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Effectiveness of Erythropoetin Alpha and Eryhtropoetin Beta in Patients With End-Stage Kidney Disease with Anemia Undergoing Hemodialysis: A Meta-Analysis Study

Vincentius William Sunur [1)], Timothy Sulistio[1)], Vega Adisyahputra[1)], Vita Safira[1)], Ronald Pratama Adiwinoto[2)], Yuswanto Setyawan[3)]

1) Faculty of Medicine, Universitas Hang Tuah
2) Department of Public Health Sciences, Fakultas Kedokteran Hang Tuah
3) Department of Internal Medicine, RSPAL dr. Ramelan Surabaya,
Faculty of Medicine Universitas Hang Tuah

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ABSTRACT

Background: One of the causes of anemia in ESRD (End Stage Renal Disease) is due to lack of erythropoietin (EPO) production. The use of short-lived ESA preparations such as Erytrhopoietin alpha and Erytrhopoietin beta still differs in opinion about the effectiveness between the two ESA agents. So the purpose of this study is to review the findings from various studies to provide a better understanding of the effectiveness of the use of ESA.

Subjects and Method: The results of the study sought were the effectiveness of erythropoietin alpha and erythropoietin beta which were assessed by the hemoglobin levels in the study. This study uses a meta-analysis design in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Data search using PUBMED, ResearchGate, and ScienceDirect databases.

Results: A total of 458 studies were identified through database sources. After adjusting for inclusion and exclusion criteria, there were 6 studies to be reviewed in a meta-analysis with a total of 220 patients given erythropoietin alpha therapy and 227 patients given erythropoietin beta therapy. The results of the meta-analysis showed that there was no significant difference in the erythropoietin alpha and erythropoietin beta groups after 1 month of therapy (P=0.20, MD=0.16, 95%CI = -0.57 until 1.17, I2=0%, P=0.56), nor after 3 months of therapy (P=0.19, MD=-0.27, 95%CI =-0.68 until 0.13, I2=0%, P=0.58).

Conclusion: There was no significant difference between the effectiveness of erythropoetin alpha and erythropoetin beta in increasing patients' hemoglobin levels. These two ESA agents are effective in increasing hemoglobin levels in ESRD patients.

Keywords: ESRD, Erythropoietin alpha, erythropoietin beta, hemoglobin

Correspondence:
Vincentius William Sunur. Faculty of Medicine, Universitas Hang Tuah. Jl. Arief Rachman Hakim No. 150 Sukolilo Regency, Surabaya, East Java 60111, Indonesia. Email: wsunur@gmail.com

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BACKGROUND

Chronic kidney disease is defined as kidney damage or decreased kidney function for at least 3 months, regardless of etiology. Kidney damage can be pathological in the native or transplanted kidney, confirmed by radiography, biopsy, or by clinical markers such as increased albuminuria, i.e. albumin-to-creatinine ratio (ACR) >30 mg/g (3.4 mg/mMol), or changes in urine sediment; decreased kidney function refers to a decrease in the glomerular filtration rate (GFR), which is usually estimated (eGFR) from serum creatinine concentrations (Wilson et al., 2021). End-Stage Renal Disease (ESRD) is defined as a decrease in the glomerular filtration rate below 15 ml/min (Akbari et al., 2015).

Anemia, defined as a serum hemoglobin (Hb) level ≤12 gm/dL in women and ≤13 gm/dL in men, is a common complication of chronic kidney disease. The prevalence of anemia tends to correlate with the severity of the underlying kidney disease, ranging from 8.1% in patients with stage 1 chronic kidney disease to 53.4% in stage 5/end-stage chronic kidney disease/ ESRD (Shahab & Saifullah Khan, 2020). Anemia is caused by inadequate erythropoietin production, resistance to erythropoietin, shortened red blood cell lifespan, uremic toxins, and inflammation. Among the various complications, anemia is often associated with poor clinical outcomes in chronic kidney disease and increased mortality. Anemia is more common and more severe when the estimated glomerular filtration rate (eGFR) decreases. The prevalence of anemia increases as CKD progresses: 8.4% in stage 1 to 53.4% in stage 5/ESRD. (Georgatzakou et al., 2016; Portolés et al., 2021; Shaikh et al., 2023; Thavarajah & Choi, 2019)

One of the causes of anemia in ESRD is due to a lack of erythropoietin (EPO) production. Erythropoietin (EPO) is a glycoprotein hormone naturally produced by renal peritubular cells, which stimulates the production of red blood cells. In chronic kidney disease, there is damage to the structure and function of the kidneys, disrupting the process of red blood cell formation and causing decreased hemoglobin levels in the blood. Erythropoiesis-stimulating agents (ESAs) have been used to manage anemia in chronic kidney disease (CKD) with the aim of reducing transfusion requirements and symptoms of anemia. (Schoener & Borger, 2023; Thavarajah & Choi, 2019) Currently available ESA preparations consist of short-acting agents (epoetin alfa and epoetin beta) and long-acting agents (darbepoetin and methoxy polyethylene glycol–epoetin beta), as well as biosimilar ESA agents (Hodson & Strippoli, 2021).

ESA preparations available in Indonesia are: epoetin/erythropoetin alpha, epoetin/erythropoetin beta, and C.E.R.A which is an ESA agent with a longer half-life (PERNEFRI, 2011). Although there have been various studies to evaluate the effectiveness and safety of using ESA agents with a short half-life (erythropoetin alpha and beta), there is still debate and disagreement between the results of these studies. The study by Dashti et al. is in accordance with the KDIGO guidelines that there is no difference in effectiveness between the 2 agents (Dashti et al., 2021; KDIGO, 2012). However, the studies of Ahsan et al., Faizah et al., Widodo et al. and Prasetya et al. concluded different results between the effectiveness of ESA (Ahsan et al., 2021; Faizah et al., 2022; Prasetya et al., 2019; Widodo et al., 2021). In previous meta-analysis studies on ESAs discussing the prevention rate of transfusion requirements and patient mortality, no one has concluded the effectiveness between these two ESA

agents in increasing hemoglobin levels (Amato et al., 2018; Chung et al., 2023). Therefore, the purpose of this meta-analysis is to review the findings of various existing studies to provide a more comprehensive understanding of the effectiveness of ESA use in increasing hemoglobin levels in ESRD patients. In this study, we will conduct a meta-analysis of the latest studies conducted between 2018 and 2023 to evaluate the effects of using epoetin alpha or erythropoietin alpha and epoetin beta or erythropoietin beta so that we can provide an up-to-date understanding of this topic.

SUBJECTS AND METHOD

1. Study Design

This study was conducted using a meta-analysis design in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. This study is a meta-analysis, which is an analysis with secondary processing. Therefore, no ethical approval is required.

2. Inclusion and Exclussion Study Criteria

Randomized controlled trials (RCTs) examining the effects of Erythropoetin Alpha and Erythropoietin Beta in Patients With End-Stage Kidney Disease with Anemia Undergoing Hemodialysis were included in the systematic review. Inclusion criteria include studies in the period 2018-2023, studies with research designs: experimental (Randomized Controlled Trial, Clinical Trial, and quasi-experimental) and observational (prospective cohort), open access studies. The study population was patients with chronic kidney disease with complications of anemia with samples given erythropoietin alpha or erythropoietin beta intervention, the results of the study sought: in the form of the effectiveness of erythropoietin alpha and beta as assessed by hemoglobin levels.

3. Definition of Operational Variables

Erythropoetin Alpha is a drugs classified as erythropoiesis stimulating agents to activate the erythropoiesis process and stimulate the release of reticulocyte cells.

Eryhtropoetin Beta is a a drug that is part of the synthesis of erythropoietin which can function to produce red blood cells from protein sources.

End-Stage Kidney Disease is a a condition where kidney function begins to decline gradually.

Anemia is a problem of not having enough healthy red blood cells or hemoglobin to carry oxygen to the body's tissues.

Hemodialysis is a treatment for advanced kidney failure that filters wastes, salts and fluid from body blood.

4. Study Instruments

Data search using the PUBMED, Research Gate, and ScienceDirect databases with the keywords "End stage kidney disease; Chronic Kidney Disease; Anemia; epoetin alpha; epoetin beta; Erythropoietin alpha; Erythropoietin beta" and obtained 458 studies.

5. Data analysis

The study selected articles based on specific criteria and adhered to PRISMA flowchart guidelines. Data analysis utilized Rev-Man 5.4.1 software to determine effect sizes and evaluate heterogeneity consistency (I2) among the selected research findings.

RESULTS

1. Study Characteristics Results

Figure 1 is a PRISMA flow diagram illustrating the process of searching and selecting selected studies. A total of 97 studies were identified through Research Gate, 23 studies in PUBMED, and 338 studies in Science Direct with a total of 458

studies. There were 114 studies after studies published not in the 2018-2023 period were excluded. 110 studies after duplicates were excluded. There were 70 studies excluded with the type and design of the study not meeting the criteria, leaving 40 studies. Then 33 studies were excluded because the title and abstract did not match. Of the 7 studies, 1 study was excluded because the treatment was not appropriate (Not comparing the effectiveness of erythropoietin alpha and beta from the beginning or baseline). The remaining 6 studies will be meta-analyzed.

Of these 6 studies, there are 2 observational studies with a prospective cohort design and 4 experimental studies. 2 studies will compare the average hemoglobin levels after 3 months of erythropoietin alpha and beta administration. 5 studies will compare after 1 month. A total of 220 patients were given erythropoietin alpha therapy and 227 patients were given erythropoietin beta therapy.

2. Meta-Analysis Results

Figure 2 describes the results of a meta-analysis between 5 studies comparing mean hemoglobin levels in g/dL after 1 month of *erythropoietin alpha* and beta therapy, there was no significant difference in the *erythropoietin alpha* and *erythropoietin beta* groups (P = 0.20, MD = 0.16, 95% CI [-0.57, 1.17], I2 = 0% [P = 0.56]).

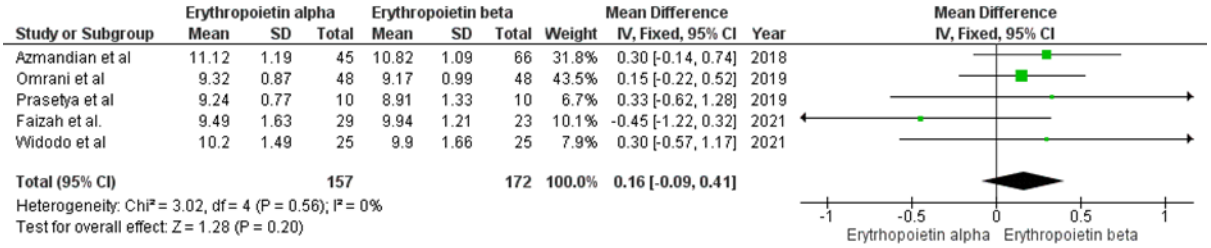
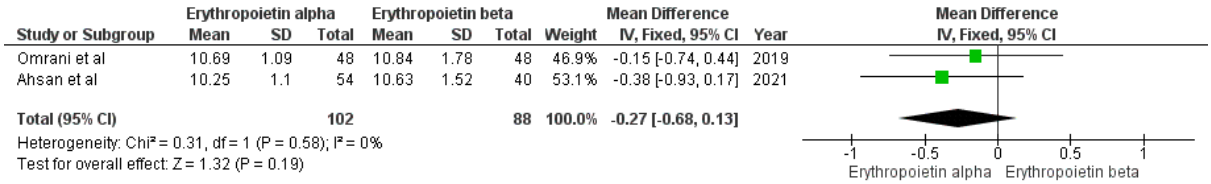


Figure 2 Forest Plot Average Hemoglobin Levels After 1 Month

It can be seen in Figure 3 explaining the results of the meta-analysis between 2 studies comparing the average hemoglobin levels after being given erythropoietin alpha and beta therapy after 3 months, there was no significant difference in the erythropoietin alpha and erythropoietin beta groups (P value = 0.19, MD = -0.27, 95% CI [-0.68, 0.13], I2 = 0%, [P = 0.58])

Figure 3 Forst Plot Average Hemoglobin Levels After 3 Months



DISCUSSION

In the results of this meta-analysis, no significant difference was found between the effectiveness of administering erythropoietin alpha and erythropoietin beta. This study ranged from 2018-2023 and there were some differences in the results between the studies. However, as written in the research by Omrani et al., erythropoietin alpha and beta are effective in increasing hemoglobin

levels in chronic kidney disease patients undergoing hemodialysis. (Omrani et al., 2019) Erythropoietin alpha and beta are two types of recombinant erythropoietin that have a structure similar to human erythropoietin. Both function as Erythropoiesis Stimulating Agents (ESAs), which stimulate the production of erythrocytes. This erythropoietin has a relatively short half-life (6–8 hours intravenously and 19–24 hours subcutaneously), and the optimal administration schedule is two or three times a week intravenously or subcutaneously (Locatelli & Del Vecchio, 2011). Erythropoietin alpha refers to human erythropoietin produced in cell culture using recombinant DNA technology, while erythropoietin beta refers to a synthetic, recombinant form of erythropoietin, a protein that stimulates red blood cell production. The difference between the two erythropoietins lies in the glycosylation chain and molecular weight, with erythropoietin alpha having a lower molecular weight than erythropoietin beta. Both erythropoietins are recombinant human erythropoietins that have a short half-life, but erythropoietin alpha has a shorter half-life. (Deicher & Hörl, 2004; PERNEFRI, 2011)

The 2012 KDIGO guidelines on the use of ESA preparations explain that there is no difference between the use of ESA preparations on patient clinical outcomes (KDIGO, 2012). However, several RCTs and observational studies have noted differences between these two fast-acting ESA agents. Several studies have shown that erythropoietin alpha is more effective in increasing patients' hemoglobin levels (Faizah et al., 2022; Prasetya et al., 2019; Widodo et al., 2021). In contrast, an observational study by Ahsan et al. concluded that erythropoietin beta is more effective (Ahsan et al., 2021). However, the Ahsan et al. study was an observational study so there was no randomization and there were confounding factors. This difference of opinion may be explained because each study had differences in the erythropoietin alpha/beta preparations given, different doses and methods of administration, differences in the number of samples, confounding factors in each individual sample, and individual characteristics of each sample in different studies. The difference in erythropoietin effectiveness may also be explained by differences in glycosylation chains and routes of administration that affect half-life and bioavailability (John et al., 2012)

This meta-analysis analyzed the effectiveness of erythropoietin alpha and beta with increasing Hb levels and there was no significant difference between the two. The results of this meta-analysis were influenced by differences in the number of samples affecting the strength of each study. Evaluation of Hb levels in the studies in this meta-analysis also affected the final results. The average evaluation in this study was carried out for 1 to 3 months, a longer evaluation of up to 6 to 9 months is needed to assess more stable Hb levels according to the KDIGO guidelines (KDIGO, 2012). In the previous meta-analysis, the final results that assessed the need for transfusion, mortality, and side effects of each ESA agent were reviewed. In this meta-analysis, no significant differences were found (Chung et al., 2023). The effectiveness in increasing patient Hb in this meta-analysis supports the 2012 KDIGO statement that there was no difference in clinical outcomes in each ESA preparation. However, this meta-analysis has limitations, namely the lack of bias assessment in this study, the lack of studies obtained, different baseline hemoglobin in each study, and the number of samples in each study that varied so that it might affect the final results of each study.

The conclusion of this study was that there was no significant difference between the effectiveness of erythropoetin alpha and erythropoetin beta in increasing the hemoglobin levels of patients. These two ESA agents are effective in increasing hemoglobin levels in ESRD patients. However, due to the limitations of this study, it is recommended for further studies with a larger number of studies.

AUTHORS CONTRIBUTION

Vincentius William Sunur; lead researcher responsible for topic selection, search, and collection of research data. Timothy Sulistio, Vega Adisyahputra, Vita Safira, Ronald Pratama Adiwinoto, Yuswanto Setyawan; analyzed the data, reviewed her research documentation.

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The study was self-funded.

CONFLICT OF INTEREST

No conflict of interest.

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