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Evaluation of erythropoietin therapy in hemodialysis patients at PKU Muhammadiyah Hospital Yogyakarta

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Abstract

Most of the patients with end-stage renal disease who undergo hemodialysis receive erythropoietin (EPO) therapy for anemia treatment. Anemia with EPO deficiency is a common complication of chronic kidney disease (CKD). EPO therapy is expected to improve anemia and quality of life of patients. This analytic observational study was conducted in a cross-sectional design. It aimed to identify the difference in red blood cell profiles, namely hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC), and quality of life of CKD patients on EPO and non-EPO therapy at PKU Muhammadiyah Hospital in Yogyakarta. The inclusion criteria were PGK ICD N18.9 outpatients who received hemodialysis therapy at this hospital and were literate, able to understand the questionnaire, and willing to be a respondent. The results showed that there was no significant difference ($p>0,05$) between the red blood cells (Hb, MCV, MCH, MCHC) of the EPO and non-EPO therapy groups. The correlation between the EPO and the quality of life of patients in all of the KDQOL domains was $p> 0.05$. Aside from the insignificant difference between the EPO and non-EPO therapy groups, the research concluded that there was no correlation between either the EPO or the non-EPO therapy with the quality of life of hemodialysis patients.

Keywords: EPO, Hb, MCH, MCV, MCHC, quality of life

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INTRODUCTION

Anemia is prevalent in patients with chronic kidney disease (CKD) who undergo hemodialysis therapy. It has been reported in 80-90% of CKD patients. It is associated with Erythropoietin (EPO) deficiency due to the inability of the kidneys to produce EPO physiologically (Sari *et al.*, 2014).

Anemia management in CKD patients mostly relies on the use of EPO (Gombotz, 2012). It is a widely accepted treatment, as well as the first-line therapy for anemia in CKD patients (Singh, 2008). Although it has many advantages, EPO drug is expensive and, therefore, burdensome for patients who must take it (Mikhail *et al.*, 2012).

In practice, there are two types of treatment for anemia of CKD, namely EPO and non-EPO. The later combines folic acid, iron, and vitamin B1. A study by Hidayati *et al.* (2012) at PKU Muhammadiyah Hospital in Yogyakarta shows that erythropoietin alpha is used in 69.05% anemia treatment whereas erythropoietin beta in 30.95%. As for the pre-oral adjuvant therapies (82.05%), most of them administer the combination of folic acid, iron, and vitamin. Only a few of them use folic acid (10.26%) and folic acid-vitamin B complex combination (7.69%).

Anemia contributes to the reduced quality of life of patients with end-stage kidney disease. Most CKD patients on hemodialysis have to receive EPO therapy or take erythropoietin-stimulating agents routinely to treat their anemia. Anemia due to EPO deficiency is a common complication of CKD. It can be treated with EPO administration, red blood cell transfusion, or the combination of both. However, the widely accepted treatment by anemic patients is the administration of EPO. Early studies found that EPO reduced the need for red blood cell transfusions and improved quality of life of CKD patients compared with no EPO administration.

This study aimed to determine the differences in the profiles of hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC) and the quality of life of CKD patients on either EPO or non-EPO therapy for their anemia management.

INSTRUMENT AND METHOD

Instrument

The instrument used in this study was the Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}) v. 1.3 published by RAND. This questionnaire was first translated into Indonesian by the UAD Language Development Center. The translation process was forward, i.e., from English to Indonesian by a translator.

Methods

This analytical observational study employed a cross-sectional approach. The subjects were patients with chronic renal failure on hemodialysis at PKU Muhammadiyah Hospital in Yogyakarta in July 2017. They were selected purposively according to the predefined inclusion and exclusion criteria. The samples were 87 patients consisting of 78 patients receiving EPO (EPO therapy group) and 9 patients receiving non-EPO (non-EPO therapy group).

The inclusion criteria were: outpatients diagnosed with CKD who underwent treatment at the hemodialysis unit of the hospital and were literate, able to understand the questionnaire, and willing to participate in the study.

The research data included Hb, MCH, MCV, and MCHC, as well as the quality of life of CKD patients on hemodialysis who suffered from anemia and managed it with erythropoietin therapy. The research method involved the design, place, and scope or object of the activities, main materials and tools, data collection technique, the operational definition of the research variables, and analysis technique. The quality of life was obtained from respondents in July 2017 using the Indonesian version of KDQOL-SF^{TM} v.1.3.

Data Analysis

This research performed an independent samples t-test on Hb, MCH, MCV, MCHC, and quality of life of the selected patients. It also used a statistical test for comparison of proportions, namely the chi-square test, to identify the presence or absence of any differences between the EPO and the non-EPO therapy groups.

RESULTS AND DISCUSSION

Hb, MCV, MCH and MCHC Profiles

Table I presents the mean values of the Hb, MCV, MCH, and MCHC of both EPO and non-EPO (iron) therapy groups.

Table I. The mean values of the red blood cell profiles of the EPO and the non-EPO therapy groups

Profiles	Hb	MCV	MCH	MCHC
($\bar{x}$ + SD)	9.28 ± 1.528	90.06 ± 6.150	29.60±1.998	32.89±0.688
Independent t–test (*P-values*)	0.068	0.124	0.164	0.415

The independent samples t-test on the red blood cell profiles (Table I) produced different p-values for each variable, namely Hb= 0.068, MCV= 0.124, MCH= 0.164, and MCHC= 0.415. These figures indicate that there is no significant difference between the red blood cell profiles of the EPO and the non-EPO (iron) therapy groups.

The mean Hb values of the EPO therapy group and the iron therapy group was 9.28 ± 1.528 (*p-value*= 0.068), representing an insignificant difference. In other words, the increased Hb levels in both therapy groups are not significantly different. Nevertheless, the red blood cell profiles showed that the mean Hb level of the EPO therapy group was 1.00 higher than the iron therapy group. Therefore, the EPO therapy is better than the iron therapy.

The same case of insignificant difference between the two groups applied to MCV, MCH, and MCHC, which are measures of anemic conditions. MCV is the average volume of erythrocytes. When thalassemia and anemia of chronic disease are excluded from the diagnosis, MVC indicates iron-deficiency anemia. The MVC was within the normal range, i.e., 82-93 femtoliters. The MCH—the average amount of hemoglobin (picogram) per erythrocyte—was also normal, i.e., 27-33 picogram/erythrocyte cell. Furthermore, the MCHC of the groups was also in the normal state, i.e., within 33-36%. MCHC describes the average concentration of red blood cells (weight per volume). As a conclusion, the MCV, MCH, and MCHC profiles in this study are normal.

Based on the blood sample data, both EPO therapy and iron therapy did not result in significant differences. The use of EPO and iron at PKU Muhammadiyah Hospital in Yogyakarta is according to the regulations issued by the Indonesian Nephrology Association (PERNEFRI, 2011). In anemia management, the targeted Hb is >10 g/dl. The European Best Practice Guidelines for the management of anemia in CKD patients state that the lower limits of normal Hb are 11.5 gr/dl in women and 13.5 gr/dl in men aged <70 years or 12.0 gr/dl in men aged >70 years (KDIGO, 2012). According to PENEFRI (2011), the EPO response is categorized as inadequate if the patient fails to achieve the desired or targeted Hb level after receiving EPO for 4-8 weeks. Iron is administered to correct the iron stores. After the iron stores are sufficient, iron therapy is continued with EPO therapy. In iron therapy, the targets are ferritin >100 μg/L and transferrin saturation >20%. However, this study did not include ferritin due to the assumption that all sampled patients suffered from EPO-deficiency anemia.

The results showed that there was no significant difference between the red blood cell profiles of the EPO and the non-EPO therapy groups. Many factors can affect Hb levels aside from the type of therapy, e.g., exercise and physical activity. The Hb levels of individuals who routinely exercise are slightly increased because tissues or cells require more O_2 (oxygen) during physical activities (Bahri *et*

al., 2009 in Saputro and Junaidi, 2015). The other factors that can affect Hb levels and red blood cells in a person are food, age, sex, activity, smoking habit, and co-occurring diseases like leukemia, thalassemia, and tuberculosis. The food contains nutrients or nutritional components that are used to promote the formation of hemoglobin (i.e., Fe or iron and protein). The Hb levels in females are easier to drop than in males, especially during menstruation (Curtale *et al.*, 2000 in Saputro and Junaidi, 2015). The consumption of, for instance, vitamin C can increase iron absorption by up to four times (Wirakusumah, 1998). According to Patimah (2007), iron is a precursor that is very necessary for the formation of hemoglobin and red blood cells (erythrocytes). Besides, vitamin C is one of the necessary antioxidants obtained from outside sources. The oral administration of vitamin C can provide potential benefits as it reduces the damages that free radicals cause to the tissues (Khassaf *et al.*, 2003).

Quality of Life

KDQOL SF-36 consists of 36 questions with eight dimensions, namely: physical function, role limitations due to physical problems, role limitations due to emotional problems, social function, mental/psychological health, vitality, body pain, and general perception of health. After the mean value of each domain had been calculated, this research categorized respondents into three groups, namely below, within, and above the average. The more the respondents below the average score in a domain, the more difficult the achievement of good quality of life in the said domain (Purwitasari, 2016). The scores and the number of respondents by domain are presented in Table II.

Kidney failure deteriorated the physical quality of half of the respondents. The quality of life of hemodialysis patients is lower than individuals in general for they tend to experience physical suffering and limitations in daily activities (Mailani, 2015). Using the SF-36 questionnaires to obtain information from 60 respondents, Senduk *et al.* (2016) can describe the relationship of anemia and the quality of life of CKD patients on hemodialysis. They explain that these patients experience a decrease in some scales, including physical functioning, physical limitations, general health, and vitality. CKD weakens the physical states and potentially reduces the patient's motivation. The symptoms of reduced physical health status are strongly associated with sleep problems and depression, all of which affect the quality of life (Mardyaningsih, 2014).

Table II. The quality of life of the respondents by KDQOL domain

Domains	Quality of Life		Number of Respondents
Domain 1 (Physical Function)	<52.4	Low	43
	>52.4	High	50
Domain 2 (Physical State)	<26.1	Low	67
	>26.1	High	26
Domain 3 (Body Pain)	<55.5	Low	38
	>55.5	High	55
Domain 4 (General Health)	<50.7	Low	46
	>50.7	High	47
Domain 5 (Mental Health)	<76.6	Low	45
	>76.6	High	48
Domain 6 (Emotional Condition)	<40.5	Low	64
	>40.5	High	29
Domain 7 (Social Function)	<67.5	Low	48
	>67.5	High	45
Domain 8 (Vital Function)	<61.6	Low	47
	>61.6	High	46

Hemodialysis patients are also susceptible to emotional problems like stress that is attributable to dietary and fluid restrictions, physical limitations, the disease itself, side effects of drugs, and dependence on dialysis, all of which decrease the quality of life. Most of the time, they suffer from depression and anxiety—psychological disorders—due to uremia symptoms, such as fatigue, sleep disorders, decreased appetite, and cognitive impairment. Depression is found in up to 50% of patients who have just started dialysis treatment. The symptoms include guilt, despair, irritability, and suicide. Patients also feel as if they have become a burden to the family and worried about any disruptions to their appearance or body image (Mailani, 2015).

Table III informs the results of the statistical test for comparison of proportions, i.e., chi-square test, on the quality of life of anemic CKD patients in both EPO and non-EPO therapy groups. The test results on all domains showed that both therapy groups did not have different quality of life. This finding is contrary to Keown *et al.* (2010), which affirm that EPO therapy can improve the quality of life of CKD patients. Factors that influence the quality of life of CKD patients on dialysis include decreased physical condition, duration of hemodialysis, compliance with adjuvant therapy, complications of CKD disease, and the severity of anemia. Decreased physical condition is a sign of a patient's poor quality of life. It is determined by age and medical history. The older the patient, the poorer the physical condition and the lower the energy produced in the body (Purwitasari, 2016).

Table III. The relationship between the administration of erythropoietin and the quality of life of CKD patients by KDQOL domain

Domains	Groups	Quality of Life		*P*-values
		Low	High	
1	EPO	38	45	0.530
	Non-EPO	5	5	
2	EPO	60	23	0.569
	Non-EPO	7	3	
3	EPO	34	49	0.616
	Non-EPO	4	6	
4	EPO	41	42	0.616
	Non-EPO	5	5	
5	EPO	41	42	0.412
	Non-EPO	4	6	
6	EPO	57	26	0.621
	Non-EPO	7	3	
7	EPO	41	42	0.186
	Non-EPO	7	3	
8	EPO	42	41	0.616

The duration of hemodialysis also plays an important role in the quality of life of patients. Patients who had received hemodialysis for a long time tended to have a high score of quality of life. At the beginning of hemodialysis, patients respond as if they have not accepted the loss of their kidney function yet. They tend to be angry with the situation, feel sad with the state of their current life, and require a prolonged adjustment to the new environment. As for the patients who have been on hemodialysis for a long time, they have a good quality of life because they are psychologically more prepared and have been able to adapt to the conditions they must live in, received more health education, and established better social relations with health workers (Astuti, 2015).

Research limitations

In this study, the data are limited to Hb levels and red blood cell profiles obtained from the medical records of patients who have received either EPO or non-EPO therapy. Due to time limitation and researcher's knowledge, the analysis excludes many other factors that can influence the increase of Hb level and red blood cells in CKD patients, such as food, compliance, and the consumption of drugs other than the ones administered in the hemodialysis ward. Therefore, further research involving a wider dataset of the determinants of Hb levels and red blood cells becomes necessary.

CONCLUSIONS

The results showed that the Hb levels and erythrocyte indices in the EPO and non-EPO therapy groups were insignificantly different. Also, there was no significant difference between the EPO and non-EPO therapy groups regarding the quality of life of CKD patients on hemodialysis.

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REFERENCES

Astuti, N.D., Syamsiatun, N.H., & Suryani, I., 2015. Faktor-faktor yang berhubungan dengan kualitas hidup pasien gagal ginjal kronik yang menjalani hemodialisa di Rumah Sakit Umum Daerah Panembahan Senopati Bantul, *Jurnal Nutricia*,17(1): 10-16.

Gombotz, H., 2012. Patient blood management: a patient-orientated approach to blood replacement with the goal of reducing anemia, blood loss and the need for blood transfusion in elective surgery, *Transfusion Medicine and Hemotherapy*., 39: 67–72.

Hidayati, Nugroho, A.E., Inayati., 2011. Evaluasi terapi anemia pada pasien ASKES dengan gagal ginjal kronis yang menjalani hemodialisis rutin Di RS PKU Muhammadiyah Yogyakarta. *Jurnal Manajement dan Pelayanan Farmasi*, 1(3) September 2011: 147-152.

Khassaf, M., Mcardle, A., Esanu, C., Vasilaki, A., Mcardle, F., Griffiths, R. D., Brodie, D. A. & Jackson, M. J., 2003, Effect of vitamin C supplements on antioxidant defence and stress proteins in human lymphocytes and skeletal muscle. *Journal Physiololgy*, 549.2: 645-652.

KDIGO, 2012. Clinical Practice Guidline for Anemia in Chronic Kidney Disease, *Kidney International Suplement*, 2: 279-335, Boston, MA, USA.

Keown, P.A., Churchil, D.A., Poulin-costello, M., Lei, L., Gantotti, S., Agodoa, I., Gitlin, M., Gandra, S.R., & Mayne, T.J., 2010. Dialysis patient treated with epoetin alfa show improved anemia symptoms: A new analysis of the Canadian Erythropoietin Study Group trial, *Hemodialysis International*, 14:168-173.

Mailani, F., 2015. Kualitas hidup pasien penyakit ginjal kronik yang menjalani hemodialisis: systematic review, *Ners Jurnal keperawatan*,11(1): 1-8.

Mardyaningsih, D.P., 2014. Kualitas Hidup pada Penderita Gagal ginjal Kronik yang Menjalani terapi hemodialysis di RSUD dr. Soediran Mangun Sumarso Kabupaten Wonogiri, *Bachelor Thesis*, Prodi Keperawatan Stikes Kusuma Husada, Surakarta.

Mikhail, A., Shrivastava, R., & Richardson, D., 2012. Clinical Practice Guidelines Anaemia of CKD, *UK Renal Association*, 5th Edition. Tersedia online www.renal.org/guidelines.

Patimah, S. 2007. Pola konsumsi ibu hamil dan hubungannya dengan kejadian anemia defisensi besi. *Jurnal Penelitian Kesehatan*. Jakarta: Fakultas Kedokteran,8-9.

PERNEFRI, 2011. Konsensus Manajemen Anemia Pada Penyakit Ginjal Kronik,Perhimpunan Nefrologi Indonesia (PERNEFRI), Jakarta.

Purwitasari, D.A., 2016. Kepatuhan terapi obat dan kualitas hidup pada pasien penyakit ginjal terminal di RS PKU Muhammadiyah Bantul, *Bachelor Thesis*, Fakultas Farmasi Universitas Ahmad Dahlan, Yogyakarta.

Saputro, D. A, & Junaidi S., 2015. Pemberian Vitamin C pada latihan fisik maksimal dan perubahan kadar hemoglobin dan jumlah eritrosit, *Journal of Sport Sciences and Fitness*, *JSSF* 4 (3) (2015): 32-40.

Sari, N. L., Srikartika, V. M., & Intannia, D., 2014. Profil dan evaluasi terapi anemia pada pasien gagal ginjal kronik yang menjalani hemodialisa di BLUD RS Ratu Zalecha Martapura Periode Juli-Oktober 2014. *Jurnal Pharmascience*, 2(1) Februari 2015: 65-71, Universitas Lambung Mangkurat.

Senduk, C.R., Palar, S., & Rotty, L.W., 2016. Hubungan anemia dengan kualitas hidup pasien penyakit ginjal kronik yang sedang menjalani hemodialisis regular, *Jurnal e-Clinic* (eCl), 4(1): 105-110.

Singh, A.K., 2008. *Anemia of Chronic Kidney Disease*, *Clin J Am*, (3): 3-6.

Wirakusumah, E. S. 1998. Perencanaan Menu Anemia Gizi Besi. Jakarta: Trubus Agriwidya: 5-11.