Original Research Paper

Volume-8 | Issue-3 | March-2018 | PRINT ISSN No 2249-555X

General Medicine

ASSOCIATION OF SERUM FERRITIN LEVEL WITH HEMATOMA EXPANSION IN PATIENTS OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE

Gupta S*	Department of Medicine, Himalayan Institute of Medical Sciences, HIHT University, Dehradun, Uttarakhand, India *Corresponding Author
Kakkar R	Department of Medicine, Himalayan Institute of Medical Sciences, HIHT University, Dehradun, Uttarakhand, India
Singh Y	Department of Medicine, Himalayan Institute of Medical Sciences, HIHT University, Dehradun, Uttarakhand, India
Mittal M	Department of Medicine, Himalayan Institute of Medical Sciences, HIHT University, Dehradun, Uttarakhand, India

ABSTRACT

Introduction: ICH patients have rapid neurological deterioration due to ongoing bleeding and enlargement of the hematoma during the first few hours. Studies have implicated a strong relation between the level of serum ferritin and the edema surrounding the hematoma within 72 hr. We hereby aim to study the serum ferritin levels and correlate them with the hematoma volume on CT head.

Aims and objectives: Measurement of serum ferritin levels and hematoma expansion in patients of spontaneous ICH and studying the correlation of serum ferritin level with hematoma expansion in patients of spontaneous ICH.

Methods: This is an observational study patients with diagnosis of spontaneous ICH were included, their hematoma volume, absolute edema and relative edema was evaluated by CT head done on day 1 and 3 along with the ICH scores and serum ferritin levels.

Results: Mean age of patients was 56.94±10.85 years with majority of males. Mean day 1 and day 3 hematoma size was 28.85±44.46 and 22.88±19.82 cm^3 respectively. Mean day 1 absolute edema size was 68.23±111.35 cm^3. while mean day 3 absolute edema size of survivors was 77.45±82.06 cm^3, Mean day 1 relative edema was 1.38±0.36. Mean day 3 relative edema of survivors was 2.38±1.16. At presentation, ICH score 1, 2 and 3 were seen in 39.2%, 37.3% and 23.5% patients.. Serum ferritin levels ranged from 10.92 to 1210.00 ng/ml. In multivariate analysis, only ICH score showed a significant association with outcome.

Conclusion: There was no significant association between S. ferritin levels and hematoma expansion in terms of absolute change in hematoma volume or absolute edema, but relative edema on day 3 showed a strong correlation with S. ferritin levels at presentation.

KEYWORDS :

Introduction:

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke accounting for approximately 10 to 20 % of all strokes with increased incidence in middle and low-income countries (1,2). Hypertensive arteriosclerosis and cerebral amyloidangiopathy (CAA) commonly amount to 80% of primary hemorrhages with higher incidence in people of Asian descent (3). Due to poorly controlled hypertension in ICH patients, sometimes it may be difficult to identify the underlying etiology. Incidentally, there is a fast progression due to ongoing bleeding and enlargement of the hematoma during the first few hours (4). Ferritin has been implicated to be a key iron-storage protein in the brain and it has been seen that numbers of ferritin-positive cells increased around the hematoma at the first day and are still at high levels 1 month later (5).

In hospitalized patients, in comparison to the edema surrounding the hematoma at the beginning, stronger relation has been implicated between the level of serum ferritin and the edema surrounding the hematoma 72 hr as in acute phase iron can compound the poisonous effect of thrombin and by accelerating the formation of the hydroxyl radicals and lipid peroxidation it can cause an oxidative injury (6). Hematoma growth becomes the principal cause of early neurological deterioration. Prospective and retrospective studies indicate that up to 38% hematoma expansion is noted within three hours of ICH onsetand that hematoma volume is a strongest predictor of 30-day mortality for all locations of spontaneous intracerebral hemorrhage as it becomes the principal cause of early neurological deterioration (7).

Therefore, if a relation is established between elevated serum ferritin levels and hematoma volume expansion in patients of spontaneous ICH, then lowering the ferritin level with iron-modifying agents or phlebotomy and using free radical scavengers could also be of therapeutic value. Thus, this study is planned to estimate the levels of serum ferritin levels in patients presenting with spontaneous ICH and correlate them with the hematoma volume on CT head.

Material and Methods:

This observational and follow up study was conducted in Medicine Department of Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun within a period of 12 months after obtaining an informed written consent from the patients and ethical clearance from the institutional ethics committee. Patients with diagnosis of spontaneous ICH who presented within 24 hrs of onset of symptoms, with age above 18 years and intracerebral hemorrhage confirmed by CT or MRI were taken. Exclusion criteria included patients with head injury, cancer, subarchanoid hemorrhage, chronic kidney disease, chronic liver disease,arterio venous malformations; patients onoral anticoagulants,current treatment for iron supplements, had underwent surgical intervention for ICH within 72 hours of presentation ,hematological malignancies and patients who consumed >40gm/day alcohol.Demographic data, history, clinical information about stroke risk factors were recorded in the study proforma, Serum Ferritin level were estimated using VIDAS immunofluroscenceanalyser version 1.0.and computed tomography of head was done using Multi detector Computed tomography – Siemen's Somatom sensation 64 slice(MDCT).

Baseline CT Head done on day of admission, follow up CT was done on day 3 theintracerebral hemorrhage volume was measured by using the formula ABC/2.The largest diameter of the hemorrhage on the slice is (A) in centimeters, and then largest diameter 90° to *A* on the same slice was measured next *(B)*. Finally, the approximate number of 10-mm slices on which the ICH was seen was calculated *(C)*. If the hemorrhage area was greater than 75% of the area,the slice was considered 1 hemorrhage slice for determining *C*, if between 25% to 75% of the area, the slice was considered half and area less than 25% was not considered a hemorrhage slice. Absolute Edema was measured and the size of absolute edema was calculated using the same technique and formula as described above.Relative edema was calculated by following the measured as described by Mehdiratta *et al.* (8) using the following formula:

$$\text{Relative Edema} = \frac{\text{(Absolute Edema size – Hematoma size)}}{\text{Hematoma size}}$$

Serum ferritin normal reference values:
Female (20-50years) : 22-112ng/ml
Male (20-50years) : 34-310ng/ml
Female (>50years) : 13-651ng/ml
Male (>50 years) : 4-665 ng/ml

The severity of hemorrhage was assessed using ICH scoring system proposed by Hemphill *et al.* (9).Patients were followed up till discharge, in-hospital outcome was noted in terms of: Improved, No change, Worsened, Death.

Data was analyzed by using statistical software SPSS 22. Data was analyzed using Independent Samples 't'-test, ANOVA and Chi-square test. Correlations were assessed using Spearman rank-correlation. Receiver-Operator Characteristic curves were drawn to find out appropriate cut-off value to predict outcome. Multivariate analysis was performed using binary logistic regression to evaluate the role of different clinical parameters with outcome (mortality±worsening). A 'p' value less than 0.05 were considered to indicate a statistically significant association.

Results:
A total of 51 patients were included, with mean age of 56.9±10.85 years, with 35 males and rest females. Unilateral weakness was the most common clinical presentation with or without altered sensorium. There were 19 (37.3%) smokers, 40 (78.4%) had history of hypertension and 13 (25.5%) had diabetes mellitus. Right side was involved in 23 patients, left in 21 while brainstem was involved in 7 cases.

Serum ferritin levels ranged from 10.92 to 1210.00 ng/ml. Mean serum ferritin levels were 193.34±236.15 ng/ml. Median value was 103.71 while interquartile range started from 36.08 and ended at 257.70 ng/ml. A total of 7 of patients had serum ferritin levels above reference range.

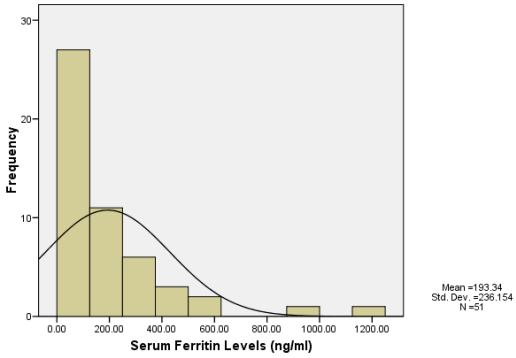

Fig. 1: Serum Ferritin Levels in all patients at admission

The change in hematoma volume between Day 1 and Day 3 interval it was found to range from -26.04 to 26.90 cm^3 with a mean of -0.38± 7.83 cm^3 while change in absolute volume was found to change from -47.20 cm^3 to 327.09 cm^3 with a mean of 23.42±58.01 cm^3. The median value was 4.85 cm^3 with interquartile range -2.75- 30.66 cm^3. The change in relative edema ranged from -0.73 to 4.33 with a mean of 1.01±1.21(Table 1).

Table 1: Day 1 and Day 3 Volume of Hematoma, Absolute Edema and Relative Edema (cm^3)

SN	Parameter	Day 1 (n=51)	Day 3 (n=49)	Comparison between Day 1 and 3 (n=49)
Hematoma Volume	Range	1.98-312	1.8-73.4	-26.04-26.90
	Mean±SD	28.85±44.46	22.88±19.82	-0.38±7.83
	Median [IRQ]	19.08 [7.85-35.64]	16.40 [8.70-31.30]	-0.72 [-3.11-3.30]
Absolute Edema	Range	3.70-789.36	4.85-434.53	-47.20-327.09
	Mean±SD	68.23±111.35	77.45±82.06	23.42±58.01
	Median [IRQ]	43.10 [19.32-75.56]	59.98 [21.90-88.14]	4.85 [-2.75-30.66]
Relative Edema	Range	0.68-1.96	0.84-5.23	-0.73-4.33
	Mean±SD	1.38±0.36	2.38±1.16	1.01±1.21
	Median [IRQ]	1.40 [1.12-1.70]	2.11 [1.53-2.92]	0.60 [0.11-1.91]

Maximum number of patients had ICH score 1 (n=20;) followed by those having ICH score 2 (n=19). At discharge 38 (74.5%) patients showed improvement, 3 (5.9%) were discharge without change, 2 (3.9%) cases had worsened whereas 8 (15.7%) cases expired.

Mean change in hematoma volume (Day 3 – Day 1) was increased and maximum among those who worsened followed by those who expired whereas reduced in those who improved and who remained unchanged. Statistically, the difference in mean change in hematoma volume among different outcomes at discharge was not significant (p=0.215).Mean change in absolute edema size and relative edema size was increased and maximum among those who worsened followed by those who expired and those who improved whereas reduced in unchanged patients. Mean change in absolute edema size was statistically significant (p=0.007), while mean change in relative edema size was not significant (p=0.671) as shown in Table1.

With increasing ICH score, a significant increase in mean day 1 and day 3 hematoma volume, absolute edema size took place (p<0.001). However, neither any association between ICH score and change in hematoma volume and absolute edema size at day 3 was observed, nor with change in absolute edema and relative edema at day 3.

Spearman correlation coefficient (ρ) values for correlation with hematoma size, absolute edema size, relative edema was evaluated at presentation, at day 3 and finally a comparison was made with change in size of hematoma, absolute edema and relative edema between day 3 and day1. There was a strong correlation seen between the relative edema size and serum ferritin levels on day 3 while none of the other correlations were significant statistically. as shown in table 2.

Table 2: Correlation Coefficients of Serum Ferritin at presentation, at day 3 and with Change in Size of Hematoma, Absolute Edema and Relative Edema at Day 3 as compared to Day 1 (Spearman rank correlation) (n=49)

SN	Time	Hematoma Size		Absolut edema		Relative edema	
		ρ	'p'	ρ	'p'	ρ	'p'
1	Presentation	-0.01	0.922	0.02	0.868	0.15	0.309
2	At day 3	-0.01	0.951	0.24	0.095	0.89	<0.00
3	Comparison between day 3 and 1	-0.19	0.201	0.03	0.852	0.18	0.213

On evaluating the data statistically for the association of serum ferritin with ICH scores, the association was not found to be significant (p=0.070) as shown in table 3.

Table 3: Association of Serum Ferritin levels with ICH Scores

SN	ICH Score	No. of cases	Serum Ferritin Levels (ng/ml)	
			Mean	SD
1.	Score 1	20	148.91	134.8
2.	Score 2	19	290.2	328.15
3.	Score 3	12	114.04	138.73

F=2.820; p=0.070 (NS)

For outcome at discharge as well as at 30 day, mean differences in serum ferritin levels did not show a significant association with outcome (p=0.300) as shown in Table 4

Table 4: Evaluation of S. Ferritin level as a predictor of outcome at discharge and outcome at 30 day

SN	Condition at discharge & day 30	S. Ferritin levels for outcome at discharge			S. Ferritin levels for outcome at day 30		
		n	Mean	SD	n	Mean	SD
1.	Better	38	171.85	151.44	14	173.10	140.99
2.	Same	2	29.97	8.64	25	160.19	161.96
3.	Worsened	3	329.82	549.20			
4.	Death	8	285.11	403.97	12	286.05	400.47
Statistical significance (ANOVA)		F= 1.173; p=0.330			F=1.234; p=0.300		

In a multi-variate analysis, with poor outcome at discharge and with mortality at day 30, being the dependent variable on independent variables S. ferritin, Volume of hematoma and ICH score, only ICH score was found to be an independent predictor as shown in Table 5 and 6.

Table 5: Multivariate Assessment of Serum Ferritin Levels with Hematoma size and ICH scores as a predictor of poor outcome (Mortality±Worsening) at discharge

		B	S.E.	Wald	df	Sig.	Exp (B)	95.0% C.I. for EXP (B)	
								Lower	Upper
Step 1 (a)	S. Ferritin	.002	.001	2.085	1	.149	1.002	.999	1.005
	Volume of hematoma at presentation	.006	.011	.286	1	.593	1.006	.985	1.027
	ICH Score	1.893	.711	7.090	1	.008	6.641	1.648	26.757
	Constant	-5.705	1.693	11.358	1	.001	.003		

a Variable(s) entered on step 1: SFerritin, VOLUME OF HEMATOMA ATPRESENTATION,

Table 6: Multivariate Assessment of Serum Ferritin Levels with Hematoma size and ICH scores as a predictor of mortality at day 30

		B	S.E.	Wald	df	Sig.	Exp (B)	95.0% C.I. for EXP(B)	
								Lower	Upper
Step 1(a)	S. Ferritin	.003	.002	3.300	1	.069	1.003	1.000	1.006
	Volume of hematoma at presentation	.009	.014	.434	1	.510	1.009	.982	1.037
	ICH Score	2.071	.831	6.212	1	.013	7.934	1.557	40.436
	Constant	-6.615	2.033	10.589	1	.001	.001		

a Variable(s) entered on step 1: SFerritin, VOLUME OF HEMATOMA ATPRESENTATION, ICHSCOREATPRESENTATION.

Discussion:

Despite newer advancements in medical and neurosurgical management modalities, ICH is generally associated with poor outcome, with an overall mortality of 40% to 50% (10). Few hematological and biochemical parameters have been wih prediction of outcome of these patients and body iron reserves, is one of the factors which has been looked upon with interest (11). Experimental studies have proven role of heme and iron metabolism in cerebral hemorrhageand of iron-modifying agents in reducing hemoglobin-induced neurotoxicity and brain edema (12).

Similar to our study, Bhatia *et al.* (11) also reported the mean age of patients as 57.32±12.84 years and proportion of males as 65.4%. Serum ferritin levels in our study ranged from 10.92 to 1210.00 ng/ml with mean levels were 193.34±236.15 ng/ml and 7 patients had S. ferritin levels above reference range. Mehdiratta*et al.* (8) found S. ferritin levels to be above 100 ng/ml in all the cases and their median were close to 300 ng/ml. Pankaj*et al.* (13) reported the serum ferritin levels to range from 20.13 ng/ml to 321 ng/ml mean value to be close to 257 ng/ml which is substantially higher as compared to present study.

Pérez de la Ossa et *al.* (14) found mean serum ferritin levels to be 183.47ng/ml, which is close to values obtained in our study. This difference could be due to difference in nutritional status, particular iron reserves and our study was done in a hilly region of northern India where iron deficiency is a common finding, particularly among elderly (15).

Mehdiratta*et al.* (8) who had the median serum ferritin levels of higher order (~300 ng/ml) had the highest increase in hematoma size (>35%) whereas in studies reporting mean serum ferritin levels in lower order had reported much lesser rise in hematoma size, *viz.* 10% (16), -7.1% (17) and -0.33% (present study) thereby suggesting a varying relationship between hematoma size and serum ferritin levels. Hematoma size has invariably been stated to be an objective criteria in assessment of severity of ICH in different studies and has been included in almost all the scoring systems including ICH scoring system (9) and FUNC (18), absolute edema and relative edema fail to do so.Mehdiratta*et al.* (8) did not specify any clinical usefulness of relative edema in their study. Similarly, Perez de la Ossa *et al.* (14) also did not find any clinical usefulness of edema growth. The ICH scores found in our study are similar with the observations of previous studies. Jamora*et al.* (19) in their study found score 4 and 5 in only 8% of their cases.

In our study, day 1 and day 3 hematoma volume, but not hematoma expansion was found to be significantly associated with outcome at discharge and this has been reported in different studies and also included in ICH scoring system by Hemphill *et al.* (9). The usefulness of absolute edema for prediction of early outcome as observed in present study has been reported by Applebroom*et al.* (20) who found it useful for only those cases where hematoma size was $\leq$30 cm^3 and in our study, in most of the cases the hematoma size was less than 20 cm^3. Our study found that relative edema at day 1 and day 3 as well as change in relative edema had no significant association with ICH score.

Importantly, no significant association of S. ferritin levels was observed with outcome at discharge. Contrarily, Erdemoglu and Ozbakir (17) reported that day 1 serum ferritin levels correlate with the severity of stroke and the size of the lesion while Milan *et al.* (21) reported their usefulness for 90-day outcome only. Perez de la Ossa*et al.* (14) also found them to be useful for prediction of functional outcome only.Pankaj*et al.* (13) in their study reported usefulness of serum ferritin for prediction of worsening and mortality in patents of stroke.

There was only strong and statistically significant correlation was seen between S.ferritin levels and change in relative edema on day 3. Mehdiratta*et al.* (8)also found a strong correlation between change in relative edema and S. ferritin levels> it is explained by the phenomenon that brain edema and iron accumulation in the perihematoma region peak 3 to 4 days after experimental ICH, and that this coincides with the timing for hemoglobin hemolysis (8).

We made an attempt to evaluate the role of serum ferritin in hematoma and edema progression in ICH cases and its usefulness in prediction of outcome as but we did not find any independent role of serum ferritin in determining the clinical course and outcome of ICH patients. Limitations our study were small sample size, and the location. Henceforth, larger sample sized multi-institutional studies are now required for better delineation of role of various hematological and biochemical factors including ferritin.

Conclusion:

No significant association of S. ferritin levels was observed hematoma expansion in terms of absolute change in hematoma volume or absolute edema. However, relative edema on day 3 showed a strong correlation with S. ferritin levels at presentation, but that was not very much significant. Outcome at discharge did not show a significant association with relative edema and hematoma volume between day 1 and day 3. Mean day 1 and day 3 absolute edema size volume values and change in absolute edema size between day 1 and day 3 were significantly higher among those who worsened and died.No significant association of serum ferritin levels was observed with outcome at discharge and at 30 day.Multivariate analysis was done and it showed higher ICH scores were significantly associated with poor outcome at discharge (worsening/death).

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