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The relationship between the serum levels of ferritin and the radiological brain injury indices in patients with spontaneous intracerebral hemorrhage

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ABSTRACT

Objective(s): Preclinical studies show that iron plays a key role in mediating neuronal injury. This study was performed in order to identify the relationship between the serum level of ferritin and severity of the brain injury which occur after an Intracerebral hemorrhage (ICH).
Materials and Methods: This was a cross sectional descriptive – analytic study, which was conducted on those patients who had suffered from an ICH and had attended Poursina Hospital. The Serum levels of ferritin were measured at admittance. A Cranial CT scan was performed at admission and also 72 hr afterward. Hematoma and edema surrounding the hematoma volumes were also measured at entrance and 72 hr afterward. Data analysis was carried out by a descriptive - analytic statistics approach and calculated later on by the Spss-20 software.
Results: In this investigation, 63 patients were studied, from which 34 (54%) were male and 29 (46%) female. The average age of the patients was 69.7± 11.9 (Min 43 and Max 94 years old). A significant relationship was observed between the level of ferritin and the edema volume surrounding the hematoma at first and next 72 hr after the patients were admitted.
Conclusion: These results delineated the effective role of iron on the edema volume elevation. More studies are essentially urged to ascertain the clinical evaluation of the curing effect of iron chelators in those patients who suffer from ICH.

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Introduction

Intracerebral hemorrhage (ICH) causes 10 to 15 percent of all brain stroke cases. The amount of mortality and morbidity caused by ICH, within 30 days, is averaged 44%. Numerous patients who have suffered from ICH have become disabled (1-3). After an ICH, the blood tends to abandon the ruptured vessels and enters the parenchyma. In the parenchyma, the blood releases its serum, after congealing and during this process ferritin is released as well. Thereby ferritin may be related to the blood or iron volume which exits in the brain tissue and it may be indirectly related to the amount of the oxidative injury that it has caused (4-6).

After ICH, the primary and secondary mechanisms are mentioned when discussing brain injury. In the primary injuries, the hematoma volume causes disruption of the construction of the brain tissue and its deconstruction. The persistence of the hematoma pressure on the surrounding constructions increases the pressure inside the brain, brain ischemia, and brain herniation, consequently leading to physiological responses to the hematoma (inflammation reaction) which cause secondary injuries (5, 7-8).

The actual mechanism that causes brain edema is not yet determined; however, the substances which exist in clots (i.e. hemoglobin, iron, thrombin, etc.) have been marked as the factors responsible for the existence of edema surrounding the hematoma. Despite the increase in the hematoma volume which takes place in the first few hours of ICH, the window

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period which is required to form the edema surrounding the hematoma, takes up a few days and this grants the sufficient amount of time to cure it (9-13). Currently, there is no available medical therapy for patients with trauma brain injury and ICH, and supportive care or invasive neurosurgical evacuation of hematoma in selective patients is all that can be done (14-15). The anti-edema treatments perform as adjuvant treatments which are used to treat ICH patients (16-18).

Animal studies have shown that the accumulation of iron in the brain commences after an ICH on the first day and reaches its maximum level by the third day, and the secondary neural injury due to the accumulation of iron, causes neural injury in a few days after the ICH (2, 4, 19). Moreover, in other animal studies, it has been reported that the treatment with iron chelators such as frouxamine can reduce the edema volume surrounding the hematoma and improve the later clinical incidents (20-23).

According to the previous investigations (24-26), few studies have been conducted to investigate the interrelationship of the level of ferritin and the radiological organic injury indices or the clinical indices in human. In this study, based on the possible role of the released tissue-iron in causing secondary injury, the relationship between the serum level of ferritin and the radiological indices which reveal the severity of the brain injury after an ICH is investigated.

Materials and Methods

The study took place at Poursina Hospital in Guilan province of Iran. This was a descriptive-analytic cross sectional study. As the criteria of the patient selection of this study, those patients were selected who had symptoms of brain stroke and ICH**,** within the first 24 hr from the onset of symptoms. (A cranial CT scan was performed via the 2slice, model GE for all patients). only under the following circumstances a patient was subtracted from the study process: those patients who suffered from anemia (having a hemoglobin rate lower than 10), those who had former physical disability, cancer, liver, kidney, heart, lung failure, those who suffered from inflammatory diseases or systematic inflectional illnesses, blood diseases; those whose edema had been treated by dexametazone or manitol, patient surgery; and those who had suspicious symptoms of causes of secondary intracranial hemorrhage (before the brain tumor, arteriovenous malformation, brain aneurysm) which had been detected at the first stages of the CT scan. The treatment conditions and the study process was explained to the under study patients and their first of kin, and a form was signed to their consent.

Sample for measuring the serum level of ferritin was obtained after the diagnosis of ICH. All patients were treated with routine protocol, and no intervention was made in the treatment process. For all patients, a follow-up brain CT scan was performed 72 hr after their admission.

In a designed check list, the followings were recorded: the demographic data, the time duration from the emergence of the symptoms until the patients' qualification for the study and their entrance to the study, the accompanying diseases, the level of awareness, blood pressure, the use of anti-placate medicine, experience of former heart diseases, former strokes, diabetes mellitus, the hemorrhage volume, the edema volume surrounding the hematoma, and the place of the hemorrhage. The hematoma volume was calculated, in the CT slice, according to the following formula ABC/2: as A = the largest diameter of hemorrhage on the CT slice, B= The largest 90° diameter 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. Also to measure C every slice was compared to the primer slice. In case the hemorrhage area was almost 75% greater than the area seen of the primer slice, it was considered as one individual slice. If the area had between 25% to 75% blood in it in comparison with the primer slice, it was considered as half a slice; and if the area was less than 25% of the primer slice, it was not considered at all. These CT hemorrhage slice values were then added to determine the value for C. All measurements for A and B were made with the use of the centimeter scale on the CT scan to the nearest 0.5 cm. A, B, and C were then multiplied and the product divided by 2, which yielded the volume of hemorrhage in cubic centimeters (24). In order to measure the edema volume surrounding the hematoma, first the total volume (of the hematoma along with the edema surrounding it) was calculated according to the above mentioned formula and later the edema volume surrounding the hematoma was gained by subtracting the hematoma volume from it. The relative edema was calculated from the ratio of the edema volume surrounding the hematoma/ the hematoma volume; and the time difference of the edema emergence at the beginning of the study and 72 hr after its symptoms, was calculated as well.

In this study, the level of ferritin was considered as the independent variable and the indices surrounding the edema of the hematoma were considered as the dependent variables, and also the primary outcomes. To describe the variables statistical measures such as average, standard deviation and frequency were used. In order to detect the existence of a correlation between the level of ferritin and the radiological injury indices,

Table 1. The descriptive statistic indices of the radiologic brain injury criteria in the patients

Variable	Number	Mean± SEM	Min	Max
Edema volume at admission , ml	63	22.08±7.08	10	49
Edema volume at 72 hr, ml	52	35.75±18.34	17	110
ICH volume at admission, ml	63	28.07±21.9	7	93
ICH volume at 72 hr, ml	52	26.04±15.54	7	64
Relative edema volume at admission, ml	63	1.16±0.62	0.26	2.86
Relative edema volume at 72 hr, ml	52	1.6±1.01	0.66	6.67
Altered ICH volume at 72 hr, ml	52	2.04±4.78	-9	19
Altered edema volume at 72 hr, ml	52	13.95±14.66	1	70

Pearson's correlation was applied, and in case the required conditions for Pearson's test was not provided, Spearman's test was used instead. Also, a linear regression test was applied to determine the factors that affect the edema volume surrounding the hematoma. Sample size was determined according to similar previous studies (23, 25) and standard error of mean of these studies. Data analysis was done by SPSS-20 software. The statistical significance was considered equal or lower than 0.05 in the present study, as well.

Results

From among all 76 patients who suffered from Intracerebral hemorrhage , 13 were dropped out of the study (2 patients were transformed to other hospitals, 2 undergone surgery, 7 took edema therapy in the first 72 hr at the beginning of the study and 2 other patients were discharged from hospital by self-agreement). From the 63 patients who did enter the study, 34 were male (54 percent) and 29 were female (46%). The average age of the patients was 69.7±11.9 from among whom the youngest was 43 and the eldest 94 years old. Fifteen patients (23%) had attended Poursina Hospital through emergency calls, and the average amount of time that took until the controlled brain CT scan was 68.41±10.01 hr.

From among all the patients who were under study, 45 (71.4 %) had high blood pressure, 16 (25.4%) diabetes mellitus, 11 (17.5%) previously had coronary artery diseases, 6 (9.5%) had a previous stroke, 12 (19%) undergone former treatments with antiplatelet drugs and 1 patient (1.6%) had ICH before.

Through the initial CT scan, 22 patients (34.9%) suffered from thalamus hemorrhage, 21 (33.3%) had putamen hemorrhage, 13 (20.6%) had lobar hemorrhage, 5 (7.9%) cerebrum hemorrhage and 2 (3.2%) suffered from brain stem hemorrhage. Also, in the initial CT scan 29 patients (46%) were detected to have Intra-Ventricular Hemorrhage (IVH). The average ferritin level in the patients was 182.03±128 µg/l of which 549 µg/l was its maximum level and 10 µg/l was the minimum. The average of National Institutes of Health (NIH) Stroke Scale, at the very beginning of the study in the patients was 15.63 ± 6.32 and the average of GCS, again at the beginning of the study, was 11.32±3.4. It is worthy to note within the first 72 hr of the study, 11 patients (17.5%) passed away. The descriptive statistic indices indicated the radiological criteria of brain injury which have been demonstrated in Table 1.

In this study, a significant statistical relation was observed between the level of ferritin and the variables of the edema volume surrounding the hematoma within the first 72 hr (P=0.001), the edema surrounding the hematoma after the first 72 hr of observing the symptoms (P=0.001), the hematoma volume at the beginning of the study (P=0.02), the hematoma volume 72 hr after being hospitalized (P=0.004), the edema surrounding the hematoma at the very beginning of the study (P=0.02) and the relative amount of edema at the beginning of the study (P=0.02). On the contrary however, no significant statistical relation was observed between the level of ferritin and the relative edema 72 hr after being hospitalized (P=0.09) and the changes in the hematoma volume (P=0.06). In addition, by applying the multi-variable linear regression analysis, the edema was related to the level of ferritin only within the 72 hr after observing the symptoms (P=0.001) and the other variables were omitted from the model.

Table 2. The variables which influence the increase of edema in the understudy patients by applying the multi-variable of linear regression analysis

Model	Unstandardized Coefficients		Standardized Coefficients Beta	t	*P-value*
	Std. Error	b			
Constant	4.22	-15.8	-	-3.75	0.001 ***
Ferritin concentration	0.01	0.06	0.6	5.88	0.001 ***
Volume of hematoma	0.09	0.9	0.5	2.3	0.026 *
Diabetes mellitus	3.08	98.1	0.8	3.56	0.001***

Based on the one variable analysis, within the 72 hr after observing the symptoms the following variables had a significant effect on the edema surrounding the hematoma: the hematoma volume (*P*=0.001), the edema surrounding, the hematoma in the initial CT scan (*P*=0.001), the level of ferritin (*P*=0.001), the amount of time from the emergence of the symptoms until the conduction of the initial CT scan (*P*=0.02) and the existence of diabetes Miletus (*P*=0.003); but factors such as high blood pressure, age, sex, and the place of the hemorrhage were variables which had no affect on the edema surrounding the hematoma within the 72 hr after the observing the symptoms. Eventually, those variables which had significant effects were analyzed by the multi-variable linear regression analysis. This analysis was used to demonstrate those factors which determine the elevation of the edema, in Table 2.

Discussion

The results of this study were in concordance with other studies (12, 25, 26) and revealed that iron does play a role in ICH secondary injury. Based on the significant relation between the level of ferritin and the initial hematoma volume, it appears that the hematoma itself is the source of ferritin and the lack of an interrelation between it and the increased amount of the hematoma volume showed that the ferritin level possibly has nothing to do with the spread of the hematoma. Also, these results showed that the level of ferritin is directly more in concordance with the edema volume surrounding the hematoma and especially with the increase of the edema volume. In other words, it is likely that iron-dependent mechanisms are influential in causing the edema surrounding the hematoma and the secondary injury related to it. As this relation was significant in this study especially in the initial CT scan, it can be suggested that perhaps the iron-dependent/iron-related mechanisms, have been influential in causing the edema from the very first hours of the study. Also, from the relation between the hematoma volume, the level of ferritin and the existence of diabetes with the increase in the amount of edema, it can be deduced that besides the iron-dependent/iron-related mechanisms there are other factors that induce edema.

In the present study, the thalamus hemorrhage was the most prevailed among the patients , which in comparison to other studies it was to some extent more (27, 28). Also, the prevalence of high blood pressure in similar studies was between 72 to 81 percent which was similar to the results (71.4) of this study (12, 29, 30). In another study, Prez *et al* Showed (2010), that there was no significant relation between the average of the levels of the ferritin serum in the ICH patients at admission, 24 hr, and 72 hr afterward (31). The study of Mehdiratta, *et al* (2008) which was to investigate the relation between the serum levels of ferritin and the edema surrounding the hematoma in 23 patients, and within 72 hr, showed that the hematoma volume had increased up to 28 percent, while the amount of the edema surrounding the hematoma had doubled (14) and both had increased much more in comparison to the present study. The reason to this difference may be in the different methodologies which have been applied in the two studies; as in this study, the ABC/2 formula was employed to measure the volume (since it was more facilitating and applicable on the patients) but in the above mentioned study, a computer program was used for the measurement (it is worthy to mention that these two methodologies which have been applied to measure the hematoma volume where compared in a study, and the result stated that there were no significant difference between them) (32). Another possible reason of these differences may be the difference in the basic characteristics of the variables used, as in Mehdiratta's study the average time that took from observing the symptoms until the conduction of the initial CT scan was 4.3 hr; and in the initial CT scan the edema volume was more than the hematoma volume itself.

Contrary to Mahdirata's study, in the present investigation none of the variables under research had a significant relation with the relative edema 72 hr later, but there was a significant relation between these variables and the relative edema in the initial CT scan at the beginning of the study. The possible reasons may be that Mahdirata's study covered fewer patients and the edema volume was much larger than expected at the beginning of the study and also the average time from observing the symptoms until the conduction of the initial CT scan in the patients was much longer.

The results of the present investigation (the relation between the level of ferritin serum and the edema surrounding the hematoma at the beginning of the study and 72 hr after the patients were hospitalized and the stronger relation between the level of ferritin serum and the edema surrounding the hematoma 72 hr after the patients were hospitalized in comparison with the edema surrounding the hematoma at the beginning of the study) confirmed this hypothesis that iron can have a role in the acute injury and also the belated brain injury (iron may perhaps have a contributing role in the acute phase but the main injury caused by it is delayed). In the 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 (4, 33). By considering the relation between ferritin and the iron-related stress oxidative metabolism, it may be possible to decrease the mortality and morbidity by affecting these metabolisms (such as iron chelators drugs). Reports on the previous studies, reveals optimal results of the curing effect of defroxamine

for ICH treatment in animal models (20-21). Yet, it is essential that more clinical evaluations be carried out concerning the curing effect of defroxamine in the treatment of ICH patients on more animal and even human models. There has been recently a study conducted on human, which showed the relative safeness of defroxamine and the satisfying rate of defroxamine tolerance in patients of ICH (34). It is suggested for further studies that the relation between the level of ferritin and the clinical consequences it has on patients, be investigated.

Of the delimitations of this study was that according to the design of this investigation (cross sectional), it is not possible to make firm judgments about the relation between the causes and effects in the study; and the same goes for the effective role of the variables and the possible intervening factors like larger hematoma volume in patients with higher levels of ferritin, the hydrostatic pressure caused by the formation of hematoma, the accumulation of clot and the activation the coagulation cascade and the formation of thrombin which according to previous studies (6, 35-36) play a role at the initial levels of the edema surrounding the hematoma.

Conclusion

Results of the current study confirm the effective role of iron on the edema volume elevation in ICH. We suggest further studies to evaluate the effect of iron chelators in patients who suffer of different model of ICH.

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Declaration of interest

The authors declare no conflict of interest.

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