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Original Research Article

A Study of Association of Serum Ferritin and Acid Base Status in Outcome of Acute Stroke Patients: A Prospective Observational Cohort Study

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Abstract

Aim: To study the effect of level of serum ferritin and acid base status with early neurological deterioration and the outcome in patients of acute stroke.

Materials and Methods: This prospective observational study was conducted on the patients of acute stroke diagnosed clinically, neurologically and radiologically and admitted in the emergency department of Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga. The study was conducted from June 2019 to June 2020. The work was started after getting the ethical approval from college ethics committee. A group of 200 patients of acute stroke with 108 patients of acute hemorrhagic stroke and 92 patients of ischemic stroke participated in the study. Serum ferritin values along with Acid-Base status were noted within 48hours of onset of symptoms considered Day 1 and subsequently on Day 6 to evaluate the outcomes. Glasgow Coma scale was used to assess the stroke severity along with CANADIAN STROKE SCALE, NIHSS (National Institute of Health Stroke Scale) in neurological assessment and further follow up of patients.

Results: Majority of the population in both groups belong to age group between 60 – 69 years with the mean age of hemorrhagic stroke 64.814 (SD 10.0793) and ischemic stroke 64.010 (SD 8.7699). Majority of the population in both groups belongs to male sex predominantly constituting 63.5% of total study population whereas 36.5% are female sex study population. Majority of hemorrhagic stroke population group have ganglio capsular hemorrhage. In ischemic stroke population the major type observed was LTPI- Left temporo parietal infarct.

Conclusion: Elevated serum ferritin is strongly associated with early neurological deterioration in patients of stroke. Iron chelation therapy in acute stroke seems to be a strong theoretical possibility. Further studies and trials are required in this field to change the scenario of stroke patients.

Keywords: serum Ferritin, neurological deterioration, acid base ,ischemic stroke, hemorrhagic stroke.

Introduction

Stroke or cerebrovascular accident (CVA) is defined as an abrupt-onset neurological deficit attributable to a focal vascular cause. [1] It is the second leading cause of death and the third leading cause of disability. [2] As per WHO, stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". [3] Radiological signs such as size, site, and extent of the infarct, surrounding edema, Glasgow coma scale score (GCS), and intracranial tension are some of the early prognostic indicators of ICH. [4] Past research has already shown that iron plays a very important role in neurotoxicity and edema formation after stroke. The possible role of serum ferritin in predicting iron-mediated free radical injury in the pathogenesis of cerebrovascular diseases is portrayed in many studies. According to Van der et al elevated serum ferritin levels were associated with higher risks of ischemic stroke. [5]

In cerebrovascular disease the oxygen free radicals increase the volume of iron in the cytosol during oxidative stress by enabling the release of iron from ferritin. Ferrous iron mediated free radical mechanisms assumed to play a major role in acute stroke. Ferritin is also considered as an acute phase reactant. Therefore, elevation of acute phase reactant indicate inflammatory burden and it gets elevated in vascular events. Although several studies were done it is very difficult to assess the prognosis of stroke. Several indicators like site of infarction, size of infarct, vessel involved, Glasgow coma scale (GCS) and oedema around the infarct to assess the severity and prognosis of ischemic stroke and in haemorrhagic stroke it includes Glasgow coma scale, and volume of haemorrhage based on CT scan and location of haemorrhage. [6]

For a Long time, serum ferritin was measured only to know the stored Iron status. Now it has been recommended that it influences the prognosis of ischemic stroke and also acts as a risk factor for ischemic episodes by enhancing atherogenesis. [7-8]

Thus, we aim to study the effect of level of serum ferritin with early neurological deterioration and the outcome in patients of acute stroke.

Materials and Methods

This prospective observational study was conducted on the patients of acute stroke diagnosed clinically, neurologically and radiologically and admitted in the emergency department of Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga. The study was conducted from June 2019 to June 2020. The work was started after getting the ethical approval from college ethics committee. A group of 200 patients of acute stroke with 108 patients of acute hemorrhagic stroke and 92 patients of ischemic stroke participated in the study.

Inclusion criteria

1. Patients should be aged above 18 years.
2. Both sexes are included.
3. Diagnosis of CVA confirmed by CT scan.
4. Patients present within 48 hrs of onset of symptoms

Exclusion criteria

1. Patient not fulfilling inclusion criteria.
2. Patients with a history of recent infection, inflammation, Anemia (Hb < 10g/dl), any former disability and neurological deficit from previous stroke, liver disorder, Hematological malignancy, brain tumor, solid tumor, heart diseases, lung diseases,

connective tissue disorders, TIA or with history of any surgery or trauma have been excluded from the study.

200 patients of acute stroke including 108 patients of acute hemorrhagic stroke and 92 patients of acute ischemic stroke included in the study. Patients of stroke presenting within 48 hours of the onset of symptoms were included in the study. As soon as the patients got admitted consent was obtained from either patient or attenders. Then complete relevant medical history, neurological examination and assessment, routine blood investigations and CT scan was done along with blood for serum ferritin and ABG estimation were taken and all the data were recorded in standardized format. History of hypertension, diabetes, smoking, alcohol and drug history were noted. Clinical evaluation was carried out noting vital parameters, Clinical signs of focal neurological deficit and signs of increased intracranial tension.

Serum ferritin values along with Acid-Base status were noted within 48hours of onset of symptoms considered Day 1and subsequently on Day 6 to evaluate the outcomes. Glasgow Coma scale was used to assess the stroke severity along with CANADIAN STROKE SCALE, NIHSS (National Institute of Health Stroke Scale) in neurological assessment and further follow up of patients.

Radiological Evaluation

All the patients were subjected to Non-contrast computed tomography (NCCT) brain after clinical and neurological evaluation.

Serum Ferritin Estimation:

After getting informed consent from all the patients, 2ml of the venous blood collected by sterile venipuncture with in 48hr of symptoms onset. Allow the samples to clot adequately before centrifugation, after that estimation of serum ferritin level using quantitative ELISA ferritin test using ADVIA centaur XP and ADIVA Centaur XPT system was used.

Principal of the procedure:

ADVIA centaur Ferritin assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses a constant amount of two anti-ferritin antibodies. The first antibody, in the lite's Reagent, is a polyclonal goat anti-ferritin antibody labeled with acridinium ester. The second antibody, in the solid phase, is a monoclonal mouse anti-ferritin antibody, which is covalently coupled to paramagnetic particles. The reagents are stored at 2-8 degree Celsius.

The system automatically performs the following steps:

- Dispenses 25μl of sample into a cuvette.
- Dispenses 100μl of lite's reagent and 450μl of solid phase and incubates for 7.5 minutes at 37 degrees Celsius.
- Separates, aspirates and washes the cuvettes with reagent water.
- Dispenses 300μl each of Acid reagent and Base reagent to initiate the chemiluminescent reaction.
- Report results according to the selected option, as described in the system operating instruction.

Arterial Blood Gas Analysis:

After getting informed consent from all the patients and taking aseptic measures 2ml of arterial blood was collected using 2ml of sterile heparinized syringe within 48hrs of symptoms onset. Sample is collected preferably from radial artery and transported to the ABG machine (SIEMENS RAPIDLAB 348EX-system) as early as possible to analyse the blood acid- base balance in stroke patients.

Statistical Methods:

The statistical software SPSS version 20 has been used for the analysis. Categorical variables were expressed as number of patients and percentage of patients across

the group using Pearson's chi-square test for independence of attributes/Fisher's t-test as appropriate. Continuous variables were expressed as mean, median and standard deviation are compared across the groups using unpaired test. Scatter plot to show the correlation. An alpha level of 5% had been taken i.e., if any p-value is less than 0.05 had been considered as significant.

Results

Table 1: Age and gender distribution of study population

		GROUP				Total	%
		H. Stroke	%	I stroke	%		
AGE	40-49	6	5.5	10	10.9	16	8.0
	50-59	27	25.0	16	17.4	43	21.5
	60-69	38	35.2	39	42.4	77	38.5
	70-79	25	23.1	26	28.3	51	25.5
	80-89	12	11.2	1	1.0	13	6.5
Gender	Female	37	34.3	36	39.1	73	36.5
	Male	71	65.7	56	60.9	127	63.5
Total		108	100.0	92	100.0	200	100.0

Majority of the population in both groups belong to age group between 60 – 69 years with the mean age of hemorrhagic stroke 64.814 (SD 10.0793) and ischemic stroke 64.010 (SD 8.7699). Majority of the population in both groups belongs to male sex predominantly constituting 63.5% of total study population whereas 36.5% are female sex study population.

Table 2: Distribution of different NCCT brain findings in hemorrhagic and ischemic stroke groups of study population

NCCT brain finding in H stroke	Frequency	Percent
R. Thal. H- Right thalamic hemorrhage	9	8.39
R. Thal.H +IVH Right thalamic hemorrhage with interventricular hemorrhage	1	0.9
LGCH- left ganglio capsular hemorrhage	28	25.9
RTPH + IVH- Right temporo parital hemorrhage with interventicular hemorrhage	5	4.6
RGCH – Right ganglio capsular hemorrhage	30	27.8
RGCH+IVH – Right ganglio capsular hemorrhage with interventricular hemorrhage	6	5.6
LTPH + IVH- left temporo parietal hemorrhage with interventricular hemorrhage.	2	1.9
LTPH- left temporo parietal hemorrhage	11	10.2
R.PAR.H- right parietal hemorrhage	1	.9
L.THAL. H- left thalamic hemorrhage	3	2.8
LGCH+IVH- left ganglio capsular hemorrhage	6	5.6
RTPH- right temporo parietal hemorrhage	6	5.6
Total	108	100.0
NCCT brain finding in I Stroke		
LGCI- left ganglio capsular infarct	17	18.5
RGCI- Right ganglio capsular infarct	10	10.9
RFPI- Right fronto parietal lobe infarct	6	6.5
LFPI- Left fronto parietal lobe infarct	6	6.5
LMCAI- Left middle cerebral artery infarct	5	5.4

RMCAI- Right middle cerebral artery infarct	2	2.2
LTPI- Left temporo parietal infarct	18	19.6
RTPI- Right temporo parietal infarct	10	10.9
RFI- Right frontal lobe infarct	9	9.8
LFI- left frontal lobe infarct	3	3.3
RFTI- Right fronto temporal infarct	2	2.2
LFTI- left fronto temporal infarct	1	1.1
RACAI- Right anterior cerebral artery infarct	2	2.2
LACAI- left anterior cerebral artery infarct	1	1.1
Total	92	100.0

Majority of hemorrhagic stroke population group have ganglio capsular hemorrhage. In ischemic stroke population the major type observed was LTPI- Left temporo parietal infarct

Table 3: Distribution of day 1 & 6 ABG findings in hemorrhagic and ischemic stroke population

Arterial Blood Gas At day 1		GROUP				Total	
		H. Stroke	%	I stroke	%		**%**
	MAC	24	22.2	0	0.0	24	12.0
	MAL	11	10.2	7	7.6	18	9.0
	NA	0	0.0	6	6.5	6	3.0
	RAC+MAL	0	0.0	1	1.1	1	0.5
	RAL	72	66.7	69	75.0	143	70.5
	RAL+MAC	1	0.9	9	9.8	10	5.0
Total		108	100.0	92	100.0	200	100.0
Arterial Blood Gas At Day 6							
	MAC	24	22.2	0	0.0	24	12.0
	MAL	11	10.2	7	7.6	18	9.0
	NA	0	0.0	6	6.5	6	3.0
	RAC+MAL	0	0.0	1	1.1	1	0.5
	RAL	73	67.6	70	76.1	143	71.5
RAL+MAC		0	0.0	8	8.7	8	4.0
Total		108	100.0	92	100.0	200	100.0

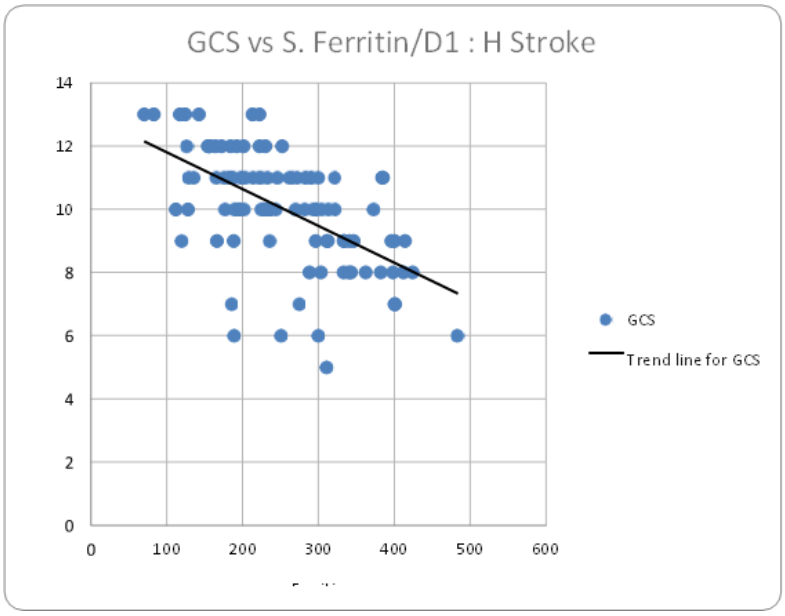

Figure 1: Pearson correlation and scatter plot analysis in hemorrhagic stroke patients: serum ferritin vs. GCS.

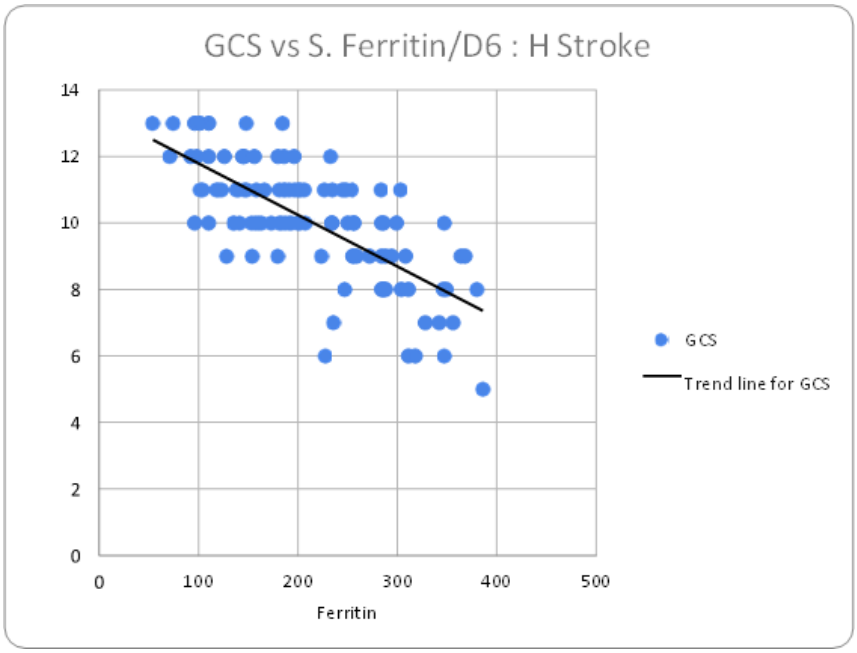

Figure 2: Pearson correlation and scatter plot analysis in hemorrhagic stroke patients: serum ferritin 6 vs. GCS.

Discussion

This study was conducted on 200 patients of acute stroke with 108 patients of acute hemorrhagic stroke and 92 patients of acute ischemic stroke. Among them 127 male patients (63.5%) and 73 female patients (36.5%) this incident data was supported Thomas kuruvill et al [9].

Majority of population in both hemorrhagic and ischemic stroke belongs to age group of 60 - 69 years with mean age for hemorrhagic population is 64.814 and ischemic stroke population is 64.01.

In our study majority of population belongs to normal BMI range constituting 59% of total study population with 38.5%

in overweight (preobese) category and less than 2.5% lies in underweight category.

Hypertension is most common risk factor present in 90% of total study population. Diabetes mellitus is present in 41.5%, smoking in 28.5%, alcoholic constitute 23.5% along with high cholesterol found in 23.5% of total study population. Most of the population has more than one risk factor associated. In our study majority of population in hemorrhagic stroke have gangliocapsular hemorrhage and temperoparietal region infraction in ischemic stroke.

ABG analysis in study population shows that simple respiratory alkalosis is seen in 70.5% of total study population. Metabolic acidosis in 12%, metabolic alkalosis in 9%, respiratory alkalosis with associated metabolic acidosis seen in 5%, no any acid base change in 3% and respiratory acidosis with associated metabolic alkalosis in 0.5% of total study population. Thus respiratory alkalosis is major acid base change seen in acute stroke patients.

Out of 200 acute stroke patients 44 patients died in study including 25 patient of ischemic stroke and 19 patient of hemorrhagic stroke. Among total of 44 patients died during the study respiratory alkalosis is seen in 28 patients (63.63%) with 13 patients of hemorrhagic stroke and 15 patients of ischemic stroke. Metabolic alkalosis in 6 patients (13.63%), respiratory alkalosis with associated metabolic acidosis in 5 patients (11.36%), metabolic acidosis in 4 patients (9.09%), respiratory acidosis associated with metabolic alkalosis in 1 patient (2.27%) of total died patients. Mortality is higher in stroke patient with respiratory alkalosis predominantly and then with metabolic alkalosis. Study by sur and shah found that patients with respiratory and metabolic alkalosis had a poor outcome about 44% mortality. [10]

Alkalemia (pH > 7.45) having respiratory and metabolic alkalosis is frequently encountered acid base change in our study on Acute Stroke Patients.

Among 108 Hemorrhagic stroke patients respiratory alkalosis (RAL) seen in 73 patients, Metabolic alkalosis (MAL) in 11 patients, Metabolic acidosis (MAC) in 24 patients. Out of 73 patients having respiratory alkalosis death occurred in 13 patients (17.8%) having pH more than 7.66, deterioration in 56 patients (76.9%) having pH between 7.56 – 7.65 and improvement in 4 patients (5.3%) having pH between 7.45-7.55. Metabolic alkalosis seen in 11 patients in which death occurred in 2 patients (18.2 %) having pH more than 7.66, deterioration in 7 patients (63.7%) having pH between 7.56-7.65 and improvement in 2 patients (18.2%) having pH between 7.45 – 7.55. Metabolic acidosis seen in 24 patients in which death occurred in 4 patients (16.7%) having pH between 7.20-7.25, deterioration in 19 patients (79.2%) having pH between 7.26 – 7.30 and improvement in 1 patients (4.1%) having pH 7.34.

Among 92 patients of ischemic stroke majority of the patients have alkalosis on ABG. Respiratory alkalosis (RAL) in 70 patients, Metabolic alkalosis (MAL) in 7 patients, mixed disorder having respiratory alkalosis with metabolic acidosis (RAL + MAC) in 8 patients, respiratory acidosis with metabolic alkalosis (RAC + MAL) in 1 patients, No acid base disorder in 6 patients. Out of 70 patients with respiratory alkalosis death occurred in 15 patients (21.4%) having pH more than 7.66, deterioration in 55 patients (78.6%) has pH between 7.56-7.65. Metabolic alkalosis seen in 7 patients in whom death occurred in 4 patients (57.1%) has pH more than 7.66, deterioration in 3 patients (42.9%) having pH between 7.56-7.65.

Respiratory alkalosis with metabolic acidosis seen in 8 patients in which death occurred in 5 patients (62.5%) having pH more than 7.56 – 7.65, deterioration in 3 patients (37.5%) having pH between 7.45 – 7.55. Respiratory acidosis with

metabolic alkalosis seen in 1 patients which later on died. No acid base disorder in 6 patients of ischemic stroke group among which 3 patients (50%) Deteriorated having pH between 7.35-7.39 and 3 patients (50%) got improved. Thus extreme of alkalemia and acedmia are having poor prognosis. Mortality is higher in pH value above 7.66 that is extreme of alkalosis with majority of patients in both hemorrhagic and ischemic stroke got deteriorated clinically or neurologically by day 6 having pH range between 7.56 to 7.65. Study conducted by Lee E. Anderson and William L. Henrich on alkalemia associated morbidity and mortality in medical and surgical patients show there was an inverse correlation between the pH value and the prognosis that is higher the pH poorer the prognosis. In their study overall mortality was 27.9% and increased as pH value rose, reaching 48.5 % when pH was more than 7.60102. Alkalemia is seen in majority of patients in both hemorrhagic and ischemic stroke and worsening of alkalemia that is increase in pH value is associated with poor outcome. [11]

Correlation between mean serum ferritin of day 1 and 6 with smoking in ischemic stroke group is non-significant. Correlation between mean serum ferritin of day 1 and 6 with smoking in hemorrhagic stroke group is significant. Correlation between mean serum ferritin of day 1 and 6 with alcohol in both hemorrhagic and ischemic stroke group is significant. Correlation between mean serum ferritin of day 1 and 6 with cholesterol in ischemic stroke group is non- significant. Correlation between mean serum ferritin of day 1 and 6 with cholesterol in hemorrhagic stroke group is significant. In our study the mortality seen in 44 patients with 19 patients of hemorrhagic stroke and 25 patients of ischemic stroke having low GCS value less than 8. 146 patients deteriorated with 82 patients in hemorrhagic stroke and 64 patients in ischemic stroke with GCS between 9-12. 10 patients is improved with 7 patient in hemorrhagic stroke and 3 patient in ischemic stroke having high GCS value 13-15. The mean age of deteriorated and improved patients in both study population is almost similar. The mean of day 1 and day 6 serum ferritin is significantly elevated in death and deteriorated patient in both the study population. The mean serum ferritin in worst prognostic group with GCS (3-8) in ischemic stroke at day 1 352.03 ng/ml (SD 95.152) and day 6 347.34 ng/ml (SD 83.5477) and in hemorrhagic stroke at day 1 335.45ng/ml (SD 78.959) and at day 6 312.00ng/ml (SD 45.50) The mean serum ferritin in bad prognostic group who were deteriorated with GCS (9-12) in ischemic stroke at day 1 214.294 ng/ml (SD 68.795) and day 6 179.987 ng/ml (SD 67.993) and in hemorrhagic stroke at day 1 231.934ng/ml (SD 72.041) and at day 6 197.5ng/ml (SD 66.283). The mean serum ferritin in good prognostic group who were deteriorated with GCS (13-15) in ischemic stroke at day 1 85.706 ng/ml (SD 15.598) and day 6 61.8 ng/ml (SD 22.137) and in hemorrhagic stroke at day 1 138.714ng/ml (SD 59.128) and at day 6 109.642ng/ml (SD 43.995). The mean serum ferritin in improved group was significantly lower than the group which is deteriorated. This holds true in ischemic and hemorrhagic stroke. The difference is significant statistically ($P < 0.05$). The admission level of serum ferritin found to be significantly to be higher in patients who were deteriorated in next 7-8 days. Hence the serum ferritin level at the base line can be used as a prognostic marker in acute stroke. This is similar to the result obtain by natalie et al in his study the mean serum ferritin value was 270.6 ng/ml in bad prognostic group. [12,13] In our study change in serum ferritin value was correlated in GCS there is negative pearson correlation with GCS and serum ferritin in both study of population of stroke. Thus 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. 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. [14,15] In brain tissue, most of the nonheme iron is in the form of ferritin, which is localized in astrocytes and microglia [16]. Ferritin synthesis in brain cells may be induced in hypoxic acidosis [17] or in response to oxidative stress to reduce the accumulation of reactive oxygen species. [18] Therefore, increased ferritin could be in part the result of a neuroprotective mechanism with the aim of sequestering toxic-free iron in the ischemic brain. At the same time an important source of reactive oxygen species is linked to disturbances in brain iron homeostasis. [19] 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. 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, whereas iron depletion or chelation reduces infarct size, brain edema, and metabolic failure in ischemia/reperfusion experimental stroke models. 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. 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.

Conclusion

Most of the patients of acute hemorrhagic and ischemic stroke have respiratory alkalosis as dominant acid base changes in this study and when severe,portend a poor prognosis.

Overall mortality is highest in both ischemic and hemorrhagic stroke patients having respiratory alkalosis as dominant change in acid base status when pH is more than 7.6.

Mixed acid base disorder carries higher mortality than single acid base disorders.

Presence of low GCS and high serum ferritin associated with poor outcome and similarly high GCS and low serum ferritin associated with good outcome.

Thus the present study concluded that elevated serum ferritin is strongly associated with early neurological deterioration in patients of stroke. Iron chelation therapy in acute stroke seems to be a strong theoretical possibility. Further studies and trials are required in this field to change the scenario of stroke patients.

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