Proceedings
The International Conference of Advancements in Nursing Care (ADNURS)
Volume 1 (2024)
E-ISSN: *On process*

Section: Medical Surgical Nursing

Boosting hemoglobin: The potent impact of erythropoietin administration

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Abstract
The prevalence of chronic kidney disease (CKD) is currently increasing. CKD patients experience kidney cell damage, leading to decreased function and insufficient erythropoietin production. This insufficiency causes a reduction in red blood cell production and results in anaemia among CKD patients. Erythropoietin Stimulating Agents (ESAs) stimulate red blood cell formation in the bone marrow. This study aimed to determine the effectiveness of erythropoietin therapy in increasing haemoglobin (Hb) levels in haemodialysis patients. The study is a retrospective observational study with descriptive analysis conducted from April 1 to April 20, 2024, at RSIY PDHI. The sample consisted of 39 respondents selected based on inclusion and exclusion criteria. The results showed that the majority of CKD patients were male (56.4%), with an average age of 55 years and an average weight of 58.32 kg. The most common employment status was self-employed (35.9%). The average Hb level before erythropoietin administration was 8.54 mg/dL. After erythropoietin therapy at a dose of 3.000 UI per week for 3 months, the average Hb level increased to 9.38 mg/dL, showing a difference of 0.83 mg/dL. Data analysis using the Wilcoxon test yielded a p-value of 0.000, which is less than the significance level α (0.05), indicating that erythropoietin therapy is effective in increasing Hb levels in haemodialysis patients.

Keywords: Haemodialysis; chronic kidney disease; erythropoietin; nursing care; interprofessional collaboration

Introduction
Chronic Kidney Disease (CKD) is characterized by kidney cell damage lasting more than three months, with symptoms including a glomerular filtration rate below or above 60 ml/person/1.73 m^2, accompanied by abnormalities in urine sediment. CKD results from various aetiologies that progressively reduce kidney function, ultimately leading to kidney failure. This condition is irreversible, and end-stage kidney disease requires transplantation and dialysis (Agustina & Purnomo, 2019). CKD can stem from multiple clinical conditions, such as kidney diseases (nephrolithiasis, glomerulonephritis) and extrarenal diseases (hypertension, diabetes mellitus, pre-eclampsia) (Sui, 2021). CKD causes approximately 850.000 deaths annually, making it the 12th most common disease globally (Kovesdy, 2022). The prevalence of kidney failure increases by 6% each year, with about 78.8% of CKD patients worldwide relying on dialysis for survival (Tonelli et al., 2020). In Indonesia, 2018 Riskesdas data indicates a population of around 252.124.458, with 713.783 individuals suffering from chronic kidney failure. Among these, approximately 150.000 patients have CKD, often caused by hypertension (Riskesdas, 2018). The Yogyakarta Special Region Provincial Health Service (DEPKES) reported 461 cases of CKD, including 175 cases in Jogja city, 168 cases in Bantul Regency, and 45 cases in Kulon Progo. The Indonesian Renal Registry (IRR) noted a significant rise in new CKD patients undergoing haemodialysis in Yogyakarta, from 359 new patients in 2017 to 2.730 new patients in 2018 (IRR, 2018).

CKD results from the kidneys' inability to maintain body balance. As a non-communicable disease, CKD progresses slowly, leading to irreversible kidney function loss. The kidneys' primary function is to filter and remove the body's metabolic waste (Loffing, Verrey, & Wagner, 2022). Treatment options for CKD include haemodialysis, Continuous Ambulatory Peritoneal Dialysis (CAPD), and transplantation. Haemodialysis, a widely used therapy, removes metabolic waste from the body, mimicking kidney filtration. In end-stage CKD, less than 15% of nephrons function, reducing the Glomerular Filtration Rate (GFR) to less than 10% of normal (Wiyono, 2018). Decreased kidney function leads to the accumulation of urea and creatinine, disrupting erythropoietin production. Erythropoietin stimulates the bone marrow to produce red blood cells. Impaired kidney function results in insufficient erythropoietin production, affecting red blood cell formation and reducing erythrocyte levels. Consequently, haemoglobin levels in haemodialysis patients decrease (Rosini et al., 2020). Erythropoietin Stimulating Agent (ESA) therapy is administered when Hb levels fall below 10 g/dL, with doses of epoetin α and β ranging from 2.000 to 5.000 IU twice a week or 80-120 units/kg/week subcutaneously (IPDI, 2021a). Hemoglobin is a vital protein responsible for transporting oxygen from the

lungs to peripheral tissues and carbon dioxide from peripheral tissues to the lungs (Wiyono, 2018). In CKD patients, decreased haemoglobin levels result from excess fluid in extracellular spaces, leading to reduced fluid and sodium excretion. Increased fluid volume causes dilution, lowering haemoglobin levels and leading to anaemia (Aristin, 2022). Anaemia in CKD patients increase the risk of significant morbidity and mortality, heightening the risk of cardiovascular events and worsening kidney failure prognosis (Wiyono, 2021). Erythropoietin therapy effectively increases Hb levels in CKD patients undergoing haemodialysis. Previous research demonstrated significant differences in haemoglobin levels before and after erythropoietin therapy in haemodialysis patients (Padantya, 2023). However, another research found no relationship between the frequency of erythropoietin therapy and increased haemoglobin levels in anaemic CKD patients undergoing haemodialysis (Nurafni, Desminingrum, & Samsiah, 2023). For this reason, the study aimed to evaluate the potent impact of erythropoietin administration on haemoglobin levels among patients with CKD receiving haemodialysis.

Method

The research employed quantitative descriptive and retrospective data collection methods. The study is a retrospective observational study with descriptive analysis conducted from April 1 to April 20, 2024, at RSIY PDHI. This approach involves analysing past events and therapy administration by measuring variables through medical records. The data source comprised secondary data from the medical records of haemodialysis patients with complete laboratory data. Sample data were selected based on specific inclusion and exclusion criteria. The inclusion criteria included stage 5 CKD patients undergoing regular haemodialysis for at least 3 months, aged 18 to 65 years, with an initial Hb level of < 10 g/dL, body weight between 40 and 80 kg, and receiving erythropoietin therapy at a dose of 3.000 IU/1 mL per week. Exclusion criteria encompassed patients who experienced acute bleeding during haemodialysis, had incomplete medical record data from laboratory results, moved to another hospital's haemodialysis center, or died. Based on these criteria, 39 respondents were included in the study. The respondents' profile was assessed using questionnaire made by authors. Wilcoxon statistical testing was used for data analysis. The ethical clearance was also obtained before study outset.

Results

The average age of respondents was 55 years, with a standard deviation of 8.51, a minimum age of 38 years, and a maximum age of 65 years. The average body weight of respondents was 58.32 kg, with a minimum weight of 40.6 kg and a maximum weight of 80 kg **(Table 4.1)**. The data shows that the majority of respondents were male, totaling 22 people (56.4%). Additionally, the majority of respondents with the highest employment status were entrepreneurs, accounting for 14 people (35.9%) **(Table 4.2)**. The average Hb value before erythropoietin therapy was 8.54 g/dL, while the average Hb value after erythropoietin therapy was 9.38 g/dL, resulting in a difference of 0.83 g/dL **(Table 4.3)**. The results of the bivariate analysis of the relationship between erythropoietin and haemoglobin levels revealed a significance value (Sig. 2-tailed) of 0.000, which is less than the threshold of α (0.05). This indicates a significant relationship between erythropoietin administration and the haemoglobin levels of haemodialysis patients.

Table 4.1 Age and weight.

Variables	N	Min	Max	Mean	SD
Age	39	38	65	55	8.51
Weight	39	40.6	80	58.32	10.12

Table 4.2. Gender dan work.

Variables	N	Percentage (%)
Gender		
Male	22	56.4
Female	17	43.6
Work		
Farmer	6	15.4
Employee	12	30.8
Entrepreneur	14	35.9
Civil servant	7	17.9

Table 4.3 Haemoglobin (Hb) levels (before and after intervention).

Variables	N	Min	Max	Mean	SD	Z	*p*
Hb before	39	7.0	10.1	8.54	0.85	-4.598	0.000
Hb after	39	7.6	10.3	9.38	0.62		

Discussion

The research results showed that the average age of the respondents was 55 years, with a standard deviation of 8.51, a minimum age of 38 years, and a maximum age of 65 years at the Haemodialysis Unit RSIY PDHI. These results indicate that the respondents are in the late adult age category. This finding is consistent with data from RSI Sultan Agung Semarang, which showed that the largest number of haemodialysis patients was in the 46–55-year age group, accounting for 48.0% (Padantya, 2023). Increasing age is associated with a progressive decrease in Glomerular Filtration Rate (GFR) and Renal Blood Flow (RBF), with a decline of around 8 ml/minute/1.73m^2 every decade starting from age 40. As individuals age, red blood cell production decreases due to diminished physiological function in all organs, particularly the bone marrow, which produces cells. Generally, women have lower haemoglobin levels than men because of menstruation, which leads to iron loss. In Indonesia, haemodialysis for CKD patients is more common among those in the early elderly group, who are often still productive and likely to prioritize their health by undergoing haemodialysis. Research at RSU Bahteramas, North Sulawesi, reported that age influences decision-making and acceptance of health-related changes, with older patients tending to refuse haemodialysis. The research results also showed that the mean body weight of respondents was 58.32 ± 10.12 kg, with a minimum weight of 40.6 kg and a maximum weight of 80 kg at the RSIY PDHI Haemodialysis Unit. Patient characteristics based on body weight are used to determine the therapeutic dose of erythropoietin. The greater the patient's weight, the higher the dose required. This study used a standardized dose of erythropoietin for each sample, namely 3.000 IU/week for 3 months. Different patient weights may lead to variations in the percentage of dose received by each patient, potentially causing differences in therapeutic outcomes. Patient characteristics based on body weight are critical for determining the appropriate therapeutic dose of erythropoietin.

The study found that the majority of respondents were male, with 22 men (56.4%). CKD can affect both men and women, but factors such as differences in work, living habits, genetics, and physiological conditions contribute to disparities. A study highlighted that men have twice the risk of chronic kidney disease compared to women, partly due to lifestyle factors like smoking, coffee and alcohol consumption, and supplement use, which can trigger systemic diseases and decrease kidney function (Provenzano et al., 2023). Cardiovascular disease is a significant risk factor for men with CKD, caused by factors including smoking, physical inactivity, diet, obesity, cholesterol, diabetes, and high blood pressure. A study found that smoking increases the risk of stage 5 CKD by 5.087 times compared to non-smokers (Kazancioğlu, 2013). Smoking in the acute phase increases sympathetic stimulation, leading to elevated blood pressure, tachycardia, and catecholamine accumulation, which in turn raises renal vascular resistance, decreasing GFR and filter fraction (Jo et al., 2020). The study results indicated that the majority of respondents were entrepreneurs (35.9%). Entrepreneurs, who manage their own businesses, often have habits like staying up late, inadequate water intake, lack of rest, and poor nutrition, which can exacerbate health issues, especially if the patient has a history of diabetes and hypertension. The research results showed the average Hb value before erythropoietin therapy was 8.5 ± 0.85 g/dl, indicating moderate anaemia. After erythropoietin therapy, the average Hb value increased to 9.38 ± 0.62 g/dl, showing an improvement of 0.83 g/dl. The significance value (Sig. 2-tailed) between the erythropoietin variable and haemoglobin levels of haemodialysis patients was 0.000 < α (0.05), indicating a significant relationship between erythropoietin therapy and haemoglobin levels. Despite the increase, Hb levels remained below the normal range for anaemia, defined as <13 g/dL for men and <11 g/dL for women (Billett, 1990). Anemia in CKD patients result from damaged parenchymal cells, reducing erythropoietin production as erythropoietin is crucial for erythropoiesis (formation of erythrocytes) in the bone marrow (Portolés, Martín, Broseta, & Cases, 2021). Decreased erythropoietin production necessitates erythropoietin therapy in haemodialysis patients. This study found a significant increase in Hb levels, although the increase was modest (0.83 g/dL). Erythropoietin treatment increases Hb levels by stimulating erythroid progenitor cell proliferation, differentiation, and survival, thereby enhancing erythrocyte production. Erythropoietin binds to receptors on CD34+ hematopoietic stem cells, activating genes that promote cell proliferation and prevent erythrocyte apoptosis, resulting in increased haemoglobin and haematocrit levels (Santos, Dias, Lima, Salgado Filho, & Miranda Dos Santos, 2020).

To achieve target Hb levels, an increase in erythropoietin dose by 50% may be necessary for patients not meeting the target. Erythropoietin hyperresponsiveness occurs when desired haemoglobin levels are not achieved despite higher doses (Santos, Dias, Lima, Salgado Filho, & Miranda Dos Santos, 2020). Erythropoietin is vital for CKD patients undergoing haemodialysis. Stage V CKD patients experience reduced kidney function, impairing fluid and waste elimination, necessitating lifelong kidney replacement therapy (haemodialysis, CAPD). Haemodialysis patients often face infections, bleeding, and anaemia due to insufficient erythropoietin production. Erythropoietin (EPO) is essential for treating anaemia in CKD. This study showed that patients receiving erythropoietin therapy at 3000 IU/week for 3 months experienced an average Hb increase of 0.83 g/dL, indicating a relationship between erythropoietin therapy and increased haemoglobin levels in haemodialysis patients. Despite proving the effectiveness of erythropoietin therapy, the study had limitations, including a small sample size due to strict inclusion and exclusion criteria, and unknown factors such as physical activity and nutritional status that could influence haemoglobin levels. Additionally, endogenous erythropoietin levels and iron status were not observed, leaving it unclear whether the therapy's effect on haemoglobin levels involved increased endogenous erythropoietin levels and iron status.

Conclusion

Based on the results of the research and discussion previously described, it can be concluded that the characteristics of the patients in this study were mostly men with an average age of 55 years, weight 58.32 kg and employment status as self-employed as many as 12 patients. Hemoglobin levels in patients undergoing hemodialysis before receiving erythropoietin therapy were an average of 8.54 g/dl and the average hemoglobin in patients undergoing hemodialysis who received erythropoietin therapy for 3 months was 9.38 g/dl. This shows that erythropoetin administration increases hemoglobin levels in patients undergoing hemodialysis with sign (0.000). Future studies should include a larger sample size to enhance the generalizability of the findings and provide more robust statistical power. Extending the follow-up period beyond three months would allow for the assessment of long-term effects and sustainability of erythropoietin therapy in increasing hemoglobin levels. It is also important to control for potential confounding variables such as nutritional status, physical activity, and concurrent medical treatments to more accurately isolate the effect of erythropoietin therapy

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