JAMA Neurology | Original Investigation

Safety and Efficacy of Atorvastatin for Chronic Subdural Hematoma in Chinese Patients
A Randomized ClinicalTrial

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IMPORTANCE Chronic subdural hematoma (CSDH) is a trauma-associated condition commonly found in elderly patients. Surgery is currently the treatment of choice, but it carries a significant risk of recurrence and death. Nonsurgical treatments remain limited and ineffective. Our recent studies suggest that atorvastatin reduces hematomas and improves the clinical outcomes of patients with CSDH.

OBJECTIVE To investigate the safety and therapeutic efficacy of atorvastatin to nonsurgically treat patients with CSDH.

DESIGN, SETTING, AND PARTICIPANTS The Effect of Atorvastatin on Chronic Subdural Hematoma (ATOCH) randomized, placebo-controlled, double-blind phase II clinical trial was conducted in multiple centers in China from February 2014 to November 2015. For this trial, we approached 254 patients with CSDH who received a diagnosis via a computed tomography scan; of these, 200 (78.7%) were enrolled because 23 patients (9.1%) refused to participate and 31 (12.2%) were disqualified.

INTERVENTIONS Patients were randomly assigned to receive either 20 mg of atorvastatin or placebo daily for 8 weeks and were followed up for an additional 16 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was change in hematoma volume (HV) by computed tomography after 8 weeks of treatment. The secondary outcomes included HV measured at the 4th, 12th, and 24th weeks and neurological function that was evaluated using the Markwalder grading scale/Glasgow Coma Scale and the Barthel Index at the 8th week.

RESULTS One hundred ninety-six patients received treatment (169 men [86.2%]; median [SD] age, 63.6 [14.2] years). The baseline HV and clinical presentations were similar between patients who were taking atorvastatin (98 [50%]) and the placebo (98 [50%]). After 8 weeks, the HV reduction in patients who were taking atorvastatin was 12.55 mL more than those taking the placebo (95% CI, 0.9-23.9 mL; $P = .003$). Forty-five patients (45.9%) who were taking atorvastatin significantly improved their neurological function, but only 28 (28.6%) who were taking the placebo did, resulting in an adjusted odds ratio of 1.957 for clinical improvements (95% CI, 1.07-3.58; $P = .03$). Eleven patients (11.2%) who were taking atorvastatin and 23 (23.5%) who were taking the placebo underwent surgery during the trial for an enlarging hematoma and/or a deteriorating clinical condition (hazard ratio, 0.47; 95% CI, 0.24-0.92; $P = .03$). No significant adverse events were reported.

CONCLUSIONS AND RELEVANCE Atorvastatin may be a safe and efficacious nonsurgical alternative for treating patients with CSDH.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02024373.

JAMA Neurol. doi:10.1001/jamaneurol.2018.2030
Published online July 30, 2018.

Supplemental content

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Chronic subdural hematoma (CSDH) is increasingly common because of the aging population. Its incidence increases from to of in the general population to . of among patients years or older. More than % of patients with CSDH have a history of traumatic brain injury. The current treatment for CSDH is surgery to remove the hematoma, but the surgery carries a recurrence rate of approximately . % in high-risk patients and a mortality rate of % to % in elderly patients. An overall mortality rate of . % is reported for patients years or older, independent of treatments. Safer and more effective nonsurgical treatments are therefore highly desirable. Dexamethasone, perindopril, and tranexamic acid have been investigated for nonsurgically treating patients with CSDH, but, to our knowledge, they have failed to show significant efficacy in controlled clinical trials. ,

We report the results of a double-blind, randomized, placebo-controlled phase II clinical trial that was designed to test the efficacy of atorvastatin for nonsurgically treating patients with mild to moderate CSDH. This trial was developed based on several lines of supporting evidence. First, the development and recurrence of CSDH is associated with localized inflammation and the overexpression of vascular endothelial growth factor, which leads to the development of immature •leakyŽ vessels and a subsequent hematoma. - Our study in a rat model of subdural hematoma supported this mechanism and further demonstrated that blocking inflammation and immature angiogenesis promoted rapid hematoma absorption. , Second, statins (-hydroxy -methylglutaryl-CoA reductase inhibitors), which were originally developed for reducing low-density lipoprotein cholesterol levels in patients with hyperlipidemia, have been shown to reduce inflammation in the vessel wall and mobilize endothelial progenitor cells for vascular repairs. - Third, our pilot and uncontrolled study of patients with CSDH found that oral atorvastatin (mg daily for - months) significantly reduced hematomas and improved clinical outcomes in % of participants, which was consistent with a systematic literature review.

Key Points

Question Can atorvastatin treat chronic subdural hematoma?

Findings In this randomized clinical trial, administering

Methods

Patients

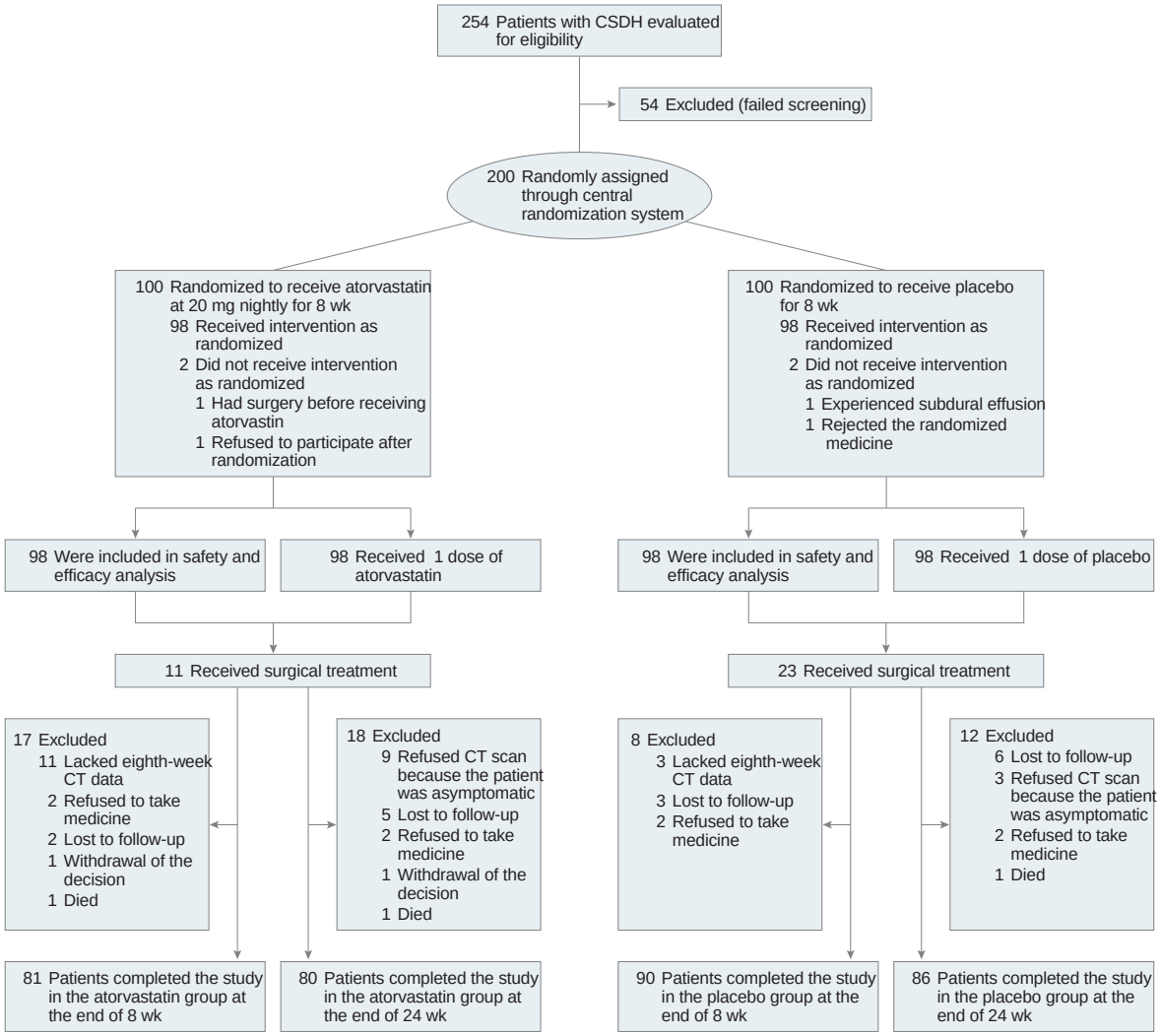
Patients who received a diagnosis of mild or moderate subdural hematoma and were treated in outpatient clinics were recruited from February , , to November , , from neurosurgical departments, all of them members of the Oriental Neurosurgical Evidence-Based Study Team (ONET). ONET was established to foster clinical and research collaborations in neurosurgery between mainland China and Hong Kong. The inclusion criteria included symptomatic patients who were age to years, a diagnosis of unilateral or bilateral supratentorial CSDH by computed tomography (CT), no previous CSDH surgery, and no statin treatment in the previous months. The clinical presentations of the patients were nonfocal, including headache, weakness of limbs, and mental decline. Patients who had a high risk of cerebral hernia, required emergency surgery, were allergic to statins, received a diagnosis of cancer, had historical and current bleeding or thrombosis with or without treatment (or were taking prophylactic antiplatelet medications), or had developed multiple organ failure were excluded. The inclusion and exclusion criteria are specified in the original report on the trial design and registration (https://clinicaltrials.gov/ct /show/NCT).

Study Design and Oversight

This trial was conducted in accordance with the International Conference on Harmonization guidelines for good clinical practice. Its study design was difference-in-difference. The data were collected by the contract research organization Beijing Stemexcel Technology Co. The trial protocol (Supplement) was approved by the ethics committees of the participating hospitals and is schematically described in Figure . During the initial screening, patients were provided with detailed information about the trial and eligible patients were recruited after providing written consent. The patients were centrally randomized using the Data Acquisition System for Electronic Data Capture, version . (Beijing Stemexcel Technology Co). The demographic information of patients who were enrolled at each study site was imported into the central randomization system, which then generated a random number that determined whether a patient received atorvastatin or placebo at a randomization ratio of : . There was no stratification during the randomization. Atorvastatin (Pfizer) and the placebo were stored at individual participating hospitals (at °… °C and while avoiding direct light), with access restricted to research nurses who were responsible for the storage, distribution, and inventory of the medications. The placebo pills were made of dextrin and had the same weight and appearance as the atorvastatin (Shandong ARURA Pharmaceutical Research & Development Co). All the patients were treated in an outpatient setting and received -day supplies of the medication in individual packages. They returned the empty packages at the end of each week to exchange them for the next week•s supply until the treatment ended.

For recruitment, each patient or guardian, assisted by a nurse coordinator who was assigned to the study, completed a short questionnaire about his or her condition, underwent physical examinations that were conducted by an attending neurosurgeon who was masked to the treatment, and received a CT scan. All data were collected onsite by nurse coordinators and submitted electronically to the data acquisition system, which also randomized the patients. All data

Figure 1. Schematic Illustration of the Trial Protocol



CSDH indicates chronic subdural hematoma; CT, computed tomography.

entries were validated by a second nurse before submission. The trial was overseen by a data monitoring board that was independent of the study investigators. This board was composed of clinicians, neurosurgeons, clinical trial experts, epidemiologists, and biostatisticians from university hospitals and the contracted trial design organization.

Atorvastatin was administered at mg per night for weeks. This dosage was chosen because it is used for patients with hyperlipidemia with minimal adverse effects ' and because atorvastatin at a higher dose (mg) was reported to increase the risk of bleeding in patients with a low body weight and uncontrolled hypertension in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. Treatment compliance was monitored by regular contact with the patients and by pill counting during patients• weekly visits to their outpatient clinics. Patients were also evaluated by plasma levels of low-density lipoprotein cholesterol on the eighth week of treatment, when the primary study variable was recorded, as an indicator of atorvastatin ingestion (compliance). After weeks of treatment, the patients were followed up for another weeks. During the trial, patients would undergo surgery to remove a hematoma when their neurological dysfunction deteriorated (worsened headache, progressive limb paralysis, or changes in levels of consciousness) or CT scan results showed a hematoma enlargement and/or a midline shift of more than cm. The decision to undergo surgery was masked to the treatment assignments.

The primary outcome of the trial was changes in HV (in milliliters) from the pretreatment baseline after weeks of treatments. Hematoma volume measured in the th, th, and th weeks after enrollment served as secondary outcomes. Hematoma volume was measured using the Tada formula on the CT scan: maximal length × maximal width × maximal thickness of a hematoma, then divided by . The location, density, and compartmentalization of the hematoma, and the presence of basal ganglia suppression and midline shift, were also

recorded. To standardize the measurements and reduce interhospital variation, CT scan images from patients who were enrolled at each study site were electronically sent to the medical imaging center of Tianjin Medical University General Hospital and analyzed by neuroradiologists who were masked to the treatment. If the coefficient of variation among HV measurements by the neuroradiologists was more than %, a fourth neuroradiologist was called in to perform an additional analysis.

The secondary outcome also included the assessment of neurological function after weeks of treatment, which was evaluated at each study site by attending neurosurgeons who were masked to the treatment. Neurological function was evaluated using the Markwalder grading scale/Gla sgow Coma Scale (eTable in Supplement), which provides a combined score of the activities of daily living (ADL) and the Barthel Index (which measures the daily living activities of patients with neurological diseases ' '), and the Glasgow Out come Scale (GOS). The GOS was originally developed to evaluate the recovery of patients with traumatic brain injury, who are much younger than patients with CSDH. A potential cofounding factor is that aging patients may require living assistance independent of CSDH, which potentially exaggerates the GOS score. For patients who underwent surgery during the trial, the HV measurements that were made immediately before surgery were recorded as the primary outcome and were compared with the baseline. Complete blood cell counts, and serum levels of alanine aminotransferase, aspartate transaminase, gamma glutamyl transpeptidase, urea nitrogen, and creatinine were measured at the baseline and at the th, th, and th weeks of the trial to evaluate hematological, liver, and kidney function.

Statistical Analysis

The data were analyzed by Beijing Stemexcel Technology Co independently of the study investigators. The results from our pilot study

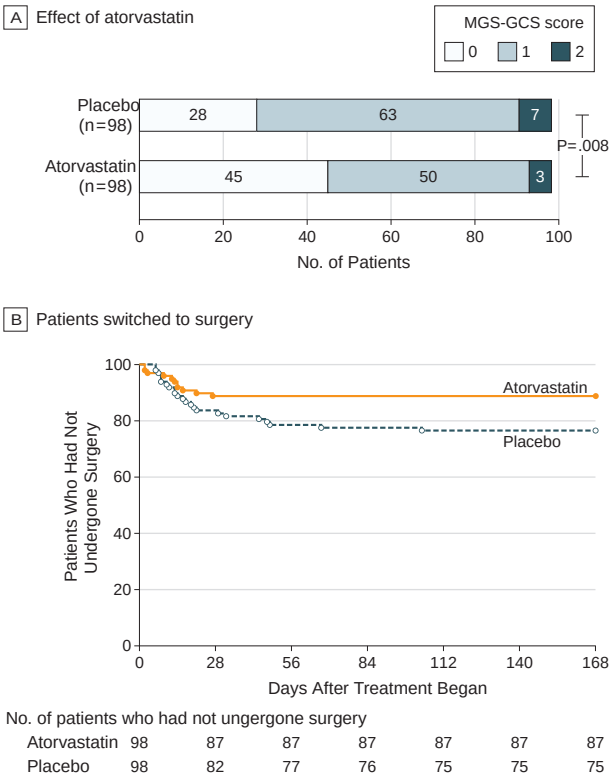
statistical difference between patients taking atorvastatin and patients taking the placebo. The concurrent use of prescription medications among the patients is listed in eTable in Supplement and was found to be randomly distributed between the groups. An extensive literature search found that none of these concurrent medications affected CSDH development or the effects of atorvastatin.

Efficacy of Atorvastatin

The reduction in HV measured after weeks of treatment (the primary outcome) was significantly greater for patients who received atorvastatin (. mL) compared with those who received the placebo (. mL) in the FAS analyses (z = . ; P = .) (Figure A). Patients taking atorvastatin were found to have a reduced HV by . mL more than patients taking the placebo (% CI, . - . mL; P = .). The data were also analyzed after adjusting for the confounding variables of age, clinical severity, and the presence of a bilateral hematoma. The adjusted results showed that HV was reduced more in patients who were taking atorvastatin than those taking the placebo (% CI, . - . mL; P = .). For the FAS analysis, the missing data from the eighth week for patients who were switched to surgery were replaced with the last available data using LOCF. The PPS analysis, which also included patients who completed weeks of treatment whether or not they underwent surgery, yielded a similar result after adjustingt for the confounding variables (Figure B). Hematoma volume was reduced by . mL more in patients who were taking atorvastatin than patients who were taking the placebo (% CI, . - . mL; P = .). When plotted as continuous variables, HV reduced gradually in patients of both groups, but the reduction was significantly greater for patients who received atorvastatin (Figures C and D), suggesting an accumulative dosing effect of atorvastatin. The HV measured at the th, th, and th weeks after enrollment (secondary outcomes) also showed a significantly greater reduction in patients taking atorvastatin than in those taking the placebo (eTable in Supplement). The plasma levels of low-density lipoprotein cholesterol were significantly lower in patients who were taking atorvastatin than in those taking the placebo (eTable in Supplement), indicating the patients• compliance in atorvastatin treatment. Together, these data suggest that atorvastatin reduced the volume of CSDH.

Consistent with the HV reduction, patients (.%) tak-

Figure 3. Neurological Function and Rate of Surgery



A, The Markwalder grading scale/Glasgow Coma Scale (MGS-GCS) was used to evaluate the effect of atorvastatin on improving the neurological function of patients with chronic subdural hematoma (scores were measured on the eighth week of treatment) (Wilcoxon test, n = 98). B, Patients were switched to surgery because of increasing hematoma volume and/or deteriorating

ments by atorvastatin (% CI, . - . ; P = .) (Figure A). When patients were ranked by ADL-BI scores as dependent living (ADL <) and independent living (ADL), more patients who taking atorvastatin than taking the placebo were found to be independent (eTable in Supplement). The GOS score measured at the eighth week was trending for atorvastatin but did not reach statistical significance between the groups (eTable in Supplement). These results suggest that atorvastatin could improve neurological function in patients with CSDH.

Patients Switched to Surgery

Thirty-four patients (. %) were switched to surgery during the trial because of increased HV and/or exacerbated neurological dysfunction ([. %] from the atorvastatin group and significantly fewer than [. %] from the placebo group) (log-rank test, P = .) (Figure B). The treatment switches were made at various times during the trial (eTable in Supplement), but most of the patients who were taking atorvastatin were switched early during the trial. Three of the patients (. %) who were taking atorvastatin were switched to surgery during the first hours of treatment before atorvastatin had reached the therapeutic dosage as defined by its pharmacokinetics. Together, these results suggest that atorvastatin reduces the need for surgery in patients with CSDH.

Subgroup Analyses

In addition to the prespecified primary and secondary outcomes, we also performed post hoc subgroup analyses. When the patients were divided into age groups, those age years or older were found to have had a significantly greater reduction in HV after weeks of treatment than those age to years (eFigure in Supplement). When patients were grouped by baseline HV, those with a hematoma of more than mL were found to have experienced a greater relative reduction in HV while taking atorvastatin than those with a hematoma of mL or less (eFigure in Supplement). We used an HV of mL to group patients because this volume has been widely used as an indication for surgery in patients with an intracranial hematoma. These results indicate that atorvastatin may be more effective for older patients and patients with larger CSDH.

Safety

Two patients died during the trial, of whom was age years and receiving atorvastatin and died of pulmonary embolism caused by multiple limb fractures on day after randomization. The other was years old receiving placebo and died of myocardial infarction on day after randomization. Their deaths were determined to be unrelated to the trial treatment by the monitoring board.

The results of routine blood and coagulation tests conducted during the trial are listed in eTable in Supplement . The laboratory measurements of liver and kidney function are listed in eTable in Supplement . Fifteen patients (%) presented with mild liver abnormalities and (%) with mild kidney abnormalities, but none required treatment. Two patients (%) were considered to have had treatment-related adverse events. One female patient developed diplopia and right-abduction nerve palsy weeks after receiving atorvastatin treatment. Her palsy disappeared and the hematoma was absorbed during the follow-up period. The other developed pruritus after weeks of participating in the trial, but the symptom remitted after days and the patient completed the trial.

Discussion

With the continuous increase in life expectancy and the therapeutic or prophylactic use of anticoagulation and antiplatelet medications, the incidence of CSDH is expected to increase significantly worldwide. Surgery has long been the first choice for treating CSDH, but it carries a considerable risk of complications and could be contradicted for patients who have mild symptoms, are at an advanced age, are taking long-term anticoagulation and/or antiplatelet medications, or are in poor physical health. Reports on the self-absorption of CSDH remain sporadic. Effective and low-cost nonsurgical treatments could significantly improve the outcomes of CSDH. This trial was designed to investigate atorvastatin as a nonsurgical

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