Original Article

Association between Serum Ferritin Concentration and Perihaematoma Oedema Volume in Patients with Supratentorial Spontaneous Intracerebral Haemorrhage

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Abstract:

Background: *Stroke (ischaemic & haemorrhagic) is a major cause of mortality and morbidity in the developed as well as in the developing countries. Perihaematoma oedema and haematoma expansion are two important points to be considered when deciding outcome of patients with ICH. Brain damage due to haematoma may be irreversible but the injury from perihaematoma oedema may be reversible. It has been seen that S. ferritin is the most reliable indicator of body iron. Treatment with iron chelators may give better outcome after ICH.*

Objective: *This study was under taken to assess the association between serum ferritin and relative perihaematoma oedema volume.*

Methodology: *This study was a cross sectional observational study that was conducted in the Departments of Neurosurgery & Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Dhaka Medical College Hospital (DMCH) from 1st March, 2014 till 30th September, 2015 on 32 patients (32) who fulfilled the selection criteria were enrolled in this study.*

Results: *In this study, male female ratio was 1:1 and the mean age was 56±15 years. Most of the ICH patients fell in the age group between 41-60 years (53%). During admission, grade-1 (GCS 3-8) level of consciousness was reported among 45% of patients. All the patients in this study presented with motor deficit that include hemiplegia 20 (62.5%) and hemiparesis 12 (37.5%). Mean value of serum ferritin was found elevated on day 4 (344±406 µg/L) in comparison to day 1 (213.4±123.5µg/L). Mean value of relative perihaematoma oedema was elevated on day 4 (4±2.7) than day 1 (1.9±1) but it was not statistically significant.*

Conclusion: *In this study after statistical analysis by Pearson's correlation test we found that there was no significant association between serum ferritin concentration and relative perihaematoma oedema on day-1 and day-4.*

Key words: *Serum ferritin concentration and relative perihaematoma oedema*

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Introduction:

Stroke is a major cause of mortality and morbidity in the developed as well as the developing countries and ranks third after coronary heart diseases and all types of cancer among the causes of death.[3,16,18,24,32] It has a prevalence of 0.3% in Bangladesh.[16,18]

Stroke is of two types, Ischaemic and Haemorrhagic stroke. Not much data about their incidence is available in Bangladesh. However, one study suggests ischaemic stroke has an incidence of 61% and that of haemorrhagic stroke is 39% of all strokes.[16]

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Hypertension is the most common risk factor, overall, in hospital based studies. The other risk factors that follow are cigarette smoking, Diabetes Mellitus, use of oral contraceptive pills and previous history of transient ischaemic attack or cerebrovascular disease.[16,18,32]

The most common areas of the brain affected are the cortical region, basal ganglia, internal capsule, insula, thalamus, cerebellum and multifocal areas. Data shows ischaemic stroke patients have higher chances of recovery (68%) as compared to haemorrhagic stroke patients (32%).[18]

In this study, we dealt with intracerebral haemorrhage leading to perihaematoma oedema and its association with serum ferritin.

Most commonly, patient having haemorrhagic stroke may present with hemiplegia/hemiparesis (85%), impaired consciousness (80%), vomiting (75%), and headache (60%). They may also present with dysarthria, motor or sensory dysphasia and nystagmus.[32]

Perihaematoma oedema and haematoma expansions are two important predictors of poor prognosis in patients with ICH.[24]

There are several mechanisms contributing to the development of brain oedema after ICH. In the first few hours there is development of hydrostatic pressure associated with growth in haematoma leading to vasogenicoedema. Clot retraction also occurs. During the first 24 hours there is thrombin formation and activation of coagulation cascade. Lastly, haemolysis of RBC occurs due to the development of Membrane Attack Complex (MAC) following complement cascade activation and haemoglobin mediated toxicity occurs.[24,37,41]

In humans, perihaematoma oedema increases rapidly in the first 48 to 72 hours after ICH and thereafter continues to increase at a slower rate for 1 to 2 weeks and then starts to decrease.[37] It has been established that haematoma induced brain damage is irreversible, however, the injury arising from perihaematoma oedema may be reversible.[37]

Animal Studies showed that brain oedema peaks on the 3rd and 4th day after ICH and neurotoxicity of haemoglobin is Iron mediated.[24] Free iron released from RBC lysis and from ferritin stores may have a role in oxidative stress, glutamate release and inflammatory response after haemorrhagic brain injury.[29,38] Iron is essential for normal brain function but iron overloading may have devastating effects. After lysis of RBCs, iron concentration in the brain can reach very high levels and contribute to brain oedema formation.[38] Whether the extent of iron mediated toxicity can be prevented by the export of iron from the brain or not, is still in experimental stages.[38] It has been seen, high serum ferritin levels measured within 12 hours from symptoms onset predict poor outcome in patients with ICH.[29,38]

Serum ferritin has been chosen as an indicator of body iron load because other measurements such as serum iron concentration, total Iron Binding Capacity and Transferrin saturation have considerable analytic and day to day variability compared to that of ferritin.[24]There is also evidence against increase in ferritin levels in reaction to stress response in patients with ischaemic stroke where Serum ferritin remains stable 48 to 72 hours after stroke and are unrelated to other biochemical markers of stress reaction.[24,29] Clinical evidence suggests that treatment with iron chelators like desferrioxamine may reduce brain oedema, improve neurological function, decrease neurological damage, disability and provide neuroprotection after experimental ICH.[24,29]

Methods and Materials:

This is a cross-sectional observational study carried out at the department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University (BSMMU) on 32 patients of all age groups having supratentorial spontaneous ICH admitted within 24 hours of onset of symptoms from 1st March 2014 to 30th September 2015. These patients were selected from Neurosurgery and Neurology department of BSMMU and Dhaka Medical College Hospital (DMCH). Non provability purposive sampling technique was followed. Male female ratio was 1:1 with mean age 56 ± 15 years. Most (53%) patients fell in the age group between 41 to 60 years. Patients with secondary causes of ICH like anticoagulant use, underlying aneurysm, atrterio-venous malformation tumor head trauma, haemorrhagic transformation of ischaemic infarcts, patients having infratentorial haemorrhage, ICH with ventricular extension who underwent medical intervention within 4 days, taking steroids, diuretics, patients with inflammatory or infectious liver, renal, haematological diseases were excluded from this study. All the patients were evaluated on the basis of detailed history, clinical examination and subsequently confirmed by plain CT scan of brain. Blood was

collected and analysed for serum ferritin level after taking written informed consent on admission. Serum ferritin and CT scan of brain were repeated on the 4th day of admission. ICH and oedema volumes were calculated both the times. Subtraction of the hematoma volume from that of the absolute oedema (the volume of hematoma and surrounding oedema) and divide the product by the hematoma volume to express the perihematoma oedema volume as a ratio of the associated hematoma volume (relative oedema volume) by using the method ABC/2. [1,19]

The Serum Ferritin test requires only about 2 ml of blood to accurately diagnose ferritin levels. Serum ferritin was performed by Chemiluminescent Microparticle Immunoassay (CMIA). Reagents for the assay are available in kit form and in automated immunoassay instruments ABBOTT Architect, i-1000 SR, immunoassay analyser.[9]

A pre-designed data collection sheet was used for each patient to collect necessary information. For statistical analysis, software SPSS (Statistical package for social science), version 20 was used. Statistical significance was set at P value <0.05. Correlation between Serum ferritin and perihaematoma oedema volume was done by Pearson's correlation test.

To measure the association and to evaluate its statistical significance we calculated by correlation coefficient (r). Larger the absolute value of 'r' stronger the relation and the sign of 'r' (positive or negative) indicates the nature of relation.

Interpretation of 'r' ('r' value range from -1 to +1)

- Positivity indicates direct or positive relation
- Negativity indicates indirect or negative relation
- Larger the absolute value of 'r' stronger the relation.

Hypothesis testing of 'r' will be done by test statistic-

$$t = \frac{\sqrt{n-2}}{\sqrt{1-r^2}}$$

df= n-1

Results:

Thirty-two patients (n=32) with mean age 56 years (SD=15) were finally examined as per inclusion criteria. Equal number of male and female patients were examined (m/f=16/16). Mean hours past from the event of ICH was 13.72±5.4 at the time of admission. During admission grade-1 (GCS, 3-8) level of consciousness was reported among 45% (n=15) and grade-2 (GCS, 9-12) among 37.5% (n=12) of patients. Analysis of risk factors shows that most common risk factor is hypertension 78%, followed by smoking 43.8%, diabetes mellitus 34.4%, ischaemic heart disease 18.8% and previous history of CVD/TIA 6.3%. In this study all patients of ICH presented with motor deficit that included hemiplegia 20(62.5%) hemiparesis 12(37.5%). Other important symptom was vomiting (78%) followed by impaired consciousness (72%), motor aphasia (68.8%), sensory aphasia (53.6%), headache (53%)and dysarthria (6.3%).

Table-I

Haematoma, oedema (absolute and relative) volume and serum ferritin at admission and day 4

Variable	Day-1 Mean ±SD	Day-4 Mean ±SD
Ferritin (µg/L)	213.4±123.5	344 ±406.3
Haematoma vol (ml)	33 ±22.4	30.3±21.3
Absolute oedema vol (ml)	85.3±59	123.2±62
Relative perihaematoma vol oedema	1.9±1	4 ±2.7

Mean (±SD) value of serum ferritin was found elevated on day-4 (344 ±406) in comparison to day-1 (213.4±123.5). Mean of absolute oedema and relative perihaematoma oedema volume was also elevated on day-4 (123.2±62, 4 ±2.7) respectively than day-1 (85.3±59, 1.9±1). But, Mean haematoma volume on day 4 (30.3±21.3) was less than that of day-1 (33.0±22.4).

On day-1 no significant correlation was found for serum ferritin with haematoma volume (r= 0.065, p= 0.725), absolute oedema volume (r= 0.043, p= 0.817) or relative perihaematoma oedema volume (r= -0.022, p= 0.903).

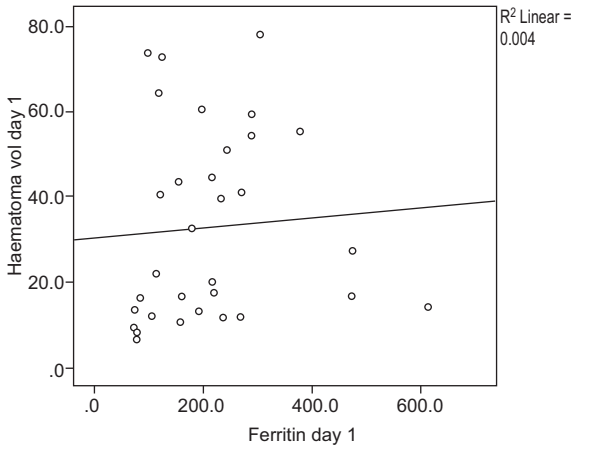


Fig.-1: *Scatterogram showing correlation between ferritin with haematoma volume on day-1*

Positive correlation of ferritin with haematoma volume on day-1 but this was not statistically significant.

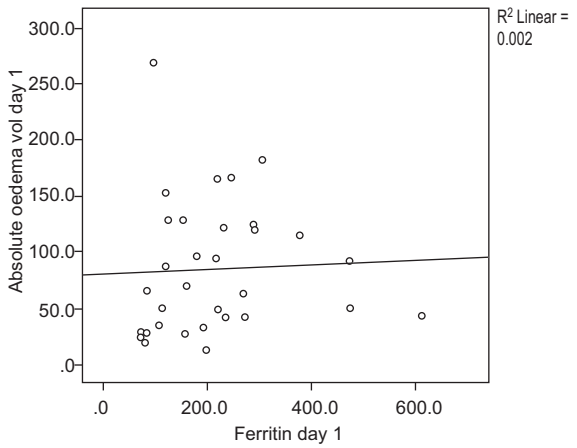


Fig.-2: *Scatterogram showing correlation between ferritin with absolute oedema volume on day-1*

Positive correlation of ferritin with absolute oedema volume on day-1 but this was not statistically significant.

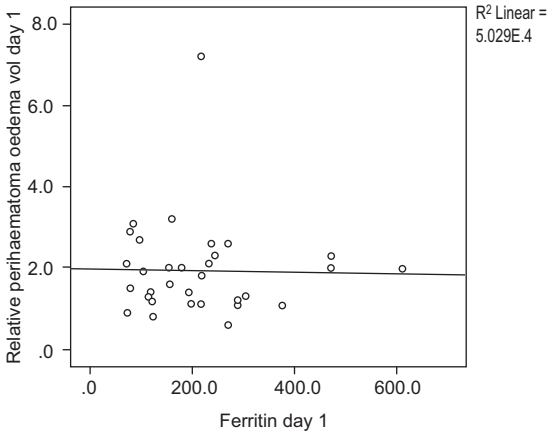


Fig.-3: *Scatterogram showing correlation between ferritin with relative peri-haematoma oedema volume on day-1*

Relative perihaematoma oedema volume has negative correlation with ferritin and that is also not statistically significant.

On day-4 no significant correlation was found for serum ferritin with haematoma volume (r= -0.106, p= 0.565), absolute oedema volume (r= -0.121, p= 0.510), or relative perihaematoma oedema volume (r= -0.057, p= 0.761).

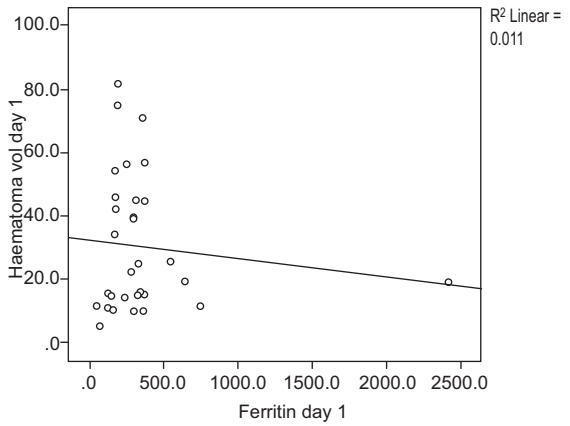


Fig.-4: *Scatterogram showing correlation between ferritin with haematoma volume on day-4*

Negative correlation of ferritin with haematoma volume on day-4 and this was not statistically significant.

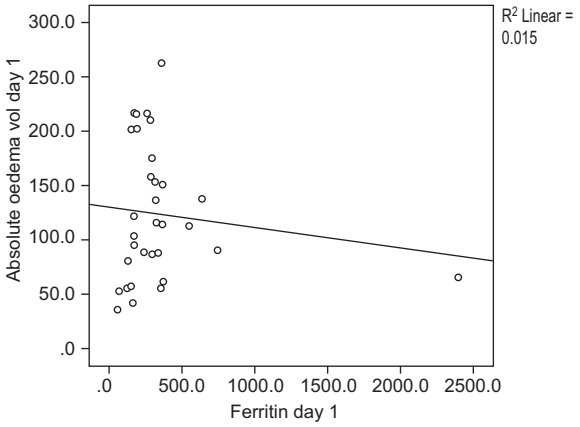


Fig.-5: *Scatterogram showing correlation between ferritin with absolute oedema volume on day-4*

Negative correlation of ferritin with absolute oedema volume on day-4 and this was not statistically significant.

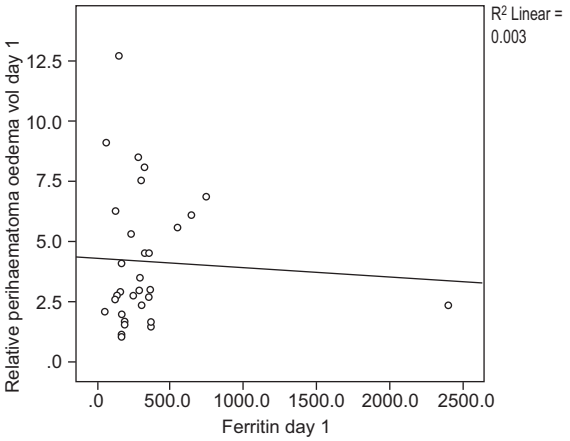
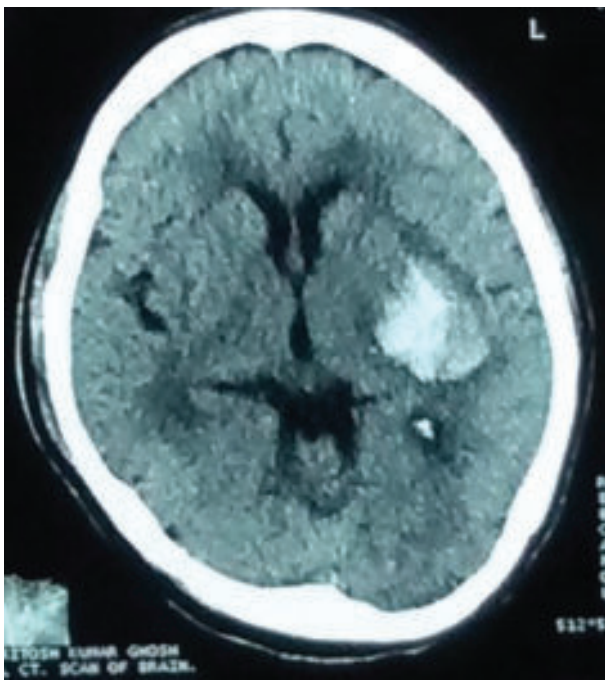


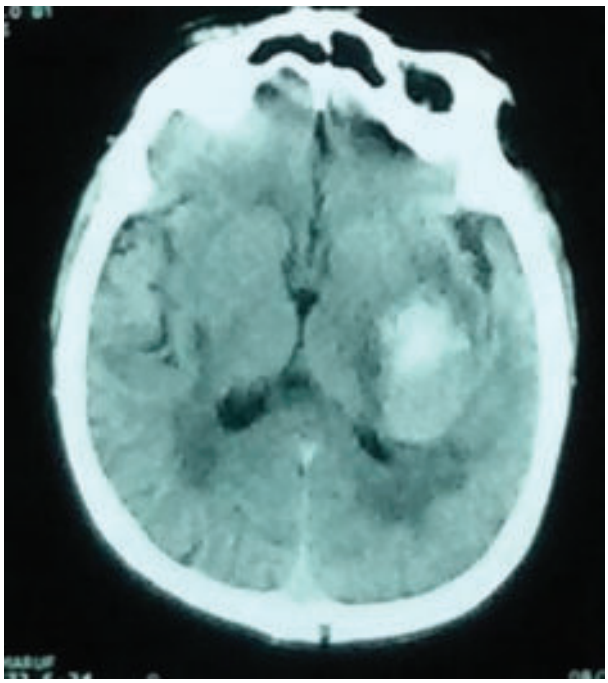
Fig.-6: Scatterogram showing correlation between ferritin with relative peri-haematoma oedema volume on day-4

Appendix – V: Figures

CASE-2

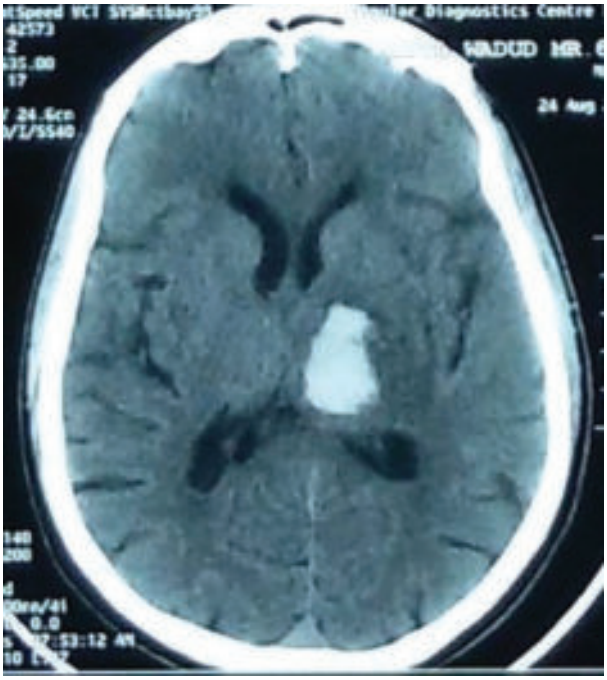


Day-1

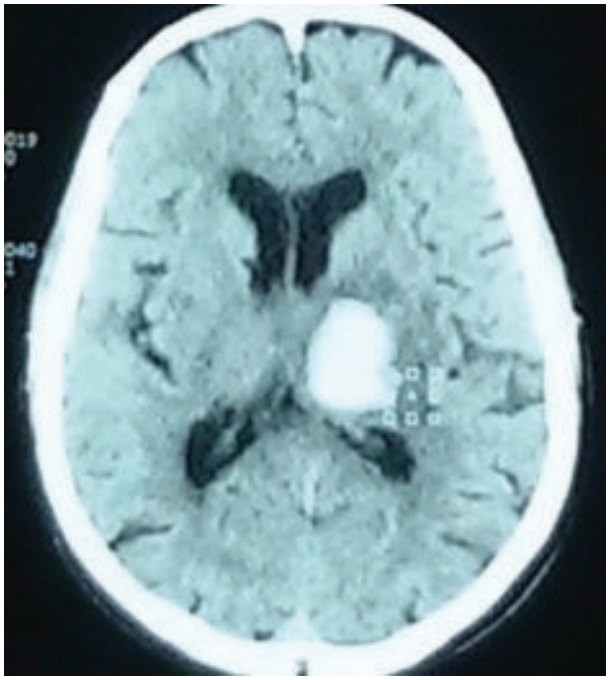


Day-4

CASE-6

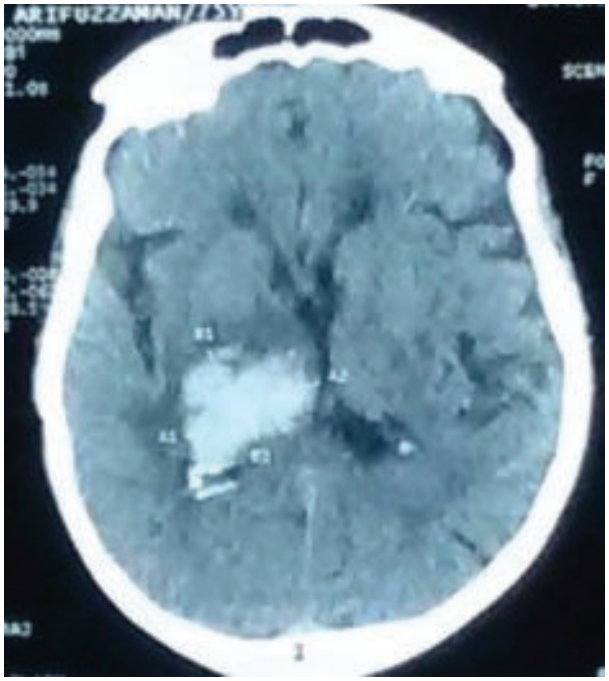


Day-1

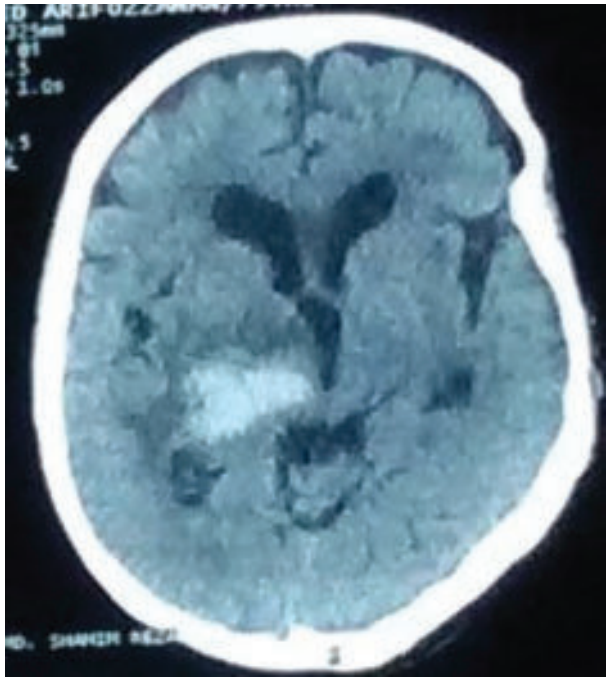


Day-4

CASE-10

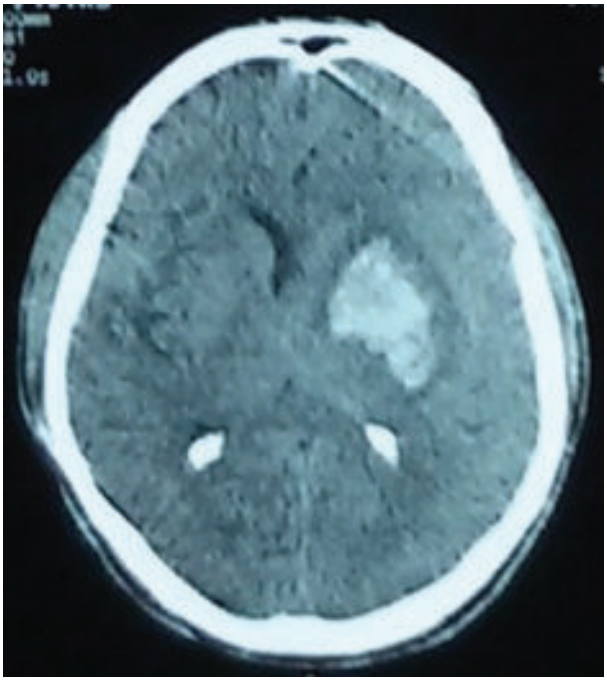


Day-1

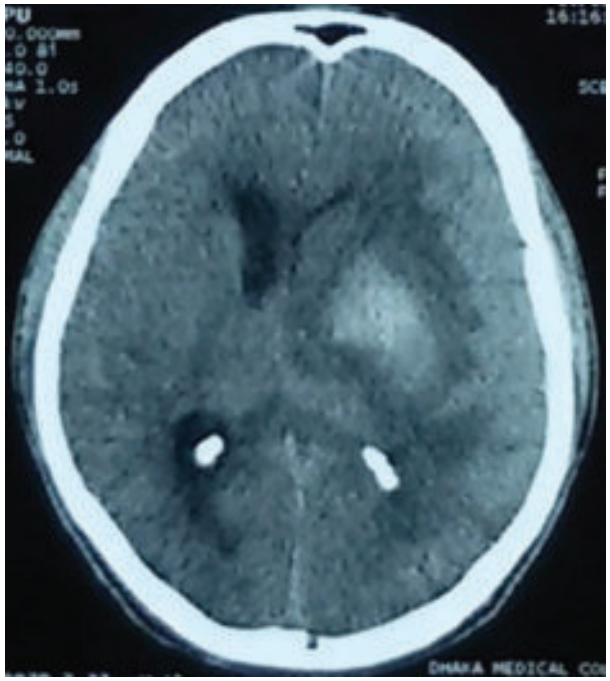


Day-4

CASE-12

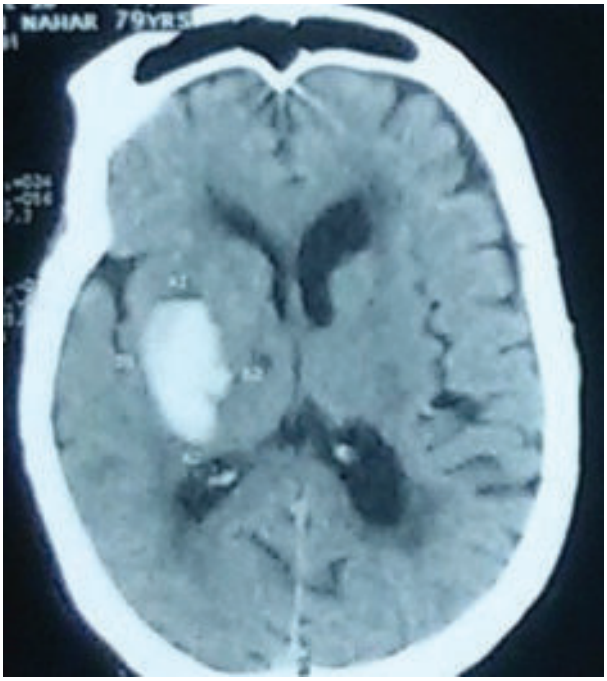


Day-1

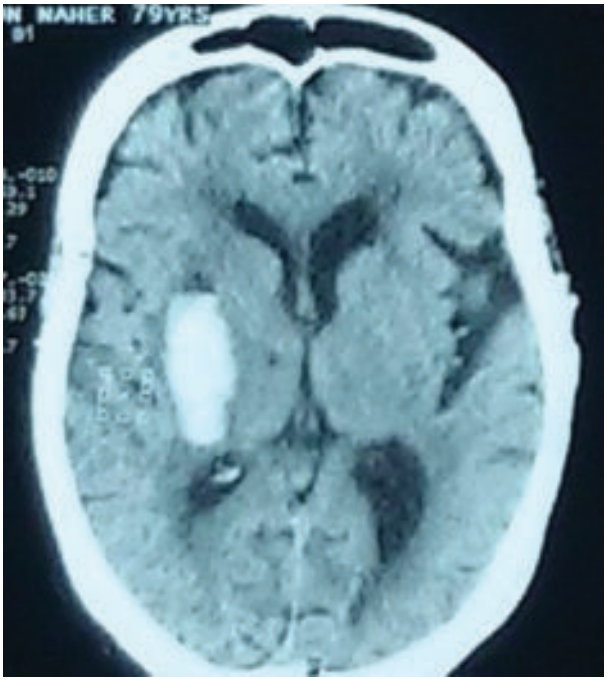


Day-4

CASE-15



Day-1



Day-4

Negative correlation of ferritin with relative perihaematoma oedema volume on day-4 and this was not statistically significant.

Discussion:

This study was carried out in the Department of Neurosurgery, BSMMU, Dhaka during the period between 1st March, 2014 to 30th September, 2015 to find out the association between serum ferritin concentration and perihaematoma oedema volume in patients with supratentorial spontaneous intracerebral haemorrhage.

The study sample comprised of 32 patients of ICH presenting within 24 hours of event. Patients were selected by non-probability purposive sampling technique based on inclusion-exclusion criteria.

Detailed clinical examination was carried out and recorded in a data collection sheet. Plain CT scan of the brain was done to confirm diagnosis. Blood was collected and analysed for serum ferritin. Serum ferritin and CT scan of the brain were repeated on the 4th day of admission. The ICH and oedema volumes were calculated both the times by using the following formula ABC/2: as A = the largest diameter of hemorrhage on the CT slice, B= The largest diameter90° to *A* on the same primer slice, and C was calculated by multiplying the approximate number of the CT slice with hemorrhage to the thickness of the slice measured in centimeters. To express the perihaematoma oedema volume as a ratio of the associated haematoma volume (relative oedema volume) the haematoma volume was substracted from that of the absolute oedema (the volume of the haematoma and surrounding oedema) and divide the product by the haematoma volume.[1,19]

The Serum ferritin test requires only about 2 ml of blood to accurately diagnose ferritin levels. Serum ferritin was performed by Chemiluminescent Microparticle Immunoassay (CMIA). Reagents for this assay are available in kit form and in automated immunoassay instruments ABBOTT Architect, i-1000 SR, immunoassay analyzer.[9]

In this study maximum number of haemorrhagic stroke was in age group 41-50 (28.1%). Previous studies showed incidence of ICH more in case of males than in females.[1] However, in this study the incidence was equal which may be due to the smaller sample size.

In this study level of consciousness of patients at admission was grade-1 (GCS 3-8) which is similar to that of another study.[32]

Analysis of risk factors were in concordance with other studies[18] and revealed that hypertension (78.1%) was the common risk factor of stroke. Other important risk factors were smoking (43.8%) and diabetes mellitus (34.4%).

All the patients in this study presented with motor deficit that included hemiplegia 20 (62.5%), hemiparesis 12 (37.5%). Other important symptom was vomiting 25 (78.1%) followed by impaired consciousness 23 (71.9%). In another study patients mostly presented with motor deficit but impaired consciousness was more common than vomiting.[32] This may be because of the delayed presentation to the hospital after the incidence of ICH as compared to other studies[1,24] and smaller sample size.

This study showed that Mean (±SD) value of serum ferritin was found elevated on day-4 (344 ±406 µg/L) in comparison to day-1 (213.4±123.5 µg/L). Mean of relative perihaematoma oedema volume was also elevated on day-4 (4 ±2.7) than day-1 (1.9±1). Statistical analysis by Pearson's correlation showed on day-1 there was no significant correlation between serum ferritin and relative perihaematoma oedema volume (r= -0.022, p= 0.903). This concurred with a previous study[24] which also showed no correlation between serum ferritin and relative perihaematoma oedema volume on day-1 but had significant correlation on day-4. Correlation between serum ferritin and relative perihaematoma oedema volume was again studied on day- 4 and it was found statistically insignificant (r= -0.057, p= 0.761). This result was similar to previous studies[1,29] which found no correlation on day-4 between serum ferritin and relative perihaematoma oedema volume but there was significant correlation on day-1.

Conclusion:

Result of this study showed that there was no significant statistical correlation between serum ferritin concentration and relative perihaematoma oedema volume on day-1 and day-4; hence, we concluded that there is no association between serum ferritin concentration and relative perihaematoma oedema volume in patients with supratentorial spontaneous intracerebral haemorrhage.

The calculation of the haematoma volume, absolute oedema volume and relative perihaematoma volume was done manually by using the formula ABC/2 and hence subject to individual discretion or biasness. Further, compared to the computer program used in other studies[24], this method was time consuming. Had longitudinal follow up of patients of ICH been included in this study it may have given a more complete picture of their prognosis.

Our findings were preliminary and needed to be further investigated in larger-scale prospective studies to identify modifiable factors determining prognosis of patients after ICH.

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