Experience with Atorvastatin in Conservative Management of Chronic Subdural Hematoma with Brief Review of Literature

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Abstract

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical procedure done in any neurosurgical unit worldwide. The majority of CSDH are operated upon and there are very few studies regarding its conservative management. Mannitol, Steroids, Tranexemic acid, middle meningeal artery embolization and Angiotensin Converting Enzyme inhibitors are some options to treat CSDH conservatively.Atorvastatin is one of the newer and novel drugs that has been used effectively to medically treat CSDH.

This is a retrospective study of 20 cases of CSDH that were managed conservatively with atorvastatin between 2015 to 2021.

A total of 20 (7.5%) cases were included in the study period (January 2015 – January 2021). Glasgow Coma Score (GCS)/ Markwalder score (MS), mode of injury if any, age, sex, symptoms and neurological findings, co-morbidities, anti-platelet use, radiological finding of midline shift at admission and outcome with Glasgow outcome score (GOS) at the end of two months after treatment recorded. Atorvastatin in dose of 20 mg daily was given for maximum of two months with repeat CT/MRI scans done at 2 months. Repeat scan was done at 2 weeks and at 2 months and all of them showed complete resolution of the CSDH radiologically. The Glasgow outcome score showed good improvement in all the cases although there was mild confusion in five of the elderly which can be attributed to age related behavior changes.

We conclude that atorvastatin can be used safely in not only elderly but also in younger subjects.

Key words: Atorvastatin, Burr hole, Chronic subdural hematoma, Glasgow Coma Score, Markwalder score

Introduction

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical procedure done in any neurosurgical unit worldwide. When CSDH is symptomatic, has mass effect, motor or sensory symptoms, large or progressing in size, deterioration of neurological findings, they are all indication for surgery unless there are other comorbidities that prevent surgical intervention. There are many surgical options from single burr hole to multiple, with or without drain, endoscopic or open and the choice depends entirely on the surgeon or on the department's policy.[1-3]

The majority of CSDH are operated upon and there are very few studies regarding its conservative management.[4-6] Surgery for CSDH may be associated with morbidity, mortality and even recurrence during follow-up.[7] In those cases which have contraindication for surgery or when the patient is not willing for surgery then conservative option remains the only choice for its management. Mannitol, Steroids, Tranexemic acid, middle meningeal artery embolization and Angiotensin Converting Enzyme inhibitors are some options to treat CSDH conservatively.[8-12] Atorvastatin is one of the newer and novel drugs that has been used effectively to medically treat CSDH.[13-16] This study reports a series of CSDH cases that refused surgery or had multiple comorbidities and thus were managed conservatively with Atorvastatin.

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Materials and Methods

This is a retrospective study of all cases of CSDH that were managed conservatively with atorvastatin between 2015 to 2021. The inclusion criteria were the presence of significant CSDH defined as thickness of more than 10 mm as seen on either Computed Tomogram (CT) or Magnetic Resonance Imaging (MRI). All cases needing emergency evacuation or present use statins and those that could not be followed up for two months from start of treatment were excluded from the study.

Glasgow Coma Score (GCS)/ Markwalder score (MS), mode of injury if any, age, sex, symptoms and neurological findings, co-morbidities, anti-platelet use, radiological finding of midline shift at admission and outcome with Glasgow outcome score (GOS) at the end of two months after treatment recorded. The risk of conservative management and the dangers of deterioration were explained in vernacular to the patient and relatives. Consent was taken and the data entered in fixed proforma. All cases that were operated due to deterioration were excluded from the study.

Atorvastatin in dose of 20 mg daily was given for maximum of two months with repeat CT/MRI scans done at 2 months. Regular two weekly monitoring of the patient was done for any drug related or clinical, biochemical/ hematological adverse effects. The outcome was determined in terms of partial or complete reduction/ disappearance of the CSDH, neurological progress and GCS improvement. Statistical data was done with SPSS v 24 (IBM, USA).

Results

A total of 25 cases were included in the study period (January 2015 – January 2021) of which five cases deteriorated and were taken for emergency surgery. During this study period a total of 265 cases were operated with 219 males and 46 females, 119 on left side and 103 on right and bilateral in 43 cases. This gives conservative management in 7.5 % of cases.

There was almost equal sex distribution. The age ranged from 15 years to 95 years with the majority more than 70 years of age. The majority (60%) were left sided and the others equally in right or bilateral. Headache, weakness of either one side or generalized and confusion were the most common symptoms. Two cases were clinically intact. History of trauma was present 46% of cases with three of them secondary to road traffic accident. These had acute subdural hematoma which was managed conservatively but presented later as CSDH. Hypertension, smoking and alcoholism were the most common symptoms associated in the cases. Majority of the CSDH were large and had mass effect with midline shift to contralateral side (55%). The GCS at admission was between 11-15 with the MS between 0-1 suggesting majority were in the good grade. The details of the patients are given in Table 1.

With relation to sex and side of lesion this subgroup showed that in both sexes the left side was more common but it was more in the female sex. Repeat scan was done at 2 weeks and at 2 months and all of them showed complete resolution of the CSDH radiologically. The Glasgow outcome score showed good improvement in all the cases although there was mild confusion in five of the elderly which can be attributed to age related behavior changes.

There was clinical improvement in 17 of the cases with 3 cases still having confusion which was probably age-related dementia. There were no side effects of the drug during the study period.

S.N.	Age (Yrs)	Sex	Side	GCS/MS	Trauma	Symptoms	Co-morbidity	Anti-platelet use	Mass effect	Outcome -GOS
1	75	F	LEFT	12/1	N	H/W/C	HTN/ALC	Y	Y	1
2	75	F	LEFT	14/0	N	H/W/C	HTN/DM	Y	N	2
3	65	F	LEFT	14/0	N	H	SMK	-	Y	1
4	70	F	LEFT	15/0	N	W	HTN/ALC	-	N	1
5	60	F	B/L	13/0	Y	W/C	-	-	N	1
6	95	M	LEFT	14/0	N	H/W/C	HTN/ALC/DM	-	N	2
7	65	M	LEFT	12/1	Y	W	-	-	Y	1
8	75	M	RIGHT	11/1	Y	C/H	HTN/ALC	Y	Y	1
9	16	F	LEFT	15/0	Y	NONE	-	-	N	1
10	82	M	RIGHT	12/1	N	H/W/C	HTN	Y	Y	1
11	63	M	RIGHT	11/2	N	W/C/H	HTN/ALC	-	Y	1
12	47	F	LEFT	15/0	Y	C/W	/ALC	-	N	1
13	79	F	B/L	12/2	N	NONE	HTN/ALC	-	Y	1

14	86	M	B/L	14/0	Y	C	HTN/ALC	Y	Y	1
15	73	M	LEFT	15/0	Y	NONE	HTN/SMK	-	Y	1
16	40	M	LEFT	13/1	N	H	-	-	Y	1
17	71	M	RIGHT	12/1	N	H/W/C	-	-	N	2
18	78	F	LEFT	14/0	Y	H/W/C	HTN	Y	N	1
19	67	F	LEFT	15/0	Y	H/C	DM	-	Y	1
20	38	F	RIGHT	13/1	N	H/W/C	ALC	-	N	1

Table 1: Showing the age, sex, side of hematoma, GCS/MS score, symptoms (H-headache, W-weakness, C-confusion), history of trauma (Y-yes, N-No), Co-Morbidity (HTN-hypertension, ALC-alcohol, SMK-smoking), antiplatelet use (Y-yes, N-No), the radiological mass effect (Y-yes, N-No) and outcome in GOS at 2 months. GCS-Glasgow coma Score, MS-Markwalder score, GOS-Glasgow Outcome Score.

Treatment drug	Mechanism of action	Level of evidence	Ongoing trials	Trial Reference
Atorvastatin	Anti-inflammatory	C	ATOCH	25
Atorvastatin with dexamethasone	Anti-inflammatory		-	
Tranexamic acid	Anti-Fibrinolytic	C	TRACS trial TORCH	29 30
Captopril	Angiotensin enzyme inhibitors	B/C	-	
Mannitol	Osmotic diuretic	C	-	
Dexamethasone Prednisolone	Anti-inflammatory		Dex-CSDH trial	36
Etizolam Ibudilast	Platelet activating receptor antagonist	C	-	
Gorei San (Japan), Xuefuzhuyutang (China)	Traditional herbal		-	

Table 2: Showing the available drugs with their mode of action, level of evidence for their use and the ongoing trials in conservative management of CSDH.

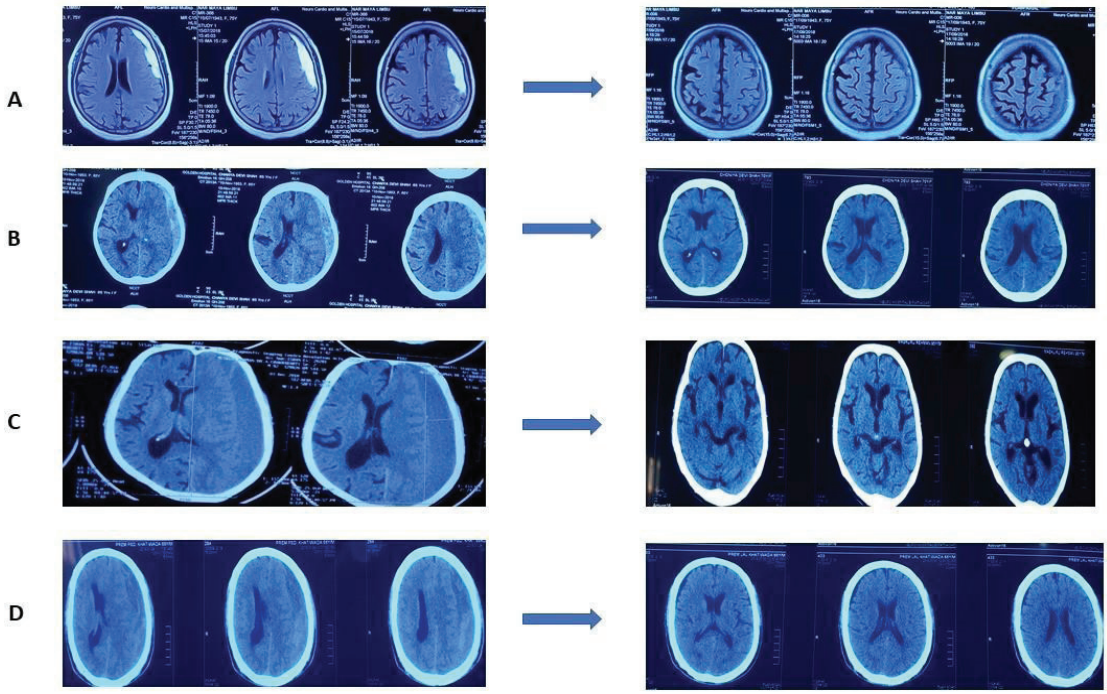

Figure 1: Radiological images of four of the cases with left sided hematoma and their complete resolution at 2 months. The cases are labelled as A to D, with the left column showing the scans before treatment and the right column after completion of treatment.

Discussion

CSDH remains one of the most common procedures in any neurosurgical center worldwide (incidence of 3.4/100,000 in age < than 65 years and 8-58/100,000 if > 65 years).[17] Majority of the neurosurgeons prefer to do a surgical evacuation with either a single or double burr hole, twist drill craniostomy and craniotomy with or without insertion of a closed drain. Since the majority of the CSDH occur in the elderly surgery can lead to serious morbidity, recurrence or even death. In cases which are at high risk due to other coexisting medical comorbidities and those who refuse surgery the option remains for conservative management. There are no studies or factors that determine whether a subdural hematoma will progress into CSDH or whether it will resolve spontaneously. In a survey done in 2008 it was found that only 25% of the neurosurgeons from United Kingdom or Republic of Ireland preferred conservative management.[18] in our study period conservative management was in only 7.5% suggesting that in Nepal the majority of CSDH are operated.

When surgery is not the option then regular follow-up with either clinically for any deterioration or with repeat serial scans is the only option to see the progression of CSDH. Medical management remains the other option with many different drugs evaluated in the conservative management of CSDH with varying results. Many factors can define the outcome of the latter management. Age more than 70 years along with cerebral atrophy and with no features of mass effect as seen radiologically, females, good Markwalder scores, absence of hemiparesis, smaller hematomas and less dense hematoma radiologically are some factors that improve with conservative management.[6,19]

Medical Management:

Atorvastatin: Atorvastatin has been widely used in medicine for its lipid and cholesterol lowering effects. In one of the earlier studies from three medical centers and then in the initial studies on rats, it was found to increase the vascular maturation-angiogenesis- by its increase of vascular endothelial growth factor and angiopoietin. Over the years more and more studies were done that confirmed the efficacy of this drug in CSDH management.[20,21] It was also shown to have anti-inflammatory that controlled the growth and expansion of CSDH which is one of the factors known for hematoma progression.[1,2] It has also led to the reduction of burr holes, increase resorption of hematoma, improved quality of life and also reduce the recurrence rate. The recommended dosage in most studies is 20 mg per day for 1 to 3 months. Some studies using 80 mg per day had an adverse effect by increasing the hematoma.

In a study that enrolled 200 cases the use of atorvastatin showed significant reduction of the hematoma volume with neurological improvement. The reduction in volume was more marked in those aged more than 65 years and there were no side effects noted due to the drug. This study also found that the effect on hematoma volume reduction was persistent till 4 months of follow-up.[22] In another meta-analysis of 6 trials found that atorvastatin was effective in reducing the rate of recurrent surgery in patients and improve neurological function in those with or without surgery (0.30, 95% CI 0.19–0.48, P<0.00001) and OR=1.75, 95% CI 1.08–2.83, P=0.02 respectively.[23] It has also been studied with combination with low dose dexamethasone that showed accelerated hematoma reduction and good neurological progress when used for 12 weeks.[24]

In this study atorvastatin was used for period of two months and showed complete resolution of the hematoma. This suggest that it need not be used for prolonged periods. The lack of any side effects has also shown its safety in CSDH management. The results seem to be the same irrespective of sex, side, age, initial GCS or MS scores and in the presence of hypertension, diabetes, smoking or alcoholism. The latter thus do not seem to play any role in the progression or expansion of CSDH. Although most studies suggest their safety in elderly this study has shown that atorvastatin can be used at all age groups. Whether in combination with other drugs remains to be studied further.

The highly anticipated ATOCH (atorvastatin on chronic subdural hematoma) trial will be completing on July 2021 and it would definitely shed more light regarding the use of this drug for CSDH.[25] In this study all the cases showed complete resolution of the CSDH at the end of two months. This suggest that long term treatment may be unnecessary once the hematoma disappears at two months. The low cost and absence of side effects makes this drug ideal for medical management.

Atorvastatin and low dose dexamethasone: these two have been studied and found that it countered the CSDH induced KLF-2 suppression in human cerebral endothelial cells and thus leading to improved outcome.[26]

Tranexamic acid: some of the factors that leads to progression of CSDH are the repeated microcapillary bleeds, activation of kinen-kallikrein system by plasmin and the subsequent inflammation with vascular leak. Tranexamic acid has an anti-fibrinolytic effect thus preventing the above cascade and resorption of the CSDH. In one of the earlier studies, it was found that 750 mg daily of this drug led to complete resorption and reduction of recurrence.[27,28] There are few trials that are studying the efficacy of this drug and the results will definitely help in future for the medical management of CSDH. Tranexamic acid in Chronic Subdural Hematomas (TRACS) trial is a multicenter, double-blind, randomized, parallel-design,

placebo-controlled, phase IIB study where the cases will receive either 750 mg of TXA daily for maximum 20 weeks or placebo until complete radiological resolution of the CSDH.[29] Tranexamic Acid to Prevent OpeRation in Chronic Subdural Hematoma (TORCH) is another ongoing double-blind placebo-controlled multi-centre randomized clinical trial of oral tranexamic 500mg twice daily for 4 weeks.[30]

Angiotensin inhibitors: Another drug that has been studied with varying results are angiotensin converting enzyme inhibitors. It was first reported in 2007 where it was found to have led in the reduction of hematoma volume and also recurrence of CSDH in a study that was conducted over 9 years.[31] The angiogenesis in CSDH has been seen with hematoma progression and hence use of this drug was theoretically proposed to help prevent the inflammation chain and reduce hematoma. In a study with preoperative use, it was found that the drugs possible led to not only increase in hematoma volume but also the rate of recurrence. The explanation was due to the increased levels of bradykinin and hence vascular permeability of the CSDH membranes.[32] In another retrospective population-based cohort of 1252 adults study found no relation of these drug use with recurrence of hematoma.[33] There are no studies to validate the advantage of using these inhibitors in the conservative management of CSDH and hence not recommended at present.

Mannitol: Mannitol is an osmotic diuretic that has been used worldwide in the management of intracranial pressure. The osmotic effect can help in the reduction of microbleeds within CSDH to allow resorption. In one of the earliest studies that involved 22 cases with mannitol treatment for 12 -106 days with 8 months to 3.5 years follow-up did not show any recurrence in the disappeared CSDH.[34] There are few other studies showing similar benefit but none are Class A level evidence to suggest recommending mannitol in the conservative treatment of CSDH.

Dexamethasone: Corticosteroids are well known to be anti-inflammatory and used in various medical diseases. They also stimulate pro inflammatory mediators like lipocortin also increase synthesis of nitric oxide. They in theory block the cascade of inflammation induced angiogenesis in CSDH and was first studied in rats with good results. This led to further studies in humans beginning 1974 and has been continuing over the decades. They have been studied and compared either alone or with surgery. In the majority of the studies, it was found to be beneficial in the reduction of the hematoma volume, shortening hospital stay, neurological improvement and recurrence rate without any major side effects, comprising a Type C recommendation. Although showing benefit it needs to be used with caution as some studies did not show any advantage and had increased incidence of hyperglycemia and nosocomial infections, Type B recommendation. The drug dosage and duration though remain unclear as there is no common consensus worldwide. Future large prospective trials studying dexamethasone in CSDH will help to clear its role in its management. At present small volume of hematoma, good MS grade, inoperable cases, multiple co-morbidities and those amenable to follow-up can be given the option of this treatment.[36] In our center we do not use steroids unless there is thick membrane which needed craniotomy and excision.

The Dex-CSDH trial (DEXamethasone in Chronic SubDural Haematoma) which is a multi-centre, pragmatic, clinical phase III, randomised, double-blind, placebo-controlled trial of dexamethasone for up to two weeks in patients diagnosed with CSDH is ongoing and has recruited 630 patients as of 25 June 2018 across 22 UK sites. The results of this trial are awaited.[37]

Platelet-activating factor receptor antagonist: these are the newer drugs that have been tried in the conservative management of CSDH based on their anti-inflammatory actions. In a study with etizolam that received 3 mg/day for 2 weeks there was significant resolution of the hematoma.[38] In another study using Ibudilast there was good correlation with hematoma reduction at end of two months suggesting it may be useful in recurrence prevention.[39]

Other Local Drugs:

Gorei-san is a Japanese Kampo herbal medicinal drug that has been used in few CSDH studies in Japan. In one of the earlier studies involving 199 cases, it was used in isolation, and with tranexamic acid with reduced recurrence in the latter group. Similar study involving 166 cases suggested similar findings but the authors do not recommend its single use in CSDH management. It has also been used in cases where surgery was performed showing reduced recurrence.[39,40] Xuefuzhuyutang is another Chinese herbal medicinal drug that has been used for treatment of cardiovascular diseases. In a single study the drug was effective in reducing the post-operative hematoma. It has not been used in conservative management of CSDH and awaits further studies.

Limitations

In this study we have only used atorvastatin without any combination with other drugs. The number of cases is also few and hence larger prospective studies are needed to prove its efficacy with high level of evidence. The study also has good grade patients and hence the role of atorvastatin for poor grade patients also remains an open topic for further research.

Conclusion

Atorvastatin remains an effective drug in the medical management of CSDH with minimal side effects. As shown in this study its effects are not limited to adults and can be used safely even in the younger age group. Larger trials will help in giving higher Class of evidence to recommend its use in CSDH. Short term 2-month treatment seems to be effective as shown in this study.

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