Therapeutic Efficacy of Erythropoietin Alpha and Erythropoietin Beta in Anemia of Chronic Kidney Disease

Sommiya Dashti, Murtaza Dhrolia, Ruqaya Qureshi, Kiran Nasir and Aasim Ahmad

Department of Nephrology, The Kidney Centre Postgraduate Training Institute, Karachi, Pakistan

ABSTRACT:

Objective: To compare the effectiveness of erythropoietin alpha and erythropoietin beta in anemia management in the hemodialysis population.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Nephrology, The Kidney Center Postgraduate Training Institute (TKC-PGTI), Karachi, from December 2019 to July 2020.

Methodology: All participants were initially started on erythropoietin alpha and then converted to erythropoietin beta after three months. The effectiveness of the erythropoietin alpha and erythropoietin beta was calculated on the basis of net change of mean hemoglobin and mean hematocrit level in the last four weeks on either erythropoietin therapy.

Results: A total of 80 patients completed the study, in which 47 (58.8%) were males while 33 (41.3%) were females. The mean age was 59.7 ± 14.7 years. The net mean hemoglobin change during last 04 weeks was– 0.19 ± 1.2 and– 0.03 ± 1.0 for erythropoietin alpha and erythropoietin erythropoietin beta, respectively (p = 0.41). The net mean hematocrit change during the last four weeks was– 0.45 ± 3.9 and– 0.49 ± 3.7 for erythropoietin alpha and erythropoietin beta, respectively (p = 0.95). The mean weekly erythropoietin dosage per Kg body weight during the last four weeks was 177.6 ± 130.4 IU/Kg/week for erythropoietin alpha and 121.3 ± 69.6 IU/Kg/week for erythropoietin beta (p = <0.001).

Conclusion: Erythropoietin alpha and erythropoietin beta have similar therapeutic efficacy in anemia management in chronic kidney disease patients. Reduced dosage of erythropoietin beta achieves and maintains the target hemoglobin level.

Key Words: *Efficacy, Erythropoietin, Anemia, Chronic kidney disease.*

How to cite this article: Dashti S, Dhrolia M, Qureshi R, Nasir K, Ahmad A. Therapeutic Efficacy of Erythropoietin Alpha and Erythropoietin Beta in Anemia of Chronic Kidney Disease. *J Coll Physicians Surg Pak* 2021; **31(12)**:1417-1421.

INTRODUCTION

Anemia is the prevalent complication of chronic kidney disease (CKD), especially Stage V,[1] and is associated with an increased risk of death and hospitalisation.[2] Anemia in CKD is typically normocytic, normochromic, and hypo-proliferative. It is multifactorial, with iron depletion; and erythropoietin deficiency being the two most common causes.[3] The availability of recombinant human erythropoietin (rHuEPO) since the early 1980s has dramatically changed the management of anemia in patients with CKD.[4,5] However, the use of erythropoiesis-stimulating agents (ESAs) presents a significant cost burden in the management of anemia of chronic kidney disease (CKD), especially in resource limited health set-up.

Correspondence to: Dr. Sommiya Dashti, Department of Nephrology, The Kidney Centre Postgraduate Training Institute, Karachi, Pakistan
E-mail: sommiyadashti@gmail.com

Received: May 21, 2021; Revised: September 11, 2021; Accepted: October 29, 2021
DOI: https://doi.org/10.29271/jcpsp.2021.12.1417

The first rHuEPO produced was erythropoietin alpha, followed by other agents as erythropoietin beta, methoxy polyethylene glycol-epoetin beta, delta, darbepoetin-alpha, omega, and several related products.[6] Among several types of ESAs, erythropoietin alpha and erythropoietin beta are two short-acting ESAs that are frequently used in the management of anemia of CKD. In some studies, both agents have shown the same efficacy in treating CKD-induced anemia.[7,8] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines also suggest that erythropoietin alpha and erythropoietin beta have the same efficacy and require the same dose to be administered to patients with CKD-induced anemia.[9]

Differences in the carbohydrate moieties of the rHuEPOs determine differences in the pharmacokinetic and pharmacodynamics properties between these agents. The terminal elimination half-life after intravenous administration of erythropoietin beta was 20% longer than that of erythropoietin alpha. After subcutaneous administration, there was delayed drug absorption with erythropoietin beta compared with erythropoietin alpha.[10] The prolonged half-life following subcutaneous administration of erythropoietin beta supports the use of subcutaneous erythropoietin beta, administered once weekly, at least in the maintenance phase of renal anemia treatment both, due to its

pharmacological as well as economic considerations.[11-13] Some studies have also shown that a reduced dose of erythropoietin beta was needed to maintain target hemoglobin (Hb) concentration.[14]

Pakistan is a resource-limited country, where less than 10% of End Stage Renal Disease (ESRD) patients receive renal replacement therapy (RRT), and up to 70% of those starting dialysis stop treatment due to cost within the first three months.[15] Erythropoietin alpha was initially the only ESA used for anemia management in hemodialysis (HD) in Pakistan (and especially in the dialysis centre) due to the availability of its less costly brand, however, expansion of market and pharmaceutical industries' competition recently allowed availability of erythropoietin beta with a comparable price to that of erythropoietin alpha. Although, widely believed that the dosage requirements of erythropoietin alpha and erythropoietin beta are the same, the proven efficacy and safety profile of erythropoietin beta, combined with the increased convenience of less frequent dosing, and reduce dose requirement is an additional benefit. This developed the authors' interest to study the effectiveness of erythropoietin alpha and erythropoietin beta in HD population because any ESA that can decrease dose requirement and financial burden on HD patient, will be of great benefit and can help more patients to reach their therapeutic targets in the management of renal anemia especially in resource limited country alike Pakistan.

The objective of this study was to compare the effectiveness of erythropoietin alpha and erythropoietin beta in anemia management in the hemodialysis population.

METHODOLOGY

This prospective quasi-experimental study was conducted in the Department of Nephrology, The Kidney Centre Postgraduate Training Institute (TKC-PGTI) after approval by the Institutional Ethical Review Committee. TKC-PGTI follows the standards defined by European best practice guidelines, and long-term maintenance HD patients dialysed for four hours three times a week.

A total of 90 patients of both genders, aged above 18 years, undergoing maintenance HD for > 3 months, with stable Hb for 3 months (defined as change in Hb, not more than or less than 2 gm/dl from mean Hb in 3 months), having adequate iron stores (defined as transferrin saturation (TSAT) $\geq$ 20%), complying with dialysis therapy and medications as advised by treating nephrologist, were enrolled in the study through non-probability consecutive sampling. Written informed consents were taken. Patients could withdraw from the study at any time and for any reason. In addition, patients could be withdrawn at the investigator's discretion in the event of inter-current illness, adverse events, or protocol violation. Patients with anemia secondary to other causes apart from CKD; decompensated liver failure, history of or active blood coagulation disorders, history of malignancy within the last five years, any red blood cell transfusion during the last three months, an event of active bleeding in 30 days before the study, major surgery within three months before study, any history of hospital admission requiring blood transfusion in the duration of the study, non-adherence to medications and women if they became pregnant, were excluded to avoid their misleading influence on the result. Exclusion criteria also included patients who were non-compliant to dialysis therapy or not receiving prescribed dialysis doses.

Hb level at the start of the study was taken as a baseline. Target Hb was 10-12mg/dl according to KDIGO guidelines.[16] Only subcutaneous injections were used for both erythropoietin alpha and erythropoietin beta. All injections were administered by experienced personnel at this dialysis centre. All participants were initially started on erythropoietin alpha as the dose as the discretion of treating nephrologist or those who were already on erythropoietin alpha, continued to receive same dose. After three months, all participants were converted to erythropoietin beta as the dose 25% less than that of erythropoietin alpha, based on pharmacokinetic difference and studies that suggest reduced dose requirement of erythropoietin beta to maintain target Hb concentration compared to erythropoietin alpha.[10,14] Hb at three month of study (that of on erythropoietin alpha), was considered as baseline Hb for erythropoietin beta. Dose was adjusted for both ESA during study period, only once a month, based on the patient response to maintained the Hb level in the target range. If the hemoglobin level increased >12 g/dl, the dose was reduced by approximately 25% (75%) of the previous dose) or *vice versa*, if Hb level decreases <10 g/dl. If the hemoglobin continues to increase, the dose was temporarily withheld until the hemoglobin begins to decrease; at that point, therapy was re-initiated at a dose approximately 25% below the previous dose. Patients were evaluated every four weeks for the study period. The first two weeks after starting both ESA were considered the washout period, and the next six weeks are considered for dose adjustment so that the steady effect of both ESA therapies can be assessed appropriately. TSAT was maintained >20% throughout the study period by adjustment of iron replacement. The clinical, demographic, and personal information of each participating patient was recorded in a proforma.

The difference in mean Hb, mean hematocrit (Hct) and mean weekly erythropoietin dosage per Kg of body weight was calculated for the last four weeks of both ESA therapies. The effectiveness of the erythropoietin alpha and erythropoietin beta was calculated based on of net change of mean Hb and mean Hct level at three months from their respective mean Hb and mean Hct level at two months in respect to the mean dosage of erythropoietin used per Kg of body weight per week during the same time period. Proportion of patients with any Hb measurement outside the target range (10-12) during the study period were also compared with Hb level above 13 g/dl was considered as safety outcome.

Data was entered and analysed by IBM version 21 of SPSS. Cleaning and coding of data was done before analysis. Mean values with standard deviation were calculated for continuous

normally distributed variables; while for skewed data, median with interquartile were also observed along with mean ± STD. For categorical variables, frequencies with percentages were obtained. Paired sample t-test was used to observe any mean difference in Hb, Hct and ESA dosage of patient in case of normally distributed data, on the other hand in case of skewed distribution; Wilcoxon sign rank test was applied to observe any differences in above mentioned parameters. Normality of data was assessed by Shapiro-Wilk test. P-value of less than or equal to 0.05 was considered significant.

RESULTS

A total of 90 participants were enrolled in the study. Two participants expired during the study period, secondary to cause unrelated to ESA complication, six participants declined the consent in middle of the study and withdrew, while two participants were lost to follow-up because of change of dialysis centre. A total of 80 patients completed the study, in which 47 (58.8%) were males, while 33 (41.3%) were females. The mean age was 59.7 ± 14.7 years. The majority of patients had CKD of unknown etiology 46 (57.5%), while the most prevalent comorbid was HTN 74 (92.5%). Table I demonstrates the baseline characteristics of the study participants.

Table I: Baseline (week 0) characteristics of study participants (n=80).

Variables	Mean (SD) & median, IQR or n (%)
Age	59.7±14.7 &61.5,18
Gender	
Male	47(58.8)
Female	33(41.3)
Dialysis Vintage	5.7±5.4 & 4,4
Cause of CKD	
Unknown	46(57.5)
Glomerulonephritis	16(20)
Diabetes	12(15)
Stone disease	4(5)
ADPKD	2(2.5)
Comorbidities	
Hypertension	74(92.5)
Diabetes	24(30)
Ischemic heart disease	17(21.3)
Weight	63.5±15.1 & 64,18
iPTH	290±287.5 & 175, 352
C-reactive protein	5.5±2.8 &5,1
Ferritin	560±550.4 & 457,363.5
Transferrin saturation	46±66.4 & 32,21.2
Hemoglobin	10.9±1.2 & 11,1.3
Hematocrit	34.4±4 & 34.9,5.5

CKD = Chronic kidney disease, ADPKD = Adult dominant polycystic kidney disease, iPTH = Intact parathyroid hormone.

The effectiveness of the erythropoietin alpha and erythropoietin beta was calculated based on the net change of mean hemoglobin and mean hematocrit level in the last four weeks on either erythropoietin therapy.

Net mean Hb change during the last four weeks was– 0.19 ± 1.2 and – 0.03 ± 1.0 for erythropoietin alpha and erythropoietin beta, respectively; which was statistically insignificant (p = 0.163 and 0.315, respectively). The net mean hematocrit change during last four weeks was –0.45 ± 3.9 and –0.49 ± 3.7 for erythropoietin alpha and erythropoietin beta, respectively; which was again statistically not significant (p = 0.338 and 0.12, respectively, Table II).

Table II: Change in hemoglobin and hematocrit in last four week.

	Erythropeoietin aplha Mean ± STD	Erythropoiethin beta Mean ± STD
Hemoglobin		
At Month 03	10.9±0.86	10.4±0.94
At Month 02	11.1±1	10.4±1
Change in last 4 weeks	-0.19 ± 1.2	- 0.03 ± 1.0
p-value	0.163	0.315
Hematocrit		
At Month 03	34.8±3 & 34.9, 3	32.5±3.5 & 33 , 4.2
At Month 02	35.2±3.5 & 35.6, 5.5	33±3.3 & 33.2, 5.4
Change in last 4 weeks	-0.03 ± 1	-0.5 ± 3.7
p-value	0.338	0.120

The mean weekly erythropoietin dosage per Kg body weight during the last four weeks was 177.6 ± 130.4 IU/kg/week for erythropoietin alpha and 121.3 ± 69.6 IU/kg/week for erythropoietin beta. Dosage of erythropoietin alpha and erythropoietin beta had a statistically significant difference for maintaining Hb level between 10 and 12 mg/dl (p<0.001). The authors observed that 29.3% less dosage of erythropoietin beta was required to achieve targeted Hb in CKD patients as compare to erythropoietin alpha (Table III).

Table III: Comparison of dosage of erythropoietin alpha and erythropoietin beta.

Doses	Erythropoietin alpha Mean±STD & Median, IQR	Erythropoietin beta Mean±STD & Median, IQR	p-value
Total dose of last 04 weeks	43343±33716 & 40000, 20000	29134±15553 & 30000, 25000	<0.001
Dosage per week	9524±6040 & 8308, 7692	5724±2692 & 5000, 7077	<0.001
Dosage per Kg per week	177.6±130 & 1355, 145	121±69.6 & 84, 68.5	<0.001

The proportion of patients with any Hb measurement outside the target range (10-12) during the study period was also compared. Hb of 15 patients during erythropoietin alpha and 25 patients during erythropoietin beta therapy fell outside the range of 10-12 g/dl.

Although, this was statistically insignificant (p = 0.176), patient during erythropoietin alpha achieved Hb>12 more than that of erythropoietin beta. One patient during erythropoietin alpha experienced Hb level above 13 g/dl, while none of the patients during erythropoietin beta experienced Hb level above 13 g/dl.

DISCUSSION

This prospective quasi-experimental study was conducted to study the effectiveness of erythropoietin alpha and erythropoietin beta in patients on hemodialysis. The potential confounding factors that can affect the response of ESA therapy on hemoglobin in hemodialysis patients, such as transferrin

saturation and ferritin, iPTH, inflammatory markers as C-reactive protein,[17] were also considered and were checked at the beginning of the study (Table I). The results of this study suggested that erythropoietin beta is similar to erythropoietin alpha in terms of their efficacy, while the mean weekly dosage per Kg requirement to maintain the Hb level within 10-12 g/dl was significantly less for erythropoietin beta as compare to erythropoietin alpha.

The mean change in Hb level during the last four weeks was comparable for erythropoietin beta and erythropoietin alpha. Similar finding was found in two different randomised controlled trials from Iran,[7,18] a study from Bosnia and Herzegovina,[8] and a brief report from UK.[14]

This is similar to the KDIGO guidelines, which suggest that erythropoietin alpha and erythropoietin beta have the same efficacy.[9] One study from Indonesia found better achievement in mean Hb level with erythropoietin alpha as compared to erythropoietin beta;[19] however, they had a very small sample size and have not taken into account the potential effect of confounding factors between the groups. They have attributed the result of their study were probably confounded by iron status, malnutrition, inadequate hemodialysis, inflammation, and usage of angiotension receptor blocker drugs. The mean change in Hct level during the last four weeks was also found comparable between erythropoietin beta and erythropoietin alpha. This corresponds with the result from a study by Loughman *et al.* from UK and Prasetya *et al*. from Indonesia.[19]

The mean weekly erythropoietin dosage per Kg body weight of patients during the last four weeks of treatment necessary to maintain the Hb level within 10–12 g/dL was 29.3% less for erythropoietin beta as compared to erythropoietin alpha. The present result corresponds with the study by Loughnan *et al.,*[14] which also found that higher doses of erythropoietin alpha are required to maintain Hb in the target level than erythropoietin beta; however, only intravenous (IV) route was analysed in their study. Azmandian *et al*. analysed both IV and Sc route and found that the mean dose of erythropoietin during the whole study was higher in the erythropoietin alpha group (mean 20.87 IU/Kg/week more than erythropoietin beta), but the difference was not statistically significant ($p = 0.1$).[7] The result of the current study contradicts the KDIGO guidelines, which suggest that erythropoietin alpha or erythropoietin beta usually starts at the same dose.[9] Ostrvica *et al*. evaluated the efficacy of epoetin alfa and beta (both IV and Sc) for correction of anemia in ESRD patients and found that patients needed approximately equal doses of erythropoietin alpha and erythropoietin beta to achieve and maintain the target level of Hb and hematocrit.[8] This study had a small sample size.

In the current trial, the proportion of patients with any Hb measurement outside the target range in erythropoietin beta was higher than erythropoietin alpha. Although, this was statistically insignificant, patients during erythropoietin alpha achieved Hb > 12 more than that of erythropoietin beta. This might correlate with Prasetya *et al.* study which conclude that erythropoietin alpha gave better achievement of increasing hemoglobin parameter than erythropoietin beta;[19] however, considering ability to maintain Hb within target range, both ESA were found similar. In the study by Azmandian *et al.,*[7] the proportion of patients with any Hb measurement outside the target range in erythropoietin alpha was higher than erythropoietin beta; and they proposed that a higher proportion of patients with maintenance success in the erythropoietin beta group suggests that erythropoietin beta is more successful than erythropoietin alpha in keeping patients in the target range of Hb level (10–12 g/dL).

Although, the current study was not designed to evaluate the safety between two ESA therapies, the authors found that only one patient on erythropoietin alpha achieved an Hb level above 13 g/dl, while none on erythropoietin beta. A study by Azmandian *et al*. found that erythropoietin beta and erythropoietin alpha have comparable safety profile.[7]

In the current study, the cost of therapy between erythropoietin alpha and erythropoietin beta was not compared, which depends on the brand and their marketed price. However, as mentioned earlier, the expansion of market and pharmaceutical industries' competition recently allows availability of erythropoietin beta in a comparable price to that of erythropoietin alpha. Therefore, less dosage requirement for erythropoietin beta will reduce the financial burden on the hemodialysis patient, and can help more patients reach their therapeutic targets in the management of renal anemia especially in a resource-limited country like Pakistan.

So far, few studies have compared the dosage of erythropoietin alpha with erythropoietin beta. Some analysed only IV route,[14,18] and its effect on Hct,[14] while some had a small sample size.[19] The authors analysed the effect of both Hb and Hct for ESA dosage, while quasi-experimental design of this study enabled the authors to exclude even subtle selection biases that can occur even in a well design RCTs, and to analyse a large number of patients on either ESA therapy so far to the best of authors' knowledge. Although a single-centre experience, small sample size and not assessing safety between both ESA are the major limitation of this study. This study can serve as a reference for the future researchers in designing and carrying out large, multicentre randomised controlled trials for efficacy and safety assessment between these two ESA therapies.

CONCLUSION

Both erythropoietin alpha and erythropoietin beta have similar therapeutic efficacy in anemia management in chronic kidney disease patients. A lower dosage of erythropoietin beta is required as compared to erythropoietin alpha to achieve and maintain target hemoglobin level.

ETHICAL APPROVAL:

This prospective quasi-experimental study was conducted after approval by the Ethical Review Committee of The Kidney Centre Postgraduate Training Institute (TKC-PGTI).

PATIENTS' CONSENT:

A written informed consent was taken from all patients.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SD: Literature search, study design and concept, questionnaire design, data collection.
MFD: Literature search, study design and concept, data analysis, data interpretation, drafting, revising it critically for important intellectual content.
RQ, KN: Revising it critically for important intellectual content.
AA: Data analysis, data interpretation, drafting, revising it critically for important intellectual content.
All authors approved the manuscript for the publication.

REFERENCES

1. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, *et al.* The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 2004; **20(9)**: 1501-10.
2. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. *J Am SocNephrol* 1999; **10(3)**:610-9. doi: 10.1681/ASN.V103610.
3. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am SocNephrol* 2012; **23(10)**:1631-4. doi: 10.1681/ASN.2011111078.
4. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *New Eng J Med* 1987; **316(2)**:73-8. doi: 10.1056/NEJM198707233170416.
5. Winearls C, Pippard M, Downing M, Oliver D, Reid C, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986; **328(8517)**:1175-8. doi: 10.1016/s0140-6736(86)92192-6.
6. Kalantar-Zadeh K. History of erythropoiesis-stimulating agents, the development of biosimilars, and the future of anemia treatment in nephrology. *Am J Nephrol* 2017; **45(3)**: 235-47. doi: 10.1159/000455387.
7. Azmandian J, Abbasi MR, Pourfarziani V, Nasiri AA, Ossareh S, Jahromi SE, *et al.* Comparing therapeutic efficacy and safety of epoetin beta and epoetinalfa in the treatment of anemia in end-stage renal disease hemodialysis patients. *Am J Nephrol* 2018; **48(4)**:251-9. doi: 10.1159/000493097.
8. Ostrvica E, Mesic E, Ostrvica D, Delic J, Delic-Custendil S, Hukic F. Effectiveness of treating the renal anemia in chronic hemodialysed patients by epoietin alpha and beta. *Med Res Arch* 2010; **64(1)**:4.
9. Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012; **2(4)**:279-335.
10. Halstenson CE, Macres M, Katz SA, Schnieders JR, Watanabe M, Sobota JT, *et al.* Comparative pharmacokinetics and pharmacodynamics of epoetinalfa and epoetin beta. *Clin Pharmacol Ther* 1991; **50(6)**:702-12.
11. Besarab A, Flaharty KK, Erslev AJ, McCrea JB, Vlasses PH, Medina F, *et al.* Clinical pharmacology and economics of recombinant human erythropoietin in end-stage renal disease: the case for subcutaneous administration. *J Am Soc Nephrol* 1992; **2(9)**:1405-16.
12. Weiss LG, Clyne N, Fihlho JD, Frisenette-Fich C, Kurkus J, Svensson B. The efficacy of once weekly compared with two or three times weekly subcutaneous epoetin β: Results from a randomised controlled multicentre trial. *Nephrol Dial Transplant* 2000; **15(12)**:2014-9. doi: 10.1093/ndt/15.12.2014.
13. Locatelli F, Baldamus CA, Villa G, Ganea A, de Francisco AL, Group S. Once-weekly compared with three-times-weekly subcutaneous epoetin β: Results from a randomised, multicenter, therapeutic-equivalence study. *Am J Kidney Dis* 2002; **40(1)**:119-25. doi: 10.1053/ajkd.2002.33920.
14. Loughnan A, Ali GR, Abeygunasekara SC. Comparison of the therapeutic efficacy of epoetin beta and epoetinalfa in maintenance phase hemodialysis patients. *Ren Fail* 2011; **33(3)**:373-5. doi: 10.3109/0886022X.2011.559675.
15. Dhrolia MF, Nasir K, Imtiaz S, Ahmad A. Dialyzer reuse: Justified cost saving for south Asian region. *J Coll Physicians Surg Pak* 2014; **24(8)**:591-6.
16. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int* 2014; **85(1)**: 49-61. doi: 10.1038/ki.2013.444.
17. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, *et al.* Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. *Am J Kidney Dis* 2009; **53(5)**:823-34. doi: 10.1053/j.ajkd.2008.12.040.
18. Omrani HR, Golmohhamadi S, Hashemian AH, Vaysmoradi AZ, Safari-Faramani R. Therapeutic efficacy of erythropoietin alfa and erythropoietin beta in hemodialysis: A randomised controlled trial. *J Ren Inj Prev* 2018; **8(1)**:44-9.
19. Prasetya AA, Suprapti B, Shanti BD. Effectivity of erythropoietin alpha compared to erythropoietin beta in patients with chronic kidney disease-anemia on hemodialysis. *Folia Medica Indonesiana* 2019; **55(2)**:82-8.