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Study of Association between Serum Ferritin And Prognosis Of Patients In Acute Ischemic And Haemorrhagic Stroke

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Abstract: *Despite lot of researches in the field of stroke, accurate prognostication of an acute attack is difficult. Several prognostic factors like site of infarction, size of infarct, size of the vessel involved, Glasgow coma scale, level of cerebral edema, intracranial tension have been found significant in cerebral infarction. Similarly in cases of cerebral hemorrhage, CT calculated volume of hematoma, GCS, site of hemorrhage etc. are important. One of the prognostic indicators which has gained great clinical interest in recent times is the level of serum ferritin. Initially considered only as a stress response to stroke, serum ferritin now is under research as a prognostic indicator.*

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I. Introduction

A Stroke or Cerebrovascular accident is defined as an abrupt onset neurological deficit attributable to a focal vascular cause. Thus the definition of stroke is clinical, and laboratory studies including brain imaging are required to support the diagnosis1.Cerebrovascular disease is the third leading cause of death after heart diseases and cancer in developed countries and is now emerging as the commonest preventable life threatening neurological problem worldwide. It makes an important contribution to morbidity and mortality in developed as well as developing countries. Improved detection and modification of risk factors could reduce the impact of this disease. Important non modifiable risk factors include age, gender, ethnicity and heredity. Modifiable risk factors include hypertension, cardiovascular disease, diabetes, hyperlipidemia, asymptomatic carotid stenosis, cigarette smoking and alcohol abuse. The protective effect of physical activity and moderate alcohol consumption was and further established as modifiable risk factors.1 Despite lot of researches in the field of stroke, accurate prognostication of an acute attack is difficult. Several prognostic factors like site of infarction, size of infarct, size of the vessel involved, Glasgow coma scale, level of cerebral edema, intracranial tension have been found significant in cerebral infarction. Similarly in cases of cerebral hemorrhage, CT calculated volume of hematoma, GCS, site of hemorrhage etc. are important. Some of the upcoming prognostic indicators are under study e.g.; hyperglycemia in stroke, infection in stroke, TNFa or interleukins etc. One of the prognostic indicators which have gained great clinical interest in recent times is the level of serum ferritin. Initially considered only as a stress response to stroke, serum ferritin now is under research as a prognostic indicator, the possible mechanisms of which are discussed under. This has also enhanced research in the therapeutic role of iron chelation in improving stroke prognosis. In most of the hospitals, nothing much can be done for stroke patients other than conservative management. Proving the therapeutic potential of iron chelation therapy will be a great advancement in the field of treatment of stroke.2,3,4,5

II. Material and Methods

A total of 50 patients of cerebrovascular accident presenting within 48hrs of symptom onset were included in the study and diagnosis of stroke was confirmed by CT scan. Neurological assessment was done by CANADIAN STROKE SCALE. Serum ferritin was performed within 48 hrs. of onset of symptoms. Neurological assessment was repeated on 6th day of admission by Canadian stroke scale. Patients were classified as clinical improvement, deterioration and death. In vitro quantitative determination of ferritin in human serum was done by electro chemiluminescence immunoassay "ECLIA" in Elecsys and cobas e immunoassay analyzer.

Study Design: Prospective cohort study
Study Location: This was a tertiary care teaching hospital based study done in Department of General Medicine, at Rajendra Institute of Medical Sciences, Ranchi
Study Duration: October 2016 to September 2017.
Sample size: 50 patients.

CANADIAN STROKE SCALE

				Date Time		
Mentation		Level of Consciousness	Alert	3		
			Drowsy	1.5		
		Orientation	Oriented	1		
			Disoriented or Nonapplicable	0		
		Speech	Normal	1		
			Expressive Aphasia	0.5		
			Receptive Aphasia	0		
Section A1	No Comprehensive Deficit	**Motor Functions:**	Weakness:			
		Face:	None	0.5		
			Present	0		
		Arm: Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Arm: Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg: Proximal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
		Leg: Distal	None	1.5		
			Mild	1		
			Significant	0.5		
			Total	0		
Section A2	Comprehensive Deficit	Face:	Symmetrical	0.5		
			Asymmetrical	0		
		Arms:	Equal	1.5		
			Unequal	0		
		Legs:	Equal	1.5		
			Unequal	0		
			Total Score			

Inclusion criteria:
1. Patient should be aged above 18 years.
2. Both sexes are included.
3. Diagnosis of CVA should be confirmed by CT scan.
4. Patient should present within 48 hrs. of onset of symptoms. Patients above 18 yrs. of age of both sexes with CT scan confirmed diagnosis of stroke presenting within 48 hrs of symptom onset.

Exclusion criteria:
1. Patient not fulfilling inclusion criteria.
2. Patients with history of recent infection or inflammation in the previous month.
3. Patient with history of malignancy.
4. Patients with anemia.

Statistical analysis

Pair wise comparison between various variable was done for different parameters. The Range, Mean value, Standard Deviation (S.D.), Standard error of Mean, 't' value and 'p' values were calculated as per the applicability by using appropriate formulas. Statistical Package of Social Sciences (SPSS) v. 22 was used for the purpose of data entry and data analysis. Chi-square test was used to find out associations (relations) between 2

categorical variables, ANOVA test was used to find out associations between multiple categorical variables. Pearson's correlation coefficient was used for numerical variables. P-value less than 0.05 was regarded as statistically significant.

III. Result

Total sample size: 50.
Males: 32.
Females: 18.
Age range: 26-85.
Followings were the findings of the present study-

Table no 1: Shows etiological distribution of patient stroke

	N	PERCENT
ISCHEMIC	23	46
HEMORRHAGIC	27	54

Table no 2: Classification of number of cases based on type and outcome

	Ischemic Stroke	Hemorrhagic stroke
No. of cases improved	16	15
No. of cases deteriorated	7	12
Total	23	27

Table no 3: Sex distribution of patients of ischemic stroke

	N	Percent
Males	14	60.86
Females	9	39.14

Table no 4: SEX DISTRIBUTION OF PATIENTS OF HEMORRHAGIC STROKE

	N	Percent
Male	18	66.66
Female	9	33.33

Table no5 : AGE DISTRIBUTION OF PATIENTS OF ISCHEMIC STROKE

Age range	N
20-30	1
31-40	1
41-50	6
51-60	7
61-70	5
71-80	2
81-90	1

Table no 6: AGE DISTRIBUTION OF PATIENTS IN HEMORRHAGIC STROKE

Age range	N
20-30	0
31-40	1
41-50	8
51-60	6
61-70	5
71-80	5
81-90	2

Table no 7: MEAN AGE OF PATIENTS AMONG DIFFERENT GROUPS

	Ischemic stroke	Hemorrhagic stroke
Mean age of patients improved	59.75 yrs	64.53 yrs
Mean age of patients deteriorated	48.14 yrs	54.58 yrs

Table no 8 : Mean serum ferritin of patients of ischemic stroke

	Mean serum ferritin
Patients improved	87.01
Patients deteriorated	458.70

Table no 9: Mean serum ferritin of patients of hemorrhagic stroke

	MEAN SERUM FERRITIN
Patients improved	96.44
Patients deteriorated	463.91

Table no 10: Descriptive statistics of serum Ferritin of patients of ischemic stroke who improved

Mean	87.013125
Median	52.44
Standard deviation	73.53128284
Range	238.2
Minimum	20.2
Maximum	258.4
Largest(1)	258.4
Smallest(1)	20.2

Table no 11 : Descriptive Statistics of Serum Ferritin of Patients of ischemic Stroke who Deteriorated

Mean	458.7014286
Median	416.16
Standard Deviation	145.4344779
Range	385
Minimum	321
Maximum	706
Largest(1)	706

Table no12 :Descriptive Statistics of Serum Ferritin of Patients of Hemorrhagic Stroke Who Improved

Mean	96.44
Median	81.97
Standard Deviation	39.44262
Range	141.87
Minimum	20.13
Maximum	162
Largest(1)	162
Smallest(1)	20.13

Table no13 : Descriptive Statistics of Serum Ferritin of Patients of Hemorrhagic Stroke who deteriorated

Mean	463.9125
Median	434.5
Standard Deviation	181.2183165
Range	604.15
Minimum	173.85
Maximum	778
Largest(1)	778

Table no 14 : t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in ischemic stroke

	improved	deteriorated
Mean	87.01313	458.701429
Observations	16	7
df	7	
t Stat	6.41268	
P(T<=t) two-tail	0.000363	
t Critical two-tail	2.364624	

INFERENCE:

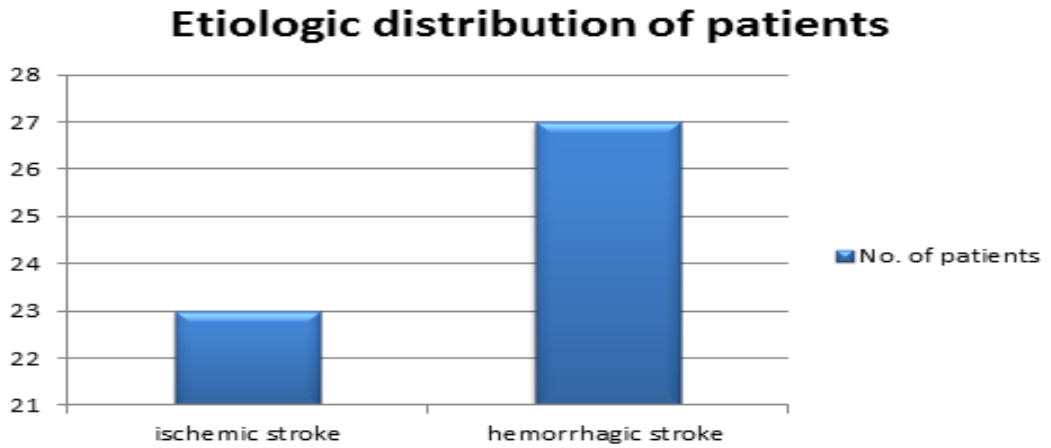
- There is statistically significant difference in means of the two groups with p<0.001.
- Mean serum ferritin in deteriorated patients is significantly higher than those who improved.

Table no 15 : t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated patients of hemorrhagic stroke.

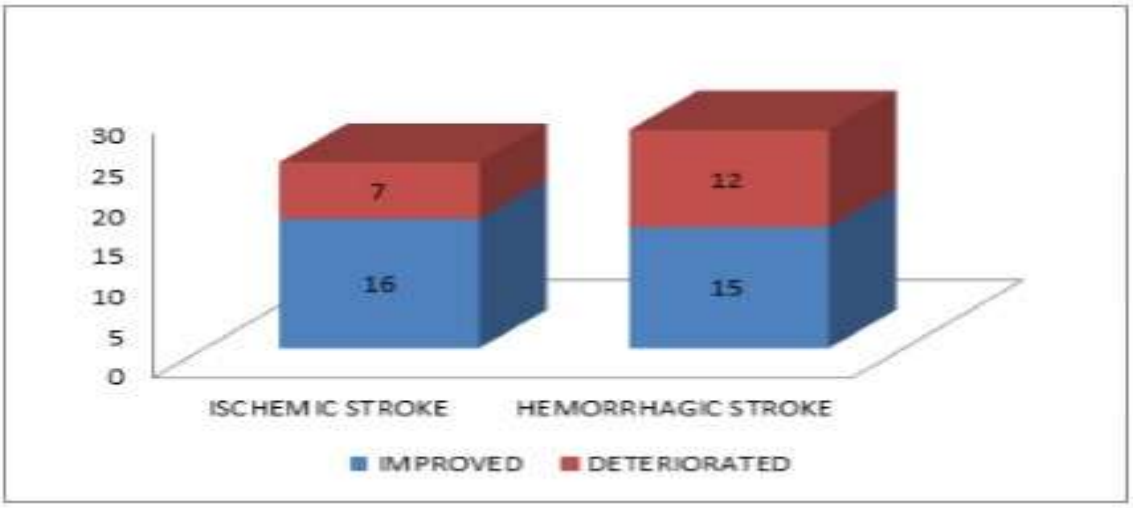
	Improved	Deteriorated
Mean	463.9125	96.44
Observations	12	15
df	12	
t Stat	6.895028	
P(T<=t) two-tail	1.66E-05	
t Critical two-tail	2.178813	

INFERENCE:

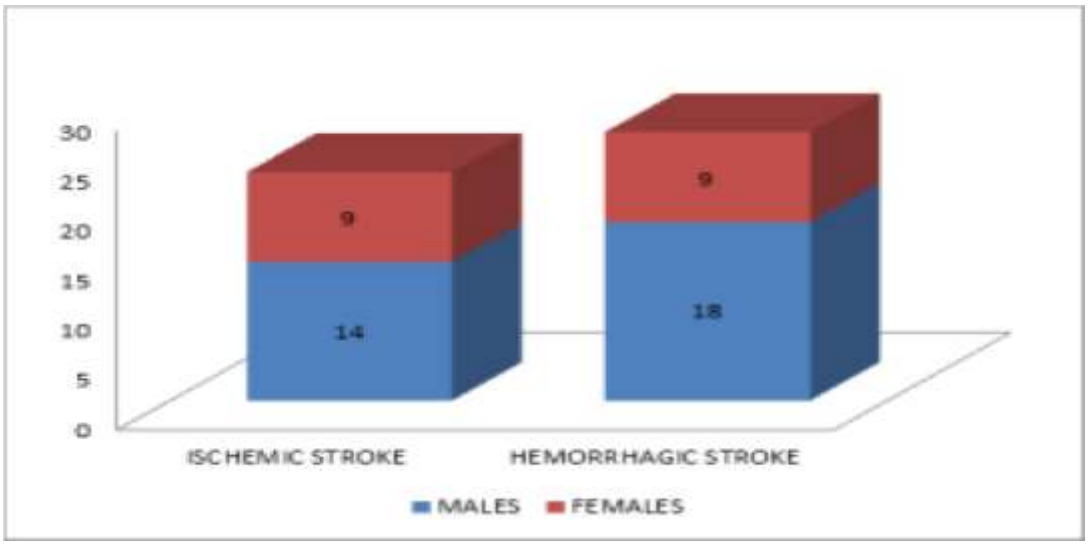
- There is highly significant difference statistically in means of the two groups with p<0.001.
- Mean serum ferritin in deteriorated patients is significantly higher than those who improved.
-



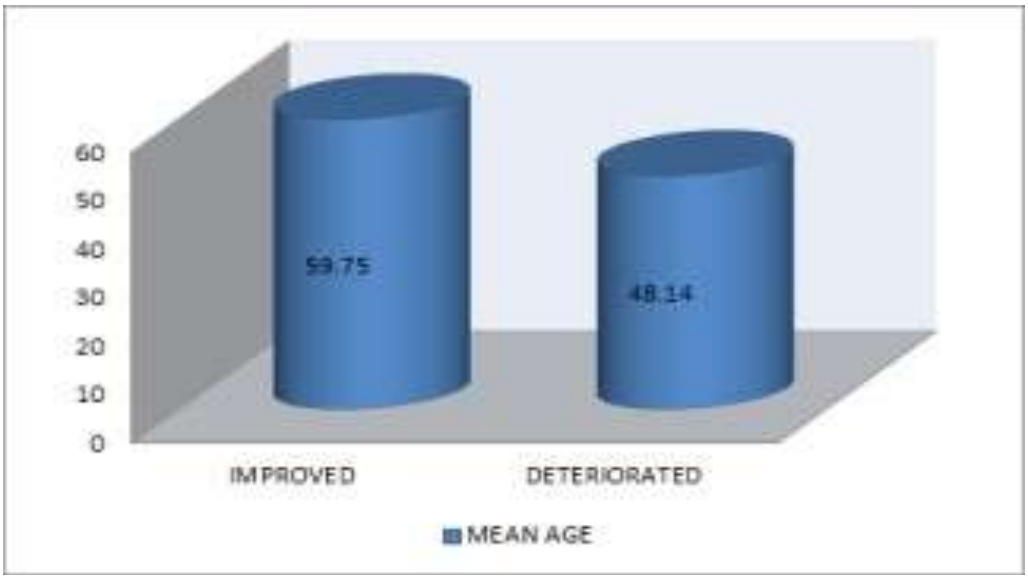
GRAPHICAL REPRESENTATION OF CLASSIFICATION OF CASES BASED ON TYPE AND OUTCOME



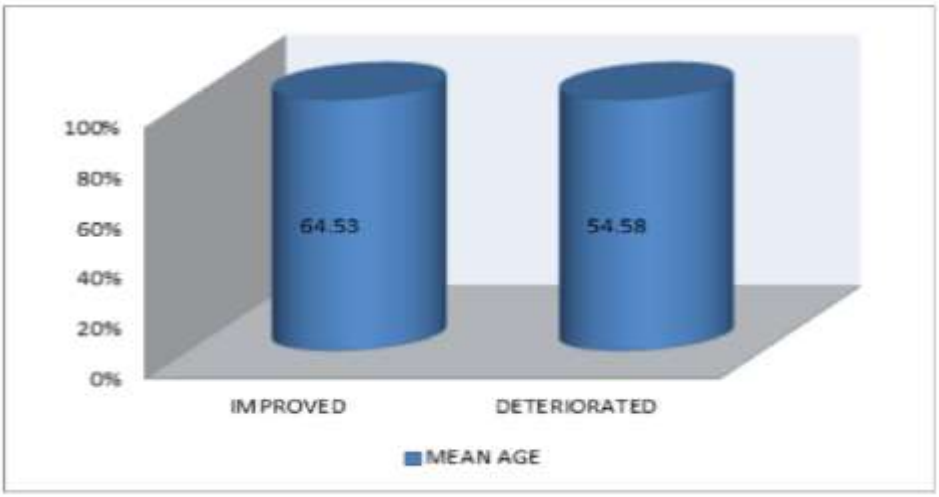
GRAPHICAL REPRESENTATION OF SEX DISTRIBUTION OF CASES



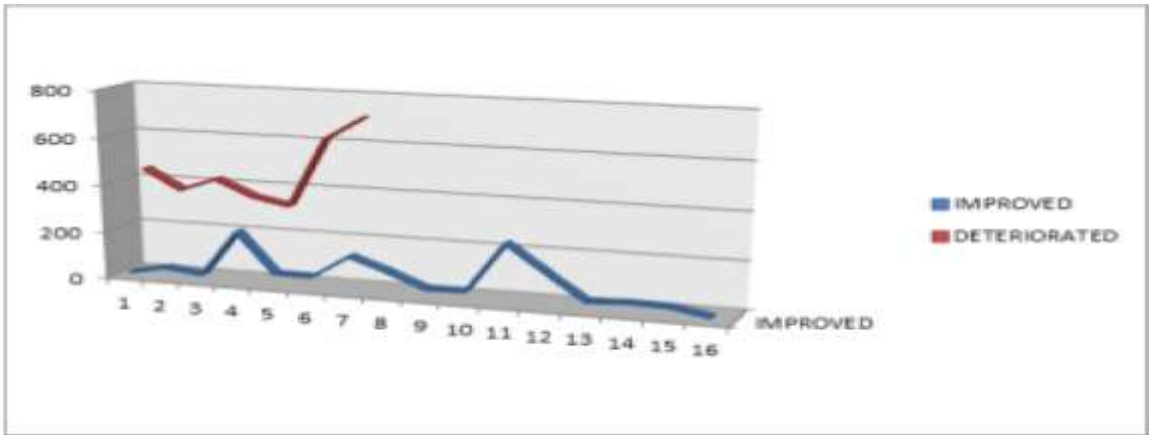
MEAN AGE OF PATIENTS OF ISCHEMIC STROKE BASED ON PROGNOSIS



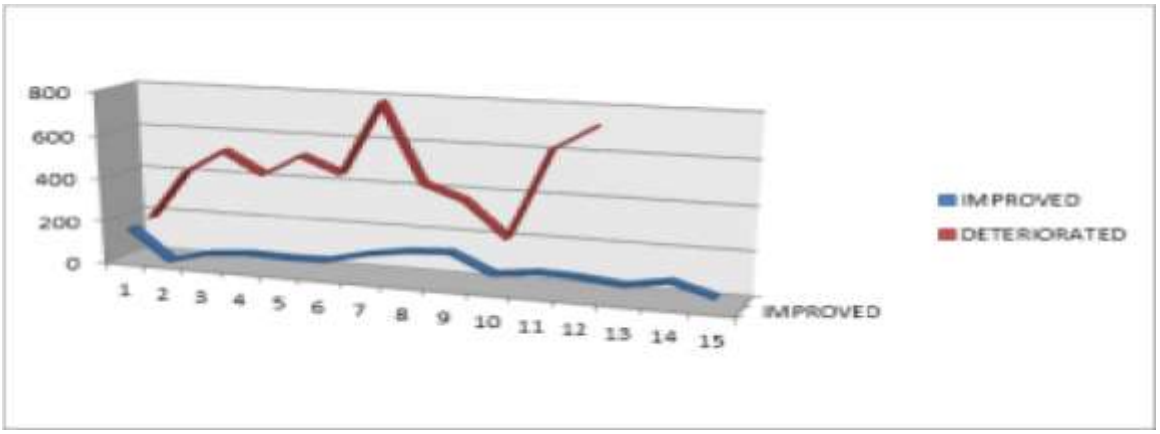
MEAN AGE OF PATIENTS OF HEMORRHAGIC STROKE BASED ON PROGNOSIS



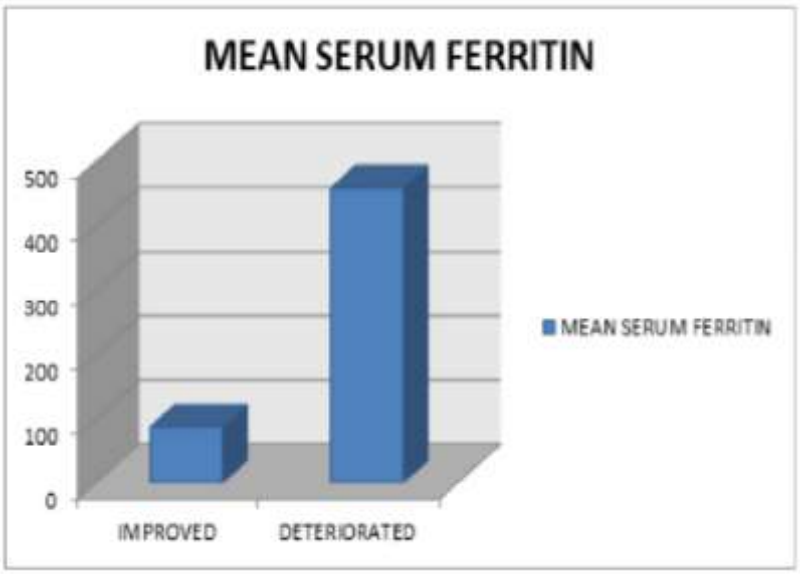
LINE DIAGRAM COMPARING SERUM FERRITIN IN PATIENTS OF ISCHEMIC STROKE BASED ON PROGNOSIS



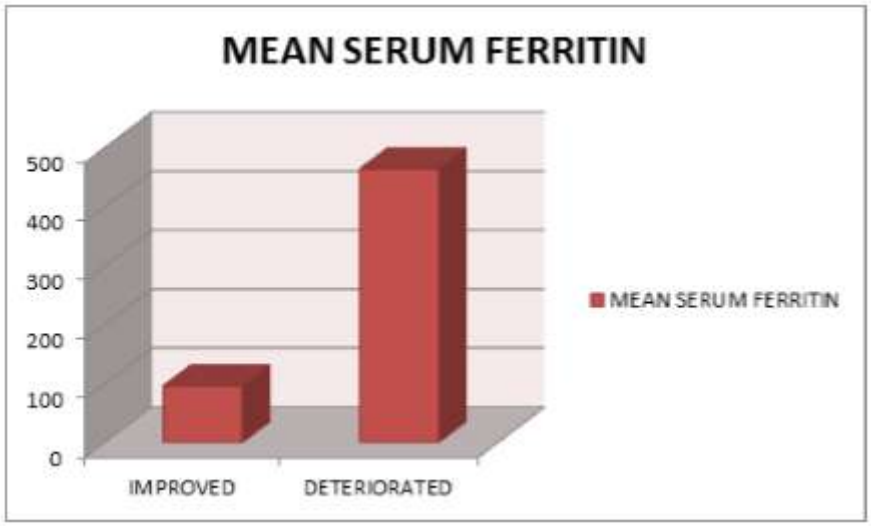
LINE DIAGRAM COMPARING SERUM FERRITN IN PATIENTS OF HEMORRHAGIC STROKE BASED ON PROGNOSIS



GRAPHICAL REPRESENTATION OF MEAN SERUM FERRITIN LEVEL OF PATIENTS OF ISCHEMIC STROKE BASED ON PROGNOSIS



GRAPHICAL REPRESENATATION OF MEAN SERUM FERRITIN LEVEL IN PATIENTS OF HEMORRHAGIC STROKE BASED ON PROGNOSIS



Results:

The total number of cases studied was 50. Out of the 50 cases studied 23 (46%) were ischemic and 27 (54%) were hemorrhagic. Among the 23 cases of ischemic stroke 14 (60.86%) were males and 9 (39.14%) were females. 16 out of 23 cases improved clinically on 6th day of assessment while 7 cases deteriorated. There was statistically insignificant difference between the mean age of the improved and deteriorated groups. Mean serum ferritin level of the group of patients improved was 85.01 and those deteriorated was 458.70. t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in ischemic stroke shows that there is statistically significant difference in means of the two groups with $p<0.001$.Mean serum ferritin in deteriorated patients is significantly higher than those who improved. Among the 27 cases of hemorrhagic stroke 18 (66.66%) were males and 9 (33.33%) were females. 15 out the 27 improved while 12 deteriorated. There was statistically insignificant difference between the mean age of the improved and deteriorated groups. Mean serum ferritin level of the group of patients improved was 96.44 and those deteriorated was 463.91. t-test assuming unequal variances to compare means of serum ferritin of improved and deteriorated groups in hemorrhagic stroke shows that there is statistically significant difference in means of the

two groups with p<0.001. Mean serum ferritin in deteriorated patients is significantly higher than those who improved.

IV. Discussion

This study shows that serum ferritin is an important independent risk factor of prognosis of stroke. High levels of serum ferritin correlate well with the early neurological deterioration of stroke patients. Therefore testing of serum ferritin can be helpful in identifying high risk patients. As seen in the observations, the mean age of the patients in the improved and deteriorated groups is almost the same. Other risk factors are evenly distributed among both the groups. But the mean serum ferritin in the improved group was significantly lower than the group which deteriorated. This holds true in both ischemic and hemorrhagic stroke. Admission levels of serum ferritin were found to be significantly higher in patients who deteriorated in next 7 days. Serum ferritin is a suitable index of the amount of cellular iron stores and, consequently, might be related to the availability of iron in the infarcted area.6,7 In brain tissue, most of the non heme iron is in the form of ferritin, which is localized in astrocytes and microglia.8Ferritin synthesis in brain cells may be induced in hypoxic acidosis9 or in response to oxidative stress to reduce the accumulation of reactive oxygen species .10Therefore, increased ferritin could be in part the result of a neuro protective mechanism with the aim of sequestering toxic-free iron in the ischemic brain. During cerebral ischemia, free iron released from intracellular stores such as ferritin catalyzes the conversion of superoxide and hydrogen peroxide into the highly reactive toxic hydroxyl radical.11,12 Experimental data support a causal role of iron overload in ischemic brain and endothelial damage. Iron intake has been associated with larger infarct volumes, higher oxidative stress, glutamate release, and inflammatory response after permanent middle cerebral artery occlusion in the rat,13 whereas iron depletion or chelation reduces infarct size, brain edema, and metabolic failure in ischemia/reperfusion experimental stroke models.14,15 In patients with acute ischemic stroke not treated with thrombolytic drugs, high serum ferritin values and high cerebrospinal fluid ferritin concentrations determined early after symptom onset have been associated with subsequent neurologic worsening, poor neurologic outcome, large infarct volume, and elevated concentrations of glutamate in blood.16,18 Serum ferritin levels are thought to be directly proportional to cellular iron stores and can be used to assess iron overload in the absence of inflammation, cancer, and infectious diseases.19,20 As early as 1981, Sullivan proposed the "iron hypothesis,"21 suggesting that the lower incidence rates of ischemic heart disease in premenopausal women compared with men and the increase of ischemic heart disease rates in postmenopausal women were results of the rise in iron stores after cessation of menses, with oxidative imbalance as the central biologic mechanism. In the Fenton reaction, Fe (II) catalyzes the formation of extremely reactive hydroxyl radicals. Interaction with lipids may initiate the formation of oxidized LDL that ultimately leads to the development of foam cells and progression of atherosclerosis.22 additionally, iron could also play a role in vascular disease by activating platelets via a protein kinase C mechanism.23 Although its initial focus was on ischemic heart disease, the hypothesis may also apply to cerebrovascular disease. Another proposed mechanism by which iron may play a role in ischemic vascular disease, which might be more relevant to stroke risk, is through ischemia/reperfusion injury. During reperfusion after cerebral infarction, there is a marked increase in oxygen-radical production as well as a releaseof iron ions, leading to progressive tissue damage and cellular death.24 Because of its specific areas rich in iron, high amounts of polyunsaturated fatty acid side chains in membrane lipids, and low concentrations of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, the brain may be especially vulnerable to oxidative stress. So far, only a few articles have reported on the association between iron and the risk of stroke in population-based studies.

Taken together, these findings suggest that iron overload is associated with following; a. Poor early neurological outcome in stroke patients. b. Iron overload may offset the beneficial effect of thrombolytic therapy. c. Iron chelation therapy may be beneficial in acute stroke if serum ferritin is high.

Studies done previously in this field showed similar results. Milan et al, Stroke 2007; 38;9095, Nov 2006 showed that increased body iron stores was associated with poor outcome in patients of ischemic stroke after thrombolytic therapy. Mehdirratta M, Kumar S, Hackney D, Schlaud G, Selim M, Stroke 2008;39;1165-1170,2008 showed positive association between serum ferritin level and perihematoma edema volume in patients of spontaneous intracerebral hemorrhage. Millerot- Serrerot et al, neurochemistry international Journal, reported similar results in ischemic stroke. In summary, patients with stroke with increased serum ferritin

concentrations have a higher risk of poor clinical outcome, hemorrhagic transformation, and brain edema than patients with low ferritin values. These findings suggest that iron overload may counterbalance the benefits of thrombolytic therapy observed in patients with low ferritin levels. If these results are confirmed in future studies, iron chelators or free radical trapping agents should be used to reduce the neurotoxic effects of iron in patients with acute ischemic stroke and those who are treated with thrombolytic therapy.

V. Conclusion

A number of evidence has suggested that elevated serum ferritin (A marker of increased body iron stores) is a definite prognostic marker of acute stroke. An elevated serum ferritin herald more intensive management protocols and care for the patient as it can predict early neurological deterioration. Secondly, it can help in decision making regarding thrombolytic therapy. Patients can be classified as those who will be benefited or not from the thrombolytic therapy. Those with elevated serum ferritin will have more chances of deterioration in post-thrombolysis period. Thirdly, iron chelation therapy can actually improve the prognosis of stroke. Many studies are on to prove actual therapeutic efficacy of iron chelation therapy (Desferrioxamine and defepirome) in acute stroke. But this study at least shows its theoretical possibility. Strict thrombolysis protocols, late presentation of patients after the crucial period of first three hours when thrombolysis can be performed and delay in radiological diagnosis due to lack of facilities does not leave much for the clinician to do in these cases except for conservative management. iron chelation therapy, if proved to be beneficial in future can take us a big leap forward in the management of acute stroke.

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