MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 610-617
DOI: 10.12659/MSM.912064

Received: 2018.07.12
Accepted: 2018.09.10
Published: 2019.01.21

Effect of Interventional Therapy on IL-1β, IL-6, and Neutrophil-Lymphocyte Ratio (NLR) Levels and Outcomes in Patients with Ischemic Cerebrovascular Disease

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental souurces

Background: This study investigated the clinical effect of interventional therapy in ischemic cerebrovascular disease (ICD).

Material/Methods: A retrospective analysis was performed on 260 ICD patients who were divided into a control group (122 patients, conventional drug treatment) and an observation group (138 patients, interventional therapy plus conventional drug treatment). Enzyme-linked immunosorbent assay was used to examine the expression of IL-1β, IL-6, and NLR. Furthermore, neurological deficit scores and Barthel index scores as well as the correlation of IL-1β, IL-6 and NLR were examined in these 2 groups.

Results: The expression of IL-1β, IL-6, and NLR significantly decreased in both groups after 1 week or 4 weeks of treatment compared with before treatment ($P<0.05$). Significant differences in neurological impairment scores were detected between these 2 groups after 4 weeks of treatment ($P<0.05$), and the control group showed higher neurological deficit scores than did the observation group ($P<0.05$). Barthel index scores were significantly higher after treatment than before treatment in the control and observation group ($P<0.05$), and the control group had lower Barthel index scores than did the observation group ($P<0.05$). Pearson correlation analysis showed that IL-1β, IL-6, and NLR expression were positively correlated in ICD patients ($P<0.05$).

Conclusions: Interventional surgery combined with conventional drug therapy can reduce serum IL-1β and IL-6 levels, decrease neurological impairment, and improve the quality of life of patients. The combined treatment group showed better outcomes than did the group that received the drug alone; therefore, combined therapy is suitable for promoting better clinical outcomes.

MeSH Keywords: Cerebrovascular Disorders • Hypoxia-Ischemia, Brain • Nervous System Diseases

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912064

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Background

Ischemic cerebrovascular disease (ICD) refers to the occurrence of ischemia and hypoxia in brain tissues due to changes in the cerebral arterial wall and hemodynamic disturbances; this disease can cause continuous or transient damage to brain tissues [1]. ICD is a common clinical disease in the elderly. Population aging is the major driver of the projected increase in the incidence of ICD, and a rising trend in the incidence is also observed in young people [2]. Studies have shown that ICD accounts for more than 75% of cerebrovascular disease, which has a great impact on human health and is the third most common disease followed by cardiovascular and coronary heart disease [3]. ICD is characterized by high incidence, high recurrence, high disability, and high mortality [4]. It is estimated that about 17 million people die of cerebrovascular diseases each year worldwide [5], and post-treatment patients have different degrees of sequelae, seriously decreasing their quality of life.

Interleukin-1 (IL-1) has a wide range of biological effects in host defense against infection; for example, it plays an important role in the immune and inflammatory responses in cerebrovascular diseases such as cerebral infarction and atherosclerosis [6]. IL-1β is one of the 3 major members of the IL-1 family. Studies have shown that enhanced expression of IL-1 after cerebral infarction aggravates the ischemic injury, and IL-1β is the main contributor to this [7]. IL-6 is the most important pro-inflammatory cytokine in the body and is normally expressed at low levels; however, its expression rapidly rises in inflammatory responses, autoimmune diseases, and malignancy [8]. Studies have shown that elevated serum IL-6 level is a risk factor for progressive cerebral infarction [9]. Neutrophil/lymphocyte ratio (NLR) has becomes a widely-used indicator of inflammation in recent years. Studies have shown that NLR has important effects in cardiovascular and cerebrovascular diseases [10].

The traditional treatment of ICD is mainly based on surgical removal of the carotid intima and supplementation with drugs, but the effect of drug treatment alone is not satisfactory. However, surgery causes severe trauma, and the recovery time is very long. Moreover, ICD occurs primarily in the elderly, and the patient's physical and surgical tolerance is often poor; therefore, more postoperative complications can occur, and the effects of the surgical treatment are limited [11]. In recent years, with the development of the medical techniques, interventional treatment has gradually become accepted. Interventional treatment has several advantages, such as less trauma, improved cerebral blood flow, and fewer complications, and this treatment procedure has thus been rapidly promoted in clinical practice. Notably, blood vessel stenosis and blood supply recovery are greatly improved by interventional therapy [12].

Therefore, this study investigated the beneficial effect of interventional therapy in ICD, and the expression of IL-1β, IL-6, and NLR during ICD treatment was also examined.

Material and Methods

Patients

A retrospective analysis was performed on 260 ICD patients who were treated in the First Hospital of Jilin University from April 2015 to June 2016. Patients were divided into the control group (drug treatment) and the observation group (interventional treatment) according to treatment methods. The control group comprised 122 patients (68 males, and 54 females), and the mean age was 57.9 years (range, 45–77 years). The observation group had 138 patients (79 males and 59 females), and the mean age was 59.2 years (range, 30–75 years). Patients were diagnosed with having ICD by 2 doctors who had more than 10-year treatment experience in this disease. The study was approved by the Medical Ethics Committee of this hospital. All patients and their families were informed and signed informed consent and were followed up for 6 months.

Inclusion and exclusion criteria

Inclusion criteria

Patients with an acute stroke caused by carotid stenosis; all patients were diagnosed by magnetic resonance imaging (MRI) and digital subtraction angiography (DSA). Patients undergoing interventional therapy met the criteria for stent implantation [13]: (1) Patients had no defects in innate immune function. (2) Patients had not undergone surgery last year. (3) The clinical data of patients were complete.

Exclusion criteria

(1) The patient age was less than 18 years old. (2) Intracranial hemorrhage occurred within 6 months, or obstruction occurred within 2 weeks before treatment. (3) Patients were allergic to the drug. (4) Patients did not cooperate with treatment or the follow-up examinations. (5) Patients had a history of intracerebral hemorrhage or brain tumor.

Drugs and reagents

Aspirin (GuoYaozhunzi: H11022079, 50 mg/tablet) was purchased from Beijing Taiyang Pharmaceutical Co. Clopidogrel bisulfate (GuoYaozhunzi: J20080090, 75 mg/tablet) was purchased from Sanofi Pharmaceutical Co. Atorvastatin calcium (GuoYaozhunzi: H20051408, 20 mg/tablet) was purchased from Pfizer Pharmaceuticals Co. IL-1β and IL-6 enzyme-linked

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immunosorbent assay (ELISA) kits were purchased from Biyuntian Institute of Biotechnology.

Treatment methods

Patients in the control group were treated with conventional drugs and patients in the observation group were treated with interventional surgery. The interventional surgery was as follows: routine local anesthesia and disinfection were performed, followed by femoral artery puncture. We used a micro-guidewire and a path map to guide the saline and urokinase into the patient along the catheter pump at a rate of 1 mL/min, and inserted the stent at the site of the arterial stenosis or embolization. All patients were administrated aspirin (100 mg/d) and clopidogrel bisulfate (75 mg/d) for 6 months. In the observation group, 1–3 enteric-coated tablets of aspirin were administered 4 days before interventional surgery, and aspirin (100 mg/d) and clopidogrel (75 mg/d) were continuously taken for 6 months after surgery. Patients in both groups were administrated atorvastatin (20 mg/d) during the treatment.

Evaluation of IL-1β and IL-6 levels

Before the treatment, blood samples were collected after an overnight fast, and the serum was isolated after centrifugation for ELISA detection. The levels of IL-1β, IL-6, and NLR were examined according to the instructions of the ELISA kit. The procedure was as follows: (1) Add 50 μL of each detection buffer to the sample and then 50 μL of the diluted detection antibody, close the plate, and incubate at 25°C for 2 h with shaking. (2) Wash with washing solution 6 times, each for 1 min, add 100 μL of diluted horseradish peroxidase-labeled streptavidin, then seal the plate again, and incubate the plate for 45 min with shaking. (3) Perform 6 washes using the wash solution, each for 1 min, and add 100 μL chromogenic substrate TMB. (4) Protect from light and incubate the plate for 15 min at 25°C. (5) Add 100 μL of stop solution. (6) Within 30 min, double-wavelength detection is performed using a microplate reader, and the maximum absorption wavelength is 450 nm. Samples were tested in 3 sets of duplicate wells, and every experiment was repeated 3 times. NLR testing was performed using the Sysmex blood routine XT-1800i instrument.

Assessment indicators

The main assessment indicators were: expression of IL-1β, IL-6, and NLR was observed in both groups before treatment and after 1 week and 4 weeks of treatment.

The secondary assessment indicators were: neurological deficit scores were observed in both groups before treatment and after 4 weeks of treatment. Total scores range from 0 to 45 points; the higher the score, the more severe the nerve injury. Barthel index scores were also observed in the 2 groups: total scores range from 0 to 100 points; the lower the value, the more severe the inability to perform daily activities. Correlations between IL-1β, IL-6, and NLR in patients with ICD were analyzed.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software, and sheets were drawn using GraphPad Prism 7 software. Count data are presented as percentage (%), and a chi-square test was used to determine the difference analysis. Measured data are expressed as mean ± standard deviation, and a paired-samples *t* test was used for analysis between these 2 groups. The curative effects at multiple time points between these 2 groups were evaluated using repeated analysis of variance. Pearson test was performed to analyze the relationship between IL-1β and IL-6 and NLR. $P<0.05$ indicates a statistical difference.

Results

Characteristics of patients

No differences in sex, age, body mass index, vascular width, smoking history, alcoholism history, hypertension history, or diabetes history were observed between the 2 groups ($P>0.05$), as shown in Table 1.

Expression of IL-1β, IL-6, and NLR before and after treatment

The serum levels of IL-1β, IL-6, and NLR were evaluated by ELISA in the 2 groups before and after treatment. No differences in the expression of IL-1β, IL-6, or NLR were found between the 2 groups before treatment ($P>0.05$) (Figures 1, 2). The expression of IL-1β, IL-6, and NLR was significantly decreased in the 2 groups after 1 week and 4 weeks of treatment compared with before treatment ($P<0.05$). The expression of IL-1β, IL-6, and NLR was significantly decreased in both groups after 4 weeks of treatment compared with the first-week treatment ($P<0.05$) (Figures 1, 2). The IL-1β, IL-6, and NLR levels were significantly lower in the observation group than in the control group after 1 and 4 weeks of treatment ($P<0.05$) (Tables 2–4).

Comparison of neurological deficit scores and Barthel index scores between these 2 groups

Neurological deficit scores and Barthel index scores were compared between these 2 groups before treatment and after 4 weeks of treatment, and no differences in pre-treatment neurological deficit scores or Barthel index scores were found between these 2 groups. Neurological deficit scores were significantly reduced after 4 weeks of treatment in both the control

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Table 1. Clinical data of two groups of patients [n (%)].

Terms	Control group (n=122)	Observation group (n=138)	t/χ^2	P value
Sex				
Male	68 (55.74)	79 (57.25)	0.179	0.673
Famale	54 (44.26)	59 (42.75)		
Age (years)	57.9±6.3	59.2±7.1	1.552	0.123
BMI (kg/m^2)	21.54±2.58	22.05±2.18	1.727	0.085
Vascular width (mm)	5.2±1.1	5.3±1.4	0.635	0.526
Smoking history				
Yes	68 (55.74)	82 (59.42)	0.360	0.549
No	54 (44.26)	56 (40.58)		
History of alcoholism				
Yes	15 (12.30)	21 (15.22)	0.464	0.496
No	107 (87.70)	117 (84.78)		
History of hypertension				
Yes	99 (77.34)	108 (78.26)	0.332	0.564
No	23 (22.66)	30 (21.74)		
Diabetes history				
Yes	70 (57.38)	88 (63.77)	1.740	0.187
No	52 (42.62)	50 (36.23)		

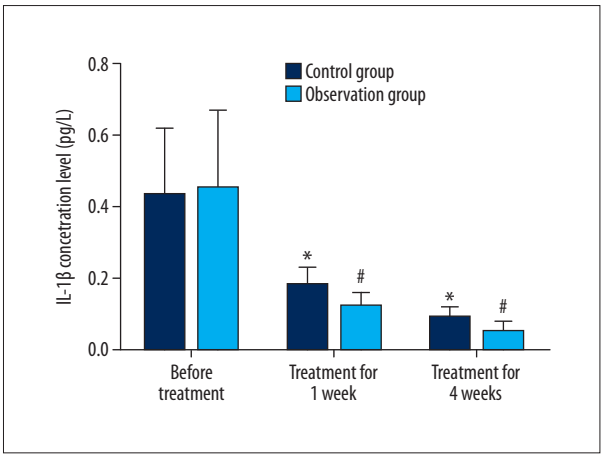

Figure 1. ELISA was used to evaluate the expression of IL-1β in the 2 groups before and after treatment. No differences were found between these 2 groups before and after IL-1β treatment. Significant differences were observed after 1 and 4 weeks of treatment in the 2 groups (* P<0.05), and IL-1β levels were higher in the control group than in the observation group after 1 and 4 weeks of treatment (# P<0.05).

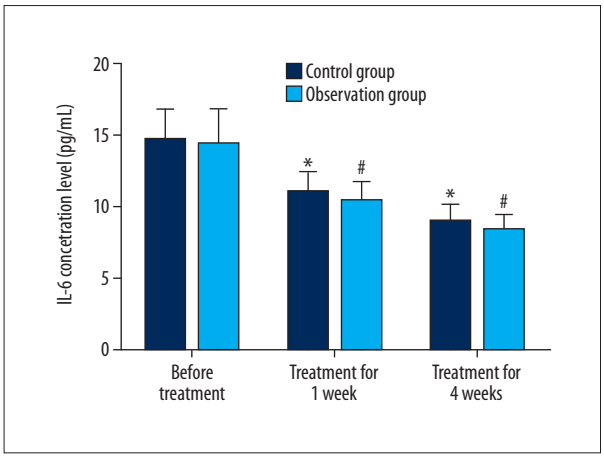

Figure 2. Expression of IL-6 was evaluated by ELISA in the 2 groups before and after treatment. No differences were observed between these 2 groups before and after IL-6 treatment. Significant differences in IL-6 levels were found after 1 and 4 weeks of treatment in these 2 groups (* P<0.05), and the control group had higher IL-6 expression than did the observation group after 1 week and 4 weeks of treatment (# P<0.05).

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Table 2. Expression of IL-1 beta before and after treatment in two groups of patients.

Group	Pretherapy IL-1β (pg/L)	Treatment for 1 week IL-1β (pg/L)	Treatment for 4 week IL-1β (pg/L)
Control group	0.43±0.19	0.18±0.05*	0.09±0.03*,**
Observation group	0.45±0.22	0.12±0.04*	0.05±0.03*,**
t value	0.779	10.737	10.729
P value	0.436	0.000	0.000

* There was a difference between before and after treatment (P<0.05). * There was a difference compared with one week after treatment (P<0.05).

Table 3. Expression of IL-6 in two groups of patients before and after treatment.

Group	Pretherapy IL-6 (pg/mL)	Treatment for 1 week IL-6 (pg/mL)	Treatment for 4 week IL-6 (pg/mL)
Control group	14.66±2.15	10.96±1.44*	8.94±1.25*,**
Observation group	14.29±2.58	10.35±1.39*	8.32±1.10*,**
t value	1.25	3.472	4.25
P value	0.214	0.001	0.001

* There was a difference between before and after treatment (P<0.05). * There was a difference compared with one week after treatment (P<0.05).

Table 4. Expression of IL-6 in two groups of patients before and after treatment.

Group	Pretherapy NLR (pg/mL)	Treatment for 1 week NLR (pg/mL)	Treatment for 4 week NLR (pg/mL)
Control group	4.15±1.58	3.52±1.05*	2.38±0.79*,**
Observation group	3.98±1.37	2.87±0.98*	1.82±0.65*,**
t value	0.929	5.161	6.267
P value	0.354	0.000	0.000

* There was a difference between before and after treatment (P<0.05). * There was a difference compared with one week after treatment (P<0.05).

group and the observation group (*P*<0.05). Neurological deficit scores were significantly higher in the control group than in the observation group (*P*<0.05) (Figure 3). Barthel index scores were significantly higher after treatment than before the treatment in both the control group and the observation group (*P*<0.05) (Figure 4). Barthel index scores were significantly lower in the control group than in the observation group (*P*<0.05) (Table 5).

Relationship between IL-1β, IL-6 and NLR

We analyzed the expression relationship between IL-1β, IL-6, and NLR at 4 weeks after treatment in the observation group, showing a positive correlation between IL-1β, IL-6, and NLR (P<0.05) (Figure 5, Table 6).

Discussion

ICD is caused by atherosclerosis in patients with arterial obstruction or stenosis, and atherosclerosis can result in abnormal blood supply in the area of obstruction or stenosis [14]. The most common clinical subtypes of ICD include transient cerebral ischemia, cerebral infarction, and cerebral artery thrombosis, and transient cerebral ischemia and acute cerebral infarction are 2 major categories [15]. Studies have shown that when brain blood flow decreases by 30% to 40%, brain tissues have low perfusion, and the conditions can easily cause acute cerebrovascular events [16]. The treatment of ICD mainly includes surgery and drug treatment. The drug treatment is a conservative treatment and involves using anti-platelet

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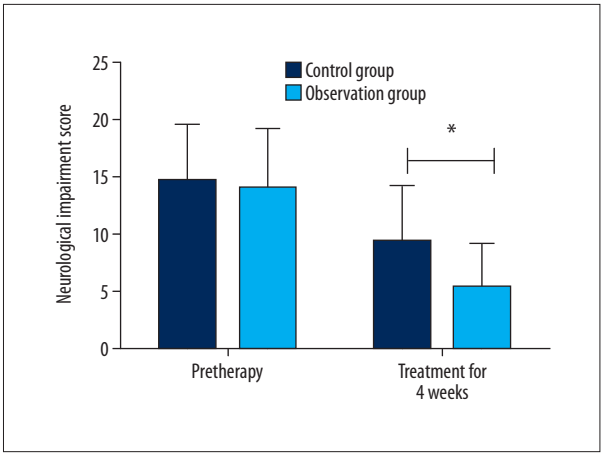

Figure 3. Neurologic impairment scores in the 2 groups before and after treatment. The scores were significantly lower after treatment than before treatment in the 2 groups (* P<0.05). The scores were higher in the control group than in the observation group after treatment (* P<0.05).

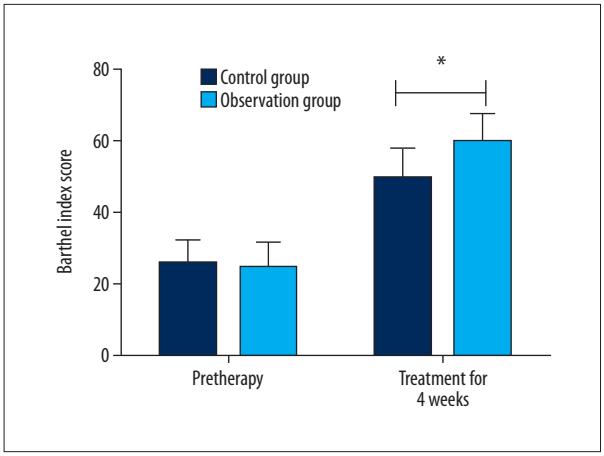

Figure 4. Barthel index scores in the 2 groups before and after treatment. The scores significantly increased in the 2 groups after treatment compared with before treatment (*P<0.05), and the scores were lower in the control group than in the observation group after treatment (* P<0.05).

Table 5. Scores of two groups before and after treatment.

Group	Neurological impairment score		Barthel index score	
	Pretherapy	Treatment for 4 weeks	Pretherapy	Treatment for 4 weeks
Control group	14.68±4.94	9.34±4.94*	25.68±12.39	49.54±22.35*
Observation group	13.99±5.26	5.36±3.84*	24.36±11.36	59.64±23.88*
t value	1.086	7.184	0.903	3.507
P value	0.278	0.000	0.368	0.001

* Indicates that there is a difference between before and after treatment (P<0.05).

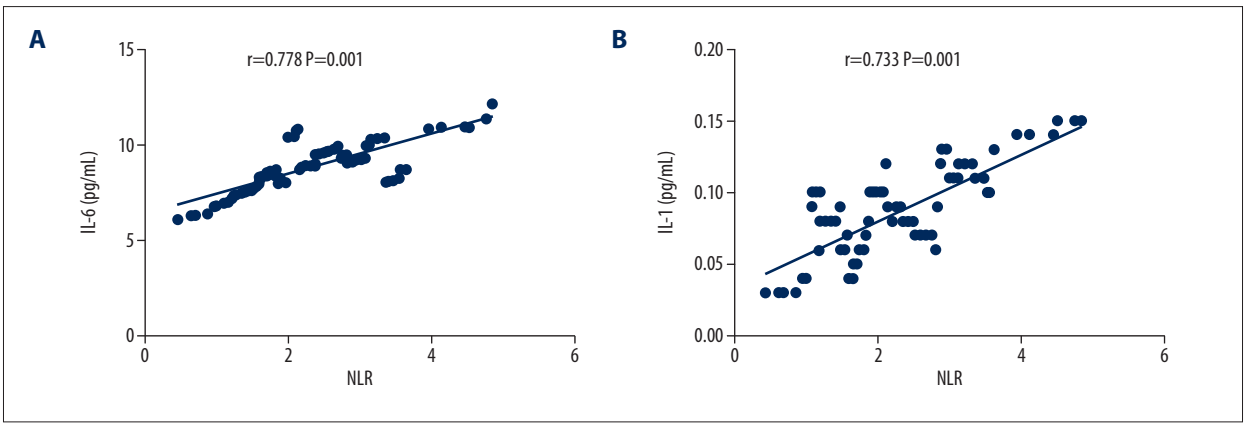

Figure 5. (**A, B**) Correlation analysis of serum IL-1 beta, IL-6, and NLR in ICD patients. Pearson correlation analysis showed that there was a positive correlation between IL-6 and NLR (r=0.778, P=0.001). Pearson correlation analysis showed that there was a positive correlation between IL-1β and NLR (r=0.733, P=0.001).

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Table 6. Relationship between IL-1 β and IL-6 and NLR.

Project	r	P
IL-1β	0.733	0.001
IL-6	0.778	0.001

aggregation and lipid-regulating medicines. The condition is controlled if it does not worsen and the width of the vascular lumen is not affected [17].

Interventional treatment was originally used for biliary stents and peripheral vascular stents, which are surgical treatments of carotid stenosis. However, with the development of the medical technique, a variety of stent systems were gradually derived and combined with self-expansion techniques to reduce the stent displacement [18]. In order to prevent the occurrence of plaque detachment during the expansion process, a variety of protective devices have also been used to provide security for the interventional treatment of vascular disease; therefore, interventional treatment has been widely promoted [19].

In this study, we compared the effects of the interventional therapy combined with the conventional drug treatment and the conventional drug treatment alone. The neurological deficit score is a scale designed specifically for the study of acute stroke treatment and is primarily used to score the neurological function of patients [20]. The Barthel index score is the most commonly used life-therapy score in the United States Rehabilitation Agency, and it is mainly used to score changes in independent living conditions before and after treatment in the elderly [21]. In this study, we scored 2 groups of patients by using these 2 scales. We found that neurological deficit scores were significantly lower in the observation group than in the control group, but Barthel index scores were significantly higher in the observation group than in the control group after treatment. The results indicate that compared with the conventional drug alone treatment, interventional surgery combined with the conventional drug treatment has a significantly better effect on ICD. Behme et al. [22] have shown that interventional surgery significantly improved the effect of acute ischemic stroke treatment. Another study showed that neurological deficit scores were significantly improved after the interventional treatment of ICD patients [23]. Zhang et al. [24] found that compared with atorvastatin treatment alone, the combination therapy (atorvastatin combined with clopidogrel) showed significantly better outcomes in terms of neurological deficit scores and Barthel index scores. In this study, both scores were also significantly improved through the combined treatment of interventional surgery and drug treatment compared with drug treatment alone. The results suggest that interventional surgery combined with drug treatment has a significantly better effect on neurological function and the activities of daily living ability of ICD patients.

In addition, we examined the expression of serum IL-1β, IL-6, and NLR in ICD patients, and found that IL-1β promoted inflammation and anticoagulation and prevented fiber accumulation. Studies have shown that IL-1β promotes the formation of thrombi, and differential expression of IL-1β is an important feature of the development of ICD [25]. Another study showed that ischemic injury was aggravated and infarct volume increased after intracerebroventricular injection of IL-1β [26]. IL-6 is one of the most important inflammatory factors in the body and can be secreted by many inflammatory cells, such as monocytes, T lymphocytes, and B lymphocytes. The increased expression of IL-6 indicates the presence of inflammation in the body [27]. Studies have shown that the higher the level of IL-6 in the serum of acute cerebral infarction patients, the worse the prognosis will be [28]. However, we found that the expression levels of IL-1β, IL-6, and NLR significantly decreased after 4 weeks of treatment compared with before treatment or at 1 week of treatment in the control group and the observation group. Moreover, significant differences in the expression of IL-1β and IL-6 were observed between these 2 groups after 1 week and 4 weeks of treatment, indicating that the combined treatment has a significantly better effect in ICD patients. Tang et al. [29] have shown that IL-6 levels increased in plasma and post-ischemic brain tissues in a focal brain ischemia animal model (occlusion of the middle cerebral artery of animals for 5 min followed by reperfusion for 24 h). Our study indicates that the combined treatment reduces the expression of IL-6; both treatment methods have a certain effect on ICD, and the combined treatment has a better effect than does drug alone treatment. We also conducted a Pearson correlation analysis on each indicator and found that there was a positive correlation between IL-1β, IL-6, and NLR, but it is unclear how it is specifically regulated.

This study has several limitations. First, the sample size was small; therefore, the accuracy of the results needs to be verified. Second, we did not perform long-term follow-ups for patients in the 2 groups. Therefore, further studies, with increased sample size and long-term follow-up, are needed to verify our results. A study showed [30] than improved cognitive performance was related to cerebral vasomotor reactivity, which is also an interesting factor that warrants further study. Several recent studies found that stroke prognosis is strongly influenced by a variety of controllable factors, such as metabolic homeostasis, perfusion and hemodynamic disturbances, and drug actions [31–33]. All these factors may act at the brain site of damage and systemic level, influencing the neurovascular recovery, secondary damage, and systemic complications. We plan to establish a method for multidimensional evaluation of stroke patients and to propose corresponding targeted treatments.

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Conclusions

In summary, interventional surgery combined with conventional drug therapy can reduce serum IL-1β, IL-6, and NLR levels, decrease neurological impairment, and improve the quality of life of patients. The combined treatment has better effects than does drug treatment alone; therefore, the combined treatment is suitable for use in clinical settings and should be promoted.

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