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Level Of Erythropoietin in Elderly Patients Presenting with Anemia of Unknown Etiology: A Retrospective Cohort Study

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Abstract

Aim: To assess the level of erythropoietin in elderly patients presenting with anemia of unknown etiology

Study Design: Retrospective cohort study

Place and duration: This study was conducted at Indus Hospital Bhong Sadiqabad, Pakistan from June 2020 to June 2021

Methodology: A total of 205 patients of age above 60 years were considered in this study. Erythropoietin level of all the patients was measured in a period of one year. All the patients were categorized into 10 groups of etiologies after a thorough review. To analyze and compare, the group with iron deficiency anemia was selected as a standard.

Results: Total 131 (63.9%) were male and 74 (36.09%) were female. Total 42 patients had anemia of unknown etiology. They had a mean erythropoietin level of 40.2 compared to 101.5 of iron deficiency anemia. However, the mean hemoglobin is 10.74 which is higher when compared to 9.55 of iron deficiency anemia.

Conclusion: The level of erythropoietin in anemia of unknown etiology was inadequately low in comparison with iron deficiency anemia. Hence, the low level of erythropoietin in such patients promotes the pathogenesis of anemia of unknown etiology.

Keywords: Anemia, Anemia of unknown etiology, elderly persons, erythropoietin

Introduction

Anemia is a common and significant problem in the geriatric population. The functioning of elderly people is dependent on the health of their blood. Therefore, anemia can disturb the lives of elderly people to a great extent. Anemia itself is a predictor of comorbidities and mortality. Impaired cognition and deficiency in performance are associated with anemia. In men, if the hemoglobin level is below 13 g/dl, they would be declared anemic. On the other hand, this value in females is 12 g/dl which is different due to multiple factors. In the elderly individuals residing in nursing homes, the incidence of anemia is 20 to 40% [1]. In the general population it is as low as 10% [2]. The elderly population has to go through routine investigations. Even with such regular monitoring, the etiology of anemia in one-third of these cases remains unclear [3].

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Erythropoietin is a hormone that is secreted from kidneys as a result of tissue hypoxia. It has a significant contribution to erythropoiesis. It has a fundamental role in the proliferation as well as differentiation of many erythroid progenitors [4]. The level of erythropoietin in anemia of unknown etiology is always seen higher. Several mechanisms have been postulated by the researchers in this regard. For an instance, some propose that inflammatory cytokines exaggerate the feedback of hematopoietic progenitor cells and hence stimulate erythropoietin production [5]. On the other hand, the capability of hematopoietic stem cells also reduces with aging. The maintenance of homeostasis is therefore disrupted in aged individuals. This factor is also responsible for anemia of unknown etiology in the geriatric population [6]. Another significant factor that is responsible for the inadequate low production of erythropoietin is anemia of unknown etiology (AUE) [7]. According to researchers, 37-45% of elderly individuals suffer from AUE [8].

Endogenous erythropoietin level in AUE is remarkably low in anemia of chronic disease and iron deficiency anemia. In contrary to that, it is high in the anemia caused as a result of chronic kidney disease [9]. It is suggestive of inference that erythropoietin is inadequately low in AUE. The present study aims to identify the response of erythropoietin production in geriatric population that has been diagnosed with AUE compared to those elderly patients who have anemia of other known etiologies such as iron deficiency anemia, chronic disease, suspected myelodysplastic syndrome (MDS), confirmed MDS, chronic kidney disease, folate deficiency, vitamin B12 deficiency, multifactorial etiology, anemia of unknown etiology and other etiology.

Methodology

This study was conducted at Indus Hospital Bhong Sadiqabad, Pakistan from June 2020 to June 2021. All the elderly patients referred to our department for anemia were taken in our study. For screening purposes, laboratory investigation of erythropoietin of all the patients was done by immunoenzymatic method and chemiluminescence method. Reference range regarded as 3 IU/L to 18.5 IU/L. The age of all the subjects was above 60 years. All the patients met the WHO criteria of anemia according to which males having hemoglobin level below 13 g/dl and females having hemoglobin below 12 g/dl were regarded as anemic. Written informed consent was taken from all the participants after an explanation of the motive and method of the research. Permission was taken from the ethical review committee of the institute.

The judgment of the etiology of the anemia in the patient was done by one of the etiologies considered in the study. Etiologies were assigned to the patients after an assessment of the patient according to the standardized criteria set as mentioned in the table below. Allocation of the patient in an etiology was done keenly and carefully after consultation from a specialist and consensus.

Criteria standardized for etiology of anemia in geriatric population

Etiology	Criteria
Iron deficiency anemia	• Serum ferritin <50 ng/mL • Absence of iron stores in bone marrow • Iron deficiency
Anemia of chronic disease	• Any chronic inflammatory disorder such as Rheumatoid Arthritis, vasculitis, autoimmune diseases and inflammatory bowel disease
Suspected MDS	• Clinical features suggestive of MDS • Laboratory investigation suggestive of MDS • Disease not confirmed by bone marrow
Confirm MDS	• Cytogenic workup done • Confirmed from bone marrow biopsy
Chronic kidney disease	• eGFR < 30 mL/min/1.73 m^2
Folate deficiency anemia	• Erythrocyte folate <340 nmol/L
Vitamin B 12 deficiency anemia	• Serum vitamin B12 < 148 pmol/L

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Multifactorial etiology	• Multiple criteria met
Anemia of unknown etiology	• Etiology is unknown • Laboratory investigations unclear • Unclear clinical examination
Other etiology	• Any other known etiology that has not been listed here

Data Collection was done from electronic and physical medical records of the patients. A screening was also done in which the erythropoietin concentration of all the patients was determined by laboratory investigation. Basic information, comorbidities and clinical examination of the patients was done when the sample for erythropoietin was collected.

The formula used for the calculation of eGFR was CKD-EPI. This formula is helpful in the prediction of the risk of renal disease and its severity in the future [10]. Due to the negative association of eGFR with hemoglobin, the cut-off value chosen for eGFR was 30 mL/min/1.73 m^2 [11]. For iron deficiency anemia, serum ferritin was used as a standard. Likewise, the values of folate and Vitamin B12 were also set for folate deficiency anemia and Vitamin b12 deficiency anemia, respectively.

Kappa and Fleiss' Kappa was used for statistical findings and analysis. A graph was constructed between erythropoietin and hemoglobin for all the groups of etiology. The least-squares method was used to construct an exponential curve. Participants who had iron deficiency anemia served as a reference group. Their erythropoietin concentrations are mentioned for approximation. A comparison of erythropoietin levels of each etiology group was done with the iron-deficiency anemia group. The software used for statistical analysis was IBM SPSS Version 26.

Results

A total of 205 participants were selected for the study after setting appropriate inclusion criteria. The research was done irrespective of the gender of the patients and 64% of the subjects were male. However, age was anticipated as an important demographic feature. No patient below the age of 60 years was selected in the study. The mean age of the participants was 74.6 years. The most common etiology seen in anemic patients is those who had confirmed diagnosis of MDS. Total 63 (30.73%) patients had confirmed MDS, 42 (20.48%) had AUE, 21 (10.24%) patients had iron deficiency anemia, 11 (5.36%) had anemia of chronic disease, 9 (4.39%) had CKD, 14 (6.8%) had suspected MDS, 13 (6.34%) had multifactorial etiology, and 29 (14.14%) had other etiology. Only 2 (0.97%) cases of Vitamin B12 deficiency were found during the study and only 0.48% patient was diagnosed case of folate deficiency anemia.

Mean values of erythropoietin, hemoglobin and eGFR are given in table 1. The mean of hemoglobin is higher in AUE comparatively. It was lowest in confirmed and suspected MDS. When compared with iron deficiency anemia, the eGFR of AUE and CKD was lower.

Table 1. Comparison of erythropoietin, hemoglobin and eGFR of each etiology group and compared to IDA

Etiology group	**N**	**EPO (IU/L) Mean**	**EPO (IU/L) p-value**	**Hemoglobin (g/dL) Mean**	**Hemoglobin (g/dL) P-value**	**eGFR (mL/min/1.73 m^2) Mean**	**eGFR (mL/min/1.73 m^2) p-value**
Iron Deficiency Anemia	21	101.5	-	9.55	-	64.2	-
Confirmed MDS	63	254.2	0.001	9.11	0.045	61.6	0.845
Suspected MDS	14	145.3	0.412	9.7	0.746	60.1	0.724
AUE	42	40.2	0.004	10.74	<0.001	54.1	0.007
Anemia of chronic disease	11	28.5	<0.001	10.22	0.282	54.8	0.205
CKD	9	24.9	0.001	9.79	0.742	19.15	0.000
Multifactorial etiology	13	103.2	0.984	9.24	0.542	35.4	0.000

Other etiology	29	280.1	0.001	9.28	0.215	64.2	0.854
Folate deficiency anemia	1	69.3	0.001	9.12	0.142	65.1	0.000
Vitamin B 12 deficiency anemia	2	85.4	0.001	9.45	0.764	68.1	0.000

Discussion

The present study has an appropriate number of subjects to give authentic results. It is observed in this study that the level of erythropoietin in AUE is lower than that in the IDA. This decreased level of concentration of erythropoietin in AUE is suggestive of its pathogenesis. When the level of EPO in iron deficiency anemia was compared to Anemia of chronic disease, AUE and CKD, the later ones showed lower levels. The eGFR of patients with CKD was significantly low. A lower level of eGFR was also observed in AUE. This low eGFR indicates that the reason behind low erythropoietin can also be a disturbance in renal function. Another reason for low EPO in AUE could be a subclinical inflammatory state due to an autoimmune or chronic inflammatory disease. Interleukin 1 and TNF-α inhibit erythropoietin synthesis in anemia of chronic disease [12]. Elderly individuals exhibit an exaggeration in the level of the inflammatory cytokine. Its rationale is not clear, however, it can be because of the aging effect of the cardiovascular system [13].

The number of bone marrow cells is reduced in old age. This leads to a decrease in the proliferation of erythropoietic stem cells. They also have a reduced reserve of bone marrow early erythroid-committed progenitors (BFU-E) as compared to young individuals [14]. This aging effect on the reserves is most likely the reason for AUE in elderly people.

The extrinsic pathway of erythropoietin may have significant participation in the pathogenesis of AUE. A low level of testosterone in sterile individuals is also a cause of anemia. Testosterone not only influences the pathway of erythropoietin but also interferes with the proliferation of BFU-E and enhances it [15].

Conclusion:

The level of erythropoietin is significantly low in elderly patients having anemia of unknown etiology. Hemoglobin and renal function is also deranged in such individuals. The results of the present study infer that decreased level of erythropoietin promotes the pathogenesis of AUE. Other mechanisms that are responsible for AUE have reduced reserves of bone marrow in aged patients, the extrinsic pathway of erythropoietin and inflammatory state due to chronic or inflammatory disease. Future interventions of pharmacology can be found by more research.

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Declaration:

Nothing to declare

Permission:

It was taken from the ethical review committee of institute

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