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Comparison of Dosage Requirement of Erythropoietin Stimulating Agent (ESA) in Maintenance of Hemoglobin Concentration in Patients Undergoing Twice Weekly Versus Thrice Weekly Hemodialysis in Pakistani Population

ORIGINAL

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Abstract

Background: Anemia is one of the major complications of patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) and is associated with left ventricular hypertrophy and also increases morbidity and mortality. Anemia in patients with CKD can be due to two major reasons; iron deficiency or erythropoietin insufficiency. Erythropoietin Stimulating Agent (ESAs) administration is the mainstay in treating anemia if the patient is iron sufficient. However, higher doses of ESAs have been associated with increased cerebrovascular and cardiovascular events. We conducted this study to see how much erythropoietin is required in our setting in iron sufficient patients to maintain hemoglobin (Hb) level and the effect of dialysis frequency on ESA doses.

Methods and Findings: A cross-sectional study was conducted at the Department of Nephrology at Ziauddin University Hospital. Patients' charts were reviewed for Hb levels and doses of ESA to maintain Hb between 10-12 mg/dl. Patients were excluded if they had iron deficiency, malignancy, were on immunosuppressive agents, had renal transplant, and with Hb >12 mg/dl or <10 mg/dl and their ferritin levels, transferrin saturation, hemoglobin concentration, frequency of hemodialysis and ESA dosage were monitored. We also compared

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these variables between patients undergoing hemodialysis thrice weekly with those undergoing hemodialysis twice a week.

A total of 105 patients were analyzed. 24 were excluded as they did not match the inclusion criteria. 81 patients were included in the study. 36 (44.4%) were males and 45 (55.6%) were females. Mean age of the patient was 56.47 ± 11.72 years. The average dose of ESA was 106.91 ± 61.47 for patients undergoing hemodialysis thrice weekly and 183.94 ± 116.71 for patients undergoing hemodialysis twice a week. Significant difference was found to exist between dosage of patients undergoing thrice weekly dialysis versus twice weekly dialysis (p=<0.001).

Our study has limitations. First our study only looked at Hb levels, iron stores and dosages of ESA, while other factors like Parathyroid Hormone (PTH) levels and Vitamin B12 were not considered that may have a role in anemia of chronic renal disease. In addition, it was a study limited to one center only and a multicenter trial should be taken to validate the results. We have reported one aspect of dialysis vintage i.e. high ESA dosage requirement

Conclusion: We found that patients undergoing hemodialysis three times a week require recommended dosage of ESA; however those undergoing hemodialysis less than three times a week require higher dosage of ESA to maintain Hb level. Here we report significant effect of hemodialysis on ESA dosage to maintain same level of Hb.

Keywords
Erythropoietin Stimulating Agents (ESAs); Anemia; Chronic Kidney Disease; Hemodialysis; Hemoglobin.

Introduction

Anemia is one of the main complications of chronic kidney disease and frequently encountered in patients undergoing hemodialysis (HD). It is associated with cardiovascular disease including left ventricular hypertrophy with resultant increase in morbidity and mortality [1]. Treating anemia is one of the cornerstones in managing patients on HD.

WHO defines anemia as hemoglobin (Hb) concentrations <13g/dl for Adult males and Hb of <12g/dl in premenopausal females [2]. In patients of HD, treatment of anemia is recommended once Hb level deceases to <10g/dl and is maintained between 10 and 11.5g/dl. [3]

Anemia in HD patients is multifactorial, with iron deficiency and lack of erythropoietin being the two most common causes [4]; other causes include GI losses, folate and Vitamin B12 deficiency and hyperparathyroidism. Hence treatment for anemia in HD patients include erythropoiesis stimulating agents (ESAs) and intravenous (IV) iron in patients who are iron deficient, being defined as transferrin saturation (TSAT) <20 % and ferritin of < 100 ng/ml. [5]

ESAs are administered to patients who are not iron deficient, in order to reduce the need for blood transfusions [6, 7] the normal starting dose of ESA is approximately 50-100IU/Kg three times per week

[8] and studies have shown that maintenance dose usually ranges between 50 and 150 U/kg three times per week, as recommended by US Food and Drug Administration (FDA). Higher doses of ESA have been associated with increased mortality and more adverse events including risks of hypertension cerebrovascular accidents (CVA) and cardiovascular events.[9]

We conducted this research to see the dosage requirement of ESA in iron sufficient patients for maintenance of Hb in our population and we also looked at the effect of dialysis vintage on ESA doses.

Method

This cross-sectional study was conducted at Hemodialysis department of Dr Ziauddin University Hospital from January 2017 to December 2017 on all HD patients undergoing dialysis for > 6 months' duration. Informed consent was taken from the patients. Charts were reviewed for Hb levels maintained over 1 month, the dose of ESA required to maintain this Hb per week, Iron profile including Ferritin levels and transferrin saturation.

Patients were excluded if they were iron deficient, those with history of malignancy, renal transplant or were on immunosuppressive agents. Patients were also excluded with history of active gastrointestinal bleeding, and those taking ESA via subcutaneous route. Patients who maintained their Hemoglobin level between 10mg/dl-12mg/dl for 1 month were included in the study that were getting ESA via intravenous route. Data was also recorded about the frequency of hemodialysis.

Statistical analysis: Data was entered on SPSS version 23. Frequencies were calculated for gender, and hemodialysis vintage (defined as frequency of hemodialysis per week). Mean and standard deviation was calculated for ESA dosage. Independent sample T test was used to compare ESA dosage in patients undergoing hemodialysis 3 times per week with those undergoing twice per week. P value of < 0.001 was considered as significant.

Results

Data of 105 patients was analyzed. 24 patients were excluded as they were iron deficient. Out of 81 patients enrolled, 36 (44.4%) were males and 45 (55.6%) were females. Mean age of the patients was 56.47 ± 11.71 years. 55/81 (67.9%) patients were on hemodialysis for more than 1 year and 26/181 (32.1%) were on hemodialysis for less than a year. 37 (45.7%) patients were getting hemodialysis thrice weekly and 44 (54.3%) were getting hemodialysis twice a week. 14 (17.3%) patients required erythropoietin dosage less than 150 units per kg whereas 67 (82.7%) patients required erythropoietin dosage greater than 150 units per kg. Average weight of patients was found to be 60.93 ± 11.85 kilogram. Laboratory findings are shown in **Table 1**.

Table 1.

Variables	Values	
Age	56.47 ± 11.712	
Gender	Males	36
	Females	45
Weight	60.93 ± 11.85	
Duration of hemodialysis	>1 year	55
	<1 year	26
Hemoglobin (g/dl)	10.42 ± 0.81	
Transferrin Saturation (%)	33.60 ± 111.96	
Ferritin (ng/ml)	539.135 ± 413.806	
Frequency of hemodialysis	3 times weekly	37
	2 times weekly	44
Erythropoietin dosage (units/kg/week)	>150	67
	< 150	14
ESA (Units/kg/wk.)	148.75 ± 102.53	

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Independent sample t tests were conducted to compare hemoglobin, ferritin, transferrin saturation and requirement of erythropoietin dosage between those patients who were getting hemodialysis thrice weekly and those who were getting hemodialysis two times per week. Statistically no significant difference was found to exist in terms of hemoglobin level, ferritin level, and transferrin saturation. However, significant difference (p=<0.001) was found to exist between ESA dosages in the two groups as shown in **Table 2**.

Table 2.

Domains/ Facets	3 times per week	2 times per week	P value
	n=37	n=44	
Hemoglobin (g/dl)	10.462 ± 0.760	10.388 ± 0.864	0.688
Transferrin saturation (%)	34.04 ± 13.43	33.23 ± 10.72	0.763
Ferritin (ng/ml)	597.64 ± 494.86	489.93 ± 328.83	0.246
ESA (Units/kg/dose)	106.91 ± 61.47	183.94 ± 116.71	<0.001

Discussion

Our study shows a strong association of dialysis vintage on dosage requirement of ESA. Patients undergoing hemodialysis less than three times per week required much higher doses to maintain Hb levels in the recommended range with same levels of iron stores.

Study conducted by Hwang et al [10] showed no difference in Hb levels in patients undergoing twice versus thrice weekly hemodialysis, however they did not look at ESA dosages. In addition, their study was conducted on patients with residual kidney function. We did not consider patient's residual kidney function; whether it has an impact is yet to be ascertained. However since majority of patients undergoing Hemodialysis at our center have little or no residual function in both groups, the results probably hold true.

Higher ESA doses have been associated with poor outcome of Hemodialysis patients. In addition, increased thromboembolic events and increased cardiovascular events and worsening hypertension [11] have been reported with higher doses of ESA. Maintaining Hb in target levels is important as Ebber and colleagues [12] have shown higher hospitalization rates in patients with lower levels of Hb.

Our study has limitations. First our study only looked at Hb levels, iron stores and dosages of ESA, while other factors like PTH levels and Vitamin B12 were not considered that may have a role in anemia of chronic renal disease. In addition it was a study limited to one center only and a multicenter trial should be taken to validate the results. We have reported one aspect of dialysis vintage i.e. high ESA dosage requirement.

In countries like ours where due to financial constraints and little or no health insurance, patients opt to undergo hemodialysis less than three times per week, while in the western world minimum hemodialysis frequency is 3 times per week and even more we need to look at the effect of dialysis vintage on quality of life and lab parameters in this population, since it may be associated with increased morbidity. In addition, we might need to consider giving these patients ESA via subcutaneous route versus IV route as it has been shown to be more efficacious with less dosing requirements. [9, 13]

Conclusion

We conclude that patients undergoing twice weekly maintenance HD require high ESA dosages to maintain hemoglobin levels compared to those that undergo 3 times per week hemodialysis and are potentially at risk of developing cerebrovascular and cardiovascular events. May be changing the route of administration might be helpful in these cases.

This article is available at: www.intarchmed.com and www.medbrary.com

Conflict of interest

Authors report that there was no conflict of interest.

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