

Clinical Efficacy and Safety of Atorvastatin for Chronic Subdural Hematoma: A Randomized Controlled Trial

KUN YANG, MING QIU*, HAN ZHAO, Z. LIU AND LIMIN ZHENG

Department Neurosurgery, Taian City Central Hospital, Taian City, Shandong Province, China

Yang *et al.*: Clinical efficacy and safety of atorvastatin

The aim of the present investigation was to observe the efficacy and safety of atorvastatin on chronic subdural hematoma patients. A total of 58 chronic subdural hematoma patients were recruited in this study, randomly divided into the control group and the atorvastatin treatment group (2 patients withdrew; n=28 each group). Before and after 24 w of treatment, the clinical outcome in patients was evaluated. The activities of daily living and neurological deficit scoring standard scores were assessed at 4, 8, 12 and 24 w after treatment. Levels of clinical biochemical indicators, serum high-sensitivity C-reactive protein, interleukin 6, matrix metalloproteinase 9 and tumour necrosis factor α were presented. Furthermore, hematoma volume was detected, which was used to assess the speed and degree of hematoma absorption. The adverse reactions and recurrence rates were recorded. The total effective rate of the atorvastatin treatment group was significantly higher than that of the control group ($p=0.024$). Following treatment, the activities of daily living score (98.3 ± 9.64) of the treatment group was significantly higher than that of the control group (83.8 ± 6.85 ; $p=0.013$). Moreover, the neurological deficit scoring standard score (13.8 ± 3.89) of the atorvastatin-treated group was distinctly lower than that of the control group (20.1 ± 4.67 ; $p=0.021$). On w 24 of treatment, compared to the control group, the serum high-sensitivity C-reactive protein, interleukin 6, matrix metalloproteinase 9 and tumour necrosis factor α levels in the treatment group were significantly reduced. Hematoma volume of the treatment group was significantly absorbed compared to the control group ($p=0.008$). There was no statistical significance in the incidence of various adverse reactions between the two groups. The recurrence rate of the control group (3.60 %) was significantly higher than that of the atorvastatin treatment group (25.00 %; $p<0.05$). These findings demonstrated that atorvastatin could reduce inflammatory response, promote hematoma absorption, protect neurological status and reduce the recrudescence rate for patients with chronic subdural hematoma.

Key words: Atorvastatin, chronic subdural hematoma, hematoma absorption, inflammatory response, recrudescence

Chronic subdural hematoma (CSDH) is increasing year by year due to the aging population^[1]. The incidence of CSDH in the population is 1.7-18/100 000 and the incidence in the elderly over 65 is higher, reaching 58/100 000^[2]. It is expected to reach 121.4/100 000 in 2030. More than 80 % of CSDH patients have a history of craniocerebraltrauma^[3]. Clinically, CSDH mainly manifests as severe headache, vomiting caused by increased intracranial pressure, accompanied by optic nerve papilledema^[4]. Moreover, some patients exhibit mental symptoms such as dementia, apathy, slow response and local brain-derived symptoms. The current treatment for CSDH is to remove the hematoma by surgery, but the risk of postoperative complications and recurrence is higher^[5]. Therefore, there is an urgent

need to explore safer and more effective non-surgical treatment.

Hematoma adventitia neovascularization and inflammatory response are the main factors for CSDH pathogenesis^[6]. Furthermore, inflammatory response is closely related to the recurrence of CSDH after surgery^[7]. More and more studies have found that increase in the hematoma absorption rate of subdural hematoma could reduce the recurrence rate of CSDH^[8]. In recent years, statins have been used to regulate angiogenesis and repair nerve damage^[9,10]. Atorvastatin can activate the Akt and Notch pathways^[11,12], thereby promote angiogenesis and functional blood vessel formation^[13]. The purpose of this study was to observe the effects of atorvastatin on clinical efficacy, neurological function

*Address for correspondence

E-mail: m16531754010_1@163.com

evaluation, serum proinflammatory factor levels, hematoma absorption, adverse reaction and recurrence rate in patients with CSDH. This study could provide novel insights into the conservative treatment of CSDH.

MATERIALS AND METHODS

Patients:

In this study, a total of 58 patients with CSDH admitted to Tai'an Central Hospital from October 2017 to December 2018 were selected as study subjects. The diagnostic criteria for CSDH were as follows, elderly people had symptoms of chronic high intracranial pressure, intellectual or mental abnormalities, especially with a history of mild head trauma for more than 3 w, who should be considered the possibility of CSDH; if computed tomography (CT) examination showed crescent or half-moon-shaped low-density or equal-density shadows on the brain surface, CSDH should be diagnosed. After confirmation of enrolment, these patients were randomly divided into a control group (n=28) and an atorvastatin treatment group (n=30). Age, gender, initial symptoms at admission, neurological function score and other basic conditions were recorded. Patients in the atorvastatin treatment group were given a prescribed course of atorvastatin, while those in the control group were treated with conventional nutritional neuropharmacology. Complications and adverse reactions in patients in the control group and the atorvastatin treatment groups were recorded. In the atorvastatin treatment group, 2 patients withdrew from the trial. All patients signed written informed consent. The study was approved by the Ethics Committee of Tai'an Central Hospital (2020-09).

Inclusion and exclusion criteria:

The inclusion criteria were as follows, patients who met the diagnostic criteria of CSDH in neurosurgery; head CT or magnetic resonance imaging (MRI) showed hematoma thickness <5 mm, no significant space-occupying effect, and midline shift <1 cm; there was no risk of cerebral hernia, and conservative treatment was feasible; patients who had undergone surgery or refused surgery on the subdural hematoma in CSDH. The exclusion criteria were, history of diabetes; those who had undergone major surgery, severe trauma, or stroke in the past 6 mo; those with cerebral hernias that were extremely dangerous and required immediate surgery; mental disorders; severe liver and kidney dysfunction; heart failure (grade α or above) or hypertension (grade β or above); intracranial hypertension; those who had

been taking aspirin or atorvastatin for a long time; allergy to atorvastatin and pregnant women.

Study design:

In this study, two numbers 0 and 1 were randomly generated by computer and distributed. All CSDH patients were assigned into 2 groups. After randomization, 30 cases were assigned in the atorvastatin treatment group and 28 cases in the control group. After CSDH patients were admitted to the hospital, the medical history collection, physical examination and basic condition analysis of the 2 groups of patients including gender, age, and average arterial pressure were recorded. Patients in the control group were treated with conventional nutritional neuropharmaceuticals. Furthermore, attention was paid to bed treatment, limited use of dehydrating agents, correction of water and electrolyte disorders, protection of gastric mucosa and improvement of heart function. Patients in the atorvastatin treatment group received 20 mg of atorvastatin daily after dinner on the basis of the treatment in the control group. Atorvastatin was purchased from Pfizer Pharmaceutical Co., Ltd. (Approval number: National Pharmaceutical Standard H20051408, specification: 20 mg/d). The course of treatment was 2 mo. During the treatment, if a treatment emergency occurred, it should be handled in accordance with the principles of neurosurgery emergency treatment.

Observation indices:

At 4, 8, 12 and 24 w after treatment, the effectiveness and safety of the treatment was assessed. The effectiveness was evaluated as follows, evaluation according to clinical effectiveness: a. hematoma elimination $\geq 99\%$, as cured; b. hematoma elimination 50-98%, as significant effectiveness; c. hematoma elimination 30-39%, as effectiveness; d. hematoma elimination $\leq 29\%$, as ineffectiveness. Herein, total effectiveness = cure + significant effectiveness + effectiveness, and total effectiveness rate = (cure + significant effectiveness + effectiveness) / total number of samples. Evaluation of the activities of daily living (ADL) and neurological deficit scoring standard (CSS). Evaluation of some characteristic biochemical indices before and after treatment. Serum high-sensitivity C-reactive protein (hs-CRP) and matrix metalloproteinase 9 (MMP-9), Interleukin 6 (IL-6) and tumour necrosis factor α (TNF- α) levels were measured. Evaluation according to the hematoma volume before

and after treatment. Safety was assessed as follows, the changes of 3 routines of hematuria and stool, liver and kidney function, blood coagulation indices and electrocardiogram before and after treatment were recorded and patient's complications and adverse reactions (ADRs) during the treatment process were recorded.

Statistical analysis:

All data were analysed using SPSS 23.0 software. The measurement data were expressed as mean±standard deviation (SD), which were assessed for normality test and homogeneity test of variance. Analysis of variance was used to compare the baseline data of the 2 groups before treatment. Before and after treatment, the paired t test was used for comparison. Analysis of variance was used for comparison between groups after treatment. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS AND DISCUSSION

In this study, 58 patients with CSDH admitted to Tai'an Central Hospital from October 2017 to December 2018 were enrolled. The initial randomization was as follows, atorvastatin treatment group (n=30); control group (n=28). Two patients in the atorvastatin treatment group withdrew, while the control group had no withdrawal. Overall, the withdrawal rate was 3.45 %. Finally, a total of 56 cases were included in the study, 28 cases in each group. There were 30 males and 26 females, aged 43-76 y, with an average age of 60.16 ± 7.89 y. After collecting the medical history, the causes of injury were found to be due to fall and injury (n=19), fall injury

(n=17), shock injury (n=11) and traffic accident (n=9). There were 42 cases with one side CSDH and 14 cases with CSDH on both sides.

Compared to before treatment, the number of cured, significant effectiveness and effectiveness patients in the atorvastatin group reached 15, 6 and 4, with a total effective rate of 89.29 %. Furthermore, the number of cured, significant effectiveness and effectiveness patients in the control group were 8, 6, and 5, while 9 were ineffectiveness, with a total effective rate of 67.86 %. Table 1 shows the clinical efficacy of the atorvastatin group and the control group. Total effective rate of atorvastatin group was significantly higher than that of the control group.

At admission, the ADL and CSS scores of CSDH patients in the atorvastatin group and control group were assessed. The results showed that there was no statistical difference between the ADL and CSS scores of the two groups of CSDH patients (Table 2). After basic care and treatment, at the end of treatment, the ADL score of CSDH patients in the control group reached 83.8 ± 6.85 , while that of the CSDH patients in the atorvastatin group reached 98.3 ± 9.64 (Table 2). There were significant statistical differences in the ADL scores between the two groups. Furthermore, at the end of treatment, the CSS score of CSDH patients in the control group was 20.1 ± 4.67 , while the CSS score of those in the atorvastatin treatment group was 13.8 ± 3.89 (Table 2). A significant difference in CSS scores was found between the groups. From the 4th w of treatment, the ADL scores of CSDH patients in the atorvastatin treatment group and the control group continued to increase, indicating that the patients' self-care ability

TABLE 1: COMPARISON OF CLINICAL EFFICACIES BETWEEN TWO GROUPS

Group	Cure	Significant effectiveness	Effectiveness	Ineffectiveness	Total effectiveness rate
Atorvastatin (n=28)	15 (53.57)	6 (21.43)	4 (14.29)	3 (10.71)	25 (89.29)
Control (n=28)	8 (28.57)	6 (21.43)	5 (17.86)	9 (32.14)	19 (67.86)
χ^2/P value					6.325/0.024

TABLE 2: COMPARISON OF ADL AND CSS SCORES BETWEEN TWO GROUPS OF CSDH PATIENTS BEFORE AND AFTER TREATMENT

Scores	Groups	Before treatment	4 w	8 w	12 w	24 w
ADL	Atorvastatin (n=28)	70.4±5.20	74.6±6.10	80.4±6.32	89.5±7.43	98.3±9.64
	Control (n=28)	71.2±5.18	72.4±6.08	76.1±4.90	81.7±5.47	83.8±6.85
	t/P value	0.176/0.678	3.764/0.037	3.002/0.028	3.228/0.045	4.387/0.013
CSS	Atorvastatin (n=28)	28.7±5.32	24.3±5.01	20.9±4.97	16.4±4.65	13.8±3.89
	Control (n=28)	28.9±5.43	26.6±5.52	23.9±5.02	22.7±4.92	20.1±4.67
	t/P value	0.100/0.873	2.746/0.047	3.002/0.038	5.203/0.036	9.307/0.021

continued to improve (Table 2). However, the self care ability of the patients in the atorvastatin group was significantly improved more than the control group. Furthermore, from w 4, the CSS scores of patients in the two groups continued to decrease, suggesting that the patients' neurological status continued to improve (Table 2). But the neurological status of the patients in the atorvastatin group was distinctly ameliorated compared to that of the control groups.

Before treatment, there was no statistical difference in serum hs-CRP, IL-6, MMP-9 and TNF- α level between the atorvastatin and control groups (Table 3). From w 4 of treatment, the levels of serum hs-CRP, IL-6 and MMP-9 for CSDH patients in the atorvastatin group were significantly higher than those in the control group and these increased in a time-dependent manner (Table 3). On w 14, serum TNF- α levels were significantly lower in the atorvastatin group than the control group. Throughout the course of treatment the levels of serum hs-CRP, IL-6, MMP-9 and TNF- α of CSDH patients in the control group remained stable but gradually decreased over time, but the extent of reduction was lower than that of the atorvastatin group. Therefore, the inflammation of CSDH patients in the atorvastatin group appeared to be better controlled.

Before treatment, there was no significant difference in hematoma volume between the atorvastatin-treated group and the control group of CSDH patients (Table 4). On w 4 of treatment, compared to the control group, the hematoma volume of CSDH patients in the atorvastatin group was significantly reduced. But because the treatment cycle was not long enough on w 4, there was no significant difference in the volume of hematoma in CSDH patients between the atorvastatin group and the control group. Starting from w 8 of treatment, the reduction of hematoma in CSDH patients in the atorvastatin group was significantly greater compared to that in the control group (Table 4). On the w 24 of treatment, the hematoma in 19 cases of CSDH patients in the atorvastatin group were completely absorbed, in 5 cases it was moderately absorbed while 2 cases were operated and in 4 cases it was lightly absorbed. Whereas in the control group, in 2 cases it was completely absorbed, in 2 cases moderately absorbed while 18 cases were operated and in 6 cases it was mildly absorbed.

In this study, ADRs were monitored by examining a series of clinical indicators such as 3 routines of blood, urine and stool, liver and kidney function, blood coagulation indices, and electrocardiogram in both groups. The

TABLE 3: COMPARISON OF CLINICAL INDICES BETWEEN TWO GROUPS OF CSDH PATIENTS BEFORE AND AFTER TREATMENT

Serum levels	Groups	Before treatment	4 w	8 w	12 w	24 w
hs-CRP (mg/l)	Atorvastatin (n=28)	6.4 \pm 0.41	5.8 \pm 0.37	5.3 \pm 0.32	4.7 \pm 0.37	3.5 \pm 0.18
	Control (n=28)	6.4 \pm 0.38	6.2 \pm 0.46	5.9 \pm 0.38	5.6 \pm 0.41	4.8 \pm 0.23
	t/P value	0.000/1.001	4.398/<0.0001	6.248/<0.0001	9.145/<0.0001	12.783/<0.0001
IL-6 (mg/l)	Atorvastatin (n=28)	27.1 \pm 10.02	26.1 \pm 8.02	24.6 \pm 5.65	22.8 \pm 5.21	19.0 \pm 4.57
	Control (n=28)	27.1 \pm 9.89	26.8 \pm 9.21	25.7 \pm 7.79	24.3 \pm 6.38	21.9 \pm 6.34
	t/P value	0.260/0.973	1.398/0.029	3.235/0.024	5.345/0.015	7.783/0.012
MMP-9 (μ g/l)	Atorvastatin (n=28)	671.5 \pm 21.68	615.3 \pm 17.96	561.9 \pm 13.84	450.2 \pm 9.98	341.9 \pm 8.66
	Control (n=28)	670.3 \pm 20.89	631.1 \pm 18.73	584.8 \pm 16.63	499.8 \pm 13.48	410.4 \pm 12.54
	t/P value	0.060/1.978	2.398/0.034	8.235/0.012	12.735/0.008	14.774/<0.0001
TNF- α (μ g/l)	Atorvastatin (n=28)	44.1 \pm 10.12	41.4 \pm 8.27	38.5 \pm 5.84	33.5 \pm 4.12	28.2 \pm 2.89
	Control (n=28)	44.0 \pm 10.35	42.7 \pm 9.67	41.1 \pm 8.97	37.8 \pm 7.73	34.9 \pm 6.78
	t/P value	0.000/2.738	1.398/0.062	1.785/0.0658	3.324/0.035	3.673/0.033

TABLE 4: COMPARISON OF HEMATOMA VOLUME BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT

Groups	Before treatment	4 w	8 w	12 w	24 w
Atorvastatin (n=28)	20.1 \pm 4.13	18.3 \pm 5.02	16.4 \pm 6.13	14.6 \pm 4.21	8.9 \pm 3.24
Control (n=28)	19.9 \pm 4.42	19.2 \pm 5.13	18.5 \pm 4.79	17.8 \pm 5.42	15.8 \pm 3.98
t/P value	0.339/0.736	0.983/0.102	1.002/0.048	2.839/0.027	3.728/0.008

Hematoma volume was expressed as mean \pm SD millilitres

results showed that the main adverse reactions in the 2 groups of CSDH patients were nausea and vomiting, abdominal discomfort, mild elevation of transaminase, dyslipidemia and rash (Table 5). However, there was no significant difference in the incidence of ADRs between the two groups. Brain CT was used to detect recrudescence rate. The recrudescence rate of patients in the atorvastatin group (3.60 %) was distinctly lower than that in the control group (25.00 %) as shown in Table 5.

This study is a randomized controlled trial on the clinical efficacy and safety of atorvastatin for CSDH. These results demonstrated that atorvastatin could reduce inflammatory response, accelerate hematoma absorption, protect neurological status and decrease the recrudescence rate for patients with CSDH. Many studies have shown that CSDH is a local inflammatory disease^[7]. Regarding the pathophysiological changes of CSDH, gradual conversion of chronic subdural effusion is the key to the formation of CSDH^[14,15]. A series of events induced by the subdural cerebrospinal fluid makes the cell layer at the edge of the dura mater tear, thereby inducing a series of self-repair mechanisms. The local inflammation is aggravated and promotes the occurrence of hematoma. Clinical studies suggested that VEGF concentration is closely related to the hematoma exudation rate, which provided a basis for the CT imaging manifestation of hematoma^[16]. Additionally, in the process of hematoma absorption in CSDH patients, VEGF concentration also indicated the speed of hematoma absorption. There are both proinflammatory and antiinflammatory response locally in CSDH^[17]. Studies have found that the concentrations of proinflammatory factors such as IL-5, IL-7, TNF- α and bidirectional inflammatory factors such as IL-6 in hematoma fluid are significantly higher than those in peripheral blood^[18-20]. Present results showed that these inflammatory factors are not only related to the formation of CSDH, but also to the mechanism of atorvastatin in the treatment of CSDH. Abnormal angiogenesis may be an important cause of CSDH. MMP-9 is a member of the matrix metalloproteinase family, which is involved

in various pathological processes of central nervous system diseases^[21-23]. Some studies have pointed out that MMP-9 may affect the occurrence of CSDH^[24]. The results of this study showed that atorvastatin can effectively reduce the serum levels of the above proinflammatory factors in CSDH patients, thereby reducing the inflammatory response.

Atorvastatin is a hydroxymethylglutaryl coenzyme A reductase inhibitor. Recent studies have found that atorvastatin has a significant therapeutic effect in addition to preventing atherosclerosis and reducing the incidence of cardiovascular and cerebrovascular diseases^[25-27]. Furthermore, it has a certain effect on stroke patients^[28]. ADL scores have been an indispensable consideration and therapeutic index in the treatment of CSDH^[29]. It has been reported that the recovery of nerve function is accompanied by angiogenesis^[30]. In the early stage of trauma, due to the lack of angiogenesis and increased vascular permeability, the absorption rate of hematoma is slow. At this time, the intracranial height due to the space-occupying effect and the toxins produced by local metabolic disorders make the neurological deficits, thereby increasing new blood vessels and accelerating hematoma absorption. In this process, low-dose statins promote angiogenesis by activating endothelial nitric oxide synthase^[31]. Consistently, present data showed that atorvastatin can accelerate hematoma absorption in patients with CSDH compared to controls.

Atorvastatin treatment of CSDH is a comprehensive treatment as it inhibits the inflammatory response, promotes angiogenesis and improve nerve function, to produce a clinical cure. Studies have shown that atorvastatin downregulated the expression of VEGF in patients with CSDH, thereby inhibiting the proliferation of vascular endothelial cells and forming new blood vessels, reducing the volume of hematoma, thereby reducing the recurrence rate of CSDH^[31,32]. In addition, atorvastatin reduces the number of neutrophils, the concentration of inflammatory factors, induces antiinflammatory effects, and reduce the recurrence of CSDH hematoma. Consistent with previous results reported, current results indicated that atorvastatin

TABLE 5: COMPARISON OF THE INCIDENCE OF ADR AND RECRUDESCENCE

Groups	ADR					Recrudescence
	Nausea and vomiting	Abdominal discomfort	Increased transaminase level	Dyslipidemia	Rash	
Atorvastatin (n=28)	1	3	1	0	2	1
Control (n=28)	2	2	1	2	3	7
χ^2	0.783	1.083	0.789	0.474	0.272	3.892
P value	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05

treatment significantly reduced the risk of recurrence of CSDH in patients. Thus, atorvastatin treatment could inhibit the inflammatory response, promote angiogenesis and improve nerve function for CSDH treatment.

These findings suggested that atorvastatin could be an ideal drug for the treatment of CSDH. But due to the relatively small sample size in this study, its clinical effect still needs to be confirmed by larger clinical trials. Nevertheless, atorvastatin could effectively treat CSDH by promoting subdural hematoma absorption and improving nerve function, thereby improving the ability of self-care and quality of life. Despite patients treated with atorvastatin experienced adverse reactions such as nausea and vomiting, abdominal discomfort and rash, it is warranted as it can significantly reduce the relapse risks. Thus, for patients with CSDH with mild symptoms, timely treatment with atorvastatin could avoid the risks and complications caused by surgery. Mechanistically, atorvastatin in the treatment of CSDH is related to the regulation of inflammation and angiogenesis, which requires in-depth research.

Conflict of interest:

All authors report no conflicts of interest in this work.

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