



Correlation between Statin use and Intracranial Haemorrhage

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Abstract

Background: Intracerebral haemorrhage (ICH) is a neurologic injury resulting in significant morbidity and mortality. Statins play a significant role in primary and secondary prevention of cardiovascular and cerebrovascular ischemic events. Despite clear benefits of statins in ischemic stroke, studies suggest there may be a link between statin therapy and development of ICH.

Aims and Objectives: To find the correlation between statin use and intracranial haemorrhage.

Methods and Results: Retrospective study among 50 patients with intracranial haemorrhage. Detailed history including co-morbid conditions (especially HTN and IHD), intensity of statin used, severity of IC bleed, fasting lipid and GCS were obtained and analysed. IC bleed was classified into mild (less than 30cc), moderate (30 to 100cc) and severe (more than 100cc) based on volume of IC bleed on CT brain. Correlation was obtained between statin use and intracranial haemorrhage.

Results and Conclusion: The study found out that statin users had larger bleed volume, low GCS, lower total cholesterol and LDL levels. Also observed in the study was higher the intensity of statins more severe is the IC bleed. IC bleed also correlated with higher age, male sex, hypertension and IHD.

Keywords: Statins, Intracranial Haemorrhage, Intracerebral Haemorrhage.

Introduction

Statins are widely prescribed for primary and secondary prevention of ischemic cardiac and cerebrovascular disease.¹The beneficial effects of statins are the result of their capacity to reduce cholesterol biosynthesis, mainly in the liver where they are selectively distributed, as well as to the modulation of lipid metabolism, derived from their effect of inhibition upon HMG-CoA

reductase. Statins have anti-atherosclerotic effects, that positively correlate with the percent decrease in LDL cholesterol. In addition, they can exert anti-atherosclerotic effects independently of their hypolipidemic action.²

Intracerebral haemorrhage, or ICH, is a devastating disease. The overall incidence of spontaneous ICH worldwide is 24.6 per 100,000 person-years. The 30-day mortality rate ranges

from 35 to 52% with only 20% of survivors expected to have full functional recovery at 6 months. Approximately half of this mortality occurs within the first 24 hours, highlighting the critical importance of early and effective treatment in the Emergency Department (ED).³

Haemorrhage results from rupture of small penetrating arteries originating from basilar arteries or the anterior, middle, or posterior cerebral arteries. Risk factors include male sex, smoking, diabetes, alcohol intake, cocaine hydrochloride use, and use of antiplatelet or anticoagulant medications. Compounding risk factors are likely to increase the risk of a patient suffering from ICH. ICH commonly occurs in the cerebral lobes, basal ganglia, thalamus, brain stem, and cerebellum.⁴

Hypocholesterolemia has been associated with increased incidence of ICH, and it has also been associated with hematoma expansion after ICH. The ERICH study (Ethnic/Racial Variations of Intracerebral Haemorrhage) was a multicenter, prospective recruitment multiethnic study of ICH. In this study they hypothesized that ICH patients who were on statin would have larger admission hematoma volume, increase risk of hematoma expansion, and higher 3-month mortality and morbidity.⁵

While the benefits of HMG coenzyme A reductase inhibitors (statins) for reducing cardiac and cerebrovascular disease risk are well established, more widespread use of statin therapy remains controversial. A particular subgroup where the advisability of statin use is unclear involves patients at high risk for intracerebral haemorrhage (ICH). The reason for added concern is the increased incidence of ICH observed among subjects randomized to statin therapy in a clinical trial of secondary stroke prevention. Since ICH survivors commonly have co-morbid cardiovascular risk factors that would otherwise warrant cholesterol-lowering medication, it is important to weigh the risks and benefits of statin therapy in this population.¹ This risk might be of major relevance to patients with prior ICH, who are at

high risk of haemorrhage, which could result from the statin-induced reductions in cholesterol levels and inhibition of platelet aggregation (Ricard et al. 2010). These concerns are particularly relevant to Asians, a population at higher risk of ICH.⁶ It needs to be acknowledged that available analyses of the impact of statins in patients with ICH are based on small numbers of patients, and almost entirely on post hoc, exploratory or observational analyses.⁷

The present study was undertaken to study the correlation of statin use and intracranial haemorrhage in individuals presented to the department of general medicine, SSIMS & RC, Davangere, Karnataka, India.

Aims and Objectives

To find the correlation between statin use and intracranial haemorrhage.

Methods of Study

We conducted a retrospective study among patients who were treated in the department of general medicine, SSIMS & RC, Davangere, Karnataka. A total of 50 patients who had intracranial haemorrhage were included.

Inclusion Criteria

- Age above 18yrs
- Patients who had intracranial haemorrhage

Exclusion Criteria

- Bleeding disorders
- Hypercoagulable states
- Trauma
- Pregnancy
- Liver disorders
- Patients on OCP

50 patients with intracranial haemorrhage were admitted in SS institute of medical sciences and research centre. Their detailed history regarding the co-morbid conditions (especially HTN and IHD), intensity of statin used, severity of IC bleed (based on volume of bleed in CT brain), fasting lipid profile (including total cholesterol, LDL, HDL, TGL) and GCS were obtained and analysed.

Statins were categorised into Low intensity statin, moderate intensity and high intensity.

| High-Intensity | Moderate-Intensity | Low-Intensity |
|--|---|--|
| Atorvastatin (40)-80 mg Rosuvastatin 20 (40) mg | Atorvastatin 10 (20) mg Rosuvastatin (5) 10mg Simvastatin 20-40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80mg Fluvastatin 40mg BID Pitavastatin 2-4mg | Simvastatin 10mg Pravastatin 10-20 mg Lovastatin 20mg Fluvastatin 20-40 mg Pitavastatin 1 mg |

IC bleed was classified based on volume of intracranial haemorrhage in CT brain into

Mild IC bleed (less than 30cc)

Moderate IC bleed (30 to 100cc)

Severe IC bleed (more than 100cc).

Statistical Analysis

Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi Square test. Mean & Sd value was calculated for continuous variables. Analysis of quantitative data between two groups was done using unpaired t test if data passes ‘Normality test’ and by Mann-Whitney test if the data fails Normality test. Comparison of three groups was done with ANOVA. Spearman correlation test was used to determine the relationship between the two variables.

P value of <0.05 was considered statistically significant. To analyze the data IBM SPSS Verion 22 for Windows was used.

Observations and Results

Out of 50 patients who developed intracranial bleed we observed that male patient accounted for 54% (27) female patient accounted for 46% (23).(Table 1)

Table 1: IC bleed and gender

| Gender | Frequency | Percent |
|--------|-----------|---------|
| Male | 27 | 54.0 |
| Female | 23 | 46.0 |
| Total | 50 | 100.0 |

Table 2 shows the frequency of people developing IC bleed according to age with age group above 60 accounting for majority of cases.

Table 2: Age group and IC bleed

| Age | Frequency | Percent |
|----------|-----------|---------|
| < 60 yrs | 8 | 16.0 |
| 60 - 69 | 13 | 26.0 |
| 70-79 | 15 | 30.0 |
| ≥ 80yrs | 14 | 28.0 |
| Total | 50 | 100.0 |

Hypertensive patient developing IC bleed accounted for 68% (34 out of 50 patients) and IHD patients accounted for 46% (23 out of 50 patients). (Table 3)

Table 3: Co-morbid conditions and IC bleed

| Co-morbid conditions | Frequency | Percent |
|----------------------|-----------|---------|
| HTN | Yes | 34 |
| | No | 16 |
| IHD | Yes | 23 |
| | No | 27 |

In table 4 we observed that IC bleed occurred in 64% patients with statin use as compared to non statin users.

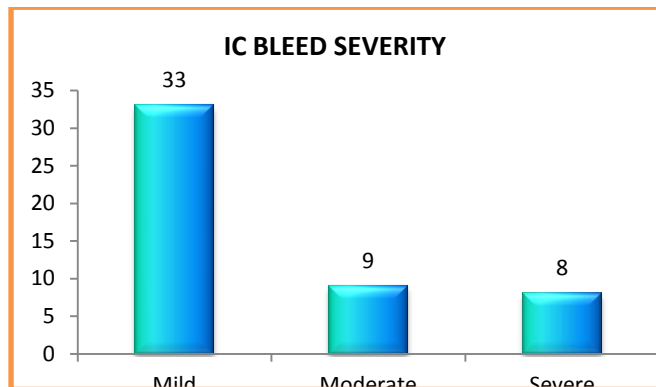
Table 4: statin use and IC bleed

| STATIN USE | Frequency | Percent |
|------------|-----------|---------|
| Yes | 32 | 64.0 |
| No | 18 | 36.0 |
| Total | 50 | 100.0 |

IC bleed has been classified in our study based on the size of bleed into mild (less than 30cc), moderate (30 to 100cc) and severe (more than 100cc). Table 5 and graph 1 depicts the severity of IC bleed based on size of bleed. 33 out of 50 patients came under the category of mild. 9 out of 50 were classified under moderate and 8 out of 50 classified under severe.

Table 5: IC bleed size and severity

| IC BLEED SIZE | | |
|---------------|-----------|---------|
| Severity | Frequency | Percent |
| Mild | 33 | 66.0 |
| Moderate | 9 | 18.0 |
| Severe | 8 | 16.0 |
| Total | 50 | 100.0 |



Graph 1: IC bleed size and severity

Most of IC bleed occurred in middle cerebral artery territory accounting for 68% shown in table 6.

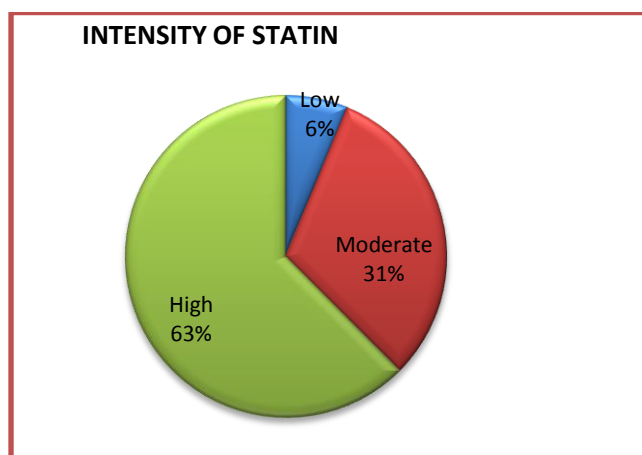
Table 6: Frequency of arterial territory involved in IC bleed

| ARTERY TERRITORY | Frequency | Percent |
|------------------|-----------|---------|
| ACA | 8 | 16.0 |
| MCA | 34 | 68.0 |
| PCA | 16 | 32.0 |

63% patients were using high intensity statins. Patients using moderate intensity accounting for 31% and low intensity 2%. (Table 7 and Graph 2)

Table 7 shows the number of patients using different intensity of statin.

| INTENSITY OF STATIN | Frequency | Percent |
|---------------------|-----------|---------|
| Low | 2 | 6.25 |
| Moderate | 10 | 31.25 |
| High | 20 | 62.50 |
| Total | 32 | 100.00 |



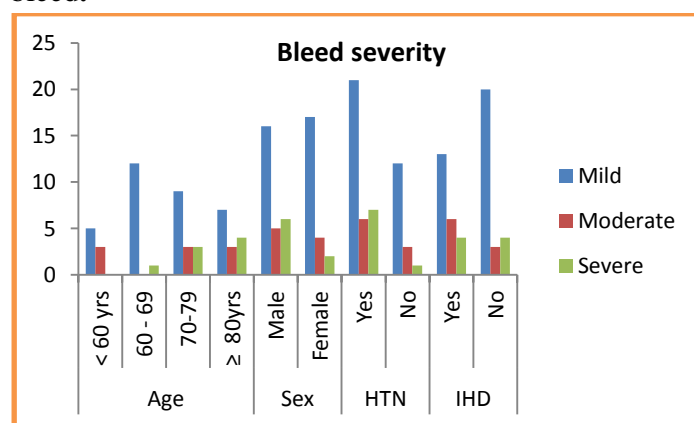
Graph 2 pie chart representation of different intensity of statin.

IC bleed was seen in majority of cases above age 60years, with severity slightly high above 80 years but without statistical significance. Considering sex, severities were slightly high in males as compared females without significant P value. Patients with history of hypertension were observed to have severe IC bleed as compared to non-hypertensives. Severity in patients with IHD showed fewer patients with mild bleed size and slightly more patients with moderate bleed size. But none of them were statistically significant. (Table 8 and Graph 3)

Table 8 tabulates the patient characteristics with severity of bleed

| Parameters | Bleed Severity | | | Chi Square | |
|------------|----------------|----------|--------|------------|----------------|
| | Mild | Moderate | Severe | | |
| Age | < 60 yrs | 5 | 3 | 0 | 9.53, P<0.146 |
| | 60 - 69 | 12 | 0 | 1 | |
| | 70-79 | 9 | 3 | 3 | |
| | ≥ 80yrs | 7 | 3 | 4 | |
| Sex | Male | 16 | 5 | 6 | 1.83, P<0.40 |
| | Female | 17 | 4 | 2 | |
| HTN | Yes | 21 | 6 | 7 | 1.69, P<0.429 |
| | No | 12 | 3 | 1 | |
| IHD | Yes | 13 | 6 | 4 | 2.179, P<0.336 |
| | No | 20 | 3 | 4 | |

Graph 3: patient characteristics with severity of bleed.



We observed that there is positive correlation between GCS and IC bleed seen in table 9.

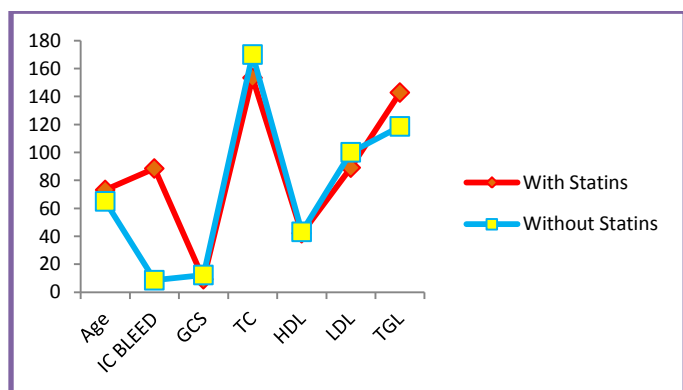
Table 9 shows the correlation between IC bleed size and other variables like age, GCS, total cholesterol, HDL, LDL, TGL

| Correlations between bleed size & other variables | | |
|---|---------|---------|
| Parameters | r Value | P Value |
| Age | .266 | P<0.06 |
| GCS | -0.837 | P<0.000 |
| TC | .146 | P<0.310 |
| HDL | .056 | P<0.696 |
| LDL | .125 | P<0.386 |
| TGL | .232 | P<0.105 |

Mean age of 73.18 ± 12.01 was observed in statin users as compared to non-statin users. IC bleed occurred in 88.56 ± 129.46 of statin users as compared with non statin users. GCS of 9.28 ± 3.83 were observed in statin users as compared to non statin users (12.33 ± 1.53). Also patients on statin had total cholesterol of 153.4 ± 22.54 as compared to non statin users. 42.2 ± 4.96 were the observed HDL levels in statin users. LDL levels of 89.1 ± 15.5 were seen in statin users. 142.8 ± 76.53 were the observed TGL levels in statin users. Of these positive correlations were observed between statin users with that of age, IC bleed, GCS, TC and LDL levels. (Table 10 and Graph 4).

Table 10 correlating between statin users and different parameters like age, IC bleed size, GCS and fasting lipid profile.

| Difference between with & without Statins | | | | |
|---|--------------------|-------------------|-----------|---------|
| Parameters | With Statins | Without Statins | t/z Value | P Value |
| Age | 73.18 ± 12.01 | 65.0 ± 14.21 | 2.159 | P<0.03 |
| IC BLEED | 88.56 ± 129.46 | 8.59 ± 10.61 | -2.418 | P<0.01 |
| GCS | 9.28 ± 3.83 | 12.33 ± 1.53 | -3.228 | P<0.002 |
| TC | 153.4 ± 22.54 | 170.0 ± 29.68 | -2.238 | P<0.03 |
| HDL | 42.2 ± 4.96 | 43.2 ± 5.39 | -0.608 | P<0.546 |
| LDL | 89.1 ± 15.5 | 100.1 ± 20.54 | -2.139 | P<0.03 |
| TGL | 142.8 ± 76.53 | 118.6 ± 38.39 | 1.254 | P<0.216 |

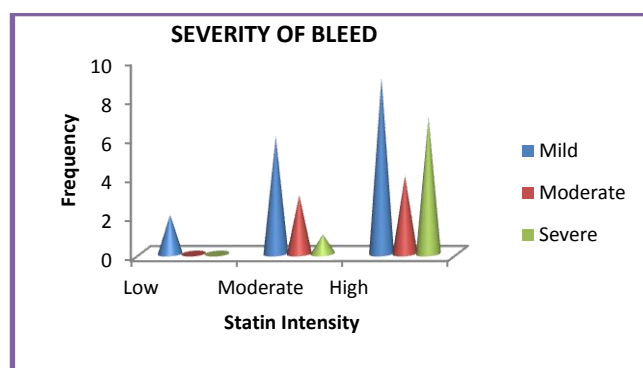


Graph 4 correlations between statin users and different parameters like age, IC bleed size, GCS and fasting lipid profile.

In table 11 and Graph 5 we observed that out of total high intensity statin users (20) mild, moderate and severe IC bleed accounted for 9,4,7 respectively. Moderate and mild intensity statin users accounted for majority of mild IC bleed (less than 30cc).

Table 11: Intensity of statin and severity of IC bleed

| Severity of Bleed | Statin Intensity | | |
|-------------------|------------------|-----------------|-------------|
| | Low (N=2) | Moderate (N=10) | High (N=20) |
| Mild | 2 | 6 | 9 |
| Moderate | 0 | 3 | 4 |
| Severe | 0 | 1 | 7 |



Graph 5: Intensity of statin and severity of IC bleed

It was observed that there was positive correlation between IC bleed size and duration of statin use, hypertension and duration of IHD. (Table 12)

Table 12: Correlations between bleed size & other variables

| Correlations between bleed size & other variables | | |
|---|---------|---------|
| Parameters | r Value | P Value |
| Duration of Statin | 0.707 | P<0.000 |
| Duration of HTN | 0.622 | P<0.001 |
| Duration of IHD | 0.761 | P<0.000 |

Mean GCS of 8.20 with a standard deviation of 3.46 was observed in patients using high intensity statin. Moderate and low intensity statin users had a GCS following IC bleed of 10.80 and 12.50 respectively (Table 13).

Table 13: Mean and standard deviation of GCS with intensity of statin

| INTENSITY OF STATIN | N | GCS Score | | ANOVA |
|---------------------|----|-----------|----------------|-----------------|
| | | Mean | Std. Deviation | |
| Low | 2 | 12.50 | 2.12 | F=2.515, P<0.09 |
| Moderate | 10 | 10.80 | 4.16 | |
| High | 20 | 8.20 | 3.46 | |

It was observed that patients who were on high intensity statin had a mean IC bleed size of 102.70 and standard deviation of 127.81. Those patients with moderate and low intensity statin had mean IC bleed of 76.36 and 8.25 respectively. This was not statistically significant.(Table 14)

Table 14: Mean and standard deviation of IC bleed with intensity of statin

| INTENSITY OF STATIN | N | IC BLEED | | Kruskal Wallis Test |
|---------------------|----|----------|----------------|---------------------|
| | | Mean | Std. Deviation | |
| Low | 2 | 8.25 | 10.96 | P<0.259, NS |
| Moderate | 10 | 76.36 | 145.57 | |
| High | 20 | 102.70 | 127.81 | |

Male patients developed a mean bleed size of 70.41 as compared to females with a significant P value. Hypertensive patients had mean bleed size of 73.46 as compared to 30.70 non hypertensive patient with a significant P value. Even in IHD patients bleed size was comparatively high but was not significant.(Table 15)

Table 15: Mean and standard deviation of IC bleed and variables like sex, HTN and IHD.

| Variables | N | IC BLEED | | Mann-Whitney U test | |
|-------------|----|----------|----------------|---------------------|---------|
| | | Mean | Std. Deviation | z Value | P Value |
| Male | 27 | 70.41 | 114.11 | -2.177 | P<0.029 |
| Female | 23 | 47.29 | 106.60 | | |
| With HTN | 34 | 73.46 | 128.31 | -3.276 | P<0.001 |
| Without HTN | 16 | 30.70 | 46.17 | | |
| With IHD | 23 | 69.63 | 107.14 | -0.848 | P<0.397 |
| Without IHD | 27 | 51.38 | 114.11 | | |

Discussion

The findings of our study shed light on the conflicting data regarding the effect of statins on outcomes after ICH. IC bleed is a complex disease and involves several factors that independently or co-dependently affect the outcome of these patients.

In our study we took 50 patients of IC bleed with almost equal gender and different age group of whom IC bleed occurred more in age group more than 60 with severity also being more in higher age group. Also the volume of IC bleed and the use of statin correlated with age with significant P value. IC bleed volume was comparatively more in male.

Patients with known history of hypertension had higher risk of IC bleed relating well to the cardiovascular effects of hypertension. IC bleed size also depended on the duration of hypertension which in turn related to the severity of IC bleed though only duration of hypertension with bleed was statistically significant. On the other hand, known case of IHD patients developing IC bleed were 23 as compared to without IHD (27). But the volume of IC bleed developing in IHD patients was comparatively more.

Almost 62% in our study were using high intensity statins. Those on statins had larger bleed volume, low GCS, and lower total cholesterol and LDL levels all of which were statistically significant. Also observed in the study was higher the intensity of statins more severe is the IC bleed. Duration of statin use also correlated with bleed size.

Another variable used in our study, ie, IC bleed showed that more patients came under mild IC bleed(less than 30cc) and most of IC bleed occurred in the MCA territory. IC bleed correlated with higher age, male sex, hypertension and IHD. P value was significant taking into consideration duration of statin use, IHD and HTN.

Conclusion

In our study of 50 patients we have found and concluded that statin use significantly leads to IC bleed and severity. Also additionally we have concluded that high intensity statin especially in elderly male with comorbidities like hypertension and diabetes have increased risk of developing IC bleed.

References

1. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Should Statins be Avoided after Intracerebral Hemorrhage ?. Arch Neurol. 2011;68(5):573–9.
2. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001;5(4):378-87.

3. Caceres JA, Goldstein JN. Intracranial Hemorrhage. *Emerg Med Clin North Am.* 2012;30(3):771–94.
4. Matre ETV, Sherman DS, Kiser TH. Management of Intracerebral haemorrhage – use of statins. *Vascular Health and Risk Management.* 2016;12:153–61.
5. Siddiqui FM, Langefeld CD, Moomaw CJ, Comeau ME, Sekar P, Rosand J et al. Use of Statins and Outcomes in Intracerebral Hemorrhage Patients. *Stroke.* 2017;48(8):1-7.
6. Tai S, Lin F, Lee C, Chang C, Wu M, Chien C. Statin use after intracerebral hemorrhage: a 10-year nationwide cohort study. *Brain and Behavior.* 2016;6(8):1-10.
7. Goldstein LB. Statin Therapy Should be Discontinued in Patients With Intracerebral Hemorrhage. *Stroke.* 2013;44:2058-9.