Differences in Pre-Post Hemodialysis Hemoglobin Levels on Erythropoietin Alpha and Beta Administration: A Systematic Review

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Abstracts: Background: Anemia Is Becoming a Complication of Chronic Kidney Disease Caused by Erythropoietin, along with Increasing Comorbidities. Erythropoietin Is a Glycoprotein Hormone to Stimulates Red Blood Cells as Its Function. There Are Several Options for Recombinant Erythropoietin, Namely Erythropoietin Alpha and Erythropoietin Beta. This Literature Review Aims to Determine the Difference in Pre-Post Hemodialysis Hemoglobin Levels on the Administration of Erythropoietin Alpha and Erythropoietin Beta.
Methods: a Systematic Review of 14 National and International Journals Was Conducted to Identify Studies That Compared Changes in Hemoglobin Levels before and after Hemodialysis with Alpha and Beta Erythropoietin Administration.
Results: the Systematic Review Found Several Studies That Compared the Difference in Hemoglobin Levels before and after Hemodialysis in Patients Receiving Alpha and Beta Erythropoietin. the Analysis Showed That There Was a Significant Difference in the Increase of Hemoglobin Levels in Both Groups of Patients. However, There Was No Significant Difference between Alpha and Beta Erythropoietin in Terms of Their Effects on Increasing Hemoglobin Levels.
Conclusion: Administration of Erythropoietin Alpha and Beta Has a Positive Effect on Increasing Hemoglobin Levels in Patients Undergoing Hemodialysis. Although There Are Differences in Their Mechanism of Action, Both Are Effective in Overcoming Anemia in Hemodialysis Patients.

1 INTRODUCTION

Chronic renal failure is a clinical syndrome caused by a decrease in kidney function that is chronic, progressive, and irreversible where the body fails to maintain metabolism and fluid and electrolyte balance (Sanjaya, A.A.G.B et all 2019). This disease is irreversible, meaning that it cannot become normal again, so the intervention carried out in patients is only to maintain existing kidney function and carry out hemodialysis to replace kidney function to eliminate body metabolism (Juwita L, Kartika IR 2019).

The World Health Organization (WHO) states that Chronic Kidney Failure (CKD) disease in the world increases by more than 30% every year. Meanwhile, in Indonesia, according to the Prevalence of Chronic Kidney Disease (CKD) aged ≥15 years based on doctor's diagnosis from 2013 patients with chronic kidney failure rose to 3.8% in 2018 (Riskesdas, 2018). According to PENEFRI (2018) from 2007 to 2018 the number of new patients who underwent hemodialysis in Indonesia with a total of 66,433 people, and 132,142 active patients on hemodialysis therapy in Indonesia. The World Health Organization (WHO) estimates that Indonesia will see a 41.4% increase in the number of people with GGK between 1995 and 2025.

The results of research by Agustina et al. (2019: 146) that there was a decrease in pre-hemodialysis hemoglobin levels from 20 respondents who had hemoglobin levels less than normal. Anemia therapy caused by CKD with epoetin therapy can improve the patient's quality of life. The types of erythropoietin include erythropoietin alpha and erythropoietin beta.

From the background described, the problem formulation in this study is: "What is the difference between pre- post hemodialysis hemoglobin levels on the administration of Erythropoietin alpha and beta". Furthermore, the purpose of this study is to determine the difference in pre- post hemodialysis hemoglobin levels on the administration of Erythropoietin alpha and beta".

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2 METHODS

This systematic review was organized based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (prism). Population, intervention, control, and outcome (PICO) questions:
P (population) hemodialysis patients
I (intervention) the use of erythropoietin alfa and beta
C (comparison control) -
O (result) hemoglobin
In this method, the steps taken are determining the topic of the literature, searching and selecting the most relevant sources and identifying keywords according to the topic, compiling and analyzing, and summarizing the findings of the article. The literature search was conducted using electronic databases that is Pubmed and Science Direct for articles published from 2018 to 2023, using words related to hemodialysis, erythropoietin alpha and beta, and hemoglobin levels. The literature search was conducted in June-July 2023 using the keywords in the database search mentioned above: "hemodialysis patients" AND "erythropoietin alfa AND beta" AND "hemoglobin". Research articles obtained from the search results were then checked for duplication and if the same article was found, it would be excluded. In searching for literature, the author selected some of the literature obtained using literature screening by reading the abstracts and titles of the studies found. After exclusion, a total search of the stored studies was conducted, concerning the PICO criteria. From the database, there were 105 initial articles due to irrelevant titles 66 articles were excluded and 11 articles were excluded due to duplicate titles. Titles and abstracts were reviewed and 14 eligible journals were identified.

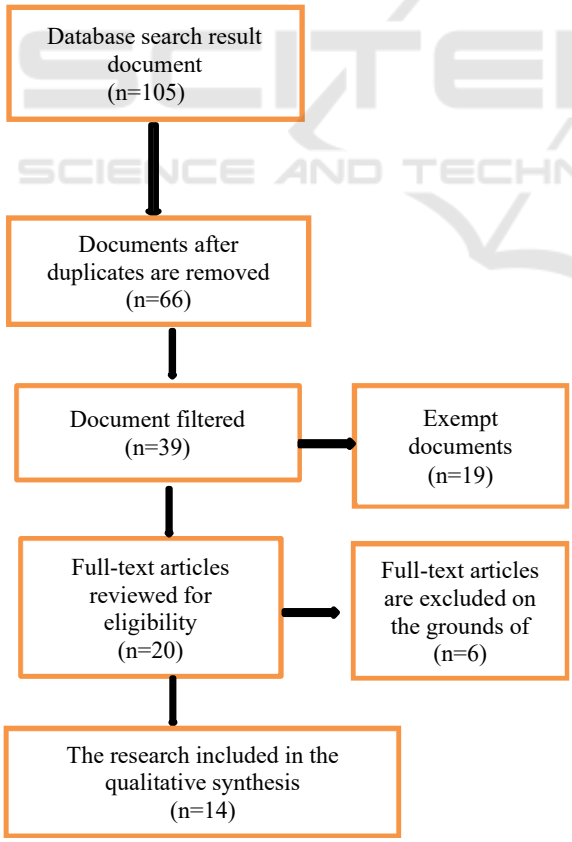

Diagram 1: Flow of Article Selection.

3 RESULTS AND DISCUSSIONS

The article selection flowchart above with a total of 14 articles selected from the initial 105 articles. All selected studies were from Indonesia (9), Iran (1), Japan (1), Saudi Arabia(1), and Pakistan (1), hemodialysis patients with anemia were assessed by measuring the patient's Hemoglobin level before and after hemodialysis.

Research conducted by Insani.N., et al. (2018) where the use of erythropoietin as part of therapy for CKD-HD anemia patients showed a relatively good and safe outcome of hematological parameters. This is indicated by an increase in the levels of each hematological parameter measured.

Research conducted by Adnan et al (2018: 276-280). This study examines the differences in red blood cell profiles, namely hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) in patients given erythropoietin and Non-erythropoietin therapy. However, this study did not explain the use of erythropoietin therapy given to the patient sample. There was an increase in hemoglobin levels by 1.00 in patients who received EPO therapy. In this study, the average MCV was 90.06 ± 6.150, MCH 29.60 ± 1.998, and MCHC 32.89 ± 0.688, so the values of the three groups were in the normal range. In addition, research conducted by Insani et al. (2018) that epoetin administration can improve hematological parameters such as erythrocytes, hemoglobin, hematocrit, MCH, MCHC, and MCV.

In research conducted by Setiawan. H., et al. (2021) where the respondents were 57 patients with chronic renal failure, analyzed that there was a significant effect of erythropoietin administration on increasing hemoglobin levels in patients with chronic renal failure undergoing hemodialysis with a p-value of 0.000 < α 0.05. Furthermore, research conducted

by Angin, et al. (2021) the results of the application of erythropoietin therapy have been proven successful in 78 patients with a percentage of 73.58% successful in treating anemia that occurs in patients with GGK.

Research conducted by Pasek, et all on 26 End Stage Renal Disease (ESRD) patients undergoing hemodialysis. The mean hemoglobin level pre-erythropoietin therapy is 8.1 gr/dl and the mean hemoglobin level post-erythropoietin therapy is 8.7 gr/dl. The results of the paired T-test of pre and post-erythropoietin therapy hemoglobin levels found a p-value of 0.001 ($p < 0.05$). There is a significant difference between hemoglobin levels before and after receiving erythropoietin therapy. Furthermore, Rahayu's research, et al. (2019) involved 36 respondents of chronic renal failure patients undergoing hemodialysis. The results showed the mean value of pre-hemodialysis hemoglobin levels of 9.3 g/dl and post-hemodialysis of 10.7 g/dl, with 91.7% of respondents experiencing an increase in post- hemodialysis hemoglobin levels. Based on these results, it is concluded that there is a significant difference in pre- and post-hemodialysis hemoglobin levels in patients with chronic renal failure.

Research conducted by Kurniawanto., at all (2018) The results of research on 10 samples of hemoglobin profiles before (Hbpre) giving EPO therapy and after giving hemoglobin (Hb-post) giving erythropoietin therapy the increase in Hb during the study, where the therapy given to patients is erythropoietin alpha (α) with two different doses of 2000 IU dose, namely 16,88%, and erythropoietin alpha (α) 3000 IU, namely 12.53%, where the results obtained were an increase of 0.16x from Hb before erythropoietin therapy was given for erythropoietin alpha (α) 2000IU and 0.12x from Hb before erythropoietin therapy was given for erythropoietin alpha (α) 3000IU. Similarly, in a study conducted by Weinhandl., (2023) almost two-thirds of the total number of patients per month had hemoglobin levels between 10.0 to 11.9 g/dL. The average use of erythropoietin was 76.7% per month, with increased use of pegylated epoetin beta. Erythropoietin dosing remained stable; epoetin alfa dosing was slightly lower than in the NHCT low target group. The prevalence of erythropoietin nonresponse was 22.2%.

Research by Faizah, et al. (2021) 52 respondents met the inclusion criteria, of which 29 patients in the alpha erythropoietin group and 23 patients in the beta erythropoietin group. The average increase in Hb of subjects using beta erythropoietin was greater than that of alpha erythropoietin. The average increase in Hb levels pre-post administration of erythropoietin beta was 0.48 g/dl while the average increase in Hb levels pre-post administration of erythropoietin alfa was 0.02 g/dl. Furthermore, research by Ahsana, et al. (2021) as many as 94 participants were involved in the analysis of patients observed after 3 months of initiation of erythropoietin preparations a significant increase in Hb levels ($p = 0.025$) in beta erythropoietin compared to alpha erythropoietin. The average increase in Hb levels was 9.80 ± 1.20 to 10.25 ± 1.10 g/l on alpha erythropoietin, and 9.66 ± 1.49 to 10.63 ± 1.52 g/l on beta erythropoietin. Furthermore, in a study conducted by Dian, et al. (2022) where a sample of 139 CKD patients used epoetin who underwent routine hemodialysis. Anemia therapy in CKD patients with the most widely used hemodialysis is epoetin alfa compared to epoetin beta. The average value of Hb increase in 3 months on epoetin beta therapy is higher than on epoetin alpha therapy and is not statistically significantly different with a value of $p>0.05$.

In Widianti's research, et all, this study calculate the total cost based on the use of erythropoietin used as anemia therapy in renal failure patients who undergo between HemapoR, EpotrexR, and NeorecormonR, so that it can be seen which one is more effective by comparing the cost-effectiveness ratio of the three drugs. The most widely used EPO consistently for 3 (three) consecutive months is NeorecormonR as much as 41.05. The most effective erythropoietin to increase Hb levels is NeorecormonR with a percentage of the number of patients whose Hb levels increased by 56.41%. Meanwhile, in AlKharboush research, et al. (2020) study involved a comparison of the potential therapeutic and economic impact of using two erythropoietin drugs (epoetin-beta and darbepoetin- alfa) in patients with stage 5 CKD for the treatment of associated anemia. Baseline serum Hb was 10.68 ±0.98 g/dL for darbepoetin-alfa patients and 11.63 ±0.32 g/dL for epoetin-beta group ($p=0.003$).

In contrast, in Prasetya research, et al. (2019) the mean increase in hemoglobin levels in the alpha erythropoietin group after treatment was 1.28 ± 0.80 g/dL ($p = 0.001$) and the beta erythropoietin group was 0.37 ± 0.95 g/dL ($p = 0.254$). A comparison of hemoglobin and hematocrit achievement in both groups showed that erythropoietin alpha gave better achievement in hemoglobin parameters ($p=0.033$). Similarly, in Azmandian research, et al. (2018) A total of 156 patients were involved in this clinical trial to compare the efficacy and safety of CinnaPoietin® (epoetin beta, CinnaGen) with Eprex® (epoetin alfa, Janssen Cilag) in the treatment of anemia in ESRD hemodialysis patients. The results showed that there

was no statistically significant difference between the treatment groups regarding the change in mean Hb (P= 0.21). However, the incidence of Hb levels above 13 g/dL was significantly lower with CinnaPoietin® (epoetin beta, CinnaGen).

4 CONCLUSIONS

Recombinant erythropoietin therapy (epoetin) in its use in Chronic Kidney Disease (CKD) patients undergoing hemodialysis can increase hemoglobin. Of the 14 journals found, 5 journals explain the effectiveness of erythropoietin in increasing hemoglobin levels, 2 journals explain the effect of either alpha or beta erythropoietin in increasing hemoglobin levels, 5 more journals explain the comparison of alpha or beta erythropoietin in increasing hemoglobin where beta erythropoietin is higher and 2 other journals explain alpha erythropoietin is higher.

From various studies that epoetin alfa epoetin beta in CKD patients undergoing hemodialysis there is no significant difference in the average change in hemoglobin. The choice between erythropoietin alpha and beta can be considered based on other factors such as side effect profile and cost.

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