRP, D-dimer, and IL-6 levels in the observation group were lower than they were in the control group, an indication that the drug combination decreased the CRP, D-dimer, and IL-6 levels compared with using just a single drug, so it may be due to the fact that the compound Danshen injection applied in the observation group was able to reduce the production of the multiple inflammatory mediators, which is consistent with the results of Long et al. [29].

The degree of neurological deficit after cerebral infarction assessment used the NIHSS scale, including multiple dimensions such as consciousness, language, movement, sensation, synkinesis, eye movement, and visual field. Fugl-Meyer is used to evaluate the motor function after cerebral infarction, and ADL is used to evaluate the activities of daily living after cerebral infarction. Studies have shown that the NIHSS, Fugl-Meyer, and ADL scores can be used as illness severity, prognosis, and efficacy evaluation indicators in ACI patients [15-17,

30]. In this study, the NIHSS scores in the observation group were significantly lower than they were in the control group, and the Fugl-Meyer and ADL scores were significantly higher than they were in the control group, which shows that the combination of drugs promoted the recovery from the disease compared with a single drug.

Chen et al. observed 101 patients with first-episode ACI. The results revealed that the PSQI scores in the cerebral infarction group were significantly lower than they were in the non-cerebral infarction patients [31]. The study concluded that the ACI patients often also suffered from sleep disorders, aggravated neurological deficits and worse sleep quality. Fu et al. concluded that age, depression, NIHSS scores, BI scores, and aphasia are independent risk factors for insomnia in patients with cerebral infarction [32]. Studies have shown that after the injection of compound Danshen injection in mice, it has a sedative effect that can last several hours, and it can prolong the mice's sleep time. Through EEG observations, it was shown that compound Danshen injection can reduce the spontaneous activity of the cerebral cortex and inhibit the active function of the cerebral cortex [33]. In our study, we observed that the PSQI and AIS scores in the observation group were significantly better than they were in the control group, suggesting compound Danshen injection can improve patients' sleep quality, which may be due to the sedative and tranquilizing effect of compound Danshen injections, so the study once again confirms the effect of compound Danshen injection on promoting sleep. This study further analyzed the incidence rate of adverse reactions in the two groups. The gastrointestinal reaction, bedsore, and other total adverse reaction rates in the observation group were lower than they were in the control group, indicating that the combination of drugs has a definite curative effect on the treatment of patients with ACI and is very safe.

In summary, rosuvastatin combined with compound Danshen injection is an effective ACI treatment, and it is capable of effectively enhancing patients' clinical symptoms, reducing the incidence of complications, promoting the recovery of the IL-6, CRP, and D-dimer levels and other indicators, and improving patients' sleep quality.

Disclosure of conflict of interest

None.

Address correspondence to: Fengming Bian, Department of Neurology, The Fifth Hospital in Harbin, No. 27 Jiankang Road, Harbin 150040, Heilongjiang Province, China. Tel: +86-0451-88626807; E-mail: fengming_bian@126.com

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