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Effects of atorvastatin on chronic subdural hematoma

A systematic review

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Abstract

Background: The high recurrent rate of chronic subdural hematoma (CSDH) has consistently confused the neurosurgeons, and the role of atorvastatin in the management of CSDH has remained unclear over past decade, and atorvastatin seems to be a safe and cost-effective treatment to CSDH. Therefore, it is necessary to conduct a systematic review to discuss the effect of atorvastatin in CSDH.

Method: We searched the PubMed, EMBASE, Cochrane Library, and the China Biology Medicine disc, up to March 2017, for published studies on the effects of atorvastatin in the management of CSDH, and reviewers performed a brief qualitative descriptive analysis of atorvastatin's efficacy in the management of CSDH.

Results: Three eligible studies were included in this systematic review. Results indicated that atorvastatin accelerated hematoma absorption, decreased recurrence risk, and surgical requirement.

Conclusion: Limited evidence suggests that oral atorvastatin may be beneficial in the management of CSDH. Further high-quality studies focused on dosage, duration, hematoma size are needed to further elucidate the role of atorvastatin in the management of CSDH.

Abbreviations: CI = confidence interval, CSDH = chronic subdural hematoma, OR = odds ratio, PRISMA = preferred reporting items for systematic reviews and meta-analysis, RCT = randomized controlled trial.

Keywords: absorption, atorvastatin, chronic subdural hematoma, conservative treatment, recurrence, surgery

1. Introduction

Chronic subdural hematoma (CSDH) is a common disease in neurosurgical and neurological department, with an incidence of nearly 3.4 per 100,000 in the patients younger than 65 years, 8 to 58 per 100,000 in patients older than 65 years.[1] Many areas of the world map are facing an ageing population, especially in China, the CSDH population has increased greatly. Moreover, patients with long-term use of anticoagulant agents, for example, cardiovascular ischemia patients, have a higher incidence of CSDH than those without.[2] Even though the incidence of CSDH is increasing, the treatment methods on CSDH vary greatly. General surgery techniques for CSDH include burr-hole drainage, percutaneous twist-drill drainage, craniotomy, and endoscopic surgery.[3–5] Previous studies have reported that corticosteroids, angiotensin converting enzyme inhibitors, tranexamic acid may be adjunctive to surgery, or even as a monotherapy for CSDH treatment.[2,6,7] Nonetheless, there are various surgical intervention and drug options for patients with CSDH, achieving a clinically efficient permanent cure is still far out of reach, and no explicit mechanism can explain this situation so far, we have known that high- and mixed-density of hematoma, leukemia, chronic renal failure, liver diseases are the risk factors for CSDH recurrence.[8]

However, the luster of drug agents has dimmed in recent decades as the characteristics of CSDH have become more clearly. The angiotensin-converting enzyme inhibitors have been found to inhibit the development of immature and new blood vessels in the neomembrane of hematoma.[7] Although previous studies have reported that corticosteroids and tranexamic acid may be beneficial, the evidences remain inadequate.[1,9–11] Recently, atorvastatin has been reported to be effective to CSDH treatment. Atorvastatin, a member of statins that inhibit 3-hydroxy-3-methyl glutaryl coenzyme A reductase and act by lowering the level of low-density lipoprotein cholesterol,[12] has been widely investigated in CSDH management. Wang et al[13] have reported rat model of subdural hematoma treated with atorvastatin, subsequently come to the finding that atorvastatin could reduce the hematoma through enhancing angiogenesis. However, the effect of atorvastatin on CSDH treatment has been poorly interpreted in clinical practice. Jiang et al[14] have

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registered a protocol of multicenter, randomized clinical trial investigating the effect of atorvastatin for CSDH treatment on ClinicalTrials.gov in 2013, but the results have not been published yet. To the best of our knowledge, neither randomized controlled trials (RCTs) nor reviews focused on the function of atorvastatin in the treatment of CSDH have been published so far. We therefore attempted to perform a systematic review by searching published literature to provide more insights into the understanding of atorvastatin for CSDH treatment.

2. Methods

2.1. Protocol and registration

The aim of this review is to discuss and investigate the effect of atorvastatin for CSDH treatment. We have registered a review protocol on PROSPERO, an international database of prospectively registered systematic reviews (no. 42016047070).

2.2. Ethics statement

As this systematic review is performed based on the published data, ethical approval is not required.

2.3. Inclusion criteria

We prepared and reported this systematic review in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Two reviewers conducted a literature screening independently for detailed information in comply with the participants, interventions, comparisons and outcomes, and types of study.[15] We screened the studies using following inclusion criteria: participants: CSDH patients confirmed by computed tomography or magnetic resonance imaging, and the patient age is >16 years old; intervention and comparator: atorvastatin taking was considered as the intervention. We assessed the effects in atorvastatin-used group and no atorvastatin-used group, or the outcomes before versus after atorvastatin use. Outcomes: outcomes, for example, recurrent rate, time to recurrence, hematoma volumes were assessed. Study design: we included RCTs, observational studies to assess the effect of atorvastatin. Participants with cerebral hernia or a high risk of cerebral hernia were not included.

2.4. Search strategy

We searched 4 medical databases, PubMed, EMBASE, Cochrane Library, and the China Biology Medicine disc, up to March 2017 without any language limitations for published studies. Reviewers used following combined terms as the searching strategy: ([MeSH] "Hematoma, Subdural, Chronic" or "chronic subdural hematoma" or "CSDH" and [MeSH] "Atorvastatin Calcium" or "atorvastatin"). A manual researching on the references of identified studies was performed for more related studies.

2.5. Data extraction

Two reviewers (SQ and WZ) conducted the data extraction process. The extracted detailed information of included studies was as follows: the family name of first author, publication year, country, study design, sample size, characteristics of atorvastatin use, main outcomes, and study quality. Two reviewers resolved all the disagreements by discussion; if necessary, a third reviewer to arbitration was resorted.

2.6. Summary measures and data analysis

This review aimed to assess the effect of atorvastatin on CSDH treatment. Wherever possible, we assessed recurrent rate, recurrent time, and changes of hematoma volume as the summary measures. With and without atorvastatin use was considered as the intervention in assessing the CSDH progress. We failed to conduct a meta-analysis on this topic due to insufficient studies and small sample size. Besides, different study designs did not meet the requirements of synthesizing the results. Finally, a brief qualitative descriptive analysis of current evidence was performed.

2.7. Assessment of methodological quality

We used the revised and validated version of methodological index for nonrandomized studies to assess the quality of included studies. Twelve items were selected for comparative studies to evaluate each study's methodological quality, and 8 of them were for the assessment of noncomparative studies. Each item scored from 0 to 2; 0 represented that it was not reported in the evaluated article, 1 represented that it was reported but inadequately, and 2 represented that it was reported adequately. The maximum score for the comparative studies was 24 and for the noncomparative studies was 16.[16]

3. Results

3.1. Study selection and study characteristics

Study selection was proceeded in comply with the requirement of PRISMA flow diagram.[17] According to the predeveloped search strategy, we identified 21 potential articles after removing duplicates, and we performed a full-text reading on 3 articles after scanning the title and abstract. Besides, we scanned the reference lists of reviews on CSDH treatment for more relevant articles, yet no additional articles were found, finally, 3 studies met the inclusion criteria and were included in this review[13,18] (Fig. 1). Of the included studies, 2 studies were retrospective studies[18,19] and the other 1[13] was a prospective study, and 2 studies[13,18] were performed in China, the rest 1[19] was in Hong Kong, China. More relevant information was shown in Table 1. A brief qualitative analysis in a narrative form was performed instead of meta-analysis due to the design and data limitations of included studies.

3.2. Does atorvastatin administration reduce the hematoma volume of CSDH?

Reducing the volume of hematoma is key to the treatment of CSDH, especially for conservative treatment with more advantages over surgery in CSDH management if atorvastatin really works. Therefore, we examined the effect of atorvastatin on eliminating hematoma. Only 3 studies with small sample size have described it. Wang et al[13] claimed that hematoma volume reduced from 48.70 ± 20.38 to 16.64 ± 14.28 mL with a sample size of 22 within the first month of atorvastatin treatment. Xu et al[18] conducted a retrospective study and found that the volume of hematoma was reduced from 20.83 ± 4.49 to 11.40 ± 4.46 mL with a sample size of 7 within the first month of oral administration of atorvastatin, 20 mg daily. In addition, another retrospective study showed that the improvement rate of

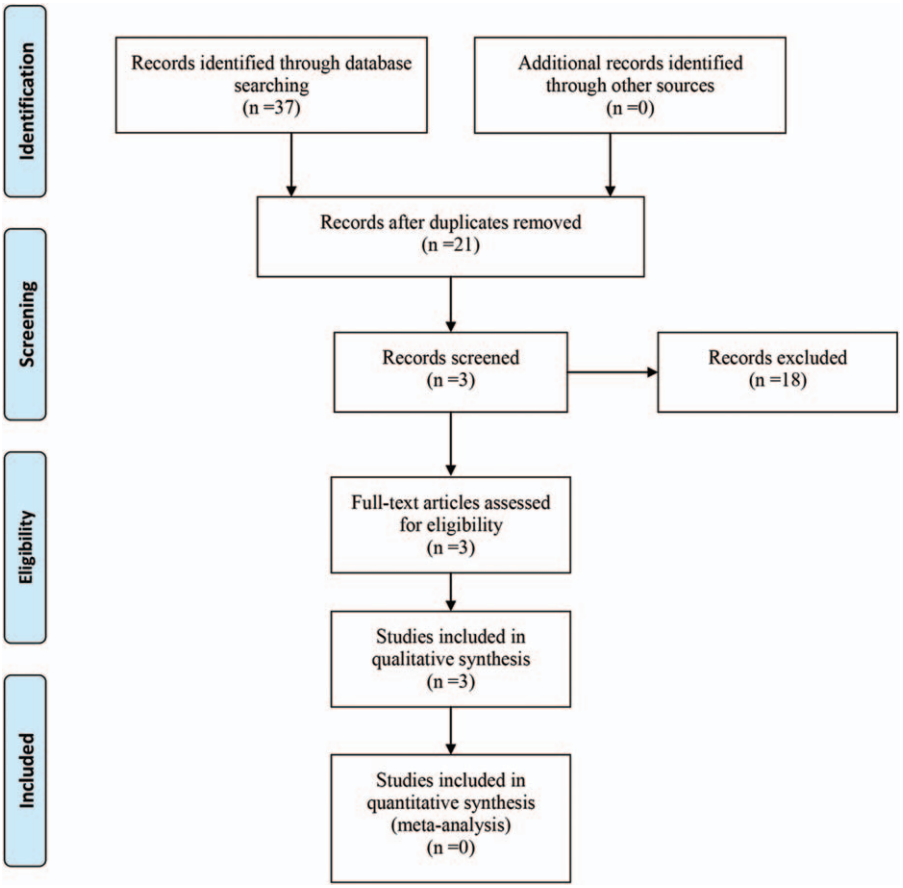

Figure 1. Flow diagram of literature search and selection process.

hematoma at third months after atorvastatin administration was 75% for the atorvastatin group versus 42% for the control group; however, the result did not have any statistically significant difference ($P = .0977$).[19]

3.3. Does atorvastatin administration decrease the recurrence rate of CSDH?

Brain swelling was incomplete accompanied by a long-time existence of subdural space in patients with CSDH, even after the hematoma had been removed; therefore, CSDH patients tended to have a higher recurrent rate. In this review, all the included studies supported that atorvastatin were closely related to the recurrence rate. Wang et al[13] firstly reported a small population of 23 participants with atorvastatin treatment. They reported that 1 patient was underwent surgery due to deteriorating condition with an increasing volume of hematoma, while 22 patients experienced improved symptoms and did not have recurrence during the follow-up period after atorvastatin intervention. Meanwhile, 1 study with 102 patients described that atorvastatin used as an adjunct to surgery could significantly decrease the risks of recurrence or prolong the time-to-recurrence hematoma.[18]

3.4. Does atorvastatin is effective in surgical CSDH treatment?

The elderly are not only at higher risk of being CSDH, but also with more risk to postoperative recurrence. How is the effect of atorvastatin in CSDH patients with surgical treatment? Chan et al reported the risk of deterioration requiring surgery was 16.7% in atorvastatin group versus 58.3% in control group. The odds ratio (OR) of burr-hole drainage was 0.143 (95% confidence interval [CI]: 0.021–0.958) with atorvastatin intervention.[19] Atorvastatin produced beneficial effects as an adjunct drug to surgery. The postoperative improvement rate was 97.4% (38/39) in atorvastatin group versus 80.9% (51/63) in control group.[18] These results showed that atorvastatin could be helpful to hematoma resolution and favored the use of atorvastatin in the management of CSDH.

3.5. Dose atorvastatin be useful for CSDH patients with antiplatelet or anticoagulant history?

All the included studies paid attention to the antiplatelet or anticoagulant history in CSDH patients treated by atorvastatin.[13,18,19] A total of 21.7% (5/23) CSDH patients had a history of aspirin treatment, whereas radiological resolution showed that all the hematomas in those patients were absorbed completely 3 months later after atorvastatin treatment.[13] In Xu et al[18] study, the history of antiplatelet or anticoagulant did not increase the risk of uncured CSDH, and the OR was 0.329 (95% CI= 0.040–2.696). In another study, no statistical difference was found in the antiplatelet or anticoagulant history between atorvastatin and control groups; however, the atorvastatin group showed better prognosis.[19]

Table 1

Characteristics of studies included in the review.

Author Year	Study design	Sample size	Sex F/M	Age, y	Atorvastatin	Follow-up	Methods of hematoma evaluation	No. of antiplatelet or anticoagulant	Hematoma changes	MINORS
Wang 2014	Prospective	23	6/17	67.87 ± 14.71	Oral, 20 mg/d for 1–6 mo (3.02 ± 1.77)	3–36 mo (18.62 ± 13.13)	CT or MRI	5	Hematoma was resolved in 17 patients and shrank in 5 patients within 3 mo, 1 had a surgery. Hematoma volume reduced from 48.70 ± 20.38 to 16.64 ± 14.28 mL	10
Xu 2016	Retrospective	109	NR	68.51 ± 12.45a 96.59 ± 28.59b	Oral, 20 mg/d for 1–6 mo	1–6 mo	CT or MRI	8a 11b	Hematoma reduced from 20.83 ± 4.49 to 11.40 ± 4.46 mL in 7 conservative patients. In 102 surgical CSDH patients, 38/39 CSDH patients were improved or cured in atorvastatin group, only 1 was uncured; 51/63 CSDH patients were improved or cured in control group, 12/63 CSDH patients were uncured ($P < .05$)	13
Chan 2017	Retrospective	24	10/14	78.3a 79.5b	Oral, 20 mg/d for 3–6 mo	3–6 mo	CT or MRI	5a 6b	Hematoma resolution at 3 m was 75% (9/12) for the atorvastatin group, vs 42% (5/12) for the control group. The risk of deterioration requiring burr-hole drainage was 16.7% (2/12) in the atorvastatin group, vs 58.3% (7/12) in the control group. The OR of deterioration requiring burr-hole drainage with atorvastatin was 0.143 (95%CI: 0.021–0.958)	13

a = atorvastatin group, b = control group, CI = confidence interval, CSDH = chronic subdural hematoma, CT = computed tomography, MINORS = methodological index for nonrandomized studies, MRI = magnetic resonance imaging, OR = odds ratio.

4. Discussion

This review is the first systematic review of published studies focused on the function of atorvastatin in CSDH patients. The results indicate that atorvastatin produces potential benefits on CSDH management. However, results of this review are not convincing and persuasive enough considering the lack of high-quality evidence. However, our review may still contribute to the understanding of atorvastatin in CSDH treatment.

Half of CSDH tended to deteriorate and required burr-hole drainage when CSDH was managed by conservative treatment.[19,20] Subsequently, atorvastatin treatment is recommended for conservation treatment, owing to its safety for asymptomatic or mildly symptomatic CSDH patients.[21] With the intervention of atorvastatin for 1 to 6 months, atorvastatin could accelerate the absorption of hematoma[13] and decrease the risk of burr-hole drainage.[19] Besides, atorvastatin is not only used by conservation treatment, but also used as an adjunct medicine to postoperation management. Previous study showed that atorvastatin decreased the risks of recurrence or prolong the time-to-recurrence after surgery.[18] To conclude, our results favored that CSDH patients might benefit from atorvastatin. The mechanisms of atorvastatin treatment should trace back to the formation of CSDH. CSDH generally comes from asymptomatic acute subdural hematoma, which arises from bleeding from bridging veins tearing or arterial rupture from a slight or moderate trauma.[22,23] Subsequent inflammation and dysfunctional angiogenesis are topic theories to CSDH growth. The accumulation of hematoma in the subdural space activates the local inflammatory reaction, and fibroblast may spread over the inner surface of hematoma neomembrane eventually.[1] Besides, the fragile and immature vessels of neomembranes may promote repeated microhemorrhage into the hematoma cyst, increase the extravasation of membrane, and make CSDH gradually enlarge.[24,25] Therefore, the local inflammatory and the nascent immature blood vessels are related to CSDH recurrence and expansion. Atorvastatin has been proven to be not only a localized inflammation inhibitor but also an angiogenesis maturation agent.[26–29] Based on similar mechanisms, a rat model of a subdural hematoma described that low-dose atorvastatin could increase the expression of angiopoietin and vascular endothelial growth factor, which may enhance vascular maturation.[30] Atorvastatin has inflammation controlling and angiogenesis maturation effects, in addition to lipid-lowering and cholesterol-lowering effects, so it has been recommended to CSDH treatment. According to the data of current published studies, atorvastatin has shown its clinical advantages, for example, it may accelerate hematoma resolution,[13,18,19] decrease the recurrent rate,[18] and reduce the burr-hole drainage requirement.[19] However, only a few studies have been reported so far, the atorvastatin for CSDH treatment is still in exploratory stage; therefore, the use of atorvastatin in clinic background should be treated with caution.

Previous study referred that the CSDH size might not be associated with improvements, whereas preoperative anticoagulation treatment may be related to reoperation rate,[31] our result implied that antiplatelet or anticoagulant history was not related to hematoma resolution. Xu et al[18] reported 19 CSDH patients with antiplatelet or anticoagulant treatment, and their result did not support that the use of antiplatelet or anticoagulant was an independent risk factor. What is more, Wang et al[13] performed a prospective study showing that the hematomas of 5 CSDH patients with antiplatelet treatment disappeared, and several

recent studies found that antiplatelet or anticoagulant medications were not related to hematoma growth or hematoma recurrence.[32–34]

Though some studies focused on the atorvastatin's efficacy in CSDH treatment have been published, no any dose-ranging reports have been found. Of all included studies and a RCT protocol, oral intake of a 20 mg atorvastatin daily for 1 to 3 months is currently the main option for atorvastatin treatment.[14,18,19] A previous meta-analysis with 7 RCTs included have found that atorvastatin 80 mg/d can increase the risk of intracerebral hemorrhage.[35] In this review, all the included studies have taken atorvastatin 20 mg/d as the intervention, and no studies have reported related adverse events. In the future, more high-quality RCTs, with dosage and duration analysis, taking atorvastatin as an adjunct to surgery or as a monotherapy, are needed when assessing the efficacy of atorvastatin.

5. Limitations

Several limitations of this systematic review should be addressed. First, there are just 3 included studies with observational design and small sample size; the high-quality evidence are lacking for our study. Second, all the studies were performed in China, the results cannot be representative for global population, more studies in other countries are needed to generalize the conclusions. Third, none of the included studies have reported the adverse effects of atorvastatin treatment, the safety of atorvastatin has not been fully understood yet.

6. Conclusion

Limited evidence suggests that oral atorvastatin may be beneficial in the management and prognosis of CSDH. Future high-quality studies are needed to further understand the role of atorvastatin in CSDH treatment.

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