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Original Research

Assessing the Effectiveness and Safety of Erythropoietin Treatment in Individuals with Chronic Kidney Disease

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ABSTRACT:

Background: Anemia is a prevalent complication of chronic kidney disease, and the interconnection between hematopoiesis (the process of blood cell formation) and the kidneys was initially acknowledged by Richard Bright in 1835. He identified the link between anemia and chronic renal failure. A substantial portion of the health issues experienced by patients with renal failure can be attributed to the complications arising from chronic anemia, underscoring the importance of managing anemia as part of their overall care. **Methods**: This study was conducted. Study Period was for 2 years who are on haemodialysis for duration of six months to two years. For this a total number of 92 participants were screened. All 92 patients were given erythropoietin [EPOFIT] manufactured by INTAS pharmaceuticals by subcutaneous route. **Results**: During the course of the study, patients will undergo a series of laboratory investigations at specific time points. At the beginning of the study and at its conclusion, assessments will be made for parameters including hemoglobin (Hb), hematocrit (Hct), reticulocyte count, red blood cell (RBC) counts, serum ferritin levels, and transferrin saturation (TSAT). **Conclusion**: Out of the 92 patients included in the study, a majority of 62 patients responded to the regular conventional dose of 50 units/kg/dose of erythropoietin, while a smaller subset of 18 patients required an increased dose of 75 units/kg to achieve the target hemoglobin level. The study's findings demonstrated a progressive increase in hemoglobin levels, with 77% of patients showing improvement after 4 weeks of treatment. However, at the end of the 12-week study period, 23% of patients still had not reached the target hemoglobin level, suggesting varying responses to the treatment among the patient population.

Keywords: Erythropoietin, Anaemia, Chronic Kidney Disease, Haemoglobin.

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INTRODUCTION

Anemia is a common complication in individuals with chronic kidney disease, and the intimate connection between hematopoiesis (the process of blood cell production) and the kidneys was initially recognized by Richard Bright in 1835 when he identified the link between anemia and chronic renal failure. Much of the health challenges faced by patients with renal failure can be attributed to the consequences of their chronic anemia.Anemia is defined by the World Health Organization (WHO) as having a hemoglobin level below 13 g/dl in men and below 12 g/dl in women. The National Kidney Foundation (NKF) recommends an evaluation for anemia when hemoglobin falls below 13 g/dl in men and below 12 g/dl in women[1]. The prevalence of anemia varies with the degree of renal impairment, and it tends to worsen as kidney disease progresses. End-stage kidney failure patients almost universally experience anemia due to insufficient production of erythropoietin, a hormone that stimulates red blood cell production.The pathogenesis of uremic anemia involves several contributing factors, but inadequate secretion of erythropoietin is the primary cause. Anemia in chronic kidney disease is also associated with functional and mobility impairment, an increased risk of strokes, and a reduced health-related quality of life (QOL).Human erythropoietin is an acidic glycoprotein hormone with a molecular weight of 34 kDa.The first clinical trial involving recombinant human erythropoietin was

conducted and published between 1986 and 1987[2]. Since then, numerous studies in patients with chronic renal failure have been published, establishing erythropoietin as an effective treatment for anemia in over 95% of patients. Erythropoietin not only improves hemoglobin levels but also enhances general well-being, reduces symptoms of fatigue, increases exercise tolerance, and even improves cognitive function.

However, it's important to note that there are adverse effects associated with erythropoietin use in patients receiving hemodialysis. These side effects may include hypertension, flu-like symptoms, seizures, and complications related to vascular access.Erythropoietin amounts are typically expressed in International units (IU), where one IU exerts the same erythropoiesis-stimulating activity in rodents as 5 μmol of cobaltous chloride. Interestingly, the sugar side chains of erythropoietin do not seem to be necessary for its interaction with target cell receptors[3].Additionally, there is growing evidence to suggest that aside from its role as an erythropoietic hormone, erythropoietin functions as a paracrine tissue-protective protein, particularly in the brain, and potentially in other organs as well.A longer-acting erythropoietin analogue known as DARBEPOIETIN, which shares similarities with normal erythropoiesis-stimulating proteins, was introduced in 2001. It's worth noting that some individuals with underlying medical conditions may fall within the reference range for hemoglobin concentration, even though they have an underlying disorder.In our study, we investigated the impact of erythropoietin on various parameters among chronic renal failure patients who were experiencing anemia and undergoing maintenance hemodialysis[4]. Specifically, we assessed the effects of erythropoietin on improving hemoglobin levels, hematocrit values, red blood cell counts, reticulocyte levels, quality of life, and the occurrence of adverse effects in this patient population. This research aimed to provide insights into the efficacy and safety of erythropoietin as a treatment option for anemia in chronic renal failure patients undergoing hemodialysis.

MATERIALS AND METHODS

In this prospective, open-label observational study, a total of 92 patients with chronic kidney disease and anemia were enrolled, although six patients dropped out during the two-year study period. The primary intervention involved administering injections of Erythropoietin, with dosages tailored to the patients' body weight. Specifically, patients received injections at a rate of either 50 U, 100 U, or 150 U per kilogram of their body weight, and this treatment was provided twice a week. The study sought to assess the impact of Erythropoietin on a range of parameters, including improvements in hemoglobin levels, hematocrit values, red blood cell counts, reticulocyte levels, quality of life, and the occurrence of adverse effects among patients with chronic kidney disease and anemia who were undergoing maintenance hemodialysis[5].In this study, stringent inclusion and exclusion criteria were established to select a specific group of patients for evaluation. To be eligible for participation, patients needed to have hemoglobin levels falling within the range of greater than 5 gm/dl and less than 10 gm/dl. The study considered both male and female patients within the age group of 18 to 80 years who were suffering from chronic kidney disease and required dialysis. Furthermore, candidates were required to exhibit transferrin saturation greater than 20% and serum ferritin levels exceeding 200 ng/ml. A crucial element was obtaining informed consent from the patients to ensure their willingness to participate.

Conversely, the exclusion criteria served to identify individuals who did not meet the specific conditions necessary for this study[6]. Patients in need of immediate correction of anemia, those with elevated leukocyte counts or active inflammatory diseases, and individuals experiencing septic shock were excluded. Additionally, those with known allergies to mammalian cell products or albumin, a history of stroke or seizures, peripheral vascular diseases, or ongoing thrombotic or bleeding conditions were ineligible. Patients with a cancer diagnosis, pregnant or breastfeeding females, and those with hemoglobin levels exceeding 12 gm/dl at the outset of the study were also excluded. Likewise, individuals who had previously participated in clinical trials with investigative drugs or those who did not provide informed consent were not part of the study. These criteria were carefully defined to ensure that the study's results would be representative of a specific patient population and maintain the integrity and safety of the research.This study spanned a two-year duration and focused on individuals who had been on hemodialysis for a period ranging from six months to two years. A total of 92 participants underwent the screening process for this research.Each subject in the study underwent a comprehensive medical examination, which included an assessment of their medical history, clinical examination, collection of demographic data, an evaluation of renal function, a review of their medical and illness history, as well as inquiries about their smoking and alcohol habits, drug usage, and drug allergies[7]. Additionally, the participants were informed about the details of the study, and the treatment plan was thoroughly explained to them. Those individuals who wished to participate in the study provided their written informed consent, acknowledging their willingness to be enrolled and receive the specified treatment.

RESULTS

In our study, we initially enrolled a total of 92 patients who were suffering from chronic kidney disease with end-stage renal disease. These patients were already undergoing maintenance hemodialysis twice a week.

However, it's important to note that during the course of the study, only 80 patients completed the entire research protocol, while the remaining 12 patients chose to discontinue their participation and dropped out of the study for various reasons.

Table 1: Male, female ratio according to age groups

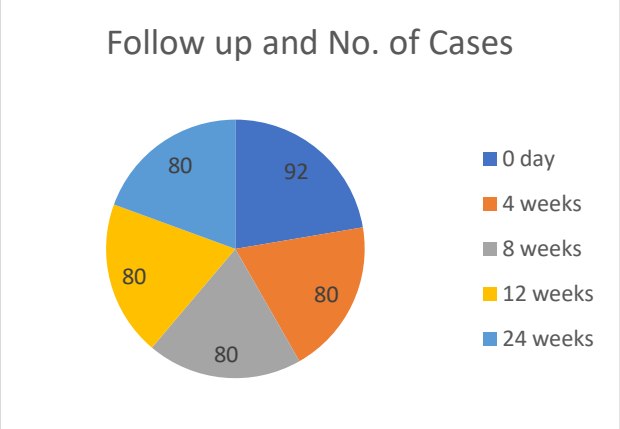
Age (Years)	Male	Female	Total No
18-40	20	12	32
61-80	4	2	6
41-60	28	26	54

The study encompassed a total of 92 patients, and these participants were systematically categorized into three distinct age groups for analysis. The largest group, comprising 54 patients, fell within the age bracket of 41 to 60 years, representing a significant portion of the study population. Additionally, 32 patients were between the ages of 18 to 40 years, and a smaller group of 6 patients were in the 61 to 80-year age range. This stratification by age facilitated a comprehensive examination of the study outcomes, allowing for the exploration of potential variations and trends within different age cohorts. Such categorization aids in the understanding of how age might influence treatment responses and clinical parameters in the context of the study's objectives.

Table 2: Changes of Hemoglobin

Follow up	No. of Cases	Hb(g/dl)	P- value
0 day	92	6.7 + 0.746	
4 weeks	80	7.785 + 0.746	<0.05
8 weeks	80	8.543 + 0.788	<0.01
12 weeks	80	9.348+ 0.669	<0.01
24 weeks	80	11.56+ 0.749	<0.01

Fig 1: Follow up and no. of cases



Among the study group, a significant portion, precisely 70% or 46 patients, presented with hemoglobin levels falling within the range of 6 to 7 gm/dl, and the average mean hemoglobin at the time of enrollment was measured at 6.7 ± 0.746 gm/dl.Following 8 weeks of therapy with 50 u/kg/dose of erythropoietin alfa, a substantial 77.5% or 62 patients demonstrated a noteworthy increase in hemoglobin levels exceeding 1.5 gm/dl compared to their baseline measurements. However, the remaining 22.5%, equivalent to 18 patients, required an increased dosage of erythropoietin, specifically 75 u/kg, to reach the target hemoglobin levels in the subsequent period of the study. These observations underscore the varying responses among the patients to the treatment regimen, with a majority achieving the desired improvement in hemoglobin levels.

Table3: Changes of reticulocyte count

Follow up (Weeks)	No. of Cases	Reticulocyte Count %	P- value
0 day	92	1.010 + 0.702	
4 weeks	80	1.110+ 0.552	<0.05
8 weeks	80	1.44 + 0.624	<0.041
12 weeks	80	1.831 + 0.422	<0.035
24 weeks	80	2.08 ±0.668	<0.016

Table 4: Changes of hematocrit

Follow up (Weeks)	No. of Cases	HCT %	P- value
0 day	9	22.20 + 2.59	
4 weeks	80	24.40+ 2.983	<0.05*
8 weeks	80	26.64+ 2.361	<0.01*
12 weeks	80	30.26+ 1.702	<0.01*
24 weeks	80	33.00+ 2.752	<0.01*

Before the initiation of the study, it is notable that all the patients enrolled exhibited a poor quality of life score across various domains. These domains included physical activity, fatigability, depression, relationships, and low mood levels. The mean score across these domains was calculated at 2.4, indicating that patients were experiencing significant challenges and limitations in their overall quality of life in these aspects. The study aimed to assess whether the treatment intervention would have a positive impact on these quality of life measures.

DISCUSSION

Effectively managing anemia in patients with chronic kidney disease (CKD) is a fundamental aspect of their overall treatment and well-being[8]. Prior to the advent of recombinant erythropoietin, patients with CKD faced significant challenges related to anemia, often requiring repeated blood transfusions. Consequently, they typically endured profound anemia, which had substantial negative effects on their quality of life and health.

The introduction of recombinant erythropoietin has marked a revolutionary shift in the management of anemia in CKD patients. It has provided a more targeted and effective approach to addressing anemia by stimulating the production of red blood cells. This advancement has not only improved hemoglobin levels but has also brought about notable improvements in patients' overall health and quality of life[9].In the context of this specific study involving 92 patients, a crucial finding emerged regarding the dosing of erythropoietin. It was observed that the majority of patients (62 out of 92) achieved their target hemoglobin levels with the regular conventional dose of 50 units/kg/dose. However, a subset of patients (18 out of 92) required a higher dose of 75 units/kg to reach the desired hemoglobin levels. This underscores the individual variability in patient responses to treatment and the need for personalized care in managing anemia in CKD.

Moreover, the study revealed a progressive increase in hemoglobin levels over the course of 12 weeks. At the 4-week mark, 77% of patients experienced improvements in their hemoglobin levels, which suggests that the treatment was effective for a majority of participants[10]. By the end of the 12-week study period, 23% of patients achieved the desired hemoglobin levels, demonstrating the benefits of the treatment over time.However, it's important to acknowledge that the management of anemia in CKD is not without potential side effects. Hypertension emerged as a common side effect among the study participants. This finding is consistent with previous research, including the CHOIR study by Singh et al[11]., which highlighted the need to strike a careful balance when targeting specific hemoglobin concentrations. While higher hemoglobin levels can be beneficial, they also come with an increased risk of adverse events, such as myocardial infarction, heart failure, stroke, and even death.

The TREAT study also echoed these concerns, emphasizing the importance of managing anemia in CKD patients in a way that minimizes the risk of adverse cardiovascular outcomes. It is a delicate balance between improving hemoglobin levels to alleviate anemia-related symptoms and avoiding potential risks associated with higher hemoglobin concentrations.

In summary, the study's findings underscore the critical role of effective anemia management in CKD patients and the positive impact of recombinant erythropoietin. However, it also emphasizes the need for individualized care and careful monitoring to strike the right balance between improving hemoglobin levels and minimizing the risk of adverse effects, particularly concerning cardiovascular health.

CONCLUSION

In the study encompassing 92 patients, it became evident that the response to erythropoietin treatment was not uniform among the participants. The majority, consisting of 62 patients, successfully achieved the target hemoglobin level using the regular conventional dose of 50 units/kg/dose of erythropoietin. However, a smaller subset of 18 patients necessitated an increased dose of 75 units/kg to attain the desired hemoglobin concentration. This discrepancy highlights the individual variability in how patients with chronic kidney disease respond to the treatment and underscores the importance of tailoring treatment plans to meet the specific needs of each patient.The study's findings also revealed a positive trend in hemoglobin levels throughout the 12-week study period. After just 4 weeks of treatment, a substantial 77% of patients experienced an improvement in their hemoglobin levels, demonstrating the efficacy of the treatment for the majority of participants. Nevertheless, at the conclusion of the 12-week study, 23% of patients still had not reached the target hemoglobin level. This observation suggests that the response to the treatment varied within the patient population.These results shed light on the complexity of managing anemia in

patients with chronic kidney disease. While the standard treatment protocol was effective for many individuals, a subset required adjustments in the form of higher doses to achieve the desired outcomes. The progressive increase in hemoglobin levels over time underscores the importance of ongoing monitoring and individualized care to optimize anemia management for these patients. The study's outcomes emphasize the need for a personalized approach to treatment to ensure the best possible results for each patient.

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