KnE Medicine

ICMEDH
The International Conference of Medicine and Health (ICMEDH)
Volume 2022

Knowledge E
enriching | engaging | empowering

Conference Paper

The Use of Folic Acid in Chronic Kidney Disease Patients With Anemia

Meilia Aisya[1], Hidajah Rachmawati[1]*, Didik Hasmono[2], Atika Putri Kusumaningtyas[3]

[1]Pharmacy Study Program, Faculty of Health Sciences, University of Muhammadiyah Malang
[2]Faculty of Pharmacy, Airlangga University[2]
[3] University of Muhammadiyah Malang General Hospital

ORCID
Hidajah Rachmawati: https://orcid.org/0000-0001-5680-0400

Abstract.
Chronic kidney disease (CKD) is defined as decreasing kidney function (GFR < 60 ml/minute/1.73 m^2) for more than 3 months. Anemia is a common complication of CKD due to a decrease in the hormone erythropoietin related to hemoglobin levels. One of the anemia therapies involves using folic acid. Folic acid helps the process of nucleoprotein synthesis and erythropoiesis maintenance. The objective of this study was to determine the pattern of folic acid applied to CKD patients with anemia at University of Muhammadiyah Malang General Hospital. Observational, descriptive, and retrospective data collection methods were used. The results showed that there were 17 patients (47%) with a single use of folic acid (3x1 mg, oral); the most common pattern of the two-combination was folic acid (3x1 mg, oral) and PRC (250 ml, intravenous [iv]), which was given to 11 patients (65%); and the most common pattern of three-combination was folic acid (3x1 mg, oral), Promavit® (3x1 tab, oral), and PRC (250 ml, iv), which was given to 2 patients or 100%. Of the 16 switch patterns, the most of common combination was a single pattern of folic acid (3x1 mg, oral) and a combination of folic acid (3x1 mg, oral) and PRC (250 ml, iv), given to 7 patients (44%).

Keywords: folic acid, anemia, chronic kidney disease

Corresponding Author: Hidajah Rachmawati

Published 15 September 2022

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the ICMEDH Conference Committee.

1. Introduction

Chronic Kidney Disease (CKD) is defined as a decreasing kidney function based on a Glomerular Filtration Rate (GFR) less than 60 ml/minute/1.73 m^2. Related to this, the most dangerous risk factor is cardiovascular disease. Based on the glomerular filtration rate, the CKD classification is divided into five stages, and a GFR value less than 15 ml/minute will lead to End-Stage Renal Disease (ESRD)[1].

According to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), using data on the percentage of CKD stages 1-4 in a population aged 18 years or older in the United States in 2013-2016, approximately 15% of adults suffered from this disease. Based on gender, the prevalence in women was higher (15%) than men (12%) [2]. According to the results of Indonesian Basic Health Research (2018), the prevalence

of CKD in the population aged over 15 years has increased by 0.38% compared to that in 2013. According to age characteristics, the highest prevalence is in the age groups of 65-74 (0.82%) and older than 75 years (0.75%). The prevalence of CKD in men (0.42%) is higher than women (0.35).

Several diseases underlying the occurrence of CKD are diabetes mellitus and hypertension [3]. Atherosclerosis and arteriosclerosis in hypertension damage the renal arteries, causing an increase in intraglomerular pressure and hyperfiltration and resulting in glomerulosclerosis [4]. In addition, increased activity of the Renin Angiotensin Aldosterone System (RAAS) can increase the angiotensin II level, which has a vasoconstrictive effect and can decrease peritubular capillary blood flow in the glomerulus and cause sclerosis, leading to kidney damage [5]. Meanwhile, in a diabetes mellitus condition, hyperglycemia can damage the blood vessels of the kidneys so that protein (albumin) can penetrate the glomerulus. The persistent proteinuria will lead to a progressive decline in kidney function and decrease the value of the glomerular filtration rate. Proteinuria, or albuminuria, accompanied by a decreasing GFR value can cause ESRD and increase diabetic patients' mortality [6][7][8].

Clinical manifestations of chronic kidney disease development are asymptomatic or do not show metabolic disturbances at the early stage (stage 1-2) in CKD patients. At stages 3 to 5 (ESRD), anemia, hypertension, electrolyte disturbances, metabolic acidosis, and osteodystrophy often appear. Signs and symptoms of CKD will develop with increasing kidney damage [9][10].

Decreased kidney function can cause a decrease in hemoglobin (Hb) levels. Anemia is a complication that often occurs in CKD patients. It occurs due to peritubular cell damage that leads to inadequate secretion of erythropoietin (EPO). The hormone EPO, produced in the kidney, plays a significant role in the proliferation and differentiation of erythrocytes [1].

Pharmacological therapy that can be given is iron supplementation, Erythropoietin-stimulating agent (ESA) therapy at Hb level below 10.0 g/dl. In addition, anemia due to folate and vitamin B12 deficiency and undergoing hemodialysis can be treated with folic acid and vitamin B12. Another therapy that can be given when the Hb level is below 7.0 g/dl is Packed Red Cells (PRC) transfusion [11][8].

Folic acid is one of the pharmacological therapies that can be given to chronic kidney disease patients. Folic acid has a major role in DNA synthesis and erythropoiesis maintenance. A decrease in DNA synthesis can cause the manifestation of macrocytic anemia. Folic acid is water-soluble, so it is easily lost in patients undergoing hemodialysis. In these conditions, routine supplementation with a dose of 1-5 mg/day can be

given. Target therapy recommendations based on hemoglobin levels are 11.5-12.0 g/dl [12][13][14].

2. Research Methods

This research was observational, not by intervening or treating the sample. The method used was a descriptive design and retrospective data collection by processing Health Medical Record data of patients diagnosed as CKD with anemia at University of Muhammadiyah Malang General Hospital in the period of January 2020-May 2021.

3. Results and Discussion

Research conducted on CKD patients with anemia who received folic acid therapy at UMM General Hospital from January 2020 to May 2021 showed a population that received folic acid therapy as many as 120 Health Medical Record data, and those who met the inclusion criteria, namely CKD patients with anemia receiving folic acid therapy, were as many as 23 samples.

3.1. Patient Demographic Data

TABLE 1: CKD Patients Distribution by Gender.

No	Gender	Number of Patient	Percentage (%)
1	Male	9	39
2	Female	14	61
	Total	**23**	**100**

Based on **Table 1**, of the 23 samples obtained, most of the patients were female (61%). In general, women have less muscle mass than men. Since muscle mass acts as a determinant of serum creatinine concentration, the creatinine value becomes less and causes an increase in the prevalence of CKD among women [15]. Anemia conditions in CKD are 2.2 times more likely in women than men because the former has lower hemoglobin concentrations [16].

Based on **Table 2**, the highest prevalence of chronic kidney disease with anemia was at the age of 56-65 years, as many as 7 patients (30%). From the age of 40, renal filtration decreases by about 1% per year. Kidney function will decrease with increasing age, as indicated by a decrease in the value of the glomerular filtration rate [17][18].

Table 2: Age Groups of CKD Patients with Anemia.

No	Age Classification *	Number of Patients	Total Percentage
1	15-30 years	3	13
2	31-45 years	3	13
3	46-55 years	6	26
4	56-65 years	7	30
5	> 66 years	4	17
Total		**23**	**100**

Table 3: Distribution of Insurance Status of CKD Patients with Anemia.

No	Insurance Status	Number of Patients	Percentage (%)
1	BPJS	23	100
2	General Patient	0	0
Total		**23**	**100**

Table 3. illustrates that from all samples, patients were covered by BPJS (Social Security Administrator for Health) (100%). After cardiovascular disease, the second-largest expenditure of BPJS was the treatment of kidney disease. Health care financing by BPJS for kidney disease, both inpatient and outpatient, has been increasing since 2014 [19].

3.2. Medical History of Patients with CKD Diagnosis

Table 4: Medical history of patients with CKD diagnosis.

No	Disease History	Number of Patients *	Percentage (%)
1	Hypertension	12	46
2	Diabetes Mellitus	10	38
3	Gout/Uric acid	1	4
4	Cardiovascular disease	2	8
5	Cholesterol	1	4
Total		**26**	**100**

Table 4. shows the prevalence of medical history of patients with chronic kidney disease, namely hypertension (46%) and diabetes mellitus (38%). Uncontrolled blood pressure can cause an increase in intraglomerular pressure and hyperfiltration, which can lead to glomerulosclerosis [4]. Whereas in diabetes mellitus, hyperglycemia can

cause microvascular complications, resulting in glycated protein formation and causing blockage of small blood vessels in the kidneys. This damage can decrease the glomerular filtration function [6]. Anemia is an common occurrence in CKD patients. Cardiovascular compensation in the setting of anemia produces a stage of high ouput, characterized by higher heart rate and increased stroke volume. Anemia has been associated with the development of Left Ventricular Hypertrophy (LVH), and this association was found to increase the risk of myocardial infarction. This complication could contribute to acute heart failure development or exacerbation of chronic heart failure in COVID-19 patients, but the pathogenesis is incompletely understood, but some of the underlying mechanisms may include myocardial injury, acute coronary syndrome, and sustained cardiac arrhythmias [20].

3.3. Patterns of Use of Folic Acid Therapy in CKD Patients with Anemia

Table 5: Usage Pattern of Single Folic Acid in CKD Patients with Anemia.

No.	Regimen Dosage	Number of Patients *	Percentage (%)
1.	Folic Acid (3x1 mg) po	11	65
2.	Folic Acid (1x1 mg) po	2	12
3.	Folic Acid (3x400 mcg) po	4	24
Total		**17**	**100**

*One patient may receive more than one therapy and switch patterns

Based on **Table 5**, the most common pattern of single use of Folic Acid is Folic Acid (3x1 mg) po as many as 11 patients (65%). In a study by Meriyani et al. (2018) on the usage of antianemia in patients with chronic kidney failure at the Wangaya Regional General Hospital, folic acid alone was more widely used, as many as 61 patients (95.31%). Folic acid plays a role in DNA synthesis and erythropoiesis maintenance. Folate deficiency can be given daily at a dose of 1 mg. Hemoglobin will increase slowly around 2.0-3.0 g/dl after approximately two weeks of treatment [13][9].

Based on Table 6, the most common usage pattern of the two-combination of Folic Acid is Folic Acid (3x1 mg) po + PRC (250 ml) iv., as many as 11 patients (65%). In a study conducted by [18], a combination of two anemia drugs used in chronic kidney failure patients undergoing hemodialysis was PRC transfusion and Folic Acid (5%). Transfusions can be given if the hemoglobin level is less than 7.0 g/dl.

Based on Table 7, the pattern of using a three-combination of folic acid is found in 2 patients. Promavit® contains several agents that increase hemoglobin levels, namely

Table 6: Usage Patterns of Two-Combination of Folic Acid in CKD Patients with Anemia.

No.	Medication	Number of Patients	Percentage (%)
1.	Folic acid (3x1 mg) po + PRC (250 ml) (iv)	11	65
2.	Folic acid (3x400 mcg) po + PRC (250 ml) (iv)	1	6
3.	Folic acid (3x1 mg) po + Promavit®* (3x1 tab) po	4	24
4.	Folic acid (1x1 mg) po + PRC (250 ml) (iv)	1	6
Total		**17**	**100**

*Promavit® (Tuna oil 179 mg, omega-3 64.5 mg, DHA 48.5 mg, EPA 12.5 mg, folic acid 400 mcg, vitamin A 345 iu, vitamin D3 34.5 iu, vitamin B12 0.5 mcg, vitamin B6 150 mcg, Ca carbonate 100 mg, Mg oxide 62.5 mg, Fe fumarate 23.5)

Table 7: Usage Patterns of Three-Combination of Folic Acid in CKD Patients with Anemia.

No.	Medication	Number of Patients	Percentage (%)
1.	Folic acid (3x1 mg) po + Promavit®* (3x1 tab) po + PRC (250 ml) (iv)	2	100
Total		**2**	**100**

vitamin B12 and Fe Fumarate. Vitamin B12 has the same role as folic acid, which normalizes DNA synthesis during hemoglobin production [21]. Meanwhile, iron will form the core of the iron porphyrin heme ring and together with the globulin chain will form hemoglobin [22].

Table 8. shows the switching therapy, and the pattern of using anemia therapy in each patient is varied. The most common switching pattern on 7 patients (44%) was from the 1^{st} pattern, which is Folic Acid (3x1 mg) po, to the 2^{nd} pattern using Folic Acid (3x1 mg) po + PRC (250 ml) iv. The pattern of changing anemia therapy can be reviewed based on laboratory data in the form of hemoglobin levels. If the hemoglobin level is less than 7.0 g/dl, PRC transfusion can be given, and at hemoglobin levels more than 7.0-11.0 g/dl, folic acid therapy can be given to maintain the hemoglobin target.

3.4. Duration of Folic Acid Use in CKD Patients with Anemia

Based on table 9, the most common duration of Folic Acid usage in CKD patients with anemia is for 1-3 days, as many as 15 patients (65%). The duration of Folic Acid administration can be seen based on the patient's clinical condition and the hemoglobin level. The hemoglobin level will increase slowly around 2.0-3.0 g/dl after approximately two weeks of treatment [9].

Table 8: Switching Patterns (Switches).

Pattern 1	Pattern 2	Pattern 3	∑	(%)
Single	**Two-Combination**			
Folic Acid (3x1 mg) po	Folic Acid (3x1 mg) po + PRC (250 ml) (iv)		7	44
Single	**Two-Combination**			
Folic Acid (3x400 mcg) po	Folic Acid (3x400 mcg) po + PRC (250 ml) (iv)		1	6
Single	**Single**			
PRC (250 ml) (iv)	Folic Acid (3x400 mcg) po		2	13
Single	**Single**			
PRC (250 ml) (iv)	Folic Acid (3x1 mg) po		1	6
Three-Combination	**Two-Combination**			
Folic Acid (3x1 mg) po + Promavit®* (3x1 tab) po + PRC (250 ml) (iv)	Folic Acid (3x1 mg) po + Promavit®* (3x1 tab) po		2	13
Single	**Two-Combination**			
PRC (250 ml) (iv)	Folic Acid (3x1 mg) po + Promavit®* (3x1 tab) po		1	6
Single	**Two-Combination**	**Single**		
Folic Acid (3x1 mg) po	Folic Acid (3x1 mg) po + PRC (250 ml) (iv)	Folic Acid (3x1 mg) po	1	6
Single	**Two-Combination**	**Single**		
PRC (250 ml) (iv)	Folic Acid (1x1 mg) po + PRC (250 ml) (iv)	Folic Acid (1x1 mg) po	1	6
Total	**16**	**100**		

Table 9: Duration of Folic Acid Use in CKD Patients with Anemia.

No	Therapy Duration	Number of Patients	Percentage (%)
1	1-3 days	15	65
2	4-5 days	8	35
Total		**23**	**100**

3.5. Length of Treatment for CKD Patients

Table 10: Length of Treatment for CKD Patients.

No	Length of Treatment	Number of Patients	Percentage (%)
1	1-5 days	21	91
2	6-10 days	2	9
Total		**23**	**100**

Based on table 10, the longest treatment duration for chronic kidney disease patients was 6-10 days, as many as 2 patients (9%), and mostly, 21 patients (91%) were treated for 1 to 5 days.

3.6. Condition of CKD Patients on Medical Discharge

TABLE 11: Condition of CKD Patients on Medical Discharge.

Condition on Hospital Discharge	Number of Patients	Percentage (%)
Improved	23	100
Patient Discharge against Medical Advice (DAMA)	0	0
Died	0	0
Total	**23**	**100**

Table 11. shows that of 23 chronic kidney disease (CKD) patients at UMM General Hospital in the period of January 2020 to May 2021, all patients left the hospital in an improved condition.

4. Conclusion

1. There were 17 patients (47%) with a single use of Folic Acid, 17 patients (47%) with a two-combination, and 2 patients (6%) with a three-combination.
2. The most common pattern of the single-use was Folic Acid (3x1 mg) po. (given to 11 patients or 65%), the most common pattern of the two-combination was Folic Acid (3x1 mg) po and PRC (250 ml) iv (given to 11 patients or 65%), and the most common pattern of the three-combination was Folic Acid (3x1 mg) po., Promavit® (3x1 tab) po, and PRC (250 ml) iv (given to 2 patients or 100%).
3. Of the 16 switch patterns, the most common combination was a single pattern of Folic Acid (3x1 mg) po and a combination of Folic Acid (3x1 mg) po + PRC (250 ml) (iv), given to 7 patients (44%).

Acknowledgments

The researchers would like to thank all parties who have helped in the preparation of this manuscript publication.

References

[1] Marriot J, Cockwell P, Stringer S. Chronic Kidney Disease and End-Stage Renal Disease. In: Whittlese C, Hodson K, editors. Clinical Pharmacy and Therapeutics. Elsevier; 2019. p. 308.

[2] Trahan C, Lapeyraque AL, Sznajder M, et al. In malnourished adolescent with anorexia nervosa, Cockroft-Gault formula is the most relevant formula to estimate renal function. Clinical Nutrition. 2019.

[3] Alidadi A, Boroujeni E. Evaluating the prevalence and etiology of chronic renal failure. International Journal of Pharmaceutical and Biological Science Archive. 2018;6(3):1–4.

[4] Nasution SH, Syarif S, Musyabiq S. Penyakit gagal ginjal kronis stadium 5 berdasarkan determinan umur, jenis kelamin, dan diagnosa etiologi di indonesia tahun 2018 chronic kidney failure disease stage 5 based on determinants of age, gender, and diagnosis of etiology in Indonesia in 201. JK Unila. 2020;4(2):157–60.

[5] Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: core curriculum 2019. Am J Kidney Dis. 2019 Jul;74(1):120–31.

[6] Listiana D, Isgiyanto A, Alvionita I. "Hubungan Riwayat Diabetes Mellitus dengan Penyakit Ginjal Kronis Ruang Penyakit Dalam RSUD dr. M. Yunus Bengkulu.," *Jurnal Sains Kesehatan*. vol. 24, no. No.3, pp. 1–10, 2016.

[7] Rivandi J, Yonata A. Hubungan Diabetes Melitus Dengan Kejadian Gagal Ginjal Kronik. Jurnal Majority. 2015;4(9):27–34.

[8] Yang J, He W. Chronic kidney disease: Diagnosis and treatment. Springer; https://doi.org/10.1007/978-981-32-9131-7

[9] DiPiro JT, Yee GC, Posey LM, Haines ST, Nolin TD, Elingron V. Pharmacotherapy: A pathophysiologic approach. 11th ed. McGraw Hill Education; 2020.

[10] Okorie C, Annan R, Turkey H, Akhtar N, Gray F, Hamdy K, et al. Epidemiology and management of chronic renal failure: A global public health problem. Biostatistics and Epidemiology International Journal. 2018;1(1):11–6.

[11] KDIGO. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4):279–335.

[12] [12] Schaefer RM, Teschner M, Kosch M. Folate metabolism in renal failure. Nephrology Dialysis Transplantation. 2014;17(5):24-27.

[13] Alvionita WD, Masruhim MA. Pengaruh penggunaan asam folat terhadap kadar hemoglobin pasien penyakit ginjal kronik yang menjalani hemodialisis di rsud abdul wahab sjahranie. Journal Trop. Pharm. Chem. 2016;3(3):179–84.

[14] Zhong H, Lin W, Zhou T. Current and Emerging Drugs in the Treatment of Anemia in Patients with Chronic Kidney Disease. Journal Of Pharmacy & Pharmaceutical Sciences. 2020;23:278-https://doi.org/10.18433/jpps30919.

[15] Chukwuonye II, Ogah OS, Anyabolu EN, Ohagwu KA, Nwabuko OC, Onwuchekwa U, et al. Prevalence of chronic kidney disease in Nigeria: Systematic review of population-based studies. Int J Nephrol Renovasc Dis. 2018 May;11(12):165–72.

[16] Shiferaw WS, Akalu TY, Aynalem YA. Risk Factors for Anemia in Patients with Chronic Renal Failure: A Systematic Review and Meta-Analysis. Ethiop J Health Sci. 2020 Sep;30(5):829–42.

[17] Gunaseelan R, Surudarma IW, Wihandani DM, Sutadarma IW. Prevalence of anemia on chronic kidney disease and its influenced factors in Sanglah General Hospital 2015-2017, Bali. Intisari Sains Medis. 2020;11(1):248.

[18] Megawati S, Restudiarti A, Kurniasih S. Evaluation of Drug Use of Anemia in Patients Chronic Kidney Failure. Jurnal Farmagazine. 3(2):2020.

[19] Kemenkes RI, “Situasi Penyakit Ginjal Kronis,” (2017).

[20] Podestà MA, Valli F, Galassi A, et al. COVID-19 in chronic kidney disease: The impact of old and novel cardiovascular risk factors. Blood Purification. 2021.

[21] Mahmood L. The metabolic processes of folic acid and Vitamin B12 deficiency. J Health Res Rev Dev Ctries. 2014;1(1):5.

[22] Katzung BG. Basic & Clinical Pharmacology. McGraw Hill Education; 2018.