Evaluation of Effectiveness of Atorvastatin in Treating Chronic Subdural Hematoma not Requiring Surgery: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Chronic subdural hematoma (CSDH) is a chronic space-occupying lesion formed by blood accumulation between the arachnoid membrane and the dura mater. Atorvastatin is of increasing clinical interest for CSDH. We performed a meta-analysis of published randomized controlled trials (RCTs) and used objective data as the primary outcomes to provide an evidence-based analysis of the efficacy of atorvastatin for CSDH treatment. Databases of MEDLINE (via PubMed), EMBASE, the Cochrane Library, Scopus, Web of Science, ScienceDirect, Chinese National Knowledge Infrastructure (CNKI), Cqvip database (CQVIP), and Wanfang database were systematically searched for RCTs reporting the use of atorvastatin for CSDH treatment. Odds ratio (OR), standard mean difference (SMD), and 95% confidence intervals (CIs) were used as summary statistics. I-square (I^2) test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. Nine relevant RCTs with 611 patients were identified for inclusion in this meta-analysis. Compared to controls, atorvastatin treatment had a significantly higher effectiveness (OR: 7.41, 95% CI: 3.32-16.52, $P < 0.00001$, $I^2 = 0\%$), lower hematoma volume (SMD: −0.46. 95% CI: −0.71 to −0.20, $P = 0.0005$, $I^2 = 0\%$), higher activities of daily living-Barthel Index (ADL-BI) (SMD: 2.07, 95% CI: 1.06-3.09, $P < 0.0001$, $I^2 = 92\%$), and smaller Chinese stroke scale (CSS) (SMD: −1.10, 95% CI: −1.72 to −0.48, $P = 0.0005$, $I^2 = 57\%$). In view of these findings, we conclude that the outcomes of experimental group are superior to the control group with respect to effectiveness, hematoma volume, ADL-BI, and CSS based on nine RCTs with 611 patients. Atorvastatin is beneficial to CSDH patients without surgery.

Keywords: CSDH, drug therapy, hematoma volume, review, statins

Introduction

Chronic subdural hematoma (CSDH) is a chronic space-occupying lesion with occult onset and slow progression, which is formed by blood accumulation between the arachnoid membrane and the dura mater.[1,2] The mechanisms of occurrence, development, and absorption of CSDH remain unclear.[3-5] For CSDH patients with significant space-occupying effects, surgical treatment is usually the first choice, which includes burr hole drill drainage, twist drill drainage, small bone window craniotomy, and endoscope-assisted evacuation of CSDH.[6-8] Although most patients have good surgical treatment results, some patients still experience postoperative recurrence (the recurrence rate can be up to 33%).[2] CSDH patients are predominantly older, with many underlying diseases, surgical risks, and postoperative complications.[2,9] Miranda *et al*.[10] reported CSDH patients' 6-month and 1-year mortality rates after surgery to be 26.3% and 32%, respectively. Therefore, it remains clinically important to develop improved drug therapies for CSDH.

Atorvastatin is becoming increasingly used for treatment of CSDH. Atorvastatin can activate the phosphatidylinositol 3-kinase/protein kinase B/transcription factor nuclear factor-erythroid 2-related factor 2 pathway and the Notch1 pathway, attenuate dendritic cell maturation, and promote neural progenitor cell proliferation. Atorvastatin can also promote angiogenesis and significantly reduce the levels of tumor necrosis factor-α, interleukin 6, and the vascular endothelial growth factor gene, which reduce hematoma.[11-13]

He *et al*.[14] evaluated the efficacy of atorvastatin for treatment of CSDH in a meta-analysis, but the included studies in that meta-analysis were predominantly retrospective and only the reoperation incidence was evaluated. Furthermore, the recently published clinical studies on CSDH treatment were not included in that meta-analysis. Therefore, we performed

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Submitted: 13-Sep-2023 **Revised:** 14-Dec-2023 **Accepted:** 17-Dec-2023
Published: 06-Feb-2024

DOI: 10.4103/aian.aian_818_23

a meta-analysis of randomized controlled trials (RCTs) with objective outcomes to provide an evidence-based analysis of the efficacy of atorvastatin for CSDH treatment.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standards were followed for conducting this current meta-analysis.[15] Patient consent or ethical approval was not required for this study because it was built on existing data from the literature.

Search strategy

The study protocol was registered in the international prospective register of systematic reviews (PROSPERO) database (ID of CRD 42023444927). All studies were searched for using MEDLINE via PubMed, EMBASE, the Cochrane Library, Scopus, Web of Science, ScienceDirect, Chinese National Knowledge Infrastructure (CNKI), Cqvip database (CQVIP), and Wanfang database without language restrictions, with a search time from inception date until June 15, 2023 [shown in Appendix 1].

Selection criteria

Citations were screened at the title/abstract level or retrieved as full text. Articles were selected using the following inclusion and exclusion criteria. Inclusion criteria: (1) only clinical RCTs were eligible, regardless of blinding; (2) patients of either gender were diagnosed with CSDH; and (3) patients in the experimental group were treated with "atorvastatin" or "atorvastatin and other drugs." Patients in the control group received either "placebo" or "other drugs." If patients in the experimental group were administered "atorvastatin and other drugs," then patients in the control group must have been administered "the same other drugs" to determine the efficacy of atorvastatin without bias. Exclusion criteria: (1) patients who underwent surgery and (2) case reports or congresses.

Data extraction and critical appraisal

Data were independently extracted from original publications by two reviewers (BW and KQL) using our selection criteria. Discrepancies between the reviewers were resolved by consensus or a third reviewer (CYG). The following data were extracted from each study: (1) first author, (2) year of publication, (3) group, (4) age, (5) interventions, (6) atorvastatin dosage, (7) follow-up visit times, (8) number of patients, (9) atorvastatin duration, (10) number of effective patients, (11) effectiveness criterion (hematoma elimination), (12) hematoma volume, (13) activities of daily living-Barthel Index (ADL-BI) after treatment, and (14) Chinese stroke scale (CSS) after treatment.

The primary outcomes were (1) effectiveness of atorvastatin based on hematoma elimination and (2) hematoma volume. The secondary outcomes were (1) ADL-BI and (2) CSS for neurologic deficit scoring standard. Note that for continuous data, there were no differences in baseline values between the experimental and control groups.

Quality assessment of individual studies

The quality of the included studies was appraised with the standard Cochrane Collaborations tool [shown in Figure 1] by two reviewers (BW and KQL). The following items need to be explained: (1) for performance bias and detection bias, only one[16] study used the blinding method, while six[17-22] of the remaining studies were assessed with objective outcomes – thus, these six studies were appraised with low risk; (2) for attrition bias, only one[16] study described incomplete data processing – thus, the other studies were appraised with unclear risk; and (3) for selection bias, two[20,23] studies were appraised with high risk due to using order of admission as random methods. Two[17,21] studies only described random process with the terminology of "random," so these two studies were appraised with unclear risk. The other[16,18,19,22,24] studies were randomized by computer, and thus, the other studies were appraised with low risk.

All statistical tests used in our meta-analysis were performed with Review Manager 5.4 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Odds ratio (OR), standard mean difference (SMD), and 95% confidence intervals (CIs) were used as summary statistics. Dichotomous data were analyzed by using the odds ratio (OR) and computed using the Mantel Haenszel method (fixed or random model). Continuous data were analyzed by using SMD, which is computed using the inverse variance method (fixed or random model). I-square (I^2) test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines, if severe heterogeneity was present at I^2 >50%, the random effect models were chosen, otherwise the fixed effect models were used.

Results

Study characteristics

The PRISMA flowchart is shown in Figure 2. A total of 1082 articles were identified after searching. The search resulted in 510 publications after removal of duplicates. After applying the inclusion and exclusion criteria, a total of nine RCTs (three[16,18,22] from "PubMed, EMBASE, the Cochrane Library, Scopus, Web of Science, and ScienceDirect" and six[17,19-21,23,24] from "CNKI, CQVIP, and Wanfang database") were included in the systematic review. The study characteristics of these trials are summarized in Tables 1 and 2.

Study outcomes

Effectiveness of atorvastatin based on hematoma elimination

Six articles[17-22] were used to evaluate effectiveness using the criteria of "hematoma elimination ≥30%" and "hematoma elimination >50%." Four articles[17,18,20,22] used the first criterion (subgroup 1), while the remaining studies[19,21] used the second criterion (subgroup 2). Note that one article[19] used the criterion of "hematoma elimination ≥50%" for treatment effectiveness, while the other article[21] used "hematoma

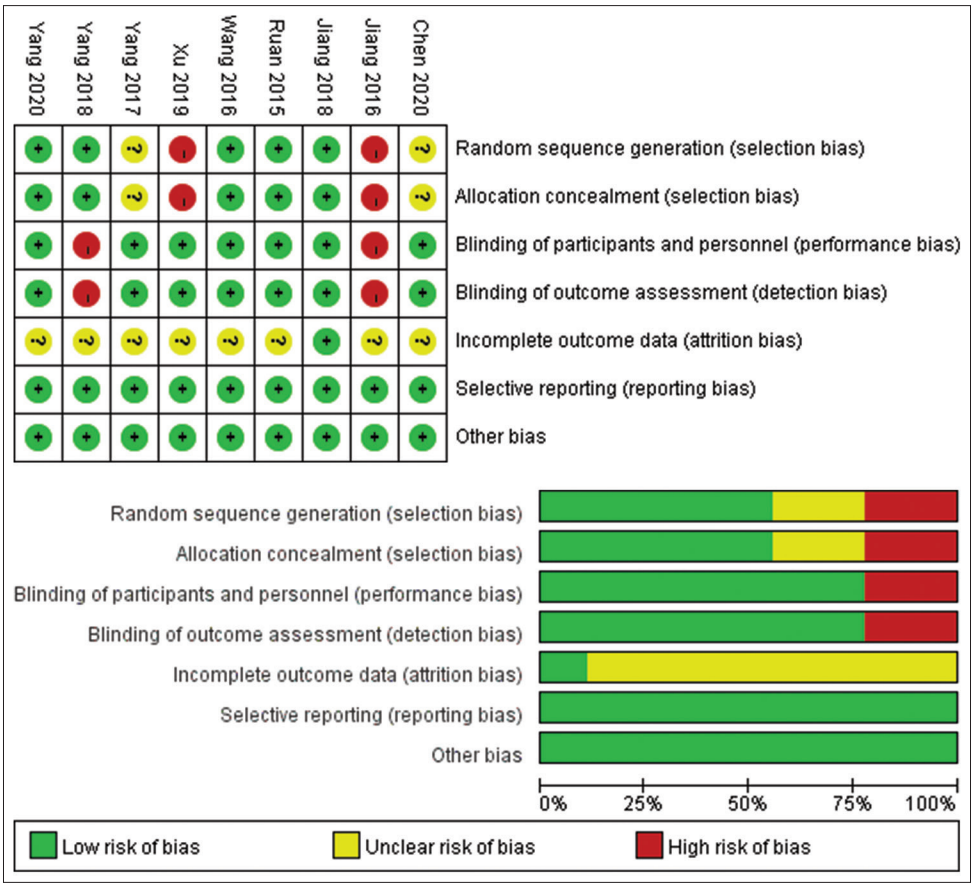

Figure 1: Risk of bias in the included articles

Table 1: Summary 1 of characteristics of studies included in our meta-analysis

First author	Year of publication	Group	Age (means±SD)	Interventions	Atorvastatin dosage	Number of patients	Atorvastatin duration	Follow-up visit times
Chen *et al*.[17]	2020	Atorvastatin	47.3±3.2	ACOD	40 mg/d	30	1 month	1 month
		Control		OD		30		
Jiang *et al*.[23]	2016	Atorvastatin	72.86±6.85	ACOD	20 mg/d	21	1 month	1 month
		Control	72.43±6.51	OD		21		
Jiang[a] *et al*.[16]	2018	Atorvastatin	58.07±48.16	Atorvastatin	20 mg/d	98	8 weeks	24 weeks
		Control	60.31±47.40	Placebo		98		
Ruan[18]	2015	Atorvastatin	56.7±8.3	ACOD	10 mg/d	11	4–6 weeks	4–6 weeks
		Control		OD		12		
Wang[19]	2016	Atorvastatin	63.67±8.41	Atorvastatin	20 mg/d	9	2 months	2 months
		Control	62.20±10.28	OD		5		
Xu and Luo[20]	2019	Atorvastatin	52.2±1.1	Atorvastatin	40 mg/d	30	2 months	2 months
		Control	51.9±1.3	OD		30		
Yang *et al*.[21]	2017	Atorvastatin	67.5±6.9	Atorvastatin	10 mg/d (A group) 20 mg/d (B group)	15 (A) 15 (B)	3 months	3 months
		Control		OD		10		
Yang *et al*.[24]	2018	Atorvastatin	72.3±5.1	ACOD	20 mg/d	60	8 weeks	8 weeks
		Control	71.2±6.5	OD		60		
Yang *et al*.[22]	2020	Atorvastatin	60.16±7.89	Atorvastatin	20 mg/d	28	2 months	24 weeks
		Control		OD		28		

[a]Jiang *et al*.[16] used median and interquartile to present age data. We converted this to mean and standard deviation using the methods of Luo *et al*.[25] and Wan *et al*.[26] The original data for age (median and interquartile) were 63.0 (24.0−88.0) for atorvastatin and 67.0 (26.0−89.0) for placebo. ACOD=Atorvastatin combined other drugs, OD=Other drugs

elimination >50%." In addition, hematoma elimination = (hematoma volume before treatment − hematoma volume after treatment)/hematoma volume before treatment ×100%. The measurement time was the same with atorvastatin duration

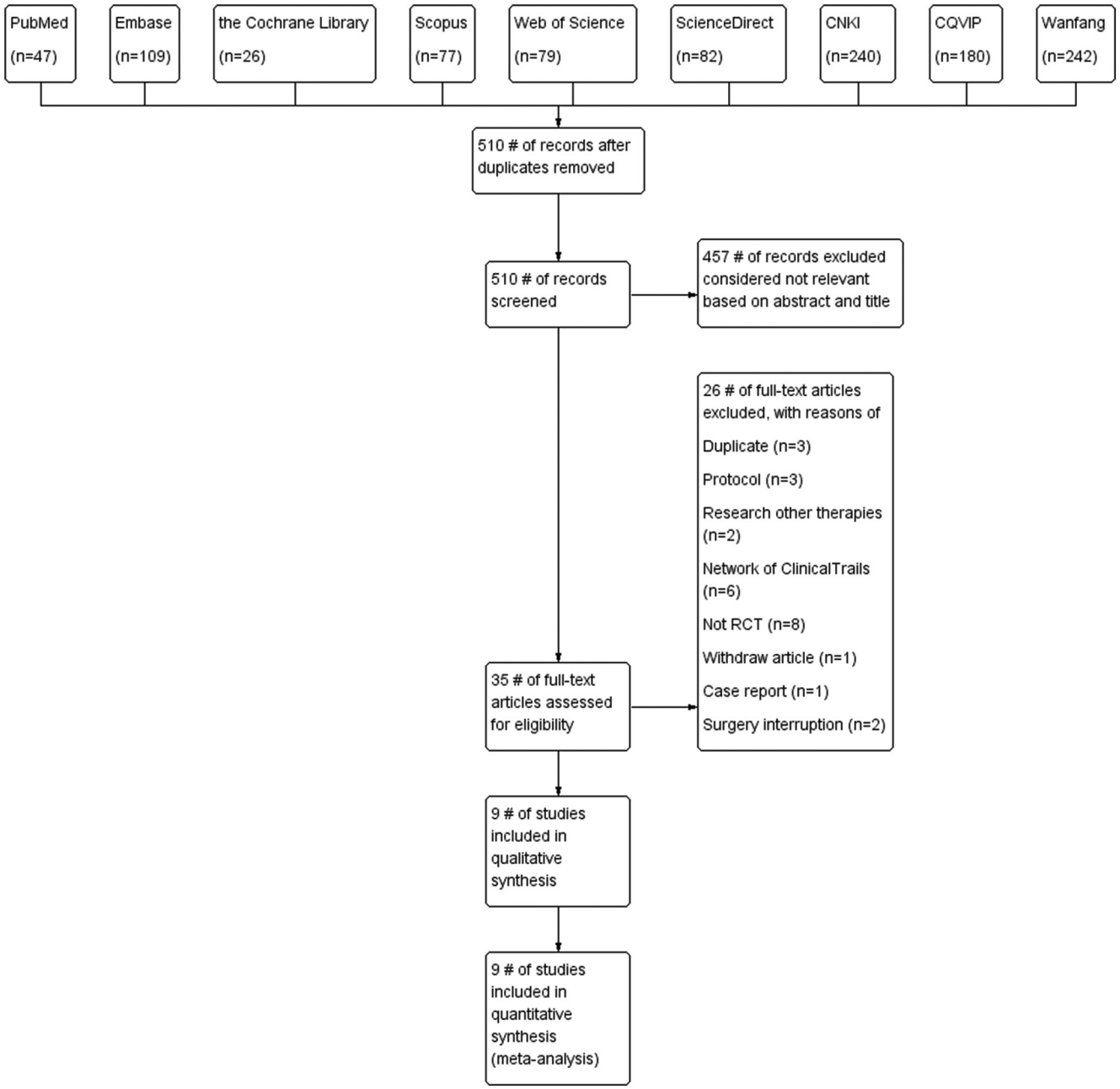

Figure 2: Flowchart of study selection

shown in Table 2, except in one article[22] which did not mention the measurement time. The meta-analysis showed that the effectiveness of atorvastatin was significantly higher in the experimental group than the control group (OR: 7.41, 95% CI: 3.32-16.52, $P < 0.00001$, $I^2 = 0\%$). There were no differences between the subgroups (subgroup 1: OR: 5.87, 95% CI: 2.28-15.15, $P = 0.0002$, $I^2 = 0\%$; subgroup 2: OR: 14.46, 95% CI: 3.25-64.29, $P = 0.0004$, $I^2 = 0\%$). The results are shown in Figure 3.

Hematoma volume

Hematoma volume was evaluated at 8 weeks after treatment. Three articles[16,19,22] were used to assess hematoma volume. The meta-analysis showed that hematoma volume of the experimental group was significantly smaller than the control group (SMD: −0.46, 95% CI: −0.71 to −0.20, $P = 0.0005$, $I^2 = 0\%$). The results are shown in Figure 4. Note that one article[16] used "median and interquartile" to present hematoma volume. We converted these data into "mean and standard deviation" using the methods of Luo *et al*.[25] and Wan *et al*.[26]

Activities of daily living-Barthel Index

Five articles[17,21-24] were used to analyze ADL-BI. In these studies, ADL-BI was evaluated from 1 to 3 months after treatment. Note that one study[22] used four visits to evaluate ADL-BI (4, 8, 12, and 24 weeks). As the evaluation time

Table 2: Summary 2 of characteristics of studies included in our meta-analysis

First author	Year of publication	Group	Number of effective patients	Effectiveness criterion (hematoma elimination)	Hematoma volume (ml, 8 weeks), means±SD[a]	ADL-BI after treatment, means±SD	CSS after treatment
Chen *et al*.[17]	2020	Atorvastatin	29	≥30%	NA	65.3±4.3	NA
		Control	24			56.4±3.6	
Jiang *et al*.[23]	2016	Atorvastatin	NA	NA	NA	73.89±4.18	15.47±3.12
		Control				66.47±3.95	19.87±3.25
Jiang[b] *et al*.[16]	2018	Atorvastatin	NA	NA	25.77±33.36	NA	NA
		Control			45.05±48.14		
Ruan *et al*.[18]	2015	Atorvastatin	10	≥30%	NA	NA	15.32±3.21
		Control	8				21.57±4.32
Wang[19]	2016	Atorvastatin	6	≥50%	7.13±10.56	NA	NA
		Control	1		18.75±16.94		
Xu and Luo[20]	2019	Atorvastatin	29	≥30%	NA	NA	NA
		Control	22				
Yang *et al*.[21]	2017	Atorvastatin	12 (A)	>50%	NA	73.52±4.30 (A)	NA
			13 (B)			74.68±4.20 (B)	
		Control	2			49.15±3.90	
Yang *et al*.[24]	2018	Atorvastatin	NA	NA	NA	79.2±12.6	NA
		Control				68.3±11.2	
Yang *et al*.[22]	2020	Atorvastatin	25	≥30%	16.4±6.13	80.4±6.32	20.9±4.97
		Control	19		18.5±4.79	76.1±4.90	23.9±5.02

[a]For evaluation of hematoma volume, Jiang *et al*.[16] included 81 atorvastatin and 90 placebo patients and Wang[19] included eight atorvastatin and four control patients. [b]Jiang *et al*.[16] used median and interquartile to present hematoma volume data. We converted this to mean and standard deviation using the methods of Luo *et al*.[25] and Wan *et al*.[26] The original data for hematoma volume (median and interquartile) were 22.6 (5.0−49.2) for atorvastatin and 41.0 (14.8−78.7) for placebo

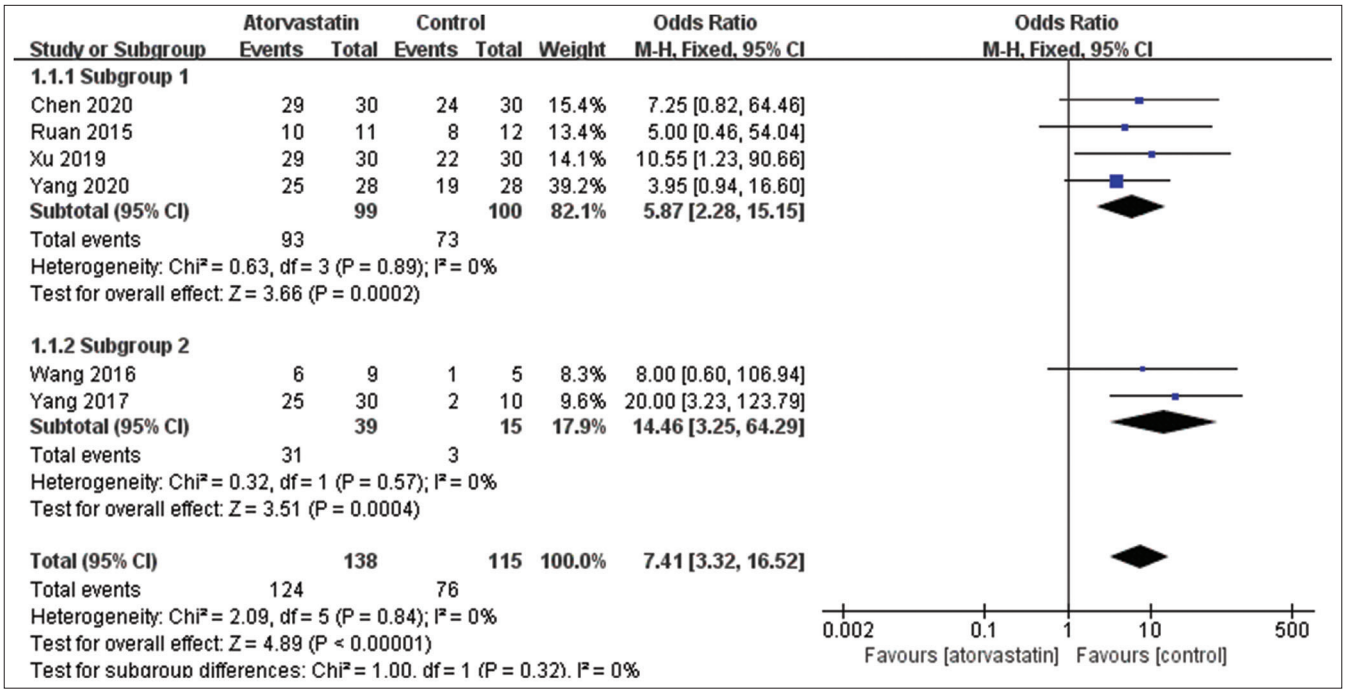

Figure 3: Effectiveness of atorvastatin based on hematoma elimination

increases, ADL-BI increases. Nevertheless, we adopted a conservative visit time (8 weeks) for evaluation of ADL-BI. The meta-analysis showed that ADL-BI of the experimental group was significantly higher than the control group (SMD: 2.07, 95% CI: 1.06-3.09, $P < 0.0001$, $I^2 = 92\%$). The heterogeneity was very high, which may relate to outcome's subjectivity and differences in the evaluation times between the studies. The results are shown in Figure 5.

CSS for neurologic deficit scoring standard

Three articles[18,22,23] were used to assess CSS. In these studies, CSS was evaluated from 4 to 8 weeks after treatment. Note that one article[22] used four visits to evaluate CSS. As for ADL-BI discussed above, we used 8 weeks for CSS evaluation time. The meta-analysis showed that CSS of the experimental group was significantly smaller than that of the control group (SMD: −1.10, 95% CI: −1.72 to −0.48, $P = 0.0005$, $I^2 = 57\%$). The results are shown in Figure 6.

Discussion

The present meta-analysis included nine articles with a total of 611 enrolled patients. The primary outcomes were effectiveness based on hematoma elimination and hematoma volume, which are objective outcomes. Barthel Index (BI) was used to evaluate patients' activities of daily living (ADL), and CSS was used to evaluate patients' neurologic function – both of these are subjective outcomes and were used as secondary outcome measures. For the objective outcomes, the effectiveness of the experimental group was significantly higher than the control group and the hematoma volume of the experimental group was smaller than the control group. For the subjective outcomes, atorvastatin significantly improved patients' ADL and neurologic function. CSDH patients are predominantly older, with many underlying diseases, surgical risks, and postoperative complications. Thus, compared to the risks associated with surgery, atorvastatin may provide better clinical outcomes for older patients.

A retrospective study by Chan *et al*.[27] found that the risk of deterioration requiring burr hole drainage was 16.7% (2/12) with atorvastatin treatment versus 58.3% (7/12) in the control group ($P = 0.0447$). This study showed CSDH with atorvastatin had a lower rate of deterioration and burr hole drainage. In a retrospective study of 89 patients receiving atorvastatin monotherapy,[28] the treatment efficacy was 87.6% (78/89) at 6 months. Furthermore, in a single-armed prospective trial of 23 patients,[29] hematoma volume reduced from 48.70 ± 20.38 ml to 16.64 ± 14.28 ml (paired-sample *t*-test, $P < 0.01$) within the first month of treatment. In that study, hematoma was completely resolved in 17 patients (77.3%) and shrank by >73.99% ± 11.17% in five patients (22.7%) at 3 months after treatment initiation. These retrospective and preliminary studies support the findings of our meta-analysis.

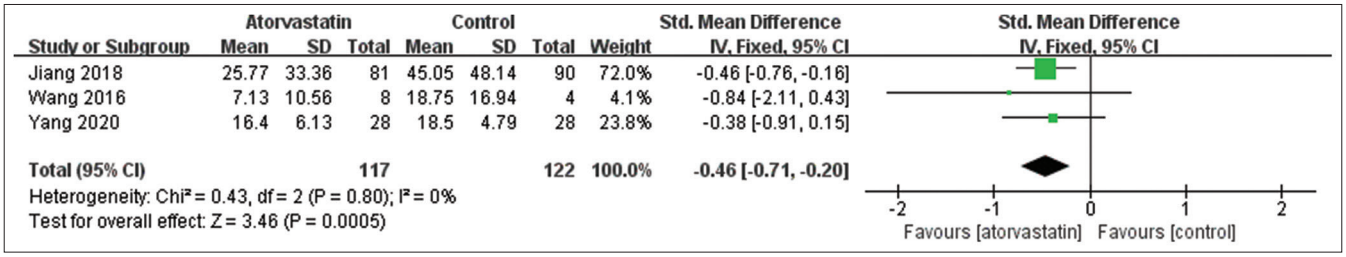

Figure 4: Hematoma volume

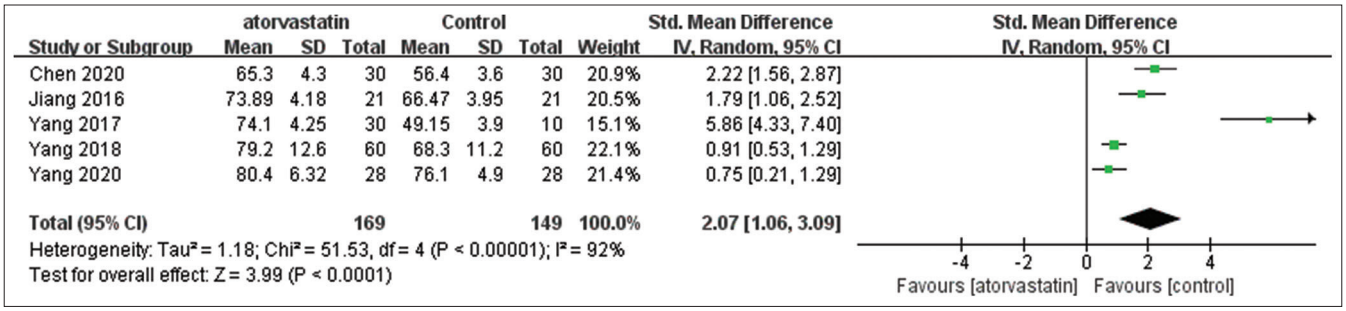

Figure 5: ADL-BI. ADL-BI = activities of daily living-Barthel Index

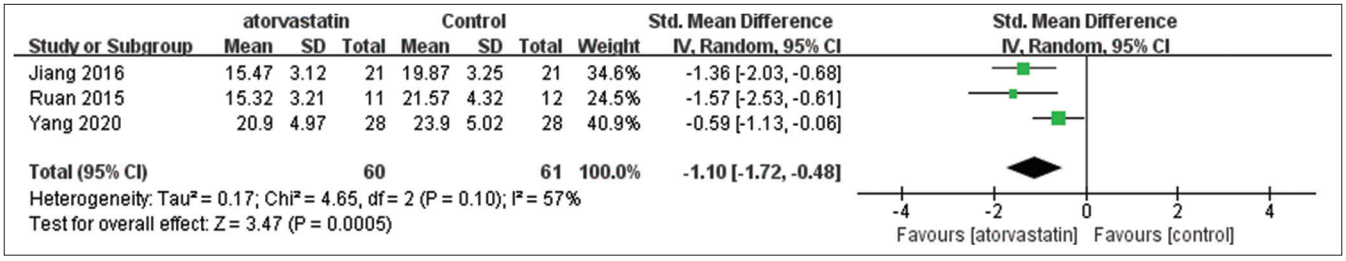

Figure 6: CSS for neurological deficit scoring standard. CSS = Chinese stroke scale

In addition, Jiang *et al*.[16] had carried out a multicenter, double-blind, randomized controlled Phase II clinical trial. The result shows atorvastatin is significantly superior to placebo. As everyone knows, Phase II clinical trial is an exploratory study and Phase III clinical trial is a confirmatory study. By ClinicalTrials.gov, a recent Phase III clinical trial (title "Efficacy of Atorvastatin in Chronic Subdural Haematoma (REACH);" ClinicalTrials.gov ID, NCT03956368) was carried out.

There are some limitations of our study. First, the article quality was not at the highest level. Four studies[17,18,21,22] were assessed with both objective and subjective outcomes. As mentioned above, although these four studies did not use the blinding method, we still appraised them with low risk in view of adopting objective outcomes. Therefore, for these four studies, there are likely performance and detection biases in the subjective outcomes due to open-label situation. Second, only one[16] study described incomplete data processing, while the remaining studies were appraised with unclear risk, which may lead to latent attrition bias. Third, because most of the nine studies[16-24] were from Chinese authors, it was difficult to avoid the bias caused by race. Fourth, most of the nine studies[16-24] did not mention the measurement methods and details of hematoma volume calculation, which may lead to some limitations. Fifth, OR and 95% CI were used as summary statistics to evaluate "effectiveness of atorvastatin based on hematoma elimination," but the 95% CI value was wider due to less sample size, which might result in uncertainty of the result. Finally, although 611 patients were enrolled, the sample size for each outcome measure was not large (effectiveness, $n = 253$; hematoma volume, $n = 239$; ADL-BI, $n = 318$; CSS, $n = 121$). Future large multi-centric trials are required to confirm our findings.

This meta-analysis proves that atorvastatin is effective based on objective data. For CSDH patients without surgery, atorvastatin is a kind of potential means of treatment. Based on the limitations of present studies, with the deepening of research, we expect there will be RCTs with larger sample size, other race, and higher standard to prove this result.

Conclusions

In view of these findings, we conclude that the outcomes of the experimental group are superior to the control group with respect to effectiveness, hematoma volume, ADL-BI, and CSS based on nine RCTs with 611 patients. Atorvastatin is beneficial to CSDH patients without surgery.

Author's contributions

Bo Wang, Kangqi Li, and Chenyu Guo were principal researchers, and contributed equally to this study. Zhe Wang contributed to the analysis of statistical data. Weiwei Zhu and Congxiao Lu were corresponding authors, who provided the study concept and provided writing support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Literature Search Query

PubMed (47 results)

#1: Search: (((((((Hematoma, Subdural, Chronic[MeSH Terms]) OR (Subdural Hematoma, Chronic[Title/Abstract])) OR (Chronic Subdural Hematoma[Title/Abstract])) OR (Chronic Subdural Hematomas[Title/Abstract])) OR (Hematoma, Chronic Subdural[Title/Abstract])) OR (Hematomas, Chronic Subdural[Title/Abstract])) OR (Subdural Hematomas, Chronic[Title/Abstract])) OR (Hemorrhage, Subdural, Chronic[Title/Abstract])) OR (CSDH[Title/Abstract])

#2: Search: ((((((((((Atorvastatin[MeSH Terms]) OR ((3R,5R)-7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid[Title/Abstract])) OR (Atorvastatin Calcium[Title/Abstract])) OR (Atorvastatin, Calcium Salt[Title/Abstract])) OR (Liptonorm[Title/Abstract])) OR (Lipitor[Title/Abstract])) OR (Atorvastatin Calcium Hydrate[Title/Abstract])) OR (Atorvastatin Calcium Anhydrous[Title/Abstract])) OR (CI 981[Title/Abstract])) OR (CI-981[Title/Abstract])) OR (CI981[Title/Abstract])) OR (Atorvastatin Calcium Trihydrate[Title/Abstract])) OR (Atorvastatin[Title/Abstract])

#3: #1 AND #2

EMBASE (109 results)

#1: 'subdural hematoma'/exp OR csdh: ab, ti OR 'subdural hematoma, chronic':ab, ti OR 'chronic subdural hematoma':ab, ti OR 'chronic subdural hematomas':ab, ti OR 'hematoma, chronic subdural':ab, ti OR 'hematomas, chronic subdural':ab, ti OR 'subdural hematomas, chronic':ab, ti OR 'hemorrhage, subdural, chronic':ab, ti

#2: 'atorvastatin'/exp OR atorvastatin: ab, ti OR (3r, 5r: ab, ti AND -7-:ab, ti AND 2-:ab, ti AND '4 fluorophenyl':ab, ti AND '5 isopropyl 3 phenyl 4':ab, ti AND phenylcarbamoyl: ab, ti AND '1h pyrrol 1 yl':ab, ti AND '-3,5-dihydroxyheptanoic acid':ab, ti) OR 'atorvastatin calcium':ab, ti OR 'atorvastatin, calcium salt':ab, ti OR liptonorm: ab, ti OR lipitor: ab, ti OR 'atorvastatin calcium hydrate':ab, ti OR 'atorvastatin calcium anhydrous':ab, ti OR 'ci 981':ab, ti OR ci981:ab, ti OR 'atorvastatin calcium trihydrate':ab, ti

#3: #1 AND #2

The Cochrane Library (26 results)

#1: MeSH descriptor: [Hematoma, Subdural, Chronic] explode all trees

#2: (Chronic Subdural Hematomas):ti, ab, kw OR (Hemorrhage, Subdural, Chronic):ti, ab, kw OR (Subdural Hematomas, Chronic):ti, ab, kw OR (Chronic Subdural Hematoma):ti, ab, kw OR (Subdural Hematoma, Chronic):ti, ab, kw (Word variations have been searched)

#3: (Hematomas, Chronic Subdural):ti, ab, kw OR (Hematoma, Chronic Subdural):ti, ab, kw OR (CSDH):ti, ab, kw (Word variations have been searched)

#4: #1 or #2 or #3

#5: MeSH descriptor: [Atorvastatin] explode all trees

#6: (Atorvastatin):ti, ab, kw OR (Atorvastatin Calcium Trihydrate):ti, ab, kw OR (Lipitor):ti, ab, kw OR (Atorvastatin Calcium Anhydrous):ti, ab, kw OR (CI981):ti, ab, kw (Word variations have been searched)

#7: (Atorvastatin Calcium):ti, ab, kw OR (Atorvastatin, Calcium Salt):ti, ab, kw (Word variations have been searched)

#8: (CI-981):ti, ab, kw OR (CI 981):ti, ab, kw OR (Liptonorm):ti, ab, kw OR (Atorvastatin Calcium Hydrate):ti, ab, kw (Word variations have been searched)

#9: #5 or #6 or #7 or #8

#10: #4 and #9

Scopus (77 results)

((TITLE-ABS-KEY("Hematoma, Subdural, Chronic") OR TITLE-ABS-KEY("Subdural Hematoma, Chronic") OR TITLE-ABS-KEY("Chronic Subdural Hematoma") OR TITLE-ABS-KEY("Chronic Subdural Hematomas") OR TITLE-ABS-KEY("Hematoma, Chronic Subdural") OR TITLE-ABS-KEY("Hematomas, Chronic Subdural") OR TITLE-ABS-KEY("Subdural Hematomas, Chronic") OR TITLE-ABS-KEY("Hemorrhage, Subdural, Chronic") OR TITLE-ABS-KEY("CSDH"))) AND ((TITLE-ABS-KEY("Atorvastatin") OR TITLE-ABS-KEY("(3R,5R)-7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid") OR TITLE-ABS-KEY("Atorvastatin Calcium") OR TITLE-ABS-KEY("Atorvastatin, Calcium Salt") OR TITLE-ABS-KEY("Liptonorm") OR TITLE-ABS-KEY("Lipitor") OR

TITLE-ABS-KEY(“Atorvastatin Calcium Hydrate”) OR TITLE-ABS-KEY(“Atorvastatin Calcium Anhydrous”) OR TITLE-ABS-KEY(“CI 981”) OR TITLE-ABS-KEY(“CI-981”) OR TITLE-ABS-KEY(“CI981”) OR TITLE-ABS-KEY(“Atorvastatin Calcium Trihydrate”)))

Web of Science (79 results)

#1: TS = (“Hematoma, Subdural, Chronic” OR “Subdural Hematoma, Chronic” OR “Chronic Subdural Hematoma” OR “Chronic Subdural Hematomas” OR “Hematoma, Chronic Subdural” OR “Hematomas, Chronic Subdural” OR “Subdural Hematomas, Chronic” OR “Hemorrhage, Subdural, Chronic” OR “CSDH”)

#2: TS = (“Atorvastatin” OR “ (3R,5R)-7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid” OR “Atorvastatin Calcium” OR “Atorvastatin, Calcium Salt” OR “Liptonorm” OR “Lipitor” OR “Atorvastatin Calcium Hydrate” OR “Atorvastatin Calcium Anhydrous” OR “CI 981” OR “CI-981” OR “CI981” OR “Atorvastatin Calcium Trihydrate”)

#3: #1 AND #2

ScienceDirect (82 results)

(“Hematoma, Subdural, Chronic” OR “Subdural Hematoma, Chronic” OR “Chronic Subdural Hematomas” OR “Hematoma, Chronic Subdural”) AND (“Atorvastatin” OR”Atorvastatin Calcium” OR “Lipitor” OR “Atorvastatin, Calcium Salt”)

CNKI (240 results)

(TKA = ‘Chronic Subdural Hematomas’ OR TKA = ‘CSDH’) AND (TKA = ‘Atorvastatin’ OR TKA = ‘Atorvastatin Calcium’ OR TKA = ‘Lipitor’)

Cqvip database (CQVIP) (180 results)

M = (Chronic Subdural Hematomas OR CSDH) AND M = (Atorvastatin Calcium OR Atorvastatin OR Lipitor)

Wanfang database (242 results)

Title or keywords:(“Chronic Subdural Hematomas” or “CSDH”) and Title or keywords:(“Atorvastatin” or “Atorvastatin Calcium” or “Lipitor”)