

Therapeutic Efficacy of Atorvastatin and Aspirin on Inflammatory Factors in Cerebral Venous Thrombosis

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Shen *et al.*: Effect of Atorvastatin and Aspirin on Cerebral Venous Thrombosis

This paper primarily discusses about the influence of atorvastatin plus aspirin on efficacy and inflammatory factors in patients with cerebral venous thrombosis. The study participants comprised 240 cerebral venous thrombosis patients selected between January 2020 and June 2022 who were grouped as a conventional group (n=107) treated with aspirin and a research group (n=133) treated by atorvastatin+aspirin based on the therapy they received. Statistical and comparative analysis were made regarding the curative efficacy, adverse events (gastrointestinal discomfort, nausea, vomiting and dizziness), inflammatory factors (interleukin-6, tumor necrosis factor-alpha, procalcitonin, high-sensitivity C-reactive protein), platelet parameters (hematocrit, platelet adhesion rate), nerve function injury (National Institute of Health Stroke Scale) and activities of daily living. Based on the analysis results, the research group had a higher overall response rate, a lower complication rate and reduced inflammatory factors, platelet parameters and National Institute of Health Stroke Scale scores than the conventional group, as well as notably higher post-treatment activities of daily living, with statistical significance. From the above, it can be concluded that atorvastatin+aspirin is significantly effective in treating cerebral venous thrombosis, validly inhibiting inflammation, improving platelet parameters, alleviating neurological impairment and enhancing patients' activities of daily living.

Key words: Atorvastatin, aspirin, cerebral venous thrombosis, therapeutic efficacy, inflammatory factors

Cerebral Venous Thrombosis (CVT) is a kind of cardio-cerebrovascular condition in brain, belongs to the most common type of cerebral infarction and often occurs in the middle-aged and elderly people, with bad living habits, diet and environmental conditions as the pathogenic factors^[1,2]. Its pathological mechanism is related to the stenosis or occlusion of the local cerebrovascular lumen caused by atherosclerosis and other reasons, which will cause the formation of local clots and thrombosis that can lead to ischemia, hypoxia and necrosis of brain tissue, seriously and negatively impacting the health of the patients^[3,4]. It also has the characteristics of acute, rapid and serious onset of disease, with high mortality and disability rates, mainly presenting with numbness of limbs, dysarthria and mouth-tongue deviation clinically^[5]. Current major treatments for CVT include thrombectomy, thrombolysis and drug therapy, however, the former two approaches, both of which are non-conservative treatments, have a high risk of intracranial hemorrhage and may threaten the life of the patients^[6,7]. Therefore, this study focuses

on the clinical treatment options for CVT patients from the perspective of pharmacotherapy to improve clinical outcomes and provide them with relatively safe and effective treatment methods.

Atorvastatin (ATO) as a statin, is a 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitor and has been shown in animal experiments that it can inhibit inflammation and platelet activation, protect vascular endothelial cells and alleviate cerebral edema^[8,9]. It has also been indicated to improve the outcomes of cerebrovascular Adverse Events (AEs) in patients with spontaneous subarachnoid hemorrhage by down-regulating Aquaporin-4 (AQP4) and Endothelin-1 (ET-1) levels and maintaining vascular autoregulation^[10]. A rat experiment reported that ATO can inhibit neuronal apoptosis in hypoxic-ischemic neonatal rats by activating a molecular pathway involved in Brain-Derived Neurotrophic Factor (BDNF), thus alleviating brain damage^[11]. While as a synthetic drug, Aspirin (ASP) has anti-inflammatory, anticoagulant and antithrombotic effects, as well as a certain preventive

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action against colorectal carcinoma, myocardial infarction and other cardiovascular events^[12,13]. One study reported that using ATO in combination with other drugs may be beneficial in further reducing the risk of reinfarction, stroke and death compared with ASP alone, suggesting that ATO+ASP may contribute to a better clinical outcome^[14].

Accordingly, we conducted relevant validation, mainly analyzing the effect of ATO+ASP on the efficacy and Inflammatory Factors (IFs) of CVT patients, which can fill the gap of the current lack in research on the role of ATO plus ASP in the treatment of CVT to some certain extent.

MATERIALS AND METHODS

General information:

The research participants were 240 CVT patients admitted to Sichuan Provincial People's Hospital between January 2020 and June 2022, including 107 patients in the conventional group (ASP therapy) and 133 patients in the research group (ATO+ASP therapy). The study was approved by the Sichuan Provincial People's Hospital Ethics Committee and informed consent was obtained from each subject. The two patient cohorts showed no statistical significance in baseline data ($p>0.05$), which was clinically comparable.

Inclusion and exclusion criteria:

The patients who met the diagnostic criteria for CVT, with the onset-to-admission time within 72 h, no contraindications to the study medication (ASP and ATO) and cooperation with the study were included in the study. Patients who received prior treatment with hemostatic, coagulation and antifibrinolytic drugs; CVT patients who are suffering combination with cerebral hemorrhage, myocardial infarction and/or coagulation dysfunction; limb paralysis and hemiplegia; history of mental illness or dysarthria and malignant tumors were excluded.

Research methods:

The conventional group was treated with ASP, which was taken once daily before meals or bedtime, 100 mg a time, for 6 mo. The research group was given ATO on the basis of ASP (the same administration method and dosage as the conventional group). ATO was taken orally at bedtime with a dose of 20 mg once a day for 6 mo.

Observation indicators:

The clinical efficacy of the drugs was analyzed by the evaluation criteria and divided into certain categories. The category cured refers to the disappearance of signs and symptoms, the recovery of language ability, the improvement of muscle strength to grade IV or above and the ability of self-care after treatment; a marked response means that the signs and symptoms basically disappear after treatment, the muscle strength is improved by 2 levels *vs.* before treatment and the language ability is basically normal; a response corresponds to the improved signs and symptoms after treatment, enhanced muscle strength by one level *vs.* before treatment, and improved language ability; non-response is translated as unaltered or worsened signs and symptoms after treatment. The Overall Response Rate (ORR) is the sum of cured, marked response and response as a percentage of the total number of patients. Post-treatment AEs such as gastrointestinal discomfort, nausea, vomiting and dizziness, were observed and recorded.

Before and after treatment, 6 ml of venous blood of upper limbs was taken on an empty stomach and the serum was separated by centrifugation to quantify Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF- α), Procalcitonin (PCT) and high-sensitivity C-Reactive Protein (hs-CRP) by Enzyme-Linked Immunosorbent Assays (ELISAs).

Venous blood (3 ml) was extracted from patients before and after treatment and centrifuged to collect the supernatant. The Hematocrit (Hct) and platelet adhesion rate were detected by Coulter LH 750 automatic blood routine analyzer.

Patients' neurological impairment and Activities of Daily Living (ADL) before and after treatment were assessed using the National Institutes of Health Stroke Scale (NIHSS) and ADL scoring system whose score range was 0-42 and 0-100, respectively. A higher NIHSS score suggests more serious neurological impairment, while a higher ADL scale score indicates a stronger ADL ability.

Statistical analysis:

Continuous variables, represented by ($\bar{x}\pm s$), were compared between groups using independent sample t tests. Categorical variables were described in the form of n (%), and inter-group differences were

identified by Chi-square (χ^2) tests. This study used Statistical Package for the Social Sciences (SPSS) 18.0 software for statistical analysis and $p < 0.05$ as the significant threshold.

RESULTS AND DISCUSSION

Baseline data of the two groups was compared and shown in Table 1. No significant inter-group differences were identified in baseline data such as sex, age, course of disease and complications between the two groups of patients ($p > 0.05$).

The treatment efficacy was evaluated and subdivided according to the criteria of cure, marked response, response and non-response. The ORR of the research group was calculated to be 92.48 %, which was significantly higher than that of 73.83 % in the conventional group ($p < 0.05$) (Table 2).

We statistically calculated the incidence rate of AEs such as gastrointestinal discomfort, nausea, vomiting, and dizziness in both cohorts, and found an obviously lower incidence of AEs in the research group, compared with the conventional group (15.89 % vs. 7.52 %) ($p < 0.05$) (Table 3).

ELISA detection of IFs such as IL-6, TNF- α , PCT and hs-CRP revealed no evident inter-group differences before treatment ($p > 0.05$) and the IFs were markedly reduced after treatment ($p < 0.05$) with even lower levels in the research group ($p < 0.05$) (fig. 1).

Measurements of platelet parameters (Hct and platelet adhesion rate) using an automatic blood routine analyzer also showed no notable inter-group differences before treatment ($p > 0.05$). After treatment, a marked reduction in these two platelet parameters was observed ($p < 0.05$), especially in the research group ($p < 0.05$) (fig. 2).

The NIHSS and ADL scores of both groups were evaluated to analyze the influences of the two drug therapies on CVT patients' neurological impairment and ADL. The two cohorts differed insignificantly in NIHSS and ADL scores before treatment ($p > 0.05$). After treatment, markedly reduced NIHSS score that was lower than that of the conventional group was determined in the research group ($p < 0.05$), while the ADL score was obviously elevated and was higher compared with the conventional group ($p < 0.05$) (fig. 3).

TABLE 1: COMPARISON OF BASELINE DATA BETWEEN THE TWO GROUPS OF PATIENTS

Indicators	Conventional group (n=107)	Research group (n=133)	χ^2/t	p
Gender				
Male	61 (57.01)	74 (55.64)	0.045	0.83
Female	46 (42.99)	59 (44.36)		
Age (years old)	63.15 \pm 5.95	62.95 \pm 5.54	0.269	0.79
Course of disease (h)	6.20 \pm 1.58	6.07 \pm 1.64	0.62	0.54
Complications				
Hypertension	37 (34.58)	41 (30.83)	0.516	0.77
Coronary heart disease	34 (31.78)	42 (31.58)		
Hyperlipidemia	36 (33.64)	50 (37.59)		

TABLE 2: COMPARISON OF CLINICAL EFFICACY OF DRUGS BETWEEN THE TWO GROUPS OF PATIENTS

Indicators	Conventional group (n=107)	Research group (n=133)	χ^2	p
Cure	29 (27.10)	72 (54.14)	-	-
Marked response	20 (18.69)	43 (32.33)	-	-
Response	30 (28.04)	8 (6.02)	-	-
Non-response	28 (26.17)	10 (7.52)	-	-
ORR	79 (73.83)	123 (92.48)	45.686	<0.001

TABLE 3: COMPARISON OF AE'S BETWEEN THE TWO GROUPS OF PATIENTS

Indicators	Conventional group (n=107)	Research group (n=133)	χ^2	p
Gastrointestinal discomfort	6 (5.61)	3 (2.26)	-	-
Nausea	3 (2.80)	2 (1.50)	-	-
Vomiting	3 (2.80)	2 (1.50)	-	-
Dizziness	5 (4.67)	3 (2.26)	-	-
Total	17 (15.89)	10 (7.52)	4.16	0.041

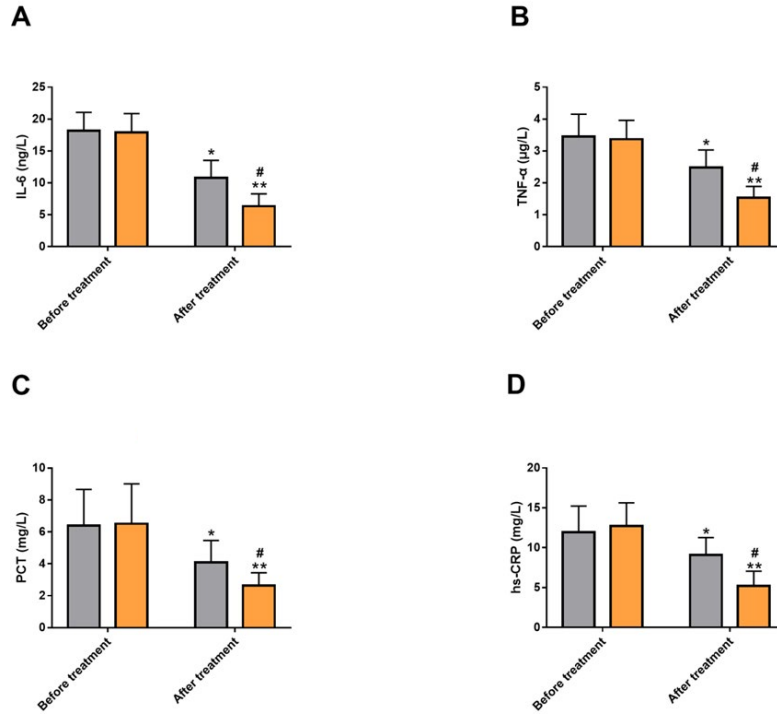


Fig. 1: Pre- and post-treatment IF's levels in two groups of patients, (A) IL-6 levels; (B) TNF- α levels; (C) PCT levels and (D) hs-CRP levels
Note: (■) Conventional group and (■) Research group, compared with before treatment * $p < 0.05$ and ** $p < 0.01$, respectively and [#] $p < 0.05$ vs. conventional group

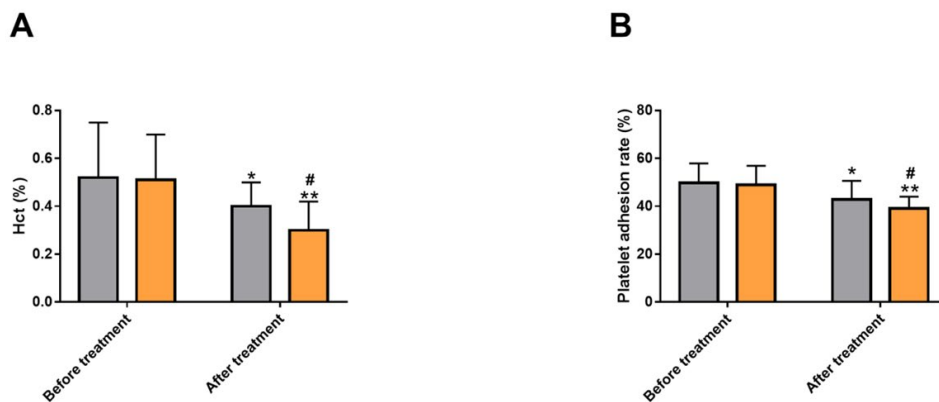


Fig. 2: Pre- and post-treatment platelet parameters in two groups of patients, (A) Hct levels and (B) Platelet adhesion rates
Note: (■) Conventional group and (■) Research group, compared with before treatment * $p < 0.05$ and ** $p < 0.01$, respectively and [#] $p < 0.05$ vs. conventional group

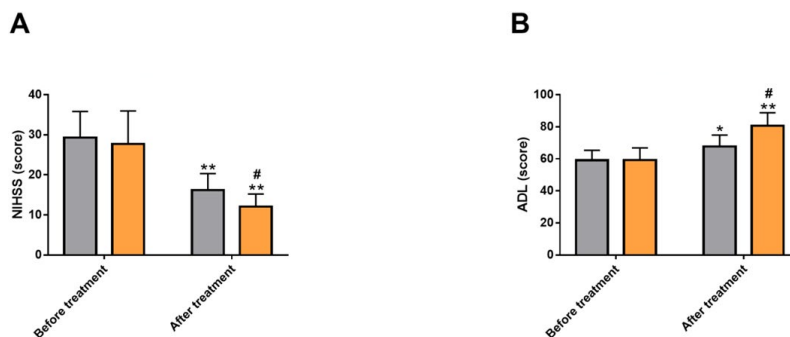


Fig. 3: Pre- and post-treatment (A) NIHSS and (B) ADL scale scores in both groups of patients

Note: (■) Conventional group and (■) Research group, compared with before treatment * $p < 0.05$ and ** $p < 0.01$, respectively and # $p < 0.05$ vs. conventional group

In this study, the efficacy was compared between the conventional group receiving ASP therapy and the research group receiving ATO+ASP. The determined ORR was found to be notably higher in the research group vs. the conventional group (92.48 % vs. 73.83 %), indicating that ATO+ASP therapy can effectively ameliorate the symptoms and signs of CVT patients and restore their language ability and muscle strength. The therapeutic mechanism of ASP in cardio-cerebrovascular diseases is associated with its inhibition of platelet aggregation, which is beneficial to prevent recurrent arterial thrombosis and thus plays a certain antithrombotic role^[15,16]. ASP has been demonstrated to reduce the risk of venous thromboembolism by 42 %^[17,18]. The cerebral vascular protective effect of ATO is related to its alleviation of cerebral vasospasm and its mediating effect on the structural and functional remodeling of vascular endothelial cells, so as to be protective of cerebrovascular auto-regulation^[19]. Vogt *et al.* proposed that the reduction of cardiovascular risk by ATO is linked to the dose- and time-dependent improvement of renal function^[20]. Through safety observation, the major AEs in both groups were determined to be gastrointestinal discomfort, followed by dizziness, and finally nausea and vomiting. Moreover, an evidently lower incidence of AEs were identified in the research group compared with the conventional group (7.52 % vs. 15.89 %), suggesting a higher safety profile of the combined treatment compared with ASP monotherapy.

Inflammation-induced necroptosis is shown to be not only related to the pathogenesis of neurodegeneration, cancer and autoimmune diseases, but also participates in the initiation and progression of ischemic diseases. Inhibition of inflammatory reaction is therefore conducive to preventing the development of pathological processes such as ischemic diseases^[21]. Besides, research has also

linked the activation of pro-IFs (IL-6 and TNF- α) to the acceleration of atherosclerosis progression, which can also lead to plaque instability under the action of various pro-IFs^[22]. ELISA results regarding IFs in the two groups revealed that the post-treatment levels of indexes such as IL-6, TNF- α , PCT and hs-CRP in the research group decreased significantly and were lower than those in the conventional group, indicating more potent inhibitory effect of the combined medication on inflammation than monotherapy in CVT patients. Similarly, it was indicated in one study that ATO+ASP inhibited the release of pro-IFs like IL-6 in bone marrow stromal cells of stroke patients, demonstrating that ATO+ASP may have a synergistic inhibitory effect on inflammatory responses^[23]. Further, according to the analysis of platelet parameters, Hct and platelet adhesion rate were notably reduced in the research group and lower than those in the conventional group after treatment, suggesting that the combined treatment can effectively improve the platelet parameters of CVT patients and thus improve their brain blood circulation. Finally, we used NIHSS and ADL scales to evaluate the neurological deficits and the ADL of the two groups, respectively. The research group treated with ATO+ASP also showed higher ADL and lower NIHSS after treatment, indicating that combined treatment can significantly improve patients' ADL ability and reduce neurological deficits. In the research of Yu *et al.* ATO+sodium ozagrel not only significantly inhibits inflammatory reactions in patients with type 2 diabetes mellitus complicated with lacunar infarction, but also alleviates neurological deficits, similar to our findings^[24]. Another study reported that ATO calcium plus ASP is not only better than ASP alone in the treatment of patients with acute ischemic stroke, but also contributes to a lower incidence of complications and shorter hospitalization time, as

well as a certain improvement effect on patients' survival outcomes^[25].

Taken together, ATO+ASP can effectively ameliorate the signs and symptoms of CVT patients and restore their language and muscle strength, with significant curative effects and a high safety profile. Moreover, it can inhibit inflammation, improve platelet parameters, alleviate neurological deficits, and improve ADL, with clinical application value.

Conflict of interests:

The authors declared no conflict of interests.

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