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Original article

Prevalence and risk factors of erythropoiesis stimulating agents hyporesponsiveness in chronic hemodialysis patients attending nephrology center of Benghazi

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Abstract

Background: Anemia is quite prevalent in end stage renal disease patients. Despite availability of different forms of erythropoiesis stimulating agents, many end stage renal disease patients are anemic according to National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines. Patient and methods: we conduct a cross sectional study between May 2022 and July 2022, targeting adult chronic hemodialysis patients, to investigate the prevalence of erythropoiesis stimulating agents hyporesponsiveness, to assess if patients are receiving the appropriate weight-based dosing of these agents, and to identify additional risk factors behind inadequate response to therapy.390 end stage renal disease patients are receiving chronic hemodialysis at nephrology center of Benghazi. Incident hemodialysis patients, patients with other hematological disease or with malignancy are excluded. Finally, 150 patients met the inclusion criteria and enrolled in the study. Results: 100 (66.7%) are male, and 50 (33.3%) are females. Age is 50.6 ±13.2 years. Erythropoiesis stimulating agents hyporesponsiveness is prevalent in chronic hemodialysis patients, 130 (86.7%) patients are anemic as their Hb levels were <11 g/dl, while only 20 (13.3%) patients have Hb levels of >/=11g/dl. There is a significant relationship between gender and ESA response, as hyporesponsiveness is more observed in male patients (P < .005). We find that 105 (70%) patients are receiving an appropriate weight-based dose, while only 45 (30%) patients were giving an inappropriate dose. When the relationship between ESA dosing and patients' response to ESA is examined, we find, that despite receiving the appropriate dose, 90 (60%) patients are ESA hyporesponsive, while only 15 (10%) are responsive to the appropriate

weight-based dose. However, no statistical association is found between ESA hyporesponsiveness and age or weekly hours of dialysis. Conclusion: despite receiving an appropriate dosage of ESA, our study population shows high prevalence of ESA hyporesponsive anemic state. New strategies should be applied to detect risk factors and adopt therapeutic measures to reduce its high prevalence in hemodialysis population.

Keywords: ESA hyporesponsiveness, hemodialysis, anemia, prevalence, risk factors

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Introduction

baseline following the first month of ESA treatment with the appropriate weight-based dose (6).

Objectives of the study:

To investigate the following issues:

1. To determine prevalence of ESA hyporesponsiveness among chronic hemodialysis patients.
2. To assess if patients are receiving the appropriate weight-based dosing of ESAs.
3. Identifying additional risk factors behind inadequate response to ESA therapy

Materials & Methods

An observational cross-sectional study was conducted between May 2022 and July 2022, at the major hemodialysis unit of Benghazi city, which hosts 390 chronic dialysis patients receiving hemodialysis therapy over a three-shift schedule. Exclusion Criteria: Incident hemodialysis patients (< six months on hemodialysis

Anemia is quite prevalent in end stage renal disease patients, and deficiency of erythropoietin is a major cause of this comorbidity (1,2). Despite availability of different forms of erythropoiesis stimulating agents, still many end stage renal disease patients are anemic according to NKF-KDOQI guidelines; which define anemia in dialysis patients as a hematocrit (HCT) value less than 33% or a hemoglobin (Hb) level less than 11 g/Dl (3). The development of erythropoiesis-stimulating agents (ESA), such as recombinant human erythropoietin (rHuEPO), has resulted in substantial health benefits for patients with CKD, thereby reducing the need for transfusion in these patients (4,5). However, a significant number of CKD patients have a reduced response to ESAs, as evidenced by the persistence of anemia despite adequate dosing, or the requirement of high doses to achieve recommended Hb targets. Initial ESA hyporesponsiveness is defined by the KDIGO guidelines as the absence of a rise in Hb concentration from

Quantitative and qualitative variables were analyzed by chi square. For the statistical analysis, Statistical Package for the Social Sciences (SPSS) software (version 25) was used. P values less than 0.05 were considered significant.

Ethical approval:

Research ethics board (ERB) of Benghazi medical center approved to conduct our study in April 2022, with protocol/ letter code (in Arabic format): (104.2022).44.1.م.ط.م.ت. Written consent was obtained from patients enrolled in this study.

Results

Out of the 390 chronic dialysis patients receiving hemodialysis therapy at the major hemodialysis unit of XXXX Center, a total of 150 patients met the criteria and agreed to participate in the study. The type of ESA provided to all patients was short acting (Epoetin alfa) and was administrated via the intravenous route. Of the sociodemographic data of the patients, 100 (66.7%) were identified as male, and 50 (33.3%) were identified as female. Age ranged from a minimum of 22 years to a maximum of 84 years, with a mean±SD of 50.6 ±13.2 years. Patients underwent dialysis every week with a mean±SD of 11.1±1.5 hours.

There is a significant relationship between gender and type of ESA response as hyporesponsiveness was more observed in male patients (P < .005). However, no statistical association was found between ESA hyporesponsiveness and age or weekly hours of dialysis (Table 1).

schedule), those with acute infections or a history of hematologic disorders such as thalassemia, sickle cell disease, Myelodysplastic syndromes (MDS), and hematologic and solid organ active malignancies and patients who had received recent therapy with medications that affect hematopoiesis; such as antiviral therapy are excluded. Point-prevalent 150 hemodialysis patients older than 18 years old undergoing hemodialysis for at least 6 months are selected as a convenient sample and enrolled in the study. Demographic data and information concerning dialysis and ESA dose were obtained and recorded through direct interviews with the selected patients. Three consecutive monthly laboratory records of patients were collected and data was entered to a specifically designed software. We used mean hemoglobin level during the 3- month period of evaluation. Also, the minimum and the maximum dose of Erythropoietin therapy received by each selected patient were calculated to evaluate if they were receiving weight-based doses. Factors associated with erythropoietin resistance were evaluated and recorded according to their availability in the patients' files; data on iron status (serum iron, total iron binding capacity (TIBC), Ferritin), dialysis adequacy (serum urea and creatinine), malnutrition (serum albumin), and hyperparathyroidism through parathyroid hormone (PTH).

Statistical Analysis

Data was presented as mean ± standard deviation (SD) for quantitative variables and summarized as frequencies and percentages for categorical variables.

Table 1. The relation between gender, age, and weekly hours of dialysis with type ESA response.

	ESA Response [n (%)]			Level of Significance
	Hyporesponsive	Responsive	Inappropriate response^	
Gender				
Male	69 (46%)	9 (6%)	22 (14.6%)	*P* = .005*
Female	21 (14%)	6 (4%)	23 (15.3%)	
Age (years)				
</= 30	8 (5.3%)	2 (1.3%)	1 (0.66%)	***P* = .169**
31-40	18 (12%)	1 (0.66%)	8 (5.3%)	
41-50	19 (12.6%)	9 (6%)	12 (8%)	
51-60	20 (13.3%)	0 (0%)	9 (6%)	
61-70	20 (13.3%)	3 (2%)	13 (8.6%)	
71-80	4 (2.6%)	0 (0%)	2 (1.3%)	
>80	1 (0.66%)	0 (0%)	0 (0%)	
Weekly hours of dialysis				
>/=12 hours				
10.5 hours	66 (44%)	10 (6.6%)	33 (22%)	*P* = .657
</=9 hours	9 (6%)	3 (2%)	3 (2%)	
	15 (10%)	2 (1.3%)	9 (6%)	

^Describing patients who are not receiving an appropriate weight-based dose of ESA. P value, *significant (P<0.05), nonsignificant (P>0.05).

appropriate dose, 90 (60%) patients were found to be ESA hyporesponsive with Hb values <11g/dl, while only 15 (10%) were responsive to the appropriate weight-based dose with Hb values of >/=11g/dl, the remaining 45 (30%) patients were considered to have an inappropriate response as they were not receiving the appropriate weight-based dose, hence making the response inappropriate (Table 2), (Figure 1).

It was found that 105 (70%) patients were receiving an appropriate weight-based dose, while only 45 (30%) patients were giving an inappropriate dose. When the relationship between ESA dosing and patients' response to ESA was examined, it was found that despite receiving the

Table 2. Relationship between ESA dose and type of ESA response.

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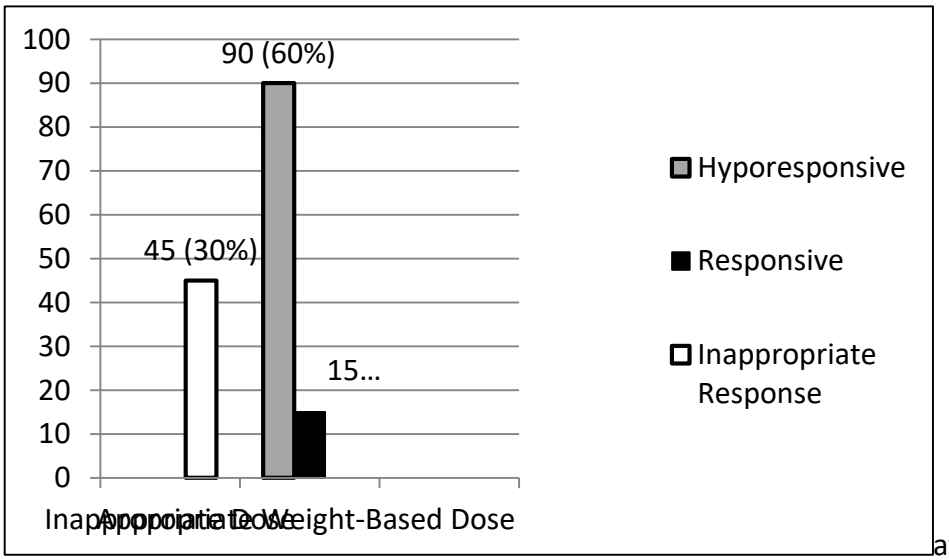
	ESA Response			Level of Significance
	Hyporesponsive	Responsive	Inappropriate response^	
Dose				*P* = .000**
Inappropriate	0 (0%)	0 (0%)	45 (30%)	
Appropriate	90 (60%)	15 (10%)	0 (0%)	

^Describing patients who are not receiving an appropriate weight-based dose of ESA. *P* value, **highly significant ($P \leq 0.001$).

Figure 1. The relationship between ESA dosing and p



atients' response to ESA. *P = 0.000*

Regarding clinical data of patients, only 28 (18.7%) were considered diabetic, while 122 (81.3%) patients did not have diabetes. 116 (77.3%) patients are hypertensive, while only 34 (22.7%) do not have hypertension. About the hepatitis C virus (HCV)13 status of patients, only 11 (7.3%) patients had positive serology for HCV, while 139

OlineISSN:2413-6096

(92.7%) had negative serology. 23 (15.3%) patients were on renin-angiotensin-aldosterone system blockers (RAAS blockers)21, while 127 (84.7%) were not on RAAS blockers. Regarding the type of vascular access, 120 (80%) patients had a fistula while 30 (20%) patients had a central venous catheter (CVC)5 as their line of access.

There was no statistical relationship between the type of ESA response and patients' clinical data (diabetes mellitus, hypertension, hepatitis C virus infection, renin-angiotensin-aldosterone system blockers, and type of vascular access).

Hb levels ranged from a minimum of 5.63 to a maximum of 12.40 with a mean±SD of 9.3±1.3. Mean corpuscular volume (MCV)23 levels ranged from a minimum of 24 to a maximum of 227 with a mean±SD of 86.2±16.4. Iron levels ranged from a minimum of 17.7 to a maximum of 274 with a mean±SD of 80.4±43.2. Regarding creatinine levels, they ranged from a minimum of 10.65 to a maximum of 237 with a mean±SD of 10.54±6.2. Urea levels ranged from a minimum of 10.65 to a maximum of 237 with a mean±SD of 125.7±39.1. Parathyroid hormone (PTH) levels ranged from a minimum of 29.9 and a maximum of 1915 with a mean±SD of 460.5±422.4. Albumin levels ranged from a minimum of 2.6 to a maximum of 5.3 with a mean±SD of 4.2±0.40 (Table 3).

There is a significant statistical association between the type of ESA response and hemoglobin level (P= .000). However, there was no statistical significance between the type of ESA response and the remaining laboratory data of patients (MCV, iron, urea, creatinine, PTH, and albumin) (Table 3).

Table 3. Laboratory data and its relation to type ESA response.

	ESA Response			Level of Significance
	Hyporesponsive	Responsive	Inappropriate Response^	
Hemoglobin				
<11 g/dl	90 (60%)	0 (0%)	40 (26.6%)	*P* = .000**
>/=11 g/dl	0 (0%)	15 (10%)	5 (3.3%)	
MCV				
<80 fl	17 (11.3%)	1 (0.6%)	6 (0.6%)	
>/=80</=100 fl	72 (48%)	13 (8.6%)	38 (25.3%)	*P* = .462
>100 fl	1 (0.6%)	1 (0.6%)	1 (0.6%)	
Iron				
<37 mcg/dl	8 (5.3%)	1 (0.6%)	4 (2.6%)	
	77 (51.3%)	14 (9.3%)	38 (25.3%)	*P* = .887

>/=37</=158 mcg/dl	5 (3.3%)	0 (0%)	3 (2%)	
>158 mcg/dl				
Urea				
</=120 mg/dl	28 (18.6%)	9 (6%)	19 (12.6%)	*P* = .073
>120 mg/dl	62 (41.3%)	6 (4%)	26 (17.3%)	
Creatinine				
</=7 mg/dl	11 (7.3%)	4 (2.6%)	5 (3.3%)	*P* = .273
>7 mg/dl	79 (52.6%)	11 (7.3%)	40 (26.6%)	
PTH				
<300 pg/ml	28 (18.6%)	6 (4%)	14 (9.3%)	
>/=300-</=540 pg/ml	16 (10.6%)	4 (2.6%)	7 (4.6%)	*P* = .747
>540 pg/ml	32 (21.3%)	2 (1.3%)	15 (10%)	
Albumin				
<3.5 g/dl	2(1.3%)	0 (0%)	0 (0%)	*P* = .509
>/=3.5 g/dl	88 (58.6%)	15 (10%)	45 (30%)	

^Describing patients who are not receiving an appropriate weight-based dose of ESA. MCV, mean corpuscular volume; PTH, parathyroid hormone. *P* value, nonsignificant (*P*>0.05), **highly significant (*P*≤0.001).

Discussion

Prevalence of Anemia

Anemia is a common complication in CKD patients and ESA therapy has been the corner-stone strategy to optimize Hb level in these patients. The results of our study showed that 130 (86.7%) patients were found to be anemic (Hb < 11 g/dl) with a mean Hb level of 9.35 ± 1.3 g/dL (2). This is in comparison with Alsaeiti K. et al. that showed a mean hemoglobin level of <10g/dl hemodialysis patients in Benghazi, Libya (2018) (7). These findings suggest that anemia prevalence in these patients has been taking an upward scale in the past couple years (8-10). Other cross-sectional studies by Kamal et al. (11), and Alemu B et al. (12), showed high percentages of anemia in hemodialysis patients, (53%) and (53.5%), respectfully. The disparity of the prevalence could be due to differences in the study methodology, variation of quality of care and quality of reporting, policy, and strategic difference (2). The present study has failed to demonstrate significant association between anemia and gender. This is in contrast to Alemu B et al. (12) which revealed that females were 2 times more likely to develop anemia than their male counterparts. Moreover, no relation was found between anemia and age as supported by Alemu B et al. (12).

ESA Hyporesponsiveness

Initial ESA hyporesponsiveness is defined by the KDIGO (2012) as the absence of a rise in Hb concentration from baseline following the first month of ESA treatment with the recommended weight-based dose. Whereas anemia in dialysis patients is defined as a HCT value less than 33% or a hemoglobin level less than 11 g/dL, according to KDIGO guidelines. Our study sample has shown that; 90 patients (60%) were found to be hypo-responsive, 15 patients (10%) were responsive, and 45 patients (30%) received inadequate dosage, demonstrating a high prevalence among dialysis patients in Benghazi when compared to other studies of similar fashion (13-16).

J Rosser et al. (17) carried out of a sample size of 93 patients, and 14 (15%) were hypo-responsive. Another study by J Luo et al. (18). demonstrated that 12,361 (12.5%) of the hemodialysis patients treated at a large dialysis facility between 2012 and 2013 (N=98,972) were found to have ESA hypo-responsiveness (19) . Locatelli F et al. (20), showed similar results. These findings may indicate inadequacies in dosage of epoetin, inefficient dialysis or other risk factors present in our patients that may affect drug efficiency.

Regarding the significance of gender with the prevalence of ESA resistance, our results showed that males were more likely to suffer ESA hypo-responsiveness (n=69 (76.7%)), and further analysis revealed a significant relationship between gender and ESA hypo-responsiveness in male patients (P < .005). Ingrasciotta Y et al. (21), also found that ESAs were in general more frequently used by males among CKD patients. It can be assumed that due to increased use of ESA's it could be a contributing factor for developing resistance to male patients.

ESA Dosage

According to KDOQI clinical practice guidelines, the appropriate epoetin dosage starts initially at 50-100 u/kg divided over two to three times per week based the patient's body weight and Hb level (22). Our study sample (150 patients), 45 patients (30%) are found to receive inappropriate doses, this may be due to lack of local guidelines to guide staff on administering adequate weight-based ESA doses and problems with drug availability. This is an issue as the correction of anemia or maintenance of Hb values in these patients depend on accurate weight-based dosing of ESAs. Previous studies (23-25) determined a significant relationship between weight and ESA dose. Thus, weight-based dosing should be put into **consideration.**

Predicting Factors of Hyporesponsiveness

Non-compliance, functional or absolute iron shortage, and inflammation are the most reported causes of ESA hyporesponsiveness. Due to the limited data available in the hospital file records, the current study discussed only the factors that could be provided by the patients' files. The most common cause of ESA hyporesponsiveness is absolute iron deficiency (defined as a ferritin concentration less than 100 µg/L with or without reduced transferrin saturation (TSAT) levels) or functional iron deficiency (defined as a ferritin concentration greater than 100 µg/L associated with a TSAT <20%) (26-28). Adequate I.V. iron therapy has now been widely recognized as a

crucial strategy for optimizing the hematologic response to ESA (29,30). Our study demonstrated that iron levels ranged from a minimum of 17.7 to a maximum of 274 with a mean±SD of 80.4±43.2 with no significant relation to ESA response. Samvat S. et al. revealed similar results (31). Ingrasciotta Y. et al. (21) reported that concomitant use of iron preparations was a protective factor against ESA hyporesponsiveness. Similarly, De Vita et al. (32) demonstrated that hemodialysis patients receiving EPO and IV iron achieved a higher hemoglobin at a lower EPO dose.

The current study used serum urea and creatinine levels as a crude measure for dialysis adequacy as the Kt/V number, which is standard parameter used for dialysis adequacy assessment, was not available. Mean serum urea was 125.7 ±39.1mg/dl and 62% of patients had a serum urea of >120 mg/dl, whereas, mean serum creatinine was 10.54 and 86.75% of patients had a serum creatinine of >7. And when examined with ESA response, no statistical relation was found. However, Kamal et al. (11) and Samvat S. et al. (31) results supported our findings. A number of prospective and retrospective studies have demonstrated a clear relationship between dialysis adequacy and the dose of Erythropoietin, not only it reduces morbidity and mortality but also improves patient response to erythropoietin therapy by removing small, and possibly middle/large molecules that may inhibit erythropoiesis, and therefore, anemia correction will be reflected in a higher percentage of patients (13, 33).

Hyperparathyroidism on the other hand has been one of the frequently implicated factors of ESA hyporesponsiveness, via direct inhibitory effects of PTH hormones on erythropoiesis, as well as indirect effect by bone marrow fibrosis (34-36). Our study confirmed that out of the 150 participants, 76 (50.7%) patients had their PTH level higher than the range recommended by KDIGO in stage CKD 5D patients (2-9 folds the upper normal range) (37). However, no statistical association was found when examined with ESA hyporesponsiveness. However, Mandolfo et al. (38) observed a 20% increase in hemoglobin level despite a 34% decrease in EPO dosage in 19 dialysis patients following parathyroidectomy. Comparable results were reported by Lee et al. (39) in 32 hemodialysis patients undergoing parathyroidectomy. Correspondingly, other statistically significant results were reported by Neves et al. (40) where 11 elderly CKD patients with secondary hyperparathyroidism showed 12% increase in hemoglobin level, without a significant change in ESA dosage, after being treated for 12 months with regular IV calcitriol.

The present study showed a mean serum albumin level of 4.2±0.40 mg/dl with only 2 patients out of the 150 participants had albumin level below 3.5mg/dl, with no significant association with hyporesponsiveness. Alemu et al. (12) and Afsar et al. (41) supported these findings. Kalantar et al (42) carried out (2002-2003) on 339 maintenance hemodialysis patients showed that serum albumin level had negative correlations with indices of refractory anemia (43). Another cross-sectional study of hemodialysis patients by Locatelli F. et al. (20) found that lower Body Mass Index (BMI) and serum albumin are more among hypo-responders to ESA. These findings suggest that improving

nutritional state in dialysis patients may also improve anemia and lead to lower required EPO dose. (44,45)

The use of RAAS blockers such as ACE inhibitors/ARBs has been linked to ESA hyporesponsiveness (46). Our data revealed that 23 patients (15.3%) were using a RAAS inhibitor, with only 18 of them showing hyporesponsiness to ESA. However, no significant association was found between the two variables. A cohort study by Ingrasciotta Y. et al. (21) confirmed that ESA hyporesponsiveness was decreased by concomitant use of high dosage ACE inhibitors/ARBs in CKD patients. On the contrary, Kamal et al. (11) and Samvat S. et al. (31) results showed that the use of ACE inhibitors/ARBs is a predictive factor for ESA hyporesponsiveness. Qureshi IZ et al. (47) showed that the monthly increase in HCT% was considerably higher in dialysis patients treated with erythropoietin and antihypertensives other than ACE inhibitors/ARBs compared to those treated with them. Previous literature showed that ACE inhibitors and ARBs are associated with a poor response to ESA therapy. It was suggested that these antihypertensive drugs may interfere with erythropoiesis as the activation of renin-angiotensin system enhances the erythropoietin production hence, its inhibition by these drugs can precipitate anemia (48,49). Another potential mechanism considered is the reduction of certain cytokines, such as interleukin-12, and/or of insulin-like growth factor-1, which physiologically stimulate erythropoiesis (50).

Hypertension and diabetes are recognized as leading causes of end-stage renal disease (51), Our study sample of 150 patients, 117 (77.3%) were hypertensive and 28 (18.3%) were diabetic and showed no significant relationship to hyporesponsiveness. These findings coincide with previous results demonstrated by Kamal et al (11) which followed 97 chronic hemodialysis patients and found that there was no statistically significant difference in response between dialysis patients regarding the clinical data and also with regard to the comorbidities which included diabetes and hypertension. Samavat et al (31) confirmed that diabetic status played no major factor in determining the level of hyperresponsiveness. These findings show that comorbidities in themselves like diabetes and hypertension may not have a direct effect on ESA hypo-responsiveness but the aftermath of these conditions, like the use of ACEi/ARBs in the treatment of hypertension, should be focused on in **further research.**

Limitations

The cross-sectional design of the study means that it can only estimate the presence and strength of the associations between the explored variables, but cannot investigate the direction of the link between the cause and EPO hyporesponsiveness. Moreover, other predicting factors of hyporesponsiveness such as inflammatory markers (CRP) and markers of nutritional deficiencies (vitamin B12 and folate) could not be investigated. Finally, although widely used in the literature, the terms hyporesponsiveness is problematic to define as one cannot measure red cell formation easily, like other authors, we used Hb levels as a surrogate.

Implementations

This study brings us one step towards a better understanding of erythropoietin therapy hyporesponsiveness, as well as the factors that are involved in the process of response to EPO. Elucidating these factors not only contributes to a better correction of anemia state, but also provides relevant clinical implications in anemia management in CKD patients to optimize the efficacy of ESA therapy.

Main research outcome points:

There is high prevalence of ESA hyporesponsiveness (60%) in chronic hemodialysis Libyan patients with hemoglobin below target level (<11 g/dL)

ESA hyporesponsiveness is more prevalent in male patients (67%) compared to female patients (33%) P <0.05

Examining the relationship between ESA dosing and patient response, it shows that, most patients are receiving appropriate weight-based ESA dosage, indicating other risk factors are underly ESA **hyporesponsiveness**

Further longitudinal (case-control) studies are required to address risk factors for ESA hyporesponsiness in chronic hemodialysis patients, despite receiving adequate ESA dosage

Conclusion

ESA hyporesponsiveness is commonly observed in patients with anemia secondary to chronic kidney disease. Our results showed that ESA hyporesponsiveness is prevalent in this population, and despite receiving an appropriate dosage of ESA, most patients were found to be hyporesponsive. Finally, the current study signifies the need for a future longitudinal study to further explore other predicting factors of ESA response, including functional/absolute iron deficiency anemia, chronic inflammatory state (CRP, IL-6), inadequate dialysis (weekly standard Kt/V) and uncontrolled hyperparathyroidism, to further explore their detrimental effect on ESA response.

Conflict of interest

No conflict, this research has been conducted without commercial or support from any manufacturers.

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