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Effects of atorvastatin on chronic subdural hematoma: A preliminary report from three medical centers

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ABSTRACT

Introduction: Chronic subdural hematoma (CSDH) is common and more prevalent in the aged population. Surgical intervention is the treatment of choice, but its outcomes may not be satisfactory because of recurrence and physical infirmity associated with aging. Aberrant angiogenesis and localized inflammation contribute to the formation of CSDH. Atorvastatin is active in promoting angiogenesis and modulating inflammation. We hypothesize that atorvastatin is effective in reducing CSDH and have tested the hypothesis in a preliminary prospective study of small cohort of patients.

Methods: Twenty-three patients with CT- or MRI-confirmed CSDH were recruited from three regional medical centers and evaluated using Markwalder's Grading Scale (MGS) and the Glasgow Coma Scale (GCS). These patients received oral atorvastatin 20 mg/day for 1–6 months (3.02 ± 1.77 months) and were followed for 3 to 36 months (18.62 ± 13.13) after the therapy. Hematoma volume, neurological functions and daily activities (measured using the Activities of Daily Life-the Barthel Index scale, ADL-BI) were compared before and after treatment with Linear Trend Chi-Square test.

Results: Twenty-two of the 23 patients experienced improvements in symptoms, and the reduction in hematoma volume from 48.70 ± 20.38 ml to 16.64 ± 14.28 ml (paired-sample *t*-test, $p < 0.01$) within the first month of the treatment. Hematoma was completely resolved in 17 patients (77.3%) and shrank by more than 73.99% ± 11.17% in 5 patients (22.7%) 3 months after the treatment was initiated. One patient experienced an initial relief of symptoms, but his condition deteriorated with an enlarged hematoma during the 4th week of treatment and underwent surgery. At 6 months, 18 patients presented no hematoma by CT or MRI and four patients, whose hematoma was completely resolved at 3 months, were not followed. None of these 22 patients relapsed during the entire follow-up period of 3–36 months. All have improved MGS, GCS, and ADL-BI. No atorvastatin-related side effects were documented.

Conclusion: Results of this preliminary prospective study show that the oral administration of atorvastatin is safe and effective in treating CSDH, offering a cost-effective alternative to surgery. A prospective randomized clinical trial is required to validate the effect of atorvastatin.

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1. Introduction

Chronic subdural hematoma (CSDH) is a common type of intracranial hematomas with an incidence of 1–13.1 per 100,000 per year [1–3]. Burr-hole drainage with or without rinse is the first choice of treatment [4]. Therapeutic endoscopy has been proposed, but its effectiveness remains to be evaluated. The incidence of recurrent CSDH may reach 25%, regardless of the type of surgery. Furthermore, most CSDHs occur in older patients, carrying a high risk of peri-operational infection, pneumonia and high-surface-tension pulmonary edema [5]. The mortality in aged CSDH patients is reported to be as high as 32% within the first year after treatment, including those treated with standard burr-hole drainage. Because of the poor prognosis of CSDH in elderly patients, some investigators believe that CSDH is not a benign disease [6,7]. Thus, alternative and more conservative therapies may be necessary for patients who have a higher risk for recurrence and/or are predicated to have poor outcomes for surgery.

There is increasing evidence that impaired angiogenesis in the neomembrane and localized inflammation play a key role in the formation of a CSDH. Impaired angiogenesis results in blood leakage from immature vessels of the neomembrane and localized inflammation hampers angiogenesis and prevents leaked blood from being absorbed [2,8–14].

3-Hydroxy-3-methylglutaryl (HMG)-COA reductase inhibitors, which is the first-line treatment for patients with high cholesterol and coronary heart disease, have been demonstrated to improve angiogenesis and reduce inflammation [15,16]. Among these drugs, atorvastatin has been widely reported to promote angiogenesis and increase circulating endothelial progenitor cells (EPCs), which are critical for the formation of new blood vessels. These effects are mediated through the activation of the endothelial protein kinase Akt/PKB, Notch1 and endothelial nitric oxide synthase (eNOS) [17–20]. Atorvastatin has also been shown to inhibit inflammation and decrease levels of proinflammatory molecules [21–23]. We hypothesize that atorvastatin is effective in reducing CSDH, by promoting membrane neovascularisation, which improves blood drainage, and reduces inflammation in CSDH. We have tested this hypothesis by investigating the safety and efficacy of atorvastatin (20 mg/night, oral) for treating patients with CSDH.

2. Patients and methods

Twenty-three patients with the evidence of CSDH were enrolled from May 2010 to February 2013 under a human subject protocol approved by the Ethics Committee of Tianjin Medical University General Hospital. All patients and/or their family members were thoroughly informed of the research and its risks. An informed consent was obtained from each patient or a patient's legal representative.

Patients enrolled in the study were evaluated using Markwalder's Grading Scale (MGS) and the Glasgow Coma Scale (GCS) at admission and during a routine clinic visit [24,25]. They were graded into the following groups according to the criteria listed in Table 1. Considering the risk of severe CSDH with increased intracranial pressure (Grade 4), this study enrolled only patients with Grades 0–3 CSDH.

2.1. Inclusion and exclusion criteria

Patients were enrolled based on the following inclusion criteria: age > 16 years and evidence of supratentorial CSDH by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI); patients with the following conditions were excluded from the study: a high risk of cerebral hernia and/or the necessity of immediate surgical intervention; liver malfunctions with an increase in alanine aminotransferase (>40 U/l) and aspartate aminotransferase (>46 U/l) in peripheral blood samples; bleeding tendency defined as prothrombin time > 15 s, INR > 1.5, activated partial thromboplastin time > 40.0 s, plasma fibrinogen > 4.0, or thrombin time > 25 s; CSDH resulting from tumor or blood disease; steroid use (dexamethasone, methylprednisolone, hydrocortisone, progesterone and estrogen) within 2 weeks prior to the enrolment; and refusal to participate in the study.

Table 1
Grading criteria for patients enrolled in the study.

Patient's Grade	Glasgow Coma Scale	Markwalder's Grading Scale
Grade 0	Glasgow Coma Scale score of 15	Normal neurological status without any symptoms
Grade 1	Glasgow Coma Scale score of 15	Without neurological deficits, but with symptoms such as headache or unsteady gait
Grade 2	Glasgow Coma Scale score of 13 to 14	Focal neurological deficits, such as drowsiness or disorientation, or variable neurological deficits, such as hemiparesis
Grade 3	Glasgow Coma Scale score of 9 to 12	With stupor but appropriate responses to noxious stimuli and several focal neurological signs such as hemiplegia
Grade 4	Glasgow Coma Scale score of less than 9	Coma with absent motor responses to noxious stimuli and decerebrate or decorticate posturing

Only patients with Grades 0–3 CSDH were selected for atorvastatin treatment in this study.

2.2. Atorvastatin therapy

A single oral dose of 20 mg atorvastatin daily (Pfizer, USA) for 1–6 months was taken by patients. Previous work reported that the most potent angiogenesis facilitation without the risk of hemorrhage was initiated by the low dose but not the high dose of atorvastatin. So in this study, the low dose of atorvastatin was chosen to be applied [26–28]. The neurological functions of patients were evaluated before the treatment and 1 week, 2 weeks, 1 month and 3 months during therapy. Patients were monitored for blood cell counts, functions of coagulation system, liver, kidney, neurological system, and gastrointestinal track, and symptoms related to the medication during the course of treatment. Conditions for switching a patient from atorvastatin to surgery include: a sudden increase in hematoma volume, a mid-line displacement of greater than 1 cm by CT or MRI scan, and deterioration in consciousness.

Steroids, angiotensin-converting enzyme inhibitor and estrogen therapy that may influence angiogenesis and promote blood circulation were proscribed during the course of atorvastatin treatment.

The atorvastatin treatment was discontinued when a hematoma disappeared completely with a stable neurological status for one month.

2.3. Evaluation and follow-up

Each patient had a CT or MRI scan of the head at the baseline before treatment. A hematoma volume was calculated based on the Coniglobus Formula given as: hematoma volume (ml) = 1/2 × the longest diameter of the hematoma layer with the largest area (cm) × the longest diameter perpendicular to the longest diameter (cm) × the thickness of the hematoma (cm). If a patient had more than one hematoma, a total volume of multiple hematomas was calculated. CT or MRI was also performed 1, 3, 6, 12, 24 and 36 months after the treatment to calculate hematoma volume. The effect of atorvastatin was evaluated by changes in hematoma volume and neurological scores at the following four levels:

(1) Poor response: hematoma volume increased with aggravated neurological symptoms;
(2) Partial response: hematoma volume decreased by less than 50%, and neurological symptoms were partially or completely resolved;
(3) Favorable response: hematoma volume decreased by more than 50% but less than 100%, and neurological symptoms were partially or completely resolved;