


**Research Article**

## Comparative Evaluation of Erythropoietin and Darbepoetin in Hemodialysis Patients

Dilip Kumar Sah<sup>1</sup>, Syed Shahzadul Haque<sup>2\*</sup>, Sweta Shah<sup>3</sup>, Shyam Sundar Yadav<sup>4</sup>

### Abstract

**Background:** An increase or depletion of body iron has harmful effects on health. Apart from iron deficiency anemia and iron overload-related organ tissue damage, there are increasing evidences that body iron status is implicated in atherosclerotic cardiovascular diseases. The purpose of this study was to determine the prevalence of iron deficiency in patients with acute ischemic stroke.

**Methods:** The prospective, observational, cross sectional study included patients with diagnosis of acute ischemic stroke from August 20<sup>th</sup>, 2016 to February 20<sup>th</sup>, 2017. Detailed history, physical examination and biochemical measurements were recorded. Patients were followed to see for outcome variable such as iron deficiency anemia.

**Results:** One hundred and forty-four (144) patients were included in this study with a male to female ratio of 2.2:1 and a mean age of 67.63 ± 3.103 years. The mean duration of stroke was 12.73 ± 6.95 hours. Co-morbidities included diabetes mellitus in 58 (40.3%), hypertension in 72 (50%), hyperlipidemia in 30 (20.8%) and obesity in 44 (30.6%) patients. There were 30 (20.8%) patients with a history of blood transfusion. Iron deficiency anemia was recorded in 15 (10.42%) patients.

**Conclusion:** Our study has revealed the presence of an iron deficiency anemia could be an underlying cause of ischemic stroke in 10.42% of patients requiring the need for assessment of iron profile and subsequently more aggressive management.

**Keywords:** Hematocrit; Hyperlipidemia; Iron Deficiency; Obesity; Stroke

### Introduction

Anemia is the most common disorder of the blood and had been proved to be highly related to the cardio-vascular diseases as well as cerebrovascular accidents [1]. However, only the subtype of sickle cell anemia was reported to be highly associated with cerebro-vascular accident (CVA) [2]. Perhaps, the most relevant studies addressing these two problems are focused on the correlation between anemia and negative outcomes after ischemic stroke [3]. The cardiovascular risk profile and overall survival has already been analyzed in the Framingham study with an interesting finding that patients with low hematocrit had mostly died of non-cardiovascular causes. The mortality due to cardiovascular events was more attributed to high hematocrit group [4]. One recent study has suggested that about 6.4 % of stroke patients have iron deficiency anemia (IDA) [5].

### Affiliation:

<sup>1</sup>Department of Nephrology, Birat Medical College Teaching Hospital Tankisinuwari, Morang, Nepal

<sup>2</sup>Department of Biochemistry, Indira Gandhi Institute of Medical Sciences, Patna, India

<sup>3</sup>Department of Obs & Gynecology, Birat Medical College Teaching Hospital Tankisinuwari, Morang, Nepal

<sup>4</sup>Department of Internal medicine, Birat Medical College Teaching Hospital Tankisinuwari, Morang, Nepal

### \*Corresponding author:

Syed shahzadul Haque, Department of Nephrology, Birat Medical College Teaching Hospital Tankisinuwari, Morang, Nepal

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Iron-deficiency anemia (IDA) results in decreased total body iron causing microcytic hypochromic erythropoiesis with decreased serum iron and ferritin with an increased total iron binding capacity. Ferro et al. have reported an association of Iron-deficiency anemia with papilledema, idiopathic intracranial hypertension, venous sinus thrombosis, and ischemic stroke [6]. The exact mechanisms underlying anemia and stroke syndromes could not be comprehended but, it is believed that iron deficiency may have a strong link to ischemic stroke. Thrombocytosis is often associated with iron deficiency and microcytosis produces a reduction in the red cell deformability and could produce a hypercoagulable state. Thrombus formation in the presence of an underlying Atherosclerotic disease could have a synergistic impact by the platelet counts and function observed in iron-deficiency anemia [7]. Anemia may also worsen regional hypoxia in areas of decreased cerebral perfusion (so-called “anemic infarction”).

Thus iron deficiency may contribute to hypercoagulable state by affecting blood flow patterns within the vessels because of reduced deformability and increased viscosity of microcytic red blood cells. Anemic patients need more blood flow to maintain compensation for the lack of oxygen [8]. Therefore, the increase in blood flow can cause endothelial damage, leading to platelet aggregation, causing a cascade for thrombus formation. Little information is available in published literature about the relationship between iron deficiency anemia and stroke. The purpose of this study was to determine the prevalence of iron deficiency in patients with stroke as a first step to make recommendations about iron prophylactic supplementation for this particular group of patients.

## Material and Methods

This study was conducted after the approval from College of Physicians and Surgeons, Pakistan. The permission was granted from Jinnah Postgraduate Medical Centre, Karachi Ethical Review Committee (ERC). All the patients (n=144) were enrolled from 20<sup>th</sup> august 2016 to 20<sup>th</sup> February 2017 in medical unit I of Jinnah Postgraduate Medical Centre, Karachi which is the referral tertiary care hospital and research institute. The inclusion criteria for induction of patients was an event leading to focal neurological deficit of sudden onset lasting for more than 24 hours with evidence of hypo-density on computerized tomography (CT) scan of brain. The criteria of exclusion were hemorrhagic stroke, long-term transfusion therapy (for more than 10 years), blood transfusion within three months prior to the study, history of other critical illness such as heart failure (diagnosed on ejection fraction (EF) < 25%, chronic obstructive pulmonary disease (COPD) diagnosed on forced expiratory volume (FEV) < 70% predicted), chronic kidney disease (CKD) diagnosed on serum creatinine > 3mg/dl or malignancy.

The patients fulfilling the selection criteria of the study were already consented for written consent at the time of admission. Baseline demographic data such as age, sex, diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, obesity, and history of blood trans-fusion was recorded. On the same day, five milliliters of blood were drawn from a convenient peripheral vein into plain tubes for assessment of iron deficiency anemia. A database was developed on SPSS 17. Mean and SD was calculated for age and duration of stroke (in hours). Frequency and percentages were calculated for age, sex, diabetes mellitus, hypertension, hyperlipidemia, obesity and history of blood transfusion along with outcome variable such as frequency of iron deficiency anemia. Effect modifier were controlled through stratification of age, sex, diabetes mellitus, hypertension, hyperlipidemia, obesity, and history of blood transfusion to see effect of these on outcome variable applying chi square test taking p value ≤0.05 as significant.

## Results

One hundred and forty-four patients fulfilling the inclusion criteria were included in this study. The mean age of study population was 67.63 ± 3.103 years. The mean duration of stroke was 12.73 ± 6.95 hours. Demographics showed that majority of patients were males 100 (69.44%) and below

**Table 1:** Demographics and clinicopathological characteristics of patients.

Variable	Categories	N (%)
Age	Mean ± SD*	67.63 ± 3.103
	< 75 years	86 (59.7)
	>75 years	58 (40.3)
Gender	Male	100 (69.4)
	Female	44 (39.5)
Iron deficiency	Yes	15 (10.4)
	No	159 (89.5)
DM*	Yes	58 (40.3)
	No	86 (59.7)
Hypertension	Yes	72 (50)
	No	72 (50)
Hyperlipidemia	Yes	30 (20.8)
	No	114 (79.1)
Obesity	Yes	44 (30.6)
	No	104 (72.2)
History of blood transfusion	Yes	30 (20.8)
	No	114 (79.1)

the age of 75 years 86 (59.72%) (Table 1). Co-morbidities included diabetes mellitus in 58 (40.3%), hypertension in 72 (50%), hyperlipidemia in 30 (20.8%) and obesity in 44 (30.6%) patients. There were 30 (20.8%) patients with a history of blood transfusion. Iron deficiency anemia was recorded in 15 (10.42%) patients (Table 1). Stratification of age, gender, DM, HTN, hyperlipidemia, obesity and history of blood transfusion is mentioned in table 2.

## Discussion

South-East Asia has emerged as the region to be affected by increased burden of anemia prevalent in 32.9% of women of all age groups [9]. Trends are very much similar in developing countries like Pakistan secondary to the consumption of cereal-based diets with a low bioavailability of iron, inappropriate personal hygiene, early marriage, repeated pregnancies, and low literacy rate as the major identifiable factors [10, 11]. Extremes of hemoglobin either low or high may have an adverse outcome. Tanne D have reported underlying anemia in 1 out of every 5 patients presented with an acute ischemic stroke [12].

Iron-deficiency anemia (IDA), defined as a decreased total body iron, is characterized by microcytic hypo-chromic erythropoiesis with low serum iron and ferritin with an elevated

**Table 2:** Stratification of age, gender, DM, HTN, hyperlipidemia, obesity and history of blood transfusion.

Variables	Iron deficiency anemia		P - value
	Yes	No	
<b>Age</b>			
Below 75 years	08	78	0.395
Above 75 years	07	51	
<b>Gender</b>			
Male	08	92	0.129
Female	07	37	
<b>Diabetes Mellitus</b>			
Yes	08	50	0.208
No	07	79	
<b>Hypertension</b>			
Yes	08	64	0.500
No	07	65	
<b>Hyperlipidemia</b>			
Yes	07	23	0.001
No	08	106	
<b>Obesity</b>			
Yes	07	37	0.129
No	08	92	
<b>History of blood transfusion</b>			
Yes	04	26	0.382
No	11	103	

total iron binding capacity [13]. Iron-deficiency anemia has been associated with papilloedema, idiopathic intracranial hypertension, venous sinus thrombosis, and ischemic stroke [14-18]. The putative mechanisms underlying anemia and stroke syndromes are not completely understood and it is believed that iron deficiency, may cause ischemic stroke by several potential mechanisms [13]. Thrombocytosis is often associated with iron deficiency and microcytosis produces a reduction in the red cell deformability and could produce a hypercoagulable state [19]. The platelet counts and function observed in iron-deficiency anemia could act synergistically to promote thrombus formation, especially in the setting of an underlying atherosclerotic disease [19]. Anemia may also worsen regional hypoxia in areas of decreased cerebral perfusion (so called “anemic infarction”) [13]. Our results have indicated no significant association between iron deficiency and co-morbidities such as DM, HTN, obesity or blood transfusion in the past but hyperlipidemia has found a significant association with iron deficiency anemia. This could have been attributed to the development of atherosclerotic plaque in the presence of hyper-coagulable state.

The risk factors for carotid artery thrombus formation in the absence of atherosclerosis are not well characterized, although cases of carotid thrombus associated with iron deficiency anemia have been reported previously [21]. Akins et al. reported 3 case reports in which young women with severe IDA and thrombocytosis secondary to menorrhagia developed carotid artery thrombosis [22]. Idbaih has also followed up 8 patients with spontaneous thrombosis of lesion-free carotid arteries and half of the patients with spontaneous thrombus had IDA, mostly secondary to menorrhagia [23]. Caplan et al. reported a young woman with severe iron- and folate-deficiency anemia with a non-adherent carotid thrombus attached to a fatty streak [24]. Yarnell et al. described a patient with menorrhagia, hypochromic microcytic anemia, platelet count of 608,000 and a stroke, whose angiogram revealed a large intraluminal mass in the carotid bifurcation [25].

Thrombus formation requires platelet activation and aggregation onto an endothelial surface with subsequent fibrin deposition. A straightforward hypothesis is that the thrombocytosis leads to thrombus formation; however, the correlation between high platelet count and thrombosis is poor. Abnormal platelet activation and function are probably more important than absolute platelet count [22]. Thus, iron deficiency may contribute to hypercoagulable state by affecting blood flow patterns within the vessels because of reduced deformability and increased viscosity of microcytic red blood cells [20]. Anemic patients need more blood flow to maintain compensation for the lack of oxygen. Therefore, the increase in blood flow can cause endothelial damage, leading to platelet aggregation, causing a cascade for thrombus formation [20]. The presence of floating thrombus in a

patient with clinical and MRI evidence of stroke represents a significant therapeutic dilemma and requires immediate decision about treatment. Thrombus in the internal carotid artery may resolve with medical management [26]. It is recommended to anti-coagulate patients with or without antiplatelet drugs immediately. Initial anticoagulation for symptomatic intraluminal carotid artery thrombosis leads to a low rate of recurrent ischemic events, and that carotid revascularization if indicated can be safely performed in a delayed manner [27].

Diabetes mellitus, hypertension, hyperlipidemia and smoking are the leading causes predisposing the occurrence of ischemic stroke. Early detection and treatment have a chance to prevent atherosclerotic changes and stroke [28]. Our cohort has increased percentage of patients with already existing comorbidities such as DM, HTN, hyperlipidemia and obesity which might have influenced the outcome in terms of ischemic stroke despite the presence of anemia in the background. Our study has certain limiting factors such as small sample size from a hospital based analysis, presence of high percentage of confounding variables such as co-morbidities. But, it has highlighted an important factor contributing adverse outcome apart from other causes contributing towards ischemic stroke. This has raised a thought about necessary analysis of blood profiling to identify iron deficiency and prompt measures in the management of acute ischemic stroke.

## Conclusion

We have identified iron deficiency anemia in 10% of cohort. These findings suggest the possibility of an underlying Iron deficiency anemia in patients causing acute ischemic stroke supporting the need for early management. Large, population based studies are required to declare anemia as a prognosticator in ischemic stroke.

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