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Comparison Of The Effectiveness And Safety Of Anemia Epoetin Alfa With Epoetin Beta Inhemodialysis Routine Patients At Haji Rsu Surabaya

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ABSTRACT

Chronic Kidney Disease (CKD) is a disorder of the structure / function of kidney> 3 months marked by pathology and renal damage marker and impairment Glomerular filtration rate (GFR). Erythropoietin is agrowth factor hematopoietic that plays a role in the formation of red blood cells 5. Research conducted by Henry et al, on the pharmacokinetics of epoetinalfa showed the results that epoetinalfa has the effectiveness of increasing Hb concentration within 2-6 weeks with a half-life of 4-5 hours. Epoetin therapy was given with indications of Hb< 10 g/dL, no absolute iron deficiency anemia Transferrin Saturation > 20%, Serum Ferritin and no severe infection. At RSU HAJI, the insurance company bears the cost of administering epoetinalfa at a dose of 3000 IU and epoetin beta at a dose of 2000 IU to anemic patients undergoing HD, with several written conditions, namely the administration of epoetinalfa/beta given twice a week ,Hb< 10 g/dL, TSAT > 20%, FS > 200 ng/L, and no severe infection. The research subjects were divided into 2 groups, namely a group of patients receiving treatment for epoetin alpha 3000 IU/2x a week and a group of patients receiving epoetin beta anemia therapy 2000 IU/2x a week, with the direction of data collection being a combination of retrospective methods. Based on the results of research that has been conducted on the comparison of the effectiveness and safety of anemia therapy with epoetinalfa and epoetin beta in routine hemodialysis patients at RSU HAJI Surabaya.

Keywords : Hemodialysis, Anemia, Epoetin, Effectiveness, Safety.

INTRODUCTION

Chronic Kidney Disease (CKD) is a disorder of the structure / function of kidney> 3 months marked by pathology and renal damage marker and impairment *Glomerular filtration rate* (GFR) <60 ml / min / 1.73 m^2Management of CKD can be given conservative therapy such as diet, drinking restrictions, and drugs (Angela Yee-Moon Wang, 2019). Giving drugs to patients with CKD can no longer provide helpTherefore, patients with CKD require renal function replacement therapy to prolong and maintain the patient's quality of life , such as kidney transplantation or

dialysi(Hiddo J.L. Heerspink , 2021).Limited donors and cost factors cause most patients in Indonesia to use dialysis as the main renal replacement therapy, one of which is HD. (Zaki Morad, MBBS, 2015)

CKD patients undergoing HD generally experience complications in the form of anemia. Anemia in CKD is closely related to decreased production of erythropoietin produced by the kidneys. This is because the kidneys are the main source of erythropoietin (Haine et al., 2021). The kidneys produce 90% of the total erythropoietin. Erythropoietin is agrowth factor *hematopoietic* that plays a role in the formation of red blood cells 5 (Nasr, 2020). Erythropoietin increases the production of reticulocytes and the initial release of reticulocytes from the bone marrow, which then lose their ribosomes and become erythrocytes(Elisa Piva MD, 2015). Anemia in CKD may result in an increase in the progression of chronic kidney damage, development of anemia in CKD condition and can cause a decrease in the delivery and use of oxygen, which can cause an increase in *cardiac*output(Jay B. Wish, 2021).As a result of these cumulative effects are *left ventricular hypertrophy* (LVH), *arterial hypertrophy, arteriosclerosis,* cardiac dilatation, arrhythmias and heart failure. So it can be said that this will increase the risk of cardiovascular and death in CKD patients. (Coyne et al., 2021)

First-line therapy for CKD anemia is to replace the deficient erythropoietin with *erythropoiesis-stimulating agents* (ESAs), more commonly known as epoetin(Sandra Ribeiro, Luís Belo, Flávio Reis, 2016). The history of using epoetin therapy in CKD anemia is that since 1989 in America, epoetinalfa is the standard therapy for anemia with CKD undergoing HD, because it can reduce morbidity and mortality(Qiyan Zheng, Huisheng Yang, Luying Sun, 2020). Research conducted by Henry *et al,* on the pharmacokinetics of epoetinalfa showed the results that epoetinalfa has the effectiveness of increasing Hb concentration within 2-6 weeks with a half-life of 4-5 hours.(M.Basora, 2015)

Based on PERNEFRI, corrective phase ESA therapy is started with 2000-5000 IU twice weekly or 80-120 units/kgBW/week subcutaneously with monitoring of Hb levels every 4 weeks(Sydney C.W.Tang, 2017). Meanwhile, the maintenance phase of ESA therapy (done when the Hb target has been reached) starts with a dose of 2000-5000 IU/week subcutaneously with monitoring of Hb levels every 4 weeks. Epoetin therapy was given with indications of Hb< 10 g/dL, no absolute iron deficiency anemia (Transferrin Saturation (TSAT) > 20%, Serum Ferritin (FS) > 100) and no severe infection. The expected therapeutic response target is an Hb increase of 0.5–1.5 g/dL in 4 weeks, with a target of achieving Hb of 10-12 g/dL in 4 weeks.The response to an increase in Hb with epoetin administration can be reduced under certain conditions(Jain, 2021). It can be affected by iron deficiency, acute infection, *inadequate dialysis*, malnutrition, folate deficiency, hyperparathyroidism, and the patient's own disease condition (Ines Silva, 2021).

Epoetin alpha and epoetin beta both have 165 amino acids, but they differ in terms of glycosylation patterns. Unit oligosaccharides of erythropoietin has a function that varies in

modulating the biological activity. The oligosaccharide portion of the epoetin beta structure is larger and more acidic than the epoetin alpha (Thompson A.M,2020). In addition, when compared with epoetinalfa, epoetin beta has an isoform with a higherbioactivity ratio *in vivo: in vitro* (Ali Reza Khoshbin, 2015). Based on a study conducted by Halstenson*et al*, regarding the pharmacokinetic and pharmacodynamic differences between epoetin alpha and epoetin beta, the results showed that the steady state (7.7%), the volume of distribution of the -phase (16.9%), and the elimination half-life (20%) of epoetin beta by intravenous administration was greater ($p<0.05$) than epoetin alfa(Dennis Stalker PhD, 2016).Comparison of these pharmacokinetic properties may affect the difference in drug side effects (ESO) of each epoetin. Reports of ESO from epoetinalfa were nausea 58%, fever 51%, *injection site reaction* 29%, vomiting 29%, hypertension 24%, pruritis 22%, insomnia 21%, dizziness 21%, headache 19%, cough 18%, edema 17%, redness 16%, *dyspnea* 14%, and *deep vein thrombosis* 11% and *pure red cell aplasia* rare(PRCA) (Alwhaibi,2021). Reports on ESO from epoetin beta were hypertension 23.4%, *GI tract* 23%, pruritis 22%, dizziness 21%, insomnia 21%, headache 19%, cough 18%, *dyspnea* 14%, *upper respiratory tract infection* 12.7%, *menstrual disorders* 9.1%, *lower respiratory tract infection* 8.6%, thrombosis 8.2%, joint disorders 7%, hyperkalemia 7%, *overhydration* 7%, infection 5.7%, *injection site reaction* 5.7%, and rare PRCA (Bejar Rafael, 2014).

At RSU HAJI, the insurance company (BPJS) bears the cost of administering epoetinalfa at a dose of 3000 IU and epoetin beta at a dose of 2000 IU to anemic patients undergoing HD, with several written conditions, namely the administration of epoetinalfa/beta given twice a week ,Hb< 10 g/dL, TSAT > 20%, FS > 200 ng/L, and no severe infection. If there is an iron deficiency FS <200 ng/L and TSAT <20%, this must be overcome first by giving iron preparations(P.Fenaux, 2017).Based on research conducted by Loughnan A *et al*, the results showed that epoetin beta and epoetinalfa were equally effective in increasing Hb and Hct levels, but epoetin beta was effective at a smaller dose than epoetinalfa ($p<0.001$)(Robert Provenzano MD, 2016). In addition, research evidence or current therapeutic guidelines only say that the clinical effect of epoetin therapy is the same, but there is no difference in terms of target time, safety and the length of time the therapeutic effect can last after administration of epoetin alpha and epoetin beta(Steven Fishbane, 2019). So that these reasons are considered for conducting a study "Comparison of the Effectiveness and Safety of Epoetin Alpha Anemia Therapy with Epoetin Beta in Routine Hemodialysis Patients at RSU HAJI Surabaya", with adesign*quasy experimental.*

METHODS

This research was conducted with adesign*quasi experimental*, with the method of *Non-equivalent Control Group Design.* The research subjects were divided into 2 groups, namely a group of patients receiving treatment for epoetin alpha 3000 IU/2x a week and a group of patients receiving epoetin beta anemia therapy 2000 IU/2x a week, with the direction of data collection being a combination of retrospective methods (as initial data / *baseline*). and prospective. Retrospective or

prospective data retrieval was carried out at the HD Installation section of the HAJI RSU Surabaya during the study period, namely 3 months from March 22 to June 22 2016, with a total of 50 patients who completed the final stage (25 patients in each group).

The independent variables were Hb levels <10 g/dl, Hct levels <30%, epoetinalfa therapy and epoetin beta therapy which included dose, frequency of administration, route of administration, and duration of administration. The dependent variable is the effectiveness and safety of epoetinalfa and epoetin beta anemia therapy. The effectiveness is the target Hb level (10-12 g/dL), the target Hct level (> 30%), and the time to target Hb*target*and*time in target*. Safety is the side effects of drugs due to anemia therapy of epoetinalfa or epoetin beta. Controlled variables were TSAT and serum ferritin levels, malnutrition/liver cirrhosis, blood loss, dialysis adequacy, cancer, folic acid administration, dialysate flow rate (Qd), blood flow velocity (Qb),type *dialyzer*, dialysate type, dialysate temperature, and speed of ultrafiltration Confounding variables are drug factors such as Azathioprine, mycophenolatemofetil (MMF), ACE inhibitors, Statins, Angiotensin II *receptor blockers* (ARB); Patient factors which include age and gender; and the underlying disease of CKD (Tang,2018).

Tabel 1. Variables

Independent Variables	Operational Definition
Dosage Administration of epoetinalfa&epoetin beta	Dosage of epoetinalfa and epoetin beta during the research process, in this case 2000 IU for epoetin beta per administration and 3000 IU for epoetinalfa per administration
Frequency of epoetinalfa&epoetin beta administration	Frequency of administration of epoetinalfa and epoetin beta to patients during the research process, in this case 2x a week
Route of administration of epoetinalfa&epoetin beta	The route of administration of epoetinalfa and epoetin beta during the research process, namely subcutaneously
Hemoglobin (Hb)	Levels Hb levels for the first time before being given epoetinalfa/beta, namely Hb levels <10g/dL
Hematocrit levels (Hct)	Hct levels for the first time before being given epoetinalfa/ beta i.e. Hct levels <30%
Duration of administration of epoetinalfa and beta	Time interval from the first administration of epoetinalfa/beta to the end of the prospective study period
Variable Dependent	Operational Definition
Effectiveness	Is an anemia condition that is resolved by looking at the difference between the initial Hb level or Hct level (since the patient first received epoetin alpha or beta therapy) with

	the final Hb level or Hct level (when the prospective study ends). In this case, the target Hb level is 10-12 g/dl and the target Hct level is >30%.
	Time to target is the time span since anemia therapy is given until the minimum Hb target has been determined (Hb 10 g/dL).
	*Time in target*is the time span required by anemia therapy to produce Hb levels that can stay within the target range (Hb 10 – 12 g/dL).
	Time Below target is the time span required for anemia therapy to produce Hb levels that fall back below the target after previously reaching the target (Hb<10 g/dL).
	Time Over Target is the time span required for anemia therapy to reach Hb levels above the target (Hb> 12 g/dL).
Safety	There are no drug side effects in the study subjects due to efforts to overcome anemia with epoetinalfa or epoetin beta

Controlled Variables	Operational Definition
Transferrin Saturation Levels (TSAT)	TSAT levels before the first time the patient received epoetin alpha or beta therapy, namely >20%
Serum levels ferritin	Serum ferritin levels before the first time the patient received epoetin alpha or beta therapy were > 200 ng/ml
Folic acid	Folic acid was always given before administration of epoetin alpha or beta therapy.
Malnutrition/liver cirrhosis The	condition declared as malnutrition/liver cirrhosis in this study is that in addition to the doctor's diagnosis (from medical record data), albumin levels show <3 g/dl.
Blood	loss The condition of sudden blood loss during the research process, namely Hb level <7 g/dl
Cancer	Patients diagnosed with cancer by a doctor based on medical record data
Adequate dialysis	frequency and duration of HD received by an HD patient. In this case, dialysis adequacy will be calculated (URR value indicator >65%, Kt/V >1.8)
Blood flow rate (Qb)	Blood flow rate (Qb) in patients with HD ranges from 200-270 ml/min. Qb used in this study tailored to the clinical conditions of patient

rate flow of dialysate (Qd)	flow rate of dialysate (Qd) in patients on HD were used in this study range from 500 ml / min
type of dialyzer	type of dialyzer used for hemodialysis in this study is a Hollow fiber dialyzer high flux / FB-130
Type of dialysate The	type of dialysate used in HD during the study is bicarbonate.
DialysateThe dialysate	temperaturetemperature used when HD patients are adjusted to the patient's temperature conditions, namely 36-37 ^{0}C
Ultrafiltration	Speed Ultrafiltration speed used when HD patients, in this case adjusted to the patient's clinical condition, which ranges from 1-10 L/hour
Variable Confounding	Operational Definition
PatientThe patient's	ageage since the first time receiving epoetin alpha/beta therapy until the end of the prospective study period and patient age data based on the date of birth on the patient's ID card or this data can be obtained from the medical record.
Patient	gender The gender of patients with chronic kidney disease who underwent hemodialysis at the HAJI Surabaya general hospital were female and male.
Factors drugs other used by patients with	medications that can affect changes in hemoglobin in therapy epoetinalfa and epoetin beta, ie azathioprine, mycophenolatemofetil (MMF), ACE inhibitors, Statins, Angiotensin II receptor blockers (ARBs).
Diseases that underlie the occurrence of CKD	The underlying diseases in chronic kidney disease are grouped into two, namely diabetes mellitus and non-diabetes (hypertension and *polycystic kidney disease*).

The target population in this study were patients with chronic kidney disease who received anemia therapy with Epoetinalfa or Epoetin beta and underwent routine hemodialysis twice a week at RSU HAJI Surabaya. While the affordable population in this study were patients with chronic kidney disease who received anemia therapy with Epoetinalfa or Epoetin beta and underwent routine hemodialysis twice a week at RSU HAJI Surabaya, according to the research criteria.

3 Inclusion Criteria for this study. First, Patients with chronic kidney anemia (Hb<10 g / dL), Hct<30% who underwent routine hemodialysis 2x a week for 4-5 hours with a stable condition at the Hemodialysis Installation of RSU HAJI Surabaya during the study period. Second,

Patients received anemia therapy with epoetinalfa 3000 IU/2x a week or epoetin beta 2000 IU/2x a week, with adequate iron status (serum ferritin >200 ng/ml and transferrin saturation >20%) thrird,Patients >18 years old and stating their willingness to be involved in the study, evidenced by signing the *Statement of Consent Form*.

Exclusion criteria were: patients with a doctor's diagnosis of cancer and malnutrition or liver cirrhosis Dropout 2 criteria Patients died, resigned or transferred to another hospital or did not come back to the HD Installation of HAJI RSU, before completing all stages of the study and Acute conditions requiring medical intervention /psychiatric threatening condition

Calculation of sample size

$$n = \frac{\left\{Z_{1-\alpha/2}\sqrt{[2P(1-P)]} + Z_{1-\beta}\sqrt{[P_1(1-P_1)+P_2(1-P_2)]}\right\}^2}{(P_1-P_2)^2}$$

Description :

n : number of samples

$Z_{1-\alpha/2}$: degree of significance

P : population proportion

The value used is $P_1 = 0.34$; $P_2 = 0.66$; = 0.05; and = 0.10, so the number of samples in this study are:

$$n = \frac{\{1.960\sqrt{[2(0.80)(0.20)]} + 1.282\sqrt{[0.34(0.66)+0.66(0.34)]}\}^2}{(0.34-0.66)^2}$$

n = 19,53 atau 20 sampel

The sampling technique used was themethod, *total sampling* namely the sample was taken from the entire target population during the data collection period. In this study, the sample was divided into two groups determined by the clinical responsible physician at the HD Installation of the HAJI RSU.

Interventions in this study will be divided into 2 groups, namely: epoetinalfa 3000 IU anemia therapy group twice a week and 2000 IU epoetin beta anemia therapy group 2x a week, group selection is determined by the clinical doctor in charge of the hemodialysis installation at RSU HAJI;and during the intervention monitoring the effectiveness and safety of therapy (Carrillo,2016).

Collectiondatacollectiondata collection including Hb, Hct, BUN, Cr, Ferritin, TSAT and side effects were recorded before and during subjects receiving epoetin therapy, until shortly before the prospective study phase was carried out. Samples that match the research criteria will be given an explanation of the research procedure along with the benefits and risks, then their willingness to fill out aasked. *Statement of Consent Form*

Datacollectiondata collection including Hb, Hct and side effects were recorded and followed continuously during and during subjects receiving epoetin therapy, until the end of the study data recording period.

In this study, data analysis was carried out in inferential and descriptive statistics. Inferential statistical analysis used is *paired t test* (if data is normally distributed) or *Wilcoxon* (if data is not normally distributed), *t test* unpaired(if data is normally distributed) or *Mann Whitney* (if data is not normally distributed), *chi square* and ANCOVA (Ji Lanpeng, Liu Peng, Robert Stephan,2019).

RESULTS AND DISCUSSION

The total patients who completed to the end of the study were 50 patients (25 patients in each group). There was nobetween the two groupssignificant differencefromthemean*baseline* (hemoglobin/hematocrit/systolic BP/BPdiastolic) (Appendix 1). This means that the initial state of anemia in the two anemia treatment groups (group I and group II) is *comparable* so that the two anemia treatment groups can be compared.

Group I compared to group II: group I (treated with epoetin alpha anemia 3000 IU/2x a week) was significantly more effective than group II (treated with epoetin beta anemia 2000 IU/2x a week). In group I it was shown by an increase in the Hb value of 7.9 g/dl ± 0.71 (Hb before epoetinalfa therapy) to 10.2 g/dl ± 1.49 (Hb after epoetinalfa therapy) while in group II it was shown with an increase in Hb value of 7.7 g/dl ±0.62 (Hb before epoetin beta therapy) to 8.9 g/dl ±1.66 (Hb after epoetin beta therapy) (Appendix 2). Regarding the comparison of *time to target* and *time in target* in groups I and II, they cannot be compared because in group I the target was achieved while in group II it was not achieved (Appendix 3 and 4). Then regarding the achievement of the Hb target or the length of Hb in the target range, it cannot be determined because the patient's Hb measurement is only done once a month, so it is not certain when the Hb will reach the target or how long the Hb level will continue in the target range.

Group I compared to group II: based on the occurrence and non-occurrence of ESO, it was found that there was no significant difference inthe incidence of side effects between group I (the epoetinalfa group) andgroup II (group giving epoetin beta) (Appendix 5). However, based on the occurrence of the resulting ESO, it was found that there was a significant difference inthe incidence of side effects that occur/arise between group I (groupepoetinalfa) and group II (epoetin beta administration group) (Appendix 5). As indicated by the percentage of ESO >10% in group I, there were 4 types of ESO, namely dizziness 28% (6 patients), cough 18.4% (7 patients), itching 14.9% (2 patients), and fever 14.9% (5 patients) compared to group II there were 3 types of ESO namely dizziness 25.9% (3 patients), digestive tract disorders 15.5% (5 patients), and itching 13.8% (2 patients) (Appendix 6).

One of the side effects of giving *erythropoietin* as a therapy for anemia is hypertension. Observation of blood pressure for ESO hypertension can only be done when the patient returns home, so it is necessary for the patient to have a BP measuring device at home. However, patients who have a blood pressure measuring device at home are very limited (only 10 patients from each anemia therapy group), so in this study to ensure the occurrence of side effects of hypertension from epoetin alpha/beta, statistical tests were carried out on systolic or diastolic blood pressure data. . Then, after performing statistical tests on the comparison of systolic and diastolic blood pressure to the two groups, namely the comparison of intradialytic and interdialytic BP in each group, the comparison of retrospective and prospective BP in each group, as well as the comparison of retrospective BP between groups I and II was not found. there is a difference that shows the presence of ESO therapy of anemia against hypertension (Appendix 7). There was a significant difference, only showing an increase in blood pressure due to hemodialysis complications.

CONCLUSION

Based on the results of research that has been conducted on the comparison of the effectiveness and safety of anemia therapy with epoetinalfa and epoetin beta in routine hemodialysis patients at RSU HAJI Surabaya, the conclusions a. There was a significant difference in the increase in the initial hemoglobin with the final hemoglobin in each anemia treatment group ($p<0.05$) andThere was a significant difference in the difference in Hb levels between the epoetinalfa group and the beta epoetin group, that is, epoetinalfa was better than epoetin beta ($p<0.05$).

The period of *time to target* and *time in target* for each anemia therapy group cannot be determined because the patient's Hb measurement is only done once a month, so it is not certain when the Hb will reach the target or how long the Hb level will remain within the target range. Comparison of *time to target* and *time in target* between the two anemia therapy groups could not be determined because epoetinalfa reached the Hb target while epoetin beta did not reach the target. There was no significant difference in the incidence of side effects between the two anemia therapy groups ($p>0.05$).

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