Association of Dialysis Adequacy, Physical and Emotional Symptoms with Erythropoietin-stimulating agent Responsiveness in Iraqi Patients Undergoing Hemodialysis

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Abstract:

Background: Erythropoietin (EPO)-deficient anemia occurs in patients with chronic kidney disease (CKD). Erythropoietin-stimulating agents (ESAs) are the standard treatment for CKD anemia, but patient responses vary. Hemodialysis patients are often anemic due to hypo erythropoiesis and their chronic inflammatory state. Inadequate dialysis is considered one of the factors that are linked to ESA hypo responsiveness. Dialysis patients may experience many symptoms that lower their quality of life. End stage renal disease (ESRD) symptoms are assessed using Dialysis Symptom Index (DSI).

Objective: The current study was designed to measure the association between physical, and emotional symptoms and ESA responsiveness. Also, to determine how dialysis adequacy affects response level.

Materials and Methods: The current study included 150 CKD anemic patients in a multicenter dialysis unit. patients were examined for the response to Epoetin alfa (Eprex) after 12 weeks in this cross-sectional study. Clinical, demographic, and laboratory data were collected. The erythropoietin resistance index (ERI) evaluated the effect of erythropoietin dosage on hemoglobin levels. Dialysis adequacy (Kt/V) measured the efficacy of dialysis. The severity of symptoms was evaluated using the 30-question Dialysis Symptom Index (DSI).

Results: 150 patients in all were enrolled, with a mean age of 51.6 ± 14.9 for the male patients. There was a significant difference in kt/v among study groups, mainly between hypo response and resistance groups (P-value < 0.01). However, there was no statistically significant difference in the DSI mean (P = 0.4). kt/v was positively correlated with the duration of dialysis and parathyroid hormone (PTH) (R = 0.27, P-value < 0.001), (R = 0.19, P-value = 0.01). additionally, The DSI was strongly connected with the age of the patients (R = 0.18, P-value = 0.02).

Conclusion: One of the main causes of Eprex resistance in this study was insufficient dialysis. Patients who received longer hemodialysis sessions exhibited higher hemodialysis sufficiency. However, there was no significant association between DSI and degree of response across research groups, and older hemodialysis patients experienced higher dialysis-related symptoms.

Keywords: ESRD, Anemia, ESA, Kt/V, dialysis symptom index.

ارتباط كفاية غسيل الكلى والأعراض الجسدية والعاطفية مع الاستجابة ل عامل محفز للإريثروبويتين لدى المرضى العراقيين الذين يخضعون لغسيل الكلى

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الخلاصة:

الخلفية: يحدث فقر الدم الناجم عن نقص الإريثروبويتين في المرضى الذين يعانون من مرض الكلى المزمن. العوامل المحفزة للإريثروبويتين هي العلاج القياسي لفقر الدم، لكن استجابات المريض تختلف. غالبا ما يعاني مرضى غسيل الكلى من فقر الدم بسبب نقص كريات الحمر وحالتهم الالتهابية المزمنة. يعتبر غسيل الكلى غير الكافي أحد العوامل المرتبطة بنقص استجابة ESA. قد يعاني مرضى غسيل الكلى من العديد من الأعراض التي تقلل من جودة حياتهم. يتم تقييم أعراض الداء الكلوي بمراحله الأخيرة باستخدام مؤشر أعراض غسيل الكلى.

الهدف: تم تصميم الدراسة الحالية لقياس العلاقة بين الاعراض الجسدية والعاطفية والاستجابة لل ESA. أيضًا، لتحديد كيفية تأثير كفاية غسيل الكلى على مستوى الاستجابة.

الطريقة: شملت الدراسة الحالية ١٥٠ مريضًا مصابا بمرض الكلى المزمن وفقر الدم في وحدة غسيل الكلى لمراكز متعددة. تم فحص المرضى للاستجابة ل ESA(Eprex) بعد ١٢ أسبوعًا في هذه الدراسة المقطعية. تم جمع البيانات السريرية والديموغرافية والمخبرية. قيم مؤشر مقاومة إرثروبويتين تأثير جرعة إرثروبويتين على مستويات الهيموجلوبين. قام Kt / V بقياس فعالية غسيل الكلى. تم تقييم شدة الأعراض باستخدام مؤشر أعراض غسيل الكلى المكون من ٣٠ سؤالاً.

النتائج: تم تسجيل ١٥٠ مريضاً بمتوسط عمر ٥١.٦ ± ١٤.٩ للذكور. كان هناك فرق معنوي في kt / v بين مجموعات الدراسة، بشكل رئيسي بين استجابة نقص الاستجابة ومجموعات المقاومة (P<٠.٠١). ومع ذلك، لم يكن هناك فرق معتد به إحصائيا في متوسط DSI (P=٠.٤). ارتبط kt / v بشكل إيجابي مع مدة غسيل الكلى وهرمون الغدة الدرقية (R=٠.٢٧ ,p <٠.٠٠١)، (R=٠.١٩ ,p =٠.٠١) بالإضافة إلى ذلك، ارتبط مؤشر DSI ارتباطًا وثيقًا بعمر المرضى (R=٠.١٨ ,p =٠.٠٢).

الاستنتاج: أحد الأسباب الرئيسية لمقاومة Eprex في هذه الدراسة هو عدم كفاية غسيل الكلى. أظهر المرضى الذين خضعوا لجلسات غسيل كلى أطول كفاءة أعلى في غسيل الكلى. ومع ذلك، لم يكن هناك ارتباط بين DSI ودرجات الاستجابة عبر مجموعات البحث، وعانى مرضى غسيل الكلى الأكبر سنًا من أعراض مرتبطة بغسيل الكلى.

الكلمات المفتاحية: الداء الكلوي بمراحله الأخيرة، فقر الدم، ESA، Kt / V، مؤشر أعراض غسيل الكلى.

Introduction

Chronic kidney disease (CKD) involves long-term renal impairment or an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 for three months [1]. CKD can leads to end-stage renal disease (ESRD) which is characterized by severe renal failure and a GFR of less than 15 mL/min.The US Renal Data System reported 124,411 new ESRD diagnoses in 2015. 20,000 new cases occur annually [2]. Iraq indicated ESRD prevalence is 52 pmp, and the Ministry of Health reported in 2018 that there has been an increase of almost 20% annually in the number of individuals with chronic renal disease who require hemodialysis therapy worldwide [3,4]. ESRD may rise sharply in the following decades due to population aging and an increasing prevalence of diabetes and hypertension [5]. ESRD symptoms might include a variety of physiological abnormalities. These include volume overload that cannot be treated with diuretics, hypertension that is difficult to control with medication, anemia, mineral

and bone disorders, and metabolic imbalances [2].

Maintenance dialysis patients have physical and emotional issues and severe symptoms that increased dialysis patient mortality [6]. Up to 50% of dialysis patients suffer from musculoskeletal pain, dialysis-associated pain, peripheral neuropathy, and peripheral vascular disease. Secondary hyperparathyroidism produces bone pain, whereas polycystic kidney disease causes chronic stomach discomfort [7].

Non-pain symptoms also lower the quality of life of ESRD patients. Patients report fatigue, pruritus, sleepiness, dyspnea, edema, dry mouth, muscle cramps, restless legs syndrome, loss of appetite, poor concentration, sleep disturbance, and constipation [7]. Validated evaluation tools can improve patient-provider communication about symptom presence and severity. The Dialysis Symptom Index (DSI) is used to assess particular symptoms in CKD and ESRD patients [6].

Hemodialysis (HD) and peritoneal dialysis (PD) are the main lifesaving treatments for ESRD patients. Hemodialysis is the most common form of dialysis and according to the United State Renal Data System (USRDS), 400,000 people in the United States are on hemodialysis [8,9]. Hemodialysis aids in the removal of excess water and toxins from the body by transferring blood from the patient to a specific machine (artificial kidney) and then returning it to the patient's bloodstream [10]. The usual hemodialysis (HD) session lasts four hours, three times a week. The adequacy of hemodialysis refers to how well toxins and waste products are removed from the patient's blood. The urea removal indexes help to calculate the adequacy of hemodialysis ([11].

The gold standard indicator of dialysis adequacy for assessing the removal of uremic toxins during dialysis is Kt/V. Multiplying the dialyzer urea clearance (K) by the time spent on dialysis (t) and dividing the resulting number by the patient's urea distribution volume (V) yields the Kt/V ratio. A Kt/V value of ≥1.3 is considered to be on target [12,13]. The insufficient dose of dialysis is a crucial factor that leads to anemia in these patients[14].

Anemia is a prevalent complication of CKD patients and as kidney function declines, anemia typically becomes more severe [15]. This medical issue can cause symptoms that lower the quality of life, such as tiredness, shortness of breath, trouble sleeping, headaches, and impaired cognitive capacity [16]. Decreased erythropoietin (EPO) synthesis and iron deficiency, are the principal causes of anemia in CKD [17].

Erythropoietin stimulating agents (ESAs) are the standard treatment for CKD anemia and improve outcomes. Dialysis patients should maintain hemoglobin levels of 11–12 g/dL with ESA therapy. Approximately 10-15% of individuals receiving erythropoietin therapy may be less receptive to the treatment [18,19]. Inadequate dialysis is considered one of the factors that are linked to ESA hypo responsiveness [20].

The current work was designed to quantify the association between the severity of physical and emotional symptoms and ESA responsiveness, using DSI. Also, to determine how dialysis adequacy affects response level.

Materials and Methods

This cross-sectional study examined the response to ESA (Eprex) therapy after 12 weeks for ESRD and anemia patients on regular HD. It included 150 patients from dialysis units in Al-Emamian Al-Kadumian Medical City, AL-Karama Teaching Hospital, and Balad General Hospital by using the GAMPRO AK98 and Fresenius dialysis system.

The inclusion criteria were patients with age over 18 years with baseline

hemoglobin (Hb) less than 11 gm/dl and had 3-4-hour regular hemodialysis sessions (1–3) per week who received Eprex for 12 weeks. Patients who did not get treatment regularly and had a history of blood loss, active bleeding, active hemolysis, blood transfusion during ESA treatment, kidney transplant, polycystic disease, hematologic condition, and cancer were excluded.

Age, gender, smoking history, length and frequency of dialysis, ESA dose (IU/W), body mass index (BMI), iron type and dosage, comorbidities like coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, other medications like Angiotensin converting enzyme inhibitor (ACEi), Angiotensin receptor blockers (ARBs), and statins, and dialyzer type (high flux or low flux) were collected by using a data sheet. After 3 months of treatment, blood samples were collected pre-dialysis and before heparin, while the baseline Hb level was obtained from patient file. Erythropoietin resistance index (ERI) was calculated over three months by dividing the weekly weight-adjusted EPO dose (IU/kg/week) by the hemoglobin level (g/dL). Individuals were classified as responsive (ERI= 5), hyporesponsive (ERI=5-15), or resistant (ERI>15) [21]. To assess dialysis adequacy, the kt/v was activated during the first minutes and recorded 5 minutes before the end. After three months of treatment, symptom severity was assessed by the 30-question DSI. Dialysis Symptom Index scores range from 0 to 120, with higher ratings indicating more severe symptoms [6].

Statistical analysis

The data were statistically analyzed by using Excel and R (version 4.2.2). As statistical tests, mean, standard deviation, median with range, percentage, $\chi 2$ test with yates' correction or Fisher's exact test, ANOVA test (one way), Kruskal-Walli's rank-sum tests, post-hoc test, Pearson's product-moment, and Spearman's rank correlation coefficient were used. Statistical significance was determined as a P-value of ≤ 0.05.

Results

A total of 150 patients were enrolled, among whom 58.6% were male, with a mean age of 51.6 ± 14.9 years. As shown in **Table 1**.

Table 1: Patient's demographics and disease characteristics.

Characteristics	Overall, N= 150
Age, years	51.6 ± 14.9
≥ 50 years	88 (58.6%)
18-50 years	62 (41.4%)
Gender	
Males	86 (57.3%)
Females	64 (42.7%)
BMI, kg/m^2	26.0 ± 5.7
>24.9	79 (52.7%)
18.5-24.9	64 (42.1%)
<18.5	7 (4.3%)
Co-exiting disease (No. of diseases)	1.5 ± 0.8
Yes	135 (90.0%)
No	15 (10.0%)
Drug use(ACEi, ARBs, statin)	

Characteristics	Overall, N= 150
Yes	101 (67.3%)
No	49(32.7%)
Type of dialyzer	
low flux	82 (54.6%)
high flux	68 (45.4%)
Smoking status	
Non-smoker	132 (88.0%)
Smoker	18 (12.0%)
Duration of dialysis	36.6 ± 27.7
≥ 24 (months)	103 (68.7%)
< 24 (months)	47 (31.3%)
Frequency of dialysis times/w	2.6 ± 0.5
3	96 (64.0%)
2	53 (35.3%)
1	1 (00.7%)

Data are expressed as Mean ± SD; N: number, %: percentage. (ACEi: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blockers).

In this study, dialysis adequacy (Kt/V) had a significant effect on erythropoietin response (p=0.016). The difference was mostly between hypo response and resistance groups (P-value < 0.01), as demonstrated in **Table 2**.

Table 2: Patients responsiveness according to dialysis adequacy

Characteristics	Response, N = 3	Hypo-response, N= 81	Resistance, N = 66	P-value
Dialysis Adequacy (Kt/V)	0.96 ± 0.1	0.99 ± 0.2	0.88 ± 0.2	**0.016**

Data are expressed as Mean ± SD; *p*-value recorded using One-way ANOVA, post-hoc test, P <0.05: Significant.

We also found that dialysis patients with higher ERI levels had higher symptom severity scores. There was no statistically significant difference in the DSI mean (P = 0.4), as shown in **Table 3**.

Table 3: Patient's responsiveness according to dialysis symptom index (DSI).

Characteristics	Response, N = 3	Hypo-response, N= 81	Resistance, N = 66	P-value
Dialysis Symptoms Index (DSI)	33.0 ± 21.1	44.7 ± 17.3	46.9 ± 17.6	0.4

Data are expressed as Mean ± SD; *p*-value recorded using One-way ANOVA, post-hoc test, P > 0.05: Not significant.

The results of the study's parameter correlation revealed a highly significant positive association between Kt/V and the duration of dialysis (R = 0.27, P-value< 0.001). Additionally, the patient's age and the DSI were positively correlated (R = 0.18, P-value = 0.02), as shown in **Table 4**.

Table 4: Correlation between Kt/V, DSI, and patient demographics

Characteristics	Kt/V*	P-value**	DSI*	P-value**
Age, years	-0.12	0.13	0.18	**0.02**
BMI	-0.05	0.51	0.07	0.35
Duration of dialysis	0.27	< **0.001**	-0.14	0.08
Frequency of dialysis/w	0.06	0.46	0.004	0.95

*Correlation coefficient(r); ** p-value recorded using Pearson's product-moment correlation. (Kt/V: dialysis adequacy; DSI: dialysis symptom index; BMI: body mass index).

However, there was no significant correlation was obtained between ERI and Kt/V or DSI as shown in **Table (5)**

Table 5: correlation between ERI, Kt/V, and DSI of the study groups

Characteristics	KT/V*	P-value**	DSI*	P-value**
Dialysis Symptoms Index (DSI)	-0.14	0.093		
Erythropoietin Resistance Index (ERI)	-0.02	0.77	0.11	0.15
Dialysis Adequacy (KT/V)			-0.14	0.093

*Correlation coefficient(r); **p-value recorded using Pearson's product-moment correlation

Furthermore, we also found that the parathyroid hormone (PTH) level had a direct correlation with dialysis adequacy (R = 0.19, P-value = 0.01).

Table 6: Correlation between Kt/V, DSI, and different parameters of the study groups

Characteristics	Kt/V*	P-value**	DSI*	P-value**
Medication				
Dose of Eprex iu /w	-0.04	0.58	0.10	0.19
Dose of iron (mg)	-0.05	0.61	0.01	0.90
Biochemicals				
Serum iron	0.008	0.91	-0.06	0.41
Total Iron Binding Capacity (TIBC)	-0.002	0.97	-0.07	0.39
Transferrin saturation	-0.03	0.67	-0.04	0.60
Ferritin	-0.12	0.14	0.05	0.53

Serum Ca^{+2}	-0.02	0.80	-0.01	0.88
Serum Po4	-0.06	0.40	0.05	0.51
PTH	0.20	**0.01**	-0.03	0.67
Hemoglobulin				
Hb pre-dialysis	0.03	0.68	-0.09	0.24
Hb post- dialysis	0.01	0.89	-0.14	0.08
Hb change	-0.02	0.76	-0.03	0.69

*Correlation coefficient(r); **p-value recorded using Pearson's product-moment correlation; Spearman's rank correlation.(DSI: dialysis symptom index; PTH: parathyroid hormone; Hb: haemoglobin).

Discussion

Erythropoietin stimulating agent responsiveness was assessed by ERI in generally stable chronic HD patients after three months of therapy. Also, this study examines the relationship between dialysis adequacy, dialysis symptoms index, and response levels. According to dialysis adequacy data, Kt/V has a major impact on the response to erythropoietin.

The current research found that ESA resistance was associated with lower Kt/V values, which is similar to previous study [22]. Uremic toxins degrade CKD patients' erythrocytes and diminish EPO and erythropoiesis. Dialysis causes blood loss by mechanically damaging erythrocytes. The pathophysiological mechanism linking inadequate dialysis to the lack of response to ESA is currently unknown, however, inflammation and vascular access issues may contribute to a poorer response [18]. The Kt/V of all ERI groups in the study population was less than the target level, indicating that patients were getting an inadequate dose of dialysis.

Due to various variables, including the discovery that increased blood flow rate (BFR), is associated with faster clearance. This was shown from the findings of Kt/V values of 1.2 (200-250 ml/min, 20%; 251-300, 35.6%; and more than 300, 63.3%) [23]. In this study, most patients' blood flow rates were between 200 and 250 because ESRD patients are more likely to have cardiovascular disease and cannot tolerate higher BFR. In China, excessive blood pump flow often disturbs patients and impairs heart function and hemodynamics. As a result, high blood pump flow rates are denied by Chinese hemodialysis patients. The mean set blood pump flow rate of hemodialysis in Chinese study was 223.63 19.80 mL/min, which is significantly lower than in other countries. However, long-term dialysis at a low flow rate may result in an inadequate therapy [24].

Hemodialysis session clearance is strongly correlated with dialysis time. Most of our participants didn't commit to the required time, hence the Kt/V didn't meet the target this corresponds to the Lambie, *et al.* study [25]. Hunger, anemia, premature discontinuation of HD sessions, infection, poor blood flow from vascular access, bouts of hypotension, technical reasons, study design, and sample size also affect dialysis adequacy [23].

Eprex treats anemia in CKD patients, reducing symptoms, and the DSI is a validated tool for assessing these symptoms [6,26]. Symptoms worsened when patients did not respond to treatment [27], and dialysis patients with greater ERI levels had higher ratings, but the findings revealed no significant difference in DSI across study groups.

Additionally, in this study, dialysis adequacy was positively correlated with dialysis duration ($R = 0.27$, $P < 0.001$). This is because extended HD treatment duration improves patient adaptation and efficacy. These results are in agreement with the study of Rezaiee, *et al.* (2016), who found a strong relationship between HD duration (months) and adequacy [28].

The data also demonstrated a significant positive association between age and DSI (R = 0.18, P-value = 0.02). WANG, *et al.* (2022), observed that older patients on hemodialysis had more dialysis-related symptoms. Older patients are more likely to have issues and a shorter treatment survival time [29].

The PTH level also correlated with dialysis adequacy (R = 0.19, P-value = 0.01). Previous research demonstrated no statistically significant relationship between Kt/V and PTH [30]. In HD patients, phosphate homeostasis is lost due to the progressive loss of functioning nephrons, resulting in persistent hyperphosphatemia [31]. When the product of serum phosphorus is increased, hyperphosphatemia causes the formation and progression of secondary hyperparathyroidism [32]. Hyperparathyroidism can be treated with oral binders, vitamin D analogs, or the calcimimetic cinacalcet by lowering PO4 and PTH levels. Etelcalcetide, a new IV calcimimetic given at the end of HD treatment sessions, decreases PTH in clinical trials [33,34]. Patients in our study do not adhere to their prescribed therapies due to the high cost and lack of hospital access. As a result, despite good Kt/V levels, PTH levels remained elevated. Further research with substantial sample sizes and countrywide is required. Medical staff should be trained on how to turn on the device and how to correctly calculate Kt/V to establish a detailed plan to improve HD adequacy and reduce mortality.

Conclusion: From the results obtained, inadequate dialysis was one of the main causes of ESA resistance. Patients who received longer hemodialysis sessions exhibited higher hemodialysis sufficiency. However, there was no significant association between DSI and degree of response across research groups, and older hemodialysis patients experienced higher dialysis-related symptoms. Giving the optimum HD dose could assist enhance HD adequacy.

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