



## Efficacy of Folic Acid in Anemia Treatment Among Hemodialysis Patients in Jakarta, Indonesia

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### ABSTRACT

Treatment with Recombinant human erythropoietin (rHU-EPO) has led to a better outcome and hope. Besides causing an increase of Hb, the quality of life has also improved. Our study is to determine how effectively folic acid manages anemia in hemodialysis patients. The design of the study is Prospective Longitudinal Study was designed to carry out this research. A total of 54 patients with 27 males and 27 females and divided into two groups (22 patients received folic acid and 32 patients received the combination of folic acid and Rhu-EPO) were included from hemodialysis ward of Cempaka Putih Islamic Hospital Jakarta. Patients were further categorized into two categories of hemoglobin (Hb) level; < 9.4 for folic acid, and ≥ 9.4 mg/dl for combination of folic acid and Rhu-EPO. The results showed, the age of hemodialysis patients who used anemia medication mostly, occurred between 60 – 69 years old. An equal number was showed by folic acid in two categories of that Hb level (50%), while the combination of folic acid and Rhu-EPO was 40.6 % for the first category (< 9.4 mg/dl) and 59.4 % for the second category (≥ 9.4 mg/dl). A significance relationship was showed by either hemodialysis patients who used single folic acid or a combination of folic acid and Rhu-EPO (0.000, P-value < 0.05). No significant correlation was observed between gender and anemia medication (folic acid and the combination of folic acid and Rhu-EPO), while the P value for both types medication was 0.133 and 0.984 respectively (P value < 0.05). For the age categories, mean of the achieved Hb level for the second and the third age category of hemodialysis patients who used folic acid was higher than the combination of folic acid and Rhu-EPO, while 2.150 and 1.800 mg/dl, respectively for folic acid, and 1.900 and 1.691 mg/dl for the combination of folic acid and Rhu-EPO. No significance correlation was observed between age categories and for both anemia medication, (0.099 and 0.400, respectively, P value < 0.005). The study concludes that folic acid is effective to turn-up hemoglobin level of hemodialysis patients with anemia although it is not as effective as Rhu-EPO.

**Keywords:** Anemia, Recombinant human erythropoietin (rHU-EPO), Chronic Renal Failure, Hemoglobin Level.

### INTRODUCTION

End-Stage Renal Disease (ESRD) is rising in developing countries<sup>1</sup> In America, ESRD incidence increased from 53.000 to 93.000 per year<sup>2</sup>. Gilbertson and colleagues in a Markov model study predicted 136.166 incident ESRD patients per year<sup>2</sup>. Besides that, a study conducted by Prodjosudjadi and Suhardjono showed, the prevalence of End-Stage Renal failure patients who were doing hemodialysis per one million population in Indonesia from 2002 to 2006 around 10,2 %, 11,7%, 13,8%, 18,4% and 23,4%<sup>3</sup>.

Anemia is found in renal failure patients (80%-95%) with many factors playing roles in the pathogenesis<sup>1</sup>. Anemia is one of the complications of ESRD<sup>4</sup>. It can increase morbidity and mortality among ESRD patients<sup>4</sup> According to the Third National Health and Nutrition Examination Survey (NHANES III), around 13, 5 million patients have creatinine clearance (CrCl) ≤ 50 ml/minute and around 800.000 patients among them have a hemoglobin < 11 g/dl<sup>5</sup>.

The main factor of anemia among ESRD patients is a deficiency of erythropoietin (EPO)<sup>6</sup>. According to KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (2012), giving Recombinant human

erythropoietin (rhu-EPO) is better than blood red transfusion because transfusion can increase the risk of infection and it can cause the risk of hemolytic, non-hemolytic, accumulation of iron, immunosuppression, and also suppress endogenous erythropoietin<sup>7</sup> rhu-EPO consists of 166 amino acid glycoproteins and it can increase erythrocyte cells and also increase the oxygen in the cells<sup>8</sup>.

According to National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF K/DOQI), for chronic kidney disease patients the iron target to maintain the EPO in their body is ≥ 100 ng/ml for ferritin and ≥ 20% for transferrin saturation<sup>7</sup>. EPO can increase hemoglobin (Hb) and also hematocrit (Hct)<sup>9</sup>

Anemia treatment with rhu-EPO has given the good result among ESRD patients [9] but the cost of that medicine has forced the physicians to replace the rhu- EPO with folic acid in the majority of Indonesia hospitals. The research relates to this topic is almost unfounded. Because of this reason, the research about this might be necessary to be done.



**MATERIALS AND METHODS**

**Study Design and Setting**

Research was carried out in hemodialysis ward Cempaka Putih Islamic Hospital Jakarta, Indonesia. The study included 54 hemodialysis patients. All hemodialysis patients having 30 years or more age who got folic acid and / or rhu- EPO were included in the study. Patients having co-morbid conditions and pregnant patients were excluded from the study.

**Ethical Approval**

Ethical approval was sourced from ethical medical committee from Faculty of Medicine in Indonesia and an approval letter, NO:728/UN2.F1/ETIK/2015 was given before data collection. Data was collected in Cempaka Putih Islamic Hospital Jakarta, Indonesia. An informed

consent form was signed from the patient before data collection.

**Data Collection and Handling**

The researcher would define the patients by the list of patients in the ward and before the data collection from the medical record, the researcher would explain about the research and its purpose to the patients. Before data collection the informed consent was signed as an agreement of the research from the patients. The data were arranged according to socio-demography status, laboratory value checked, and current medication and transferred to clinical research form (CRF). The researcher would follow-up the patients for 3 months. Data were analyzed descriptively by ANOVA test using SPSS 22 version software. Significance correlation was showed by P-value < 0.05.

**Research Framework**

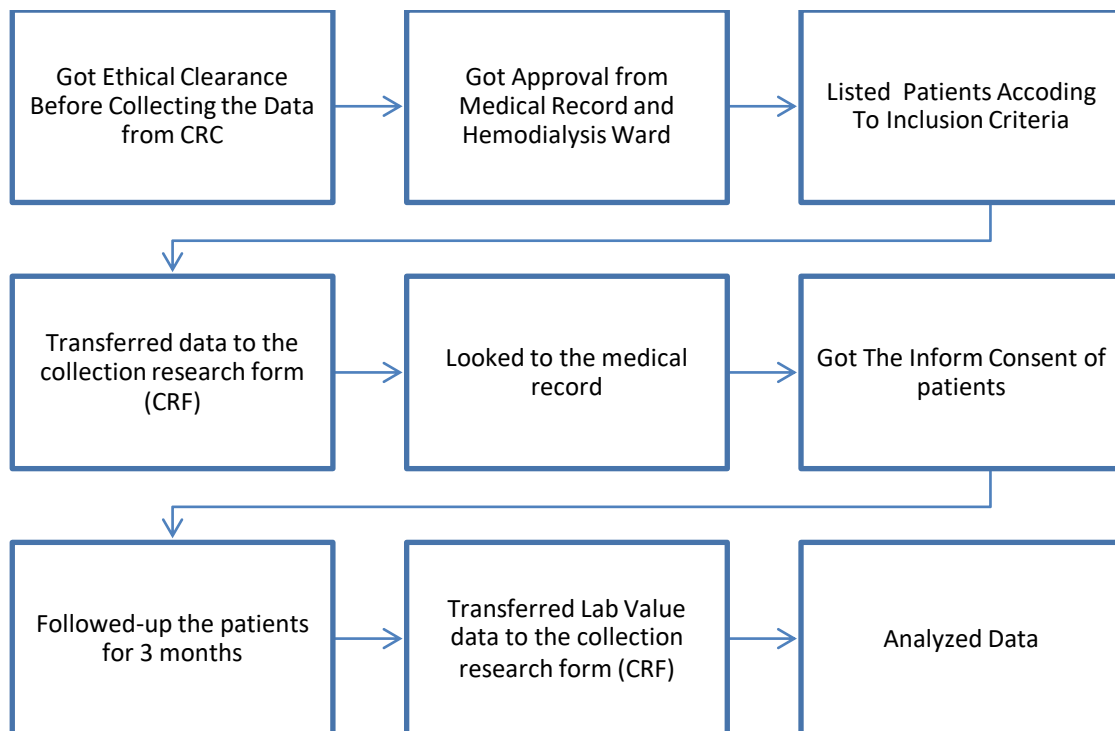


Figure 1: Descriptive Flow Chart of the Study

**RESULTS**

**1. Sociodemography**

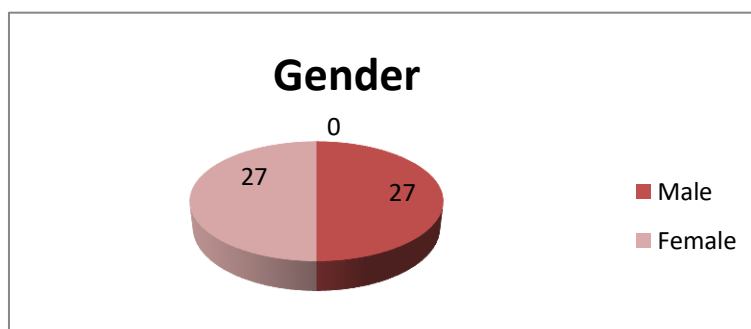
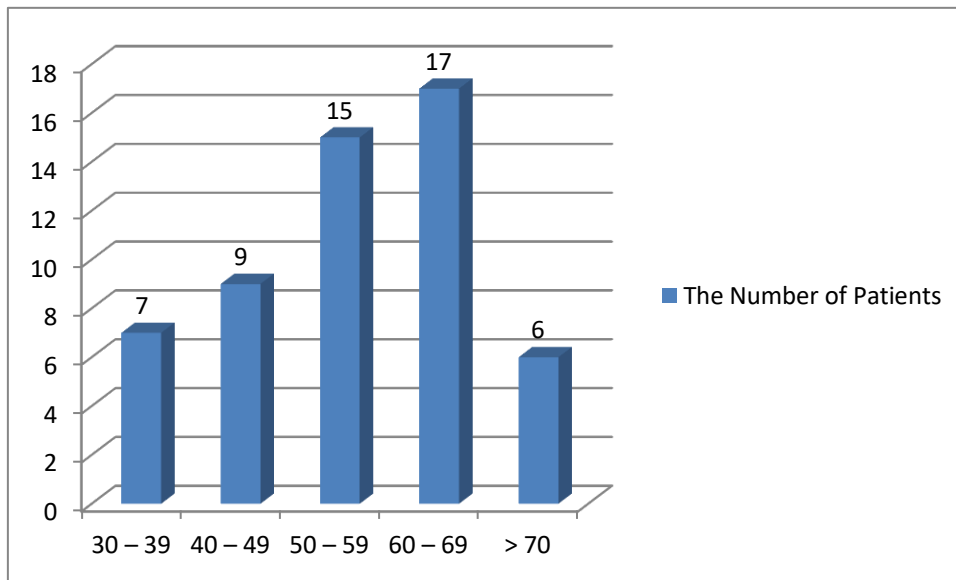
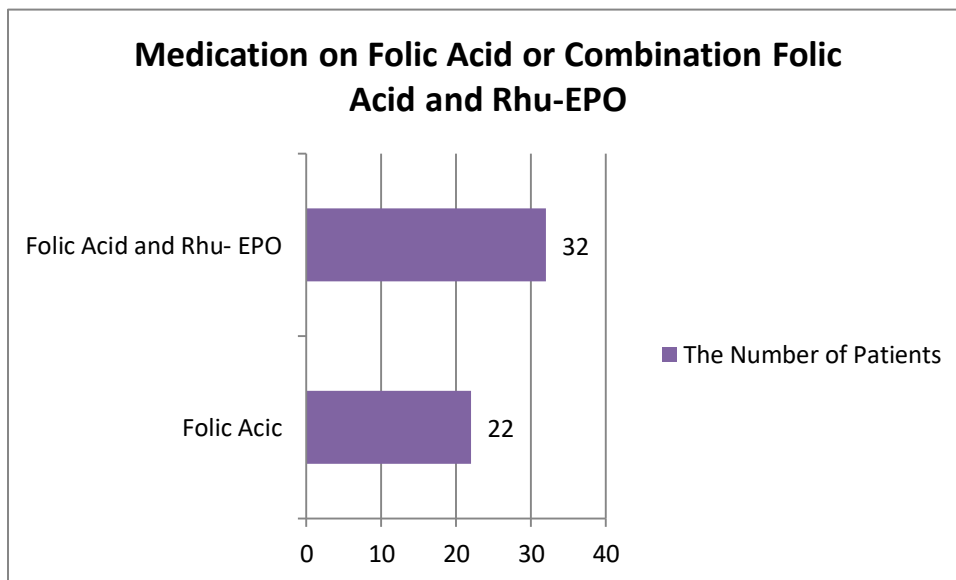


Figure 1: The number of patients based on gender (Of the total 54 patients, 27 patients were male and female).



**Figure 2:** Discriptive Data of the Patients on the Basis of Age

There were 5 age categories of the patient in this study ; 30- 39, 40 – 49, 50 – 59, 60 – 69, >70. Patients with age 60 - 69 years have a large number of anemia patients with 17 patients.



**Figure 3:** Distribution of Patients on the Basis of Medication

There were two types of anemia medication in this study, folic acid and combination folic acid and Rhu-EPO. The combination of Anemia medication between folic acid and Rhu-EPO was more prevalence than single folic acid medication.

**Table1.** Distribution of Patients on Achieving Hb Level After Folic Acid Therapy, Combination Folic Acid and *Rhu*-EPO

Hb level (mg/dl)	Folic acid		Folic acid and <i>Rhu</i> -EPO	
	Patients	Percentage (%)	Patients	Percentage (%)
< 9.4	11	50	13	40.6
≥ 9.4	11	50	19	59.4

In this study, there was two categories of Hb level ;  $< 9.4$ , and  $\geq 9.4$  mg/dl for folic acid and combination folic acid and Rhu-EPO anemia medication. An equal number was showed by folic acid in two categories of that Hb level (50%), while the combination of folic acid and Rhu-EPO was 40.6 % for the first category ( $< 9.4$  mg/dl) and 59.4 % for the second category ( $\geq 9.4$  mg/dl).

**Table 2:** Correlation Between Hb level Before and After Hemodialysis (HD)

Hb Level	Folic Acid		Folic Acid and Rhu-EPO	
	Mean of Hb Level (mg/dl) $\pm$ SD	P value*	Mean of Hb Level (mg/dl) $\pm$ SD	P value*
Before HD	8.214 $\pm$ 0.149	0.000	7.681 $\pm$ 0.132	0.000
After HD	9.786 $\pm$ 0.566		9.603 $\pm$ 0.348	

\* Paired Samples T-Test

Hb level reading was taken twice; before HD and after HD for both. The significance relationship was showed by either single folic acid or a combination of folic acid and Rhu-EPO of anemia medication (0.000, P-value  $< 0.05$ ). The high of Hb level mean was appeared by after HD at more than 9 mg/dl for both. The mean of Hb level before hemodialysis for patients who received folic acid was higher than the combination (8.214 mg/dl) but the patients who were treated by the combination had an improvement of mean of Hb higher than folic acid (around 2 mg/dl for the combination of folic acid and Rhu-EPO and around 1.5 mg/dl for folic acid).

**Table 3:** Correlation Between Gender and Achievement of Hb Level After Using Folic Acid and Combination of Folic Acid and Rhu-EPO Anemia Medication

Gender	Folic Acid		Folic Acid and Rhu-EPO	
	Mean of the Achieved Hb Level $\pm$ SD	P value*	Mean of the Achieved Hb Level $\pm$ SD	P value*
Male	1.188 $\pm$ 0.048	0.133	2.716 $\pm$ 0.063	0.984
Female	1.721 $\pm$ 0.178		2.692 $\pm$ 0.109	

\* One-Way Anova

For gender, either male or female, mean of the achievement of Hb Level for the combination of folic acid and Rhu-EPO was almost same (2.7 mg/dl), while for folic acid was slightly different in male and female (1.188 mg/dl & 1.721 mg/dl respectively). No significant correlation was showed between gender and anemia medication (folic acid and the combination of folic acid and Rhu-EPO), while the P value for both types medication was 0.133 and 0.984, respectively (P value  $< 0.05$ ).

**Table 4:** Correlation Between Age and Achieved HB Level After Folic Acid, combination of Folic Acid and Rhu-EPO Anemia Medication

Age	Folic Acid		Folic Acid and Rhu-EPO	
	Mean of the Achieved Hb Level $\pm$ SD	P value*	Mean of the Achieved Hb Level $\pm$ SD	P value*
30 – 39	1.050 $\pm$ 0.077	0.099	4.800 $\pm$ 0.079	0.400
40 – 49	2.150 $\pm$ 0.070		1.900 $\pm$ 0.056	
50 – 59	1.800 $\pm$ 0.098		1.691 $\pm$ 0.031	
60 – 69	1.160 $\pm$ 0.036		2.742 $\pm$ 0.054	
> 70	1.400 $\pm$ 0.127		4.920 $\pm$ 0.062	

\* One-Way Anova Test

For the age categories, mean of the achieved Hb level for the second and the third age category of folic acid was higher than the combination of folic acid and Rhu-EPO, while 2.150 and 1.800 mg/dl, respectively for folic acid, and 1.900 and 1.691 mg/dl for the combination of folic acid and Rhu-EPO. No significance correlation was found between age categories and anemia medication, (0.099 and 0.400, respectively, P value  $< 0.005$ ).

## DISCUSSION

Erythropoietin recombinant is one of the anemia medication for hemodialysis patients<sup>9</sup> but it is costly for low economic patients so, for anemia medication they just take folic acid. It can be seen that fourth age group (60-69) of hemodialysis patients who got anemia medication have a large number of anemia medication for hemodialysis patients (Figure 3). D. Wright and his

colleagues conducted a study in 2015 and the result showed that the mean age of hemodialysis patients was above 60 years old<sup>10</sup>.

In the current study, we compared two types of anemia medication for hemodialysis patients; folic acid and the combination of folic acid and Rhu-EPO. It is described that the hemodialysis patients who used the combination folic acid and Rhu-EPO more prevalence (Figure 3), because usually patients who are doing hemodialysis have a problem with deficiency of endogenous erythropoietin<sup>11</sup>. Deficiency of endogenous erythropoietin will cause anemia and definitely hemoglobin patients will also lower than normal value. Giving erythropoietin recombinant will discover that problem quickly. For low economic patients, the price of Rhu-EPO is expensive so, they just receive folic acid as an anemia medication. Folic acid is one of the supplement to increase red blood cells<sup>7</sup>.

Current study results showed that the patient's number who had Hb level < 9.4 mg/dl and ≥ 9.4 mg/dl was equal for folic acid anemia medication while the combination of folic acid and Rhu-EPO was 40.6% and 59.4 %, respectively for Hb level < 9.4 mg/dl and ≥ 9.4 mg/dl (Table 1). The increasing of the patient's number was seen by the combination of folic acid and Rhu-EPO. Rhu-EPO can increase Hb level significantly due to decreasing of endogenous erythropoietin in hemodialysis patients<sup>7</sup>. In the present study data showed mean Hb level before hemodialysis for patients who used folic acid was higher than the combination of folic acid and Rhu-EPO (Table 2). The improvement of the mean of Hb level after hemodialysis between patients who used folic acid and the combination of folic acid and Rhu-EPO was almost same (1.5 mg/dl and 2 mg/dl respectively). In present study, folic acid gave an impact for increasing Hb level.

Data described mean of the achieved Hb level for folic acid on the basis of gender showed that, female patients had a higher value than male patients (1.188 mg/dl) but for the combination folic acid and Rhu-EPO, male patients (2.716 mg/dl) had a slightly higher than female patients (Table 3). Some factors can be possible for explain this finding such as differentiation in absorption and compliance.

Present study results showed that mean of the achieved Hb level for the second and the third age category of folic acid was higher than the combination of folic acid and Rhu-EPO, while 2.150 and 1.800 mg/dl, respectively for folic acid, and 1.900 mg/dl and 1.691 mg/dl for the combination of folic acid and Rhu-EPO.

Erythropoietin is produced by the kidneys and a small part (± 10%) by the liver<sup>12</sup>. Stimulate erythropoietin function is CFUE erythroid progenitor cells (Colony Forming Unit erythroid) for differentiation and maturation resulting erythroblasts and accelerate the release of reticulocytes<sup>12</sup>. Erythropoietin levels in normal individuals range between 10-12 mU / ml<sup>9</sup>. In a healthy kidney, if there is a decrease in hemoglobin and oxygen

saturation in the blood, then hypoxia is occurring erythropoietin and it stimulates the production of up to 100-1000 mU / ml<sup>7</sup>. In chronic renal failure, hypoxemia due to anemia stimulus will cause the kidneys do not produce erythropoietin<sup>7</sup>. This may be due by cells that produce erythropoietin already damaged. Thus, in patients with chronic renal failure without influenced by gender or age, will still have a submaximal response to the stimulus anemia.

## CONCLUSION

In the conclusion, folic acid is effective to increase hemoglobin level of hemodialysis patients with anemia although it is not as effective as rHU-EPO. However, a large sample size and a multicenter study would be more helpful to find the efficacy of folic acid in hemodialysis patients with anemia.

## LIMITATION OF STUDY

The study was conducted prospectively by collecting any available data directly from the patient. The medical record was not computerized so some of the data were missing hence could not be added to further improve the strength of the findings, especially for laboratory value.

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