A Prospective Study of the Effect and Safety of Atorvastatin on the Recurrence of Chronic Subdural Hematoma after Burr Hole Surgery

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Abstract

Introduction Chronic subdural hematoma (CSDH) is a common neurosurgical condition. Recent studies showed efficacy of atorvastatin in reducing the requirement of surgical treatment. This study aimed to evaluate the efficacy and safety of atorvastatin in reducing the recurrence of CSDH after burr hole surgery.

Methods This prospective study included patients with CSDH who underwent burr hole surgery. Atorvastatin at 20 mg per day was administered to all patients for 4 weeks postoperatively. The major outcome was the recurrence rate of CSDH at 8 weeks following the operation.

Results Seventy-three patients who completed the 4-week course of atorvastatin were included. The mean age was 73.9 years. The most common cause of CSDH was falling. The mean hematoma volume was 106.3 mL. There was no adverse effect of atorvastatin in all of 73 patients. During the 8-week postoperative period, recurrent CSDH was found in 2 of 73 (2.7%) patients. In a comparison of the recurrence rate of CSDH between patients with use of atorvastatin from the present and previous studies (2.6–4.8%), and patients without use of atorvastatin from previous studies (9.8–19%), a marked reduction in recurrent CSDH after burr hole surgery was found in patients with use of atorvastatin.

Conclusion An administration of atorvastatin of 20 mg daily for 4 weeks following burr hole surgery is safe and may be helpful in reducing the recurrence rate of CSDH after burr hole surgery.

Keywords
- atorvastatin
- burr hole
- chronic subdural hematoma
- recurrence

Introduction

The incidence of chronic subdural hematoma (CSDH) has been found to be 1 to 13.1/100,000 persons/year.[1,2] A recent study in Japan found an increasing incidence and earlier onset of CSDH.[3] Surgical drainage of retained subdural blood with a significant pressure effect remains the major treatment for CSDH.[4] There are several reported factors associated with recurrent CSDH after surgery, such as an elderly age, antiplatelet or anticoagulant intake, separated type of CSDH,

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and bilateral CSDH.[5–9] Our previous study showed that the overall recurrence rate of CSDH after burr hole surgery was 9.8%.[10]

The pathophysiology of CSDH is a cascade of inflammatory processes that occur with encapsulated blood or fluid collected in the subdural space following a minor head trauma.[11] Therefore, some studies have focused on anti-inflammatory medication, such as dexamethasone and lipid-lowering drugs (e.g., atorvastatin), to reduce the recurrence of CSDH after surgery.[12,13] A recent trial of dexamethasone showed fewer recurrent cases, but less favorable outcomes and more adverse events.[14] Studies of atorvastatin use in rodents[15,16] and humans[17–21] found that it led to a reduction in CSDH volume without the requirement for surgery and showed no adverse effects. While all of these studies showed the efficacy of atorvastatin in reducing the need for surgical treatment, they did not show its efficacy in preventing recurrence in surgical cases. Consequently, we conducted the present prospective study to evaluate the efficacy of atorvastatin in reducing the recurrence of CSDH after burr hole surgery, which is the most common surgical therapy for CSDH.

Materials and Methods

Patient Population

Adult patients with CSDH who were operated on at Siriraj Hospital between May 2019 and December 2020 were included in this prospective study. All the patients were diagnosed as CSDH according to their symptoms, such as headache, seizure, or focal neurologic deficits, and by brain imaging, either cranial computerized tomography (CT) or magnetic resonance imaging, showing radiographic features corresponding with CSDH. Patients who had a history of statin allergy, previous ventriculoperitoneal or lumboperitoneal shunting, and who regularly used atorvastatin were excluded from this study. The included patients underwent single or double burr hole surgery with drainage of the chronic hematoma. The patients were operated by various neurosurgeons with a common standard burr hole technique. Numbers of burr hole were based on extension of the chronic subdural blood, and catheters for gravitational drainage of residual subdural blood were always placed approximately 3 to 5 days postoperatively. The CSDH characteristics based on Nakaguchi's classification[9] and volume were recorded and the demographic data of all the patients were collected. Atorvastatin at 20 mg once daily was administered to all patients for 4 weeks, starting as soon as they could have an oral diet postoperatively.

During the 8-week follow-up period, patients who discontinued atorvastatin before 4 weeks postoperatively, or who needed antiplatelet or anticoagulant treatment, or who had coexisting thrombocytopenia were withdrawn from the study. Adverse effects of atorvastatin were clinically assessed throughout the study.

Patients with recurrent CSDH were defined as patients who had recurrent neurologic symptoms and their cranial radiographic study showing persistent or increasing CSDH that finally required reoperation during the 8-week follow-up period.

This study was approved by the Ethics Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand; Certificate of Approval (COA) number SI 355/2019. All the patients' data retained full confidentiality in compliance with the Declaration of Helsinki.

Outcome Assessment

The outcome was the recurrence rate of CSDH in the 8-week postoperative period. Symptoms of recurrent CSDH, such as a headache or focal neurological deficit, were recorded. Patients with a suspicion of recurrent CSDH underwent cranial CT. If cranial CT showed CSDH that was compatible with the symptoms, that patient was diagnosed as recurrent CSDH, and surgical treatment was performed for treating the recurrent hematoma. Our recurrence rate of CSDH was compared with the results from previous studies.

Statistical Analysis

Statistical analysis was conducted using PASW Statistics (SPSS) version 18.0 software. Demographic data are presented herein as the mean $\pm$ standard deviation for continuous data and the number (percentage) for the categorical data. The chi-square test was used to compare the recurrence rate between this study and other studies. A p-value of less than 0.05 was used to determine statistically significant differences between the studies' results.

Results

In total, 75 patients were included in the study. Two individuals were withdrawn from the study before completion of the 8-week postoperative period: one died of pneumonia within the first week after the burr hole surgery, and the other discontinued atorvastatin before completion of the 4-week course due to a drug allergy presenting with a skin rash. Therefore, 73 patients who completed the 4-week course of atorvastatin after the burr hole surgery were finally included in the statistical analysis.

The included patients' demographic characteristic is shown in ►**Table 1**. There were 50 (68.5%) male and 23 (31.5%) female patients. Their ages ranged from 51 to 102 years old, with a mean age of 73.9 $\pm$ 11 years old. Of all the patients, 50 (68.5%) had hypertension, and 30 (41.1%) took antiplatelets, which were withheld during the perioperative and postoperative periods. The most common causes of CSDH were falling in 33 (45.2%) patients and an unknown cause in 21 (28.8%). Most patients presented with weakness of the extremities, headache, alteration of consciousness, and an unstable gait (49.3, 31.5, 21.9, and 20.5%, respectively). Sixty-three patients (86.3%) had an initial Glasgow Coma Scale (GCS) score of 14 to 15, while 6 (8.2%) had a GCS score of 9 to 13, and 4 (5.5%) had a GCS score of 8 or less. Regarding the hematoma appearance on cranial CT as classified according to Nakaguchi et al,[9] 35 (47.9%) were a homogeneous type, 22 (30.1%) were a separated type, and 16 (21.9%) were a laminar type. The locations of

Table 1 Patients' demographic data

Patients' characteristics	*n* (%)
Gender	
Male	50 (68.5)
Female	23 (31.5)
Age range (y)	
51–60	10 (13.7)
61–70	20 (27.4)
71–80	19 (26.0)
81–90	19 (26.0)
> 90	5 (6.8)
Causes	
Falling (with/without head injury)	33 (45.2)
Unknown	21 (28.8)
Mild head injury (not from falling)	9 (12.3)
Vehicle accident	5 (6.8)
Coagulopathy	5 (6.8)
Symptoms	
Limb weakness	36 (49.3)
Headache	23 (31.5)
Deterioration of consciousness	16 (21.9)
Unstable gait	15 (20.5)
Others	8 (11.0)
Seizure	4 (5.5)
Sensory impairment	1 (1.4)
Initial GCS score	
14–15	63 (86.3)
9–13	6 (8.2)
3–8	4 (5.5)
Hematoma location	
Left	22 (30.1)
Right	28 (38.4)
Bilateral	23 (31.5)
Hematoma volume (ml)	
< 50	8 (11.0)
51–100	29 (39.7)
101–150	24 (32.9)
> 150	12 (16.4)
Hematoma type	
Homogeneous	35 (47.9)
Separated	22 (30.1)
Laminar	16 (21.9)
Operation	
Double burr hole surgery	43 (58.9)
Single burr hole surgery	28 (38.4)
Both surgeries	2 (2.7)
Recurrence	
Present	2 (2.7)
Absent	71 (97.3)
Adverse effect of atorvastatin for 4 weeks	
Present	0 (0)
Absent	73 (100)

Abbreviation: GCS, Glasgow Coma Scale.

the hematomas were equally distributed on the left, right, and bilateral sides. The mean hematoma volume was 106.3 ± 47 mL. Double burr hole surgery was performed in 43 (58.9%) patients, 28 (38.4%) underwent single burr hole surgery, and the remaining 2 (2.7%) underwent combined double and single burr hole surgery for the treatment of bilateral CSDH.

Of the 73 patients, recurrent CSDH was found in 2 (2.7%) of the patients. Of the two cases with recurrent CSDH, the first cranial CT showed a homogenous type CSDH in one case and a separated type CSDH in the other. Both of them underwent single burr hole surgery as the primary surgical treatment for their unilateral CSDH. After that, they developed a headache on the second week after the surgery and subsequent cranial CT revealed persistent CSDH with a significant pressure effect. Subduroperitoneal shunting surgery was performed for the treatment of recurrent CSDH in both patients and their symptoms were relieved.

There was no adverse effect of atorvastatin found in the 73 patients who completed the 4-week course of atorvastatin.

Discussion

The pathophysiology of CSDH consists of a cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis in encapsulated blood or fluid collection inside the subdural space between the dura and arachnoid maters following a minor head trauma. This subdural space is a layer of cells called the "dural border cell layer." Either injury of the bridging vein or of the cortical vein resulting in an acute subdural hematoma or injury of the dural border cell layer is believed to be the initiator of CSDH formation. When hematoma has lysis, the inflammatory process in this cell layer brings about increased vascular permeability, allowing microhemorrhages and exudative fluid collection within this encapsulated subdural space, which then causes the hematoma expansion.[11,22–25] Therefore, anti-inflammatory medication may play a major role in the treatment of CSDH.

A recent randomized control trial of dexamethasone for the treatment of CSDH was reported by Li et al. Their study investigated whether the use of dexamethasone could reduce the need for surgical treatment and the recurrence of

CSDH after surgery. Even though the authors only found a small number of recurrent cases, the outcomes were less favorable and the incidence of adverse events was increased.[14] On the contrary, a randomized clinical study on the efficacy and safety of atorvastatin use in patients with CSDH revealed a reduction of the hematoma volume, a decrease in the requirement for surgical treatment, and no adverse effects of the drug.[17,21]

The recurrence rate of CSDH after surgery was not low. The results from previous studies showed an overall recurrence rate ranging from 9.8 to 15%, while a meta-analysis revealed a recurrence rate of 10.7 to 39.0%.[4,26] Most of the recurrent CSDH cases occurred within the first 3 months after surgery.[10,27] In regards to our previous prospective study, most the recurrent CSDH cases occurred within 8 weeks after the initial operation (80% of the recurrent CSDH occurred within 2 weeks, and 90% occurred within 8 weeks, postoperatively).[10] Therefore, we decided to use a follow-up period of the study of 8 weeks.

Mechanisms of atorvastatin in reduction of CDSH volume and recurrence rate of CSDH remain elusive. The major mechanisms involve inhibition of inflammatory process, promotion of vascular maturation at the neomembrane of CSDH, and antiangiogenic effect.[11,15,28] An animal study proposed by Quan et al showed that atorvastatin administration in rats with CSDH significantly increased the number of regulatory T-cells in circulation, accelerated absorption of CSDH, and improved neurological and cognitive outcomes compared with rats with CSDH treated by saline. Also, atorvastatin treatment significantly decreased the level of interleukin 6 and 8 (IL-6 and IL-8), and tumor necrosis factor-α (TNF-α). Increase in the number of regulatory T-cells and reduction of IL-6, IL-8, and TNF-α expression may be related to suppression of inflammatory reaction, and lead to absorption of CSDH and improved outcomes.[29] In the same way, Yang et al demonstrated similar results in an experimental study in rats with CSDH. They found that atorvastatin treatment effectively suppressed the expression of IL-6, IL-8, and TNF-α, increased expression of IL-10, accelerated absorption of CSDH, and improved neurological function in rats with CSDH.[30]

Regarding effect of atorvastatin on the recurrence rate of CSDH in patients undergoing burr hole surgery or twist-drill craniostomy, previous retrospective studies reported a statistically significant reduction of the recurrence rate ($p = 0.007$)[19] or uncured rate ($p = 0.045$)[18] in patients receiving atorvastatin. In the present study, we prospectively investigated the efficacy of atorvastatin in the reduction of recurrent CSDH after burr hole surgery. According to the comparison of the recurrence rate of CSDH between our

Table 2 Comparison of the recurrence rate of CSDH following burr hole surgery between the present and previous studies[10,18,19,26,27,31,32]

Authors reference	Year	*n*	Study design	Use of atorvastatin for prevention of recurrent CSDH	Follow-up	Recurrence rate (%)
Mori and Maeda[31]	2001	500	Retrospective, single center	No	12 wk	49/500 (9.8)
Weigel et al[26]	2003	3,601 (burr hole group)	Meta-analysis	No	N/A	437/3,601 (12.1)
Oh et al[27]	2010	149	Retrospective, single center	No	12 wk	18/149 (12.1)
Xu et al[18]	2016	102 (surgical group)	Retrospective, single center	Yes ($n = 39$)	3 mo	1 uncured[a]/39 (2.6)
				No ($n = 63$)		12 uncured[a]/63 (19)
Nunta-aree et al[10]	2017	75	Prospective, single center	No	8 wk	10/102 (9.8)
You et al[32]	2018	226	Retrospective, single center	No	1 mo by CT brain 1 y by telephone	34/226 (15)
Tang et al[19]	2018	245	Retrospective, single center	Yes ($n = 125$)	6 mo	6/125 (4.8)
				No ($n = 120$)		18/120 (15)
Present study	2021	73	Prospective, single center	Yes	8 wk	2/73 (2.7)

Abbreviations: CSDH, chronic subdural hematoma; CT, computerized tomography; mo, month; N/A, no available data; wk, week; y, year.
[a]Uncured case is defined as volume of chronic subdural hematoma decreased by less than 50%, recrudesced, or even increased on postoperative cranial images with aggravated neurologic symptoms.

study and previous studies with the same surgical procedure (single or double burr hole surgery) or the same duration of postoperative follow-up period (60 days), patients with use of atorvastatin for prevention of recurrent CSDH obviously had lower recurrence rate of CSDH compared with patients without use of atorvastatin (►**Table 2**).[10,18,19,26,27,31,32] These results indicate that an administration of atorvastatin following burr hole surgery may be helpful in the reduction of recurrent CSDH.

Several radiographic factors that may increase the recurrence of CSDH were reported by Nakaguchi et al. These included the hematoma characteristic as defined by Nakaguchi's classification, degree of the midline shift, and location of the hematoma. Regarding the hematoma characteristics, the separated type of CSDH carried the highest risk of recurrence (36%), followed by the homogeneous type (15%).[9] Furthermore, bilateral CSDH and a preoperative and postoperative midline shift of more than 5 mm were found to be the independent predictors of the recurrence of CSDH.[5,6] Nevertheless, owing to the scant number of recurrence cases in our present study, an association between the recurrence of CSDH and the potential risk factors for the recurrence could not be determined.

From the safety point of view, there was no adverse effect of atorvastatin found in our patients who achieved the 4-week course of the drug. This result indicates that an administration of a short course of atorvastatin after burr hole surgery is relatively safe. Several previous studies also showed safety of perioperative administration of atorvastatin in CSDH patients.[17–21] However, common adverse effects, such as allergic rash, diarrhea, indigestion, myalgia, or sore throat, must be concerned and closely monitored.

Some limitations of the present study have been encountered. For the first drawback, our study is a single-arm prospective study without control group. To improve evidence-based practice, a double-blind, randomized, placebo-controlled trial in comparison between atorvastatin and placebo for reducing the recurrence rate of CSDH after burr hole surgery is required in the future study. Moving on the next disadvantage, our results may not represent the actual recurrence rate of CSDH in the real-world practice because we eliminated confounding variables by exclusion of patients who received antiplatelet or anticoagulant drug or patients with thrombocytopenia during postoperative follow-up period. This exclusion may lower the recurrence rate in our cohort. On the contrary, in neurosurgical practice, several patients need to resume these drugs before 8 weeks after the initial surgery of CSDH due to various reasons, such as coronary artery disease or cardiac valve replacement, and risk of recurrent CSDH may be increased in such patients. The last defect of our study is a relatively short duration of postoperative follow-up period. Based on our previous study on 102 CSDH in 75 patients, 10 of 102 (9.8%) were recurrent. Of 10 recurrent CSDH, 9 (90%) developed the recurrent hematoma within 8 weeks postoperatively.[10] That was the reason why this duration was chosen as a postoperative follow-up period in the present study. However, longer follow-up in the future study is mandatory to investigate the effect of atorvastatin on prevention of recurrent CSDH in a long term.

Conclusion

An administration of atorvastatin of 20 mg daily for 4 weeks may be helpful in reducing the recurrence rate of CSDH following burr hole surgery without there being any serious adverse effects of the drug.

Authors' Contributions

D.B. contributed to the development or design of methodology, project administration, software, investigation, data collection, formal analysis, visualization, original draft preparation, and approval of the final manuscript. B.S. contributed to the development or design of methodology, formal analysis, visualization, reviewing and editing of the manuscript, and approval of the final manuscript. S.N.-a. contributed to the conceptualization, supervision, reviewing and editing of the manuscript, corresponding author, and approval of the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand; Certificate of Approval (COA) number SI 355/2019. All the patients' data retained full confidentiality in compliance with the Declaration of Helsinki.

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Conflict of Interest

None declared.

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