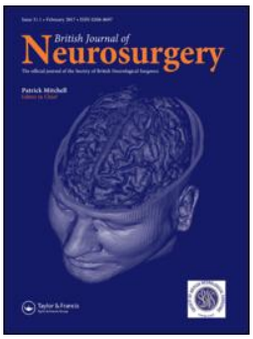

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ORIGINAL ARTICLE

The use of atorvastatin for chronic subdural haematoma: a retrospective cohort comparison study*

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ABSTRACT

Chronic subdural haematoma (CSDH) is a common neurosurgical condition. Burr-hole for drainage is an effective treatment. However, recurrence can be up to 8–33% and is associated with morbidities and mortalities. The underlying pathogenesis was postulated to be localised inflammation and pathological aberrant vessels formation. Atorvastatin, an HMG-CoA reductase inhibitor, is a type of lipid-lowering medication. In animal studies and a preliminary clinical trial, Atorvastatin was shown to be effective in the treatment of CSDH. It was found to inhibit inflammation and promote vascular maturation at the neomembrane of CSDH. Our study aimed to investigate the efficacy of Atorvastatin in CSDH. During the study period from January to December 2014, Atorvastatin was used in 12 CSDH patients with Glasgow Coma Scale (GCS) 13–15 or Markwalder's Grading Scale (MGS) Grade 0–2. They were retrospectively compared with GCS- and MGS-matched controls who had not used statin. Improvement with haematoma resolution at 3 months was 75% (9/12) for the Atorvastatin group, versus 42% (5/12) for the Control group ($p = 0.0977$). The risk of deterioration requiring burr-hole drainage was 16.7% (2/12) in the Atorvastatin group, versus 58.3% (7/12) in the Control group ($p = 0.0447$). The Odds Ratio (OR) of deterioration requiring burr-hole drainage with Atorvastatin was 0.143 (95%CI: 0.021–0.958), which favours the use of Atorvastatin in CSDH ($p = 0.0451$). The Number needed to treat (NNT) was 2.4 ($p = 0.0447$; 95%CI: 1.31–14.93). In conclusion, this retrospective cohort comparison study has shown that CSDH with Atorvastatin had a lower rate of deterioration and burr-hole drainage.

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Chronic Subdural Haematoma; elderly trauma; head injury; head trauma; manuscript; statin

Introduction

Chronic subdural haematoma (CSDH) is a common neurosurgical condition. It is more prevalent with the ageing population.[1] It is also more prevalent with the use of antiplatelet and anticoagulant medications.[2] The annual estimated incidence is 13.5 per 100,000 persons per year in the general population and for those above the age of 65 years can be up to 58.1 per 100,000 persons per year.[3] It is associated with a higher mortality with increased standardised mortality ratio up to 2.9[4] which challenge the concept of it being a benign condition.[5] Burr-hole for drainage is an effective treatment.[6] However, recurrence can be up to 8–33%.[7] The underlying pathogenesis was postulated to be pathological aberrant vessel formation[8] and localised inflammation.[9,10,11] This formed the pathophysiological basis of the use of steroid for CSDH[12,13] and its potential role as a primary non-surgical treatment of CSDH in selected groups of patients.[14] The formation of these immature vessels at the neomembrane was hypothesised to contribute to plasma extravasation and haematoma progression. Another potential choice of medication as a non-surgical treatment of CSDH is Atorvastatin, an HMG-CoA reductase inhibitor, which is a type of lipid-lowering medication. It has also been found to promote neovascularisation with vascular maturation[15] at the neomembrane of CSDH and inhibition of inflammation.[16,17] The formation of mature vessels at the neomembrane reduces vascular leakage and hence preventing haematoma progression. At the same time, the formation of mature vessels was observed to be associated with subdural haematoma absorption.[18] In an animal study, Atorvastatin was shown to be effective in the treatment of chronic subdural haematoma with haematoma volume reduction. In this animal study, Atorvastatin was suggested to have property of inhibiting inflammation by reducing the neutrophil counts in the neomembrane.[19] In a preliminary clinical trial, 75% of the patients with Atorvastatin had haematoma resolution in 3 months.[20] The aim of our study was to investigate the efficacy of Atorvastatin on CSDH and to generate a potential sample size for future randomised control trial.

Material and methods

The study design is a retrospective cohort comparison study. Data of patients with CSDH admitted to a University Hospital (Prince of Wales Hospital, Hong Kong) during the period from January to December 2014 were retrospectively collected and analysed. Inclusion criteria for analysis included (a) age of 18 or above; (b) presence of supratentorial CSDH from Computed Tomography

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(CT) Brain or Magnetic Resonance Imaging (MRI) Brain; (c) Glasgow Coma Scale (GCS) 13–15 or Markwalder's Grading Scale (MGS) Grade 0–2; (d) no indication to be operated on immediately with a low risk of brain herniation as judged by the on-call neurosurgeons. We excluded those with (a) risk of immediate brain herniation;(b) allergy to atorvastatin or other statins; (c) deranged liver function or uncontrolled hepatitis; (d) on long-term statin; (e) on long-term steroid; (f) CSDH which were secondary to underlying haematological disorders or malignancy; (g) pregnancy or on breastfeeding. CSDH patients who have not used statin, and fulfilled both the inclusion and exclusion criteria, were compared to the control. All CSDH patients would then be followed up according to departmental protocol with progress CT at one week, two weeks, one month, two months, three months and six months. Blood tests including fasting lipid, liver function test (LFT) and creatine kinase (CK) were taken at admission, three months and six months follow-up. Burr-hole drainage would be performed if there were any worsening of symptoms, deterioration in Glasgow Coma Scale (GCS), new focal neurological deficits or CT showing an increase in the size of CSDH during the follow-up period. The primary outcome was the improvement rate at 3 months, in which improvement was defined as any haematoma volume reduction from plain CT Brain. The CSDH volumes were calculated with the method of XYZ/2 that has been validated with the gold standard of computer volumetric calculation.[21] Secondary outcomes included deterioration requiring burr-hole for drainage within the 6-month follow-up period and Glasgow Outcome Scale (GOS) at 3 months and 6 months. Statistical analysis was performed with categorical frequency Chi-square test or Fisher's Exact Test. Significance was set at 5% and all statistical analyses were done with the SPSS software version 22.0 (Hong Kong S.A.R., China).

Results

During the study period from January to December 2014, we identified 12 CSDH patients with Atorvastatin who fulfilled the study inclusion and exclusion criteria. Another 12 patients with CSDH admitted during the same study period who have not used statin, and also fulfilled the inclusion and exclusion criteria were used as matched controls for analysis. The baseline characteristics were comparable in both groups (Table 1–4). Anti-platelets and warfarin were withheld during the period of conservative management. For the Atorvastatin group, 9 out of 12 (75%) improved at 3 months follow-up (with eight resolving CSDH and one resolved CSDH) (Figure 1–4). One remained static. Two deteriorated requiring burr-hole drainage. At 6 months follow-up, seven improved (four resolving CSDH and three resolved CSDH). One remained static in size. Two defaulted follow-up. For the control group, 5 out of 12 (41.7%) improved at 3 months follow up (all five with resolving CSDH). Seven deteriorated requiring burr-hole drainage. By 6 months, two had resolved CSDH while two CSDH were revolving, and one defaulted follow up. Improvement rate at 3 months was 75% (9/12) for the Atorvastatin group, versus 42% (5/12) for the Control group (p value =0.0977). Those who deteriorated requiring burr-hole drainage presented with worsening symptoms (such as headache, unsteady gait or deterioration in limb weakness), deterioration in GCS, new focal neurological deficit or CT Brain showing an increase in size or acute component during the follow-up period.

The risk of deterioration requiring burr-hole drainage within 6 months was 16.7% (2/12) in the Atorvastatin group, versus 58.3% (7/12) in the Control group (p value =0.0447). The Odds Ratio (OR) of deterioration requiring burr-hole for drainage with Atorvastatin was 0.143 (95%CI: 0.021–0.958), which favours the use of Atorvastatin in CSDH (p value =0.0451). The Number

Table 1. Baseline demographics.

	Atorvastatin	Control	p Value
Demographic			
Age (years old)	78.3 (67–91)	79.5 (58–95)	
Male gender	9/12	7/12	0.665
Admission GCS			
−15/15	0/12	1/12	0.307
−14/15	7/12	8/12	0.673
−13/15	5/12	3/12	0.665
Premorbid mobility			
– Unaided	5/12 (41.7%)	2/12 (16.7%)	0.369
– Stick	3/12 (25%)	7/12 (58.3%)	0.098
– Frame	0/12 (0%)	1/12 (8.3%)	0.307
– Wheelchair	3/12 (25%)	0/12 (0%)	0.217
– Bed-bound	1/12 (8.3%)	2/12 (16.7%)	0.537

Table 2. Social history, past medical history and medication history.

	Atorvastatin	Control	p Value
Social history			
Smoker	3/12	3/12	0.637
Drinker	0/12	1/12	0.307
Past medical history			
Diabetes	3/12	6/12	0.399
Hypertension	9/12	8/12	0.653
Dementia	5/12	8/12	0.219
CVA	5/12	6/12	0.682
IHD	0/12	3/12	0.217
Arrhythmia	2/12	4/12	0.638
DVT/PE	0/12	0/12	–
Medication history			
Aspirin	4/12 (33.3%)	4/12 (33.3%)	0.665
Plavix	0/12 (0%)	1/12 (8.3%)	0.307
Warfarin	1/12 (8.3%)	1/12 (8.3%)	0.460

CVA: cerebrovascular accident; IHD: ischemic heart disease; DVT: deep vein thrombosis; PE: pulmonary embolism.

Table 3. Baseline blood tests results.

Blood tests	Atorvastatin	Control	p Value
High cholesterol	2/12	1/12	0.537
High triglyceride	2/12	0/12	0.140
Abnormal HDL	5/12	3/12	0.665
Abnormal LDL	4/12	3/12	0.653
Deranged LFT	0/12	0/12	–
Elevated CK	0/12	0/12	–
Deranged RFT	1/12	2/12	0.537
Deranged clotting profile	1/12	1/12	0.460
Low platelet count	1/12	0/12	0.307

HDL: high-density lipoprotein; LDL: low-density lipoprotein; LFT: liver function test; CK: creatine kinase; RFT: renal function test.

Table 4. Computed tomographic characteristics of chronic subdural haematoma.

CT characteristics	Atorvastatin	Control	p Value
Laterality			
– Right	9/12	6/12	0.399
– Left	2/12	6/12	0.194
– Bilateral	1/12	0/12	0.307
Admission thickness	19.14mm (6.7mm–31mm)	12.98mm (7.8mm–21mm)	
Admission volume	60.42ml (27ml–94ml)	41.42ml (25ml–65ml)	
Admission MLS	3.26mm (0–5.4mm)	2.33mm (1–4mm)	
CT density			
– Isodense	2/12	5/12	0.369
– Hypodense	1/12	3/12	0.583
– Layered	1/12	1/12	0.460
– Mixed type	8/12	3/12	0.041

CT: Computed tomography; MLS: midline shift.

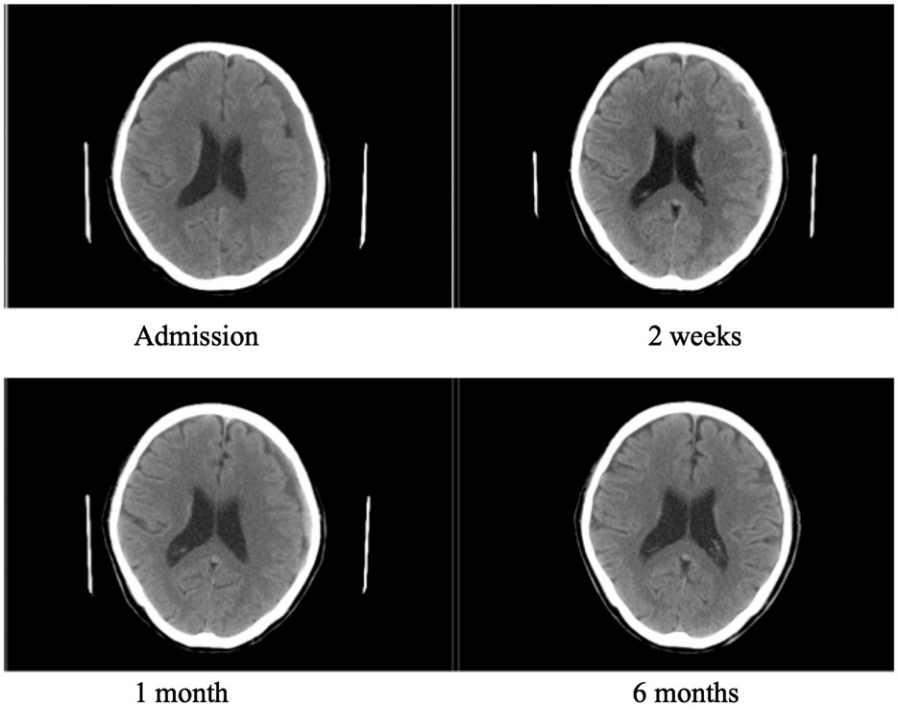

Figure 1. CT brain scan of a 79-year-old lady presented with poor memory.

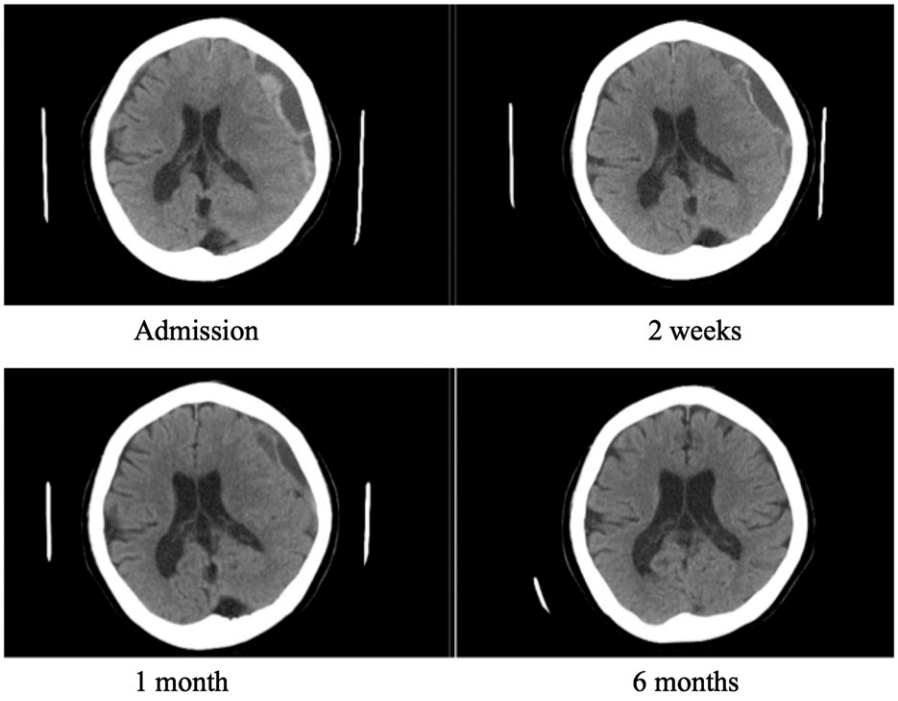

Figure 2. CT brain scan of a 70-year-old lady presented with frequent fall.

needed to treat (NNT) is 2.4 (95%CI: 1.31–14.93) (p value =0.0447). No side effect or complication arising from the use of Atorvastatin was found in this study. GOS at 3 months and 6 months had no significant difference (Table 5). For those who deteriorated while on Atorvastatin, all had burr-hole drainage performed within one month (Figure 5).

Discussion

Our results showed favourable outcome in the Atorvastatin group with a trend of haematoma resolution in a selected group of CSDH patient who were asymptomatic or minimally symptomatic. During the study period, there were 80 burr-hole drainage

operations performed for newly presented CSDH at our neurosurgical centre. They were performed as those CSDH patients were judged by the on-call neurosurgeon to have an immediate risk of herniation. This reflects the fact that only about 20% of the new CSDH admissions did not have burr-hole drainage performed during the same hospital admission and could be discharged with follow-up scans. As a result, the potential target group of CSDH patients fitting the criteria of this study who might benefit from statin was small. However, we can now provide them with a potential non-surgical option to reduce the risk of deterioration, instead of the traditional way of observation alone. When Atorvastatin was not used, about half of them ultimately required burr-hole drainage. Another difficulty in the analysis was that a substantial amount of CSDH patients were already on a statin for their pre-existing cardiovascular condition and hence could not be included for analysis. For the follow-ups, 16.7% (2/12) in the

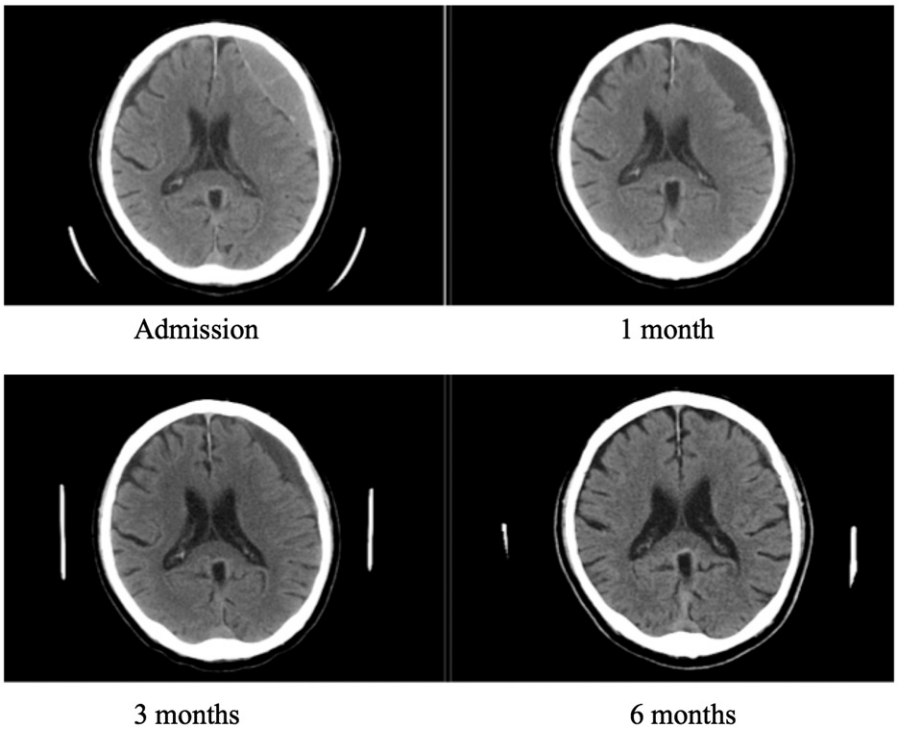

Figure 3. CT brain scan of a 81-year-old gentleman presented with confusion.

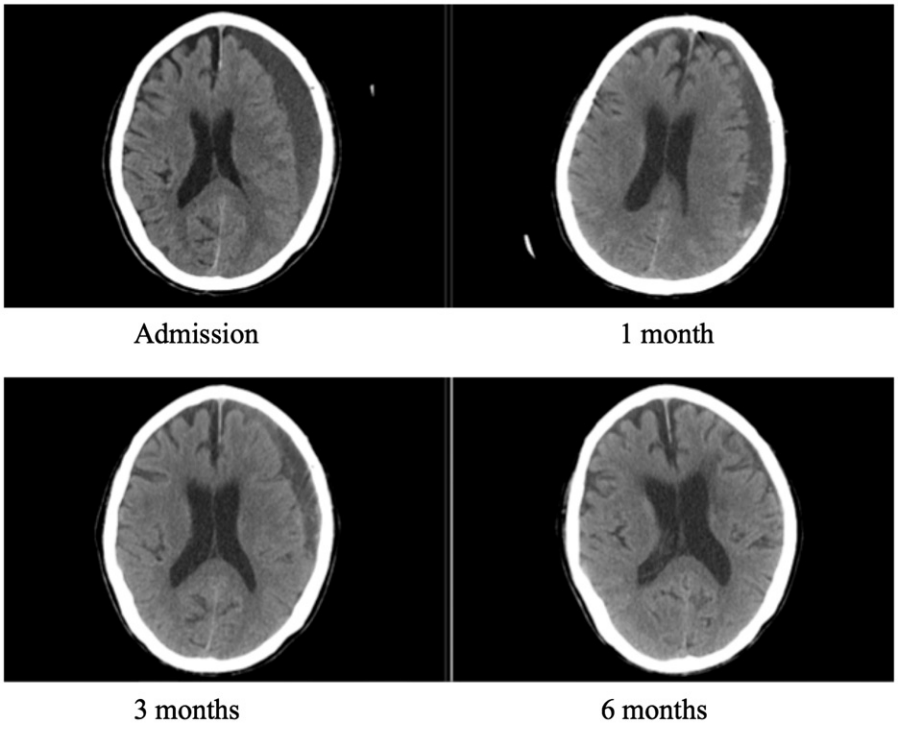

Figure 4. CT brain scan of a 75-year-old gentleman presented with unsteady gait.

statin group and 8.3% (1/12) in the control group did not attend all the follow-up appointments. Attempts were made to call back those patients for follow up, but the offer was declined by the patients as all three of them reported to have no symptoms. It was documented that they considered the CT Brain scan unnecessary. Despite defaulting the follow-up appointment, we were able to assess the GOS via phone interview, although there was no significant difference in the two groups.

As compared to burr-hole drainage, the effect of Atorvastatin on CSDH was slow and not immediate. There had been previous concerns about the potential delay in presentation for CSDH patients who would subsequently fail to respond to Atorvastatin. This formed the basis of our longer follow-up regime for these patients with CT Brain scan up to 6 months. However, to our surprise, there was no deterioration and burr-hole drainage performed beyond the first three weeks of follow up to six months. Those who did not respond to statin treatment deteriorated at Day 16 and Day 21 of follow-up. The overall deterioration with progression of haematoma was comparable to the control group in which those who did deteriorate would deteriorate within 6 weeks with no late deterioration afterwards. This data will guide us in revising our subsequent follow-up protocol by which more frequent CT scans will be done for the first 6 weeks, followed by less frequent follow-up after 6 weeks, aiming to discharge the patients after 3 months. Our study was limited by a small sample size and was retrospective in nature. The results need to be further verified with larger prospective studies. The observed effect indicates a trial would be practical with a reasonable sample size.

Table 5. Glasgow Outcome Scale (GOS) at 3 months and 6 months.

GOS	Atorvastatin	Control	*p* Value
3 months			
GOS 5 (Good recovery)	2/12	2/12	0.584
GOS 4 (Moderate disability)	9/12	10/12	0.615
GOS 3 (Severe disability)	1/12	0/12	0.307
6 months			
GOS 5 (Good recovery)	4/12	2/12	0.640
GOS 4 (Moderate disability)	7/12	10/12	0.370
GOS 3 (Severe disability)	1/12	0/12	0.307

GOS: Glasgow Outcome Scale.

There was no dose-ranging study for Atorvastatin conducted in CSDH patients in the literature. Several animal studies and clinical studies had shown that low dose Atorvastatin is associated with inflammation modulation.[15,22,23,17,24] There has only been a large dose-ranging study for Atorvastatin focusing on cholesterol level and not on the inflammatory modulation properties.[25] In this study, we were using a low dosage which was the same dose as in a previously reported preliminary study on CSDH patients.[20] This same dosage is also used in the protocol of an on-going randomised controlled trial.[26]

In this study, 58.3% in the control group deteriorated requiring burr-hole drainage. This is closely adhered to data from a previous study from our centre by Sun et al published in the British Journal of Neurosurgery in 2005 showing that 50% of CSDH treated by observation only would deteriorate requiring burr-hole drainage.[14] This formed the basis of our departmental follow-up protocol with interval CT Brain scan for all patients with CSDH whether or not operations had been performed. It was surprising to see the paucity of this kind of data in the literature. From our observation, this group of patients were either too well to be operated on during the same hospital admission (i.e. only minimal symptoms or no symptoms) or too fragile to be operated on due to underlying co-morbidities (and hence relatives inclined to proceed with operation later if the patients further deteriorated). We hope the use of Atorvastatin as a non-surgical treatment could fill up the gap in the management of CSDH by providing patients and their relatives an option when the operation is not performed for the above reasons.

The improvement rate with Atorvastatin was not significantly different from the control whereas the deterioration rate requiring burr-hole drainage was significant. This is because a proportion of patients had CSDH volumes remaining static throughout the

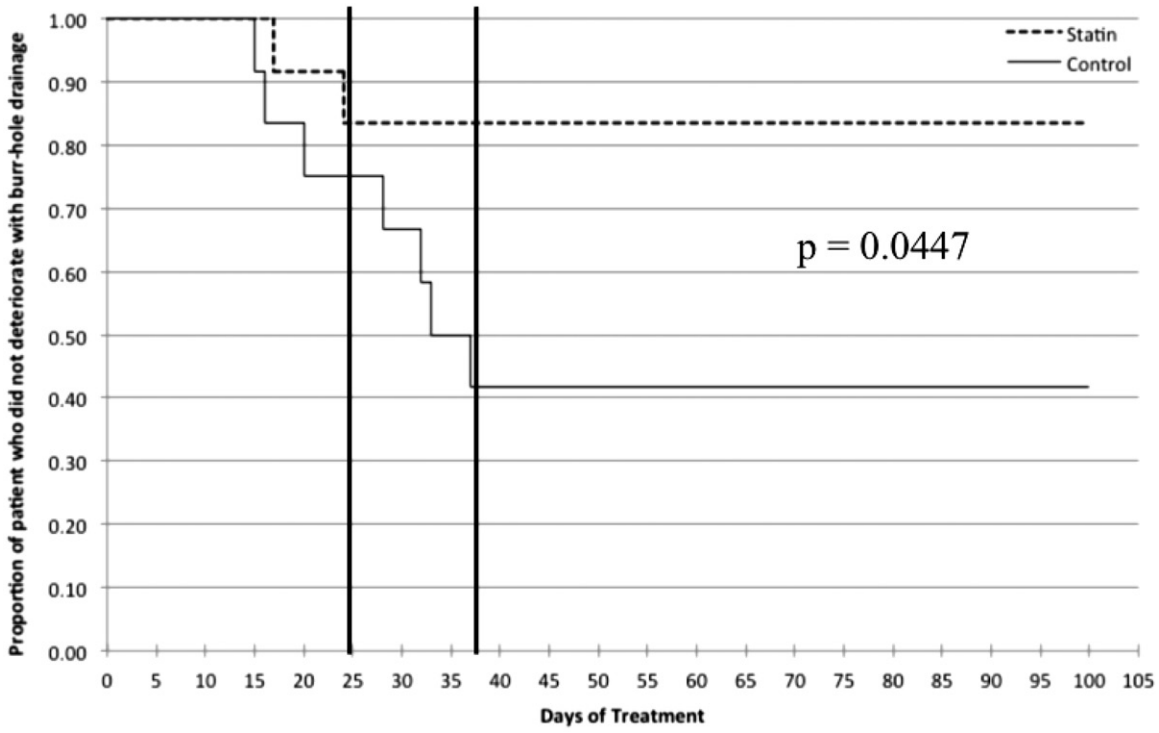

Figure 5. Kaplan–Meier Curve showing the proportion of those who did not undergo burr-hole drainage.

follow-up period and hence they were not considered as an improvement. However, these patients did not require burr-hole drainage and hence contributed to the significant secondary outcome. We acknowledge that radiological improvement is a stronger evidence of the efficacy of Atorvastatin on CSDH rather than these patients would deteriorate to require burr-hole drainage. At the same time, we should also appreciate its potential ability to prevent haematoma progression. This, in turn, would lead to less operation, which has direct clinical relevance to patients and their families. We are eager to see if this can lead to any potential improvement in functional outcome from future larger studies.

Conclusion

This retrospective cohort comparison study has shown that CSDH with Atorvastatin had a lower rate of deterioration and burr-hole drainage. This initial promising result prompts further large-scale randomised controlled trial.

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Disclosure statement

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the article.

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