

EFFECT OF SUBCUTANEOUS RECOMBINANT HUMAN ERYTHROPOIETIN ON BLOOD PRESSURE IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE (CKD) PATIENTS

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ABSTRACT

Objective: To determine the effect of subcutaneous recombinant human erythropoietin on blood pressure in pre-dialysis chronic kidney disease (CKD) patients.

Study Design: Case-series descriptive study.

Place and Duration of Study: Combined Military Hospital Peshawar, from Mar 2016 to Sep 2016.

Methodology: A total of 100 cases were enrolled. Inclusion criteria was patients of 18 to 60 years of both gender & estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² having Hb <10g/dL and pre-dialysis while Exclusion Criteria was pregnancy or lactation, BP more than 140/90 mmHg, patients on Haemodialysis and worsening renal function. Baseline BP, body weight and eGFR of anaemic chronic kidney disease patients were recorded prior to EPO Alpha therapy. Erythropoiesis-stimulating agents (ESAs) i.e. EPO Alpha (50-100 Units/kg thrice or once weekly) was administered subcutaneously. Subsequent blood pressure, body weight and eGFR monitoring was done after 2 and 4 weeks post EPO Alpha injection.

Results: Mean age range was 46.71 years with range of 20-60 years, 73 (73%) were male while 27 (27%) were females. Mean \pm SD for other quantitative variables like eGFR was 23.12 ± 5.28 , Hb levels (g/dL) was 8.62 ± 0.85 , Weight (kg) was 56.66 ± 6.62 and duration of CKD was 9.87 ± 4.02 . Frequency of Hypertension (post EPO) was 2 (2%) and *p*-value was 0.453.

Conclusion: We concluded that the frequency of hypertension in pre-dialysis patients with chronic kidney disease (CKD) receiving recombinant human erythropoietin (rhEPO) subcutaneously (SC) in low doses, is very low, so rhEPO can be used subcutaneously for treatment of anemia in pre-dialysis CKD patients.

Keywords: Anemia, Chronic kidney disease, Erythropoietin, Hypertension.

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INTRODUCTION

According to studies, approximately 71-95% of adult patients having chronic kidney disease (CKD) suffer from hypertension¹⁻². High blood pressure increases cardiovascular morbidity and mortality and also leads to a rapid decline in renal function³. Therefore, keeping blood pressure readings less than 140/90 mmHg is recommended in current guidelines for patients with CKD⁴. The production of endogenous erythropoietin falls with worsening of renal function and most of CKD patients with anemia are usually given erythropoiesis-stimulating agents (ESAs).

Patients on dialysis who were treated with higher doses of ESA showed an increased mortality mainly from cardiovascular causes in some observational studies⁵. The mechanism which causes these more frequent cardiovascular events and mortality has not been entirely identified yet. Therefore, different hypotheses have been suggested, but increase in risk of cardiovascular events due in rise in blood pressure by ESAs therapy is an important and widely accepted theory⁶.

During late 1980s at the time of introduction of ESAs in patients on haemodialysis, ESA induced hypertension was first reported and hypertension developed in approximately 20 to 30 percent of patients after ESA therapy⁷. However, with the passage of time nephrologists have

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Received: 07 Mar 2019; revised received: 20 Jul 2019; accepted: 22 Jul 2019

learnt to prevent these side effects by slowly increasing haemoglobin levels with lower doses of ESAs. The actual blood pressure may remain stable during treatment with ESAs in clinical practice, with or without adjusting the antihypertensive medication⁸.

Data on control of blood pressure in patients having CKD is limited and the pre-dialysis patients are under-represented in the available studies. Most importantly, complete information regarding the effect of treatment with ESAs on blood pressure of patients is lacking⁹. Therefore, the rationale of this study is to determine whether treatment with ESAs is associated with rise in blood pressure or not.

METHODOLOGY

This case-series descriptive study was conducted at Combined Military Hospital Peshawar from March 2016 to September 2016. Sample size (n) of 100 patients was calculated for this study using the WHO Sample size calculator for estimating a population proportion with specified absolute precision whereas confidence level of 95% and absolute precision of 0.08% was used with anticipated population size 20% and Sampling Technique was non-probability consecutive¹⁰. A total of 100 cases fulfilling the inclusion and exclusion criteria were enrolled. Inclusion Criteria included Patients of 18 to 60 years of both gender & estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² having Hb <10g/dL and pre-dialysis while exclusion criteria included pregnancy or lactation, baseline BP more than 140/90 mmHg, patients on Haemodialysis, worsening renal function (Decrease in eGFR >10ml/min/1.73 m² or development of signs of fluid overload measured after 2 and 4 weeks of starting ESA. Baseline blood pressure, body weight and eGFR of anaemic chronic kidney disease patients were recorded prior to commencement of EPO Alpha therapy. ESA i.e. EPO Alpha (50-100 Units/kg thrice or once weekly) was administered subcutaneously. Subsequent blood pressure, body weight and eGFR monitoring was done after 2 and 4 weeks post EPO Alpha injection.

Data entry and analysis were done by using SPSS 20. For both qualitative and quantitative variables, the descriptive statistics were calculated. For qualitative variables like gender and hypertension post EPO injection; frequency and percentages were calculated. For quantitative variables like age, GFR, Body weight, Hb, Duration mean and \pm standard deviation was calculated. Data was presented as Pie charts. Stratification was applied to control effect modifiers like age, weight & duration and Chi Square test (Post Stratification) was also applied and *p*-value ≤ 0.05 was considered as significant.

RESULTS

A total of 100 cases which fulfilled the given inclusion/exclusion criteria were enrolled to determine the frequency of hypertension in pre-dialysis patients having chronic kidney disease being treated with recombinant human erythropoietin.

Age distribution of the patients was done showing that 8 (8%) were between 20-29 years of age, 14 (14%) were between 30-39 years, 36 (36%) between 40 to 49 years of age, 41 (41%) between 50-59 years and 1 (1%) between 60 & above years and mean \pm SD was then calculated as 46.71 \pm 9.55 years. Patients were also distributed according to gender, which showed that 73 (73%) were male and 27 (27%) were females. Mean \pm SD for other quantitative variables like eGFR, Hb levels (g/dL), Weight (kg) and duration of CKD (years) were also calculated (table-I).

Table-I: Mean \pm SD for quantitative variables (n=100).

	eGFR (ml/min/1.73 m ²)	Hb (g/dL)	Weight (kg)	Duration of CKD (years.)
N	100	100	100	100
Mean	23.1277	8.6220	56.66	9.87
SD	5.28816	0.85299	6.627	4.024

Frequency of Hypertension (post EPO) was 2 (2%) (table-II). The data was stratified for age, weight and duration of CKD to control the effect modifiers (table-III, IV & V).

The overall *p*-value was calculated using chi square test which was 0.453. This showed that *p*-value was >0.05 which was insignificant. Thus recombinant human erythropoietin (EPO) given subcutaneously and in low dose does not cause hypertension.

Table-II: Percentage of hypertension (post epo) (n=100).

Hypertension	No. of Patients (%)
Yes	2 (2%)
No	98 (98%)

Table-III: Stratification of hypertension (post epo) with age (n=100).

Age Groups (Years)	Hypertension (Post Epo)		<i>p</i> -value
	No (%)	Yes (%)	
20-29	8	0	0.815 Fisher Exact test value: 0.808
30-39	13	1	
40-49	36	0	
50-59	40	1	
60 & Above	1	0	
Total	98 %	2%	

Table-IV: Stratification of hypertension (post epo) with weight (n=100).

Body Weight Groups (Kg)	Hypertension (Post EPO)		<i>p</i> -value
	No (%)	Yes (%)	
45-49	21	1	0.683 Fisher Exact test value: 0.684
50-54	11	0	
55-59	30	0	
60-64	25	1	
65 & Above	11	0	
Total	98%	2%	

Table-V: Stratification of hypertension (post epo) with duration of ckd (n=100).

Duration of CKD (Years)	Hypertension (Post EPO)		<i>p</i> -value
	No (%)	Yes (%)	
1-5	13	0	0.260 Fisher Exact test value: 0.373
6-10	39	1	
11-15	41	1	
16 & Above	5	0	
Total	98%	2%	

DISCUSSION

Chronic kidney disease (CKD) is gradually increasing in the South Asian countries like Pakistan and the reason of its spread is multifactorial¹¹⁻¹³. In the United States, the national

Institute of Diabetes and Digestive and Kidney Disease (NIDDK) reports that 1 in every 10 American adults has some degree of chronic kidney disease. A systematic review of observational studies revealed a global CKD prevalence of approximately 11-13% worldwide and the majority of cases are found to be Stage 3¹⁴. The See Kidney Disease (SeeKD) targeted screening project found a high proportion of individuals with risk factors for CKD and a high prevalence of unrecognized CKD. Of the 5194 patient screened, 18.8% had unrecognized CKD (estimated eGFR <60 mL/min/1.73 m²) and about 13.8% had stage 3a CKD (eGFR 45-60 mL/min/1.73 m²)¹⁵. Anemia is very common in patients with CKD and it may be responsible for few symptoms associated with decline in kidney function like fatigue, dyspnea, decreased exercise tolerance and depression. The prevalence of anemia increased with the stage of CKD, from 8.4% at stage 1 to 53.4% at stage-5 CKD¹⁶. Anemia is one of the leading cause of increased morbidity and mortality due to cardiovascular diseases in CKD patients. Moreover, it also increases the risk of hospitalization and prolongs hospital stay in these patients. Erythropoiesis-stimulating agents like recombinant human erythropoietin (rhEPO) are used to treat the anemia in CKD patients. These agents decrease the requirement for transfusion and improve symptoms related to quality of life, exercise tolerance and most importantly left ventricular hypertrophy (LVH), which is associated with increased mortality. Studies have shown that the SC dose of erythropoietin required to achieve a target Hb level is approximately 30 percent less than that required with IV administration¹⁷. Some adverse effects have also been reported when ESAs are used to attain a normal hemoglobin level¹⁸⁻¹⁹. Hypertension is one of the most common side effect of ESA therapy²⁰⁻²¹. According to studies, approximately 20 to 30 percent patients who receive erythropoietin intravenously (IV) for the anemia of CKD develop an elevation in diastolic pressure of 10 mmHg or more but there is limited data available regarding association of hypertension with the subcutaneous usage of erythropo-

ietin especially in predialysis patients. Therefore, this study was conducted to determine the frequency of hypertension in predialysis patients with chronic kidney disease receiving recombinant human erythropoietin (rhEPO) subcutaneously for their anemia.

Our final results were quite similar to the results of study conducted by Watson *et al*, published in the American Journal of Medicine, and that study demonstrated that recombinant human erythropoietin (rhEPO) given subcutaneously (SC) is an effective and safe therapy for patients with chronic kidney failure who are anemic and who are not receiving dialysis (No significant change in Mean BP was noted in 11 patients with pre-dialysis CKD treated for 12 weeks with low doses of SC recombinant human erythropoietin).

Another such study conducted by Bushra Moiz *et al*, and published in JCPSP revealed that low doses of subcutaneous (SC) recombinant human erythropoietin (rhEPO) used for the treatment of anemia in CKD, are not associated with significant rise in blood pressure in patients who are not already hypertensive (None out of 12 non hypertensive patients showed increase in BP after low doses of SC recombinant human erythropoietin used for 10 weeks). Therefore, various studies conducted in different populations concluded that predialysis CKD patients can safely use recombinant human erythropoietin (rhEPO) subcutaneously for treatment of anemia, but in low to moderate doses, with low target hemoglobin, to avoid rise in blood pressure associated with ESA therapy.

CONCLUSION

We concluded that the hypertension in predialysis patients with CKD receiving recombinant human rhEPO SC in low doses, is very low, therefore rhEPO can be used subcutaneously, to treat anemia safely in predialysis patients with CKD.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

- Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension Awareness, Treatment, and Control in Adults With CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2010; 55(3): 441-51.
- Sarafidis P, Sharpe C, Wood E, Blacklock R, Rumjon A, Al-Yassin A, et al. Prevalence, Patterns of Treatment, and Control of Hypertension in Predialysis Patients with Chronic Kidney Disease. *Nephron Clin Pract* 2012; 120(3): 147-55.
- De Goeij M, Voormolen N, Halbesma N, de Jager D, Boeschoten E, Sijpkens Y, et al. Association of blood pressure with decline in renal function and time until the start of renal replacement therapy in pre-dialysis patients: a cohort study. *BMC Nephrol* 2011; 12(1): 38-40.
- James P, Oparil S, Carter B, Cushman W, Dennison-Himmelfarb C, Handler J, et al. Evidence-based guideline for the management of high blood pressure in adults. *J Am Med Assoc* 2014; 311(5): 507-10.
- Zhang Y, Thamer M, Kaufman J, Cotter D, Hernán M. High doses of epoetin do not lower mortality and cardiovascular risk among elderly hemodialysis patients with diabetes. *Kidney Int* 2011; 80(6): 663-69.
- Singh A. What is causing the mortality in treating the anemia of chronic kidney disease: erythropoietin dose or hemoglobin level? *Curr Opin in Nephrol Hypertens* 2010; 19(5): 420-24.
- Smith K. The cardiovascular effects of erythro-poietin. *Cardio-vascul Res* 2003; 59(3): 538-48.
- Inrig J, Sapp S, Barnhart H, Patel U, Reddan D, Singh A, et al. Impact of higher hemoglobin targets on blood pressure and clinical outcomes: a secondary analysis of CHOIR. *Nephrol Dial Transplant* 2012; 27(9): 3606-14.
- Suttorp M, Hoekstra T, Mittelman M, Ott I, Franssen C, Dekker F. Effect of Erythropoiesis-Stimulating Agents on Blood Pressure in Pre-Dialysis Patients. *PLoS One* 2013; 8(12): e84848.
- Smith K. The cardiovascular effects of erythropoietin. *Cardio-vascul Res* 2003; 59(3): 538-48.
- Imran S, Sheikh A, Saeed Z, Khan SA, Malik AO, Patel J et al. Burden of chronic kidney disease in an urban city of Pakistan, a cross-sectional study. *J Pak Med Assoc* 2015; 65(4): 366-69.
- Ullah K, Butt G, Masroor I, Kanwal K, Kifayat F. Epidemiology of chronic kidney disease in a Pakistani population. *Saudi J Kidney Dis Transpl* 2015; 26(1): 1307-10.
- Alam A, Amanullah F, Baig-Ansari N, Lotia-Farrukh I, Khan FS. Prevalence and risk factors of kidney disease in urban Karachi: baseline findings from a community cohort study. *BMC Res Notes* 2014; 7(2): 179-82.
- Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016; 11(7): e0158765-72.
- Galbraith LE, Ronksley PE, Barnieh LJ, Kappel J, Manns BJ, Samuel SM, et al. The See Kidney Disease Targeted Screening Program for CKD. *Clin J Am Soc Nephrol* 2016; 11(6): 964-72.
- Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014; 9(1): e84943-46.
- Wright DG, Wright EC, Narva AS, Noguchi CT, Eggers PW. Association of Erythropoietin Dose and Route of Administration with Clinical Outcomes for Patients on Hemodialysis in the United States. *Clin J Am Soc Nephrol* 2015; 10(1): 1822-25.
- Arantes L, Crawford J, Gascon P, Latymer M, Launay-Vacher V, Rolland C, et al. A quick scoping review of efficacy, safety, economic, and health-related quality-of-life outcomes of short- and long-acting erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anemia and chronic kidney

- disease anemia. *Critical Reviews in Oncol/Hematol* 2018; 129(1): 79-90.
19. Salamin O, Kuuranne T, Saugy M, Leuenberger N. Erythropoietin as a performance-enhancing drug: Its mechanistic basis, detection, and potential adverse effects. *Molecul Cellular Endocrinol* 2018; 464(2): 75-87.
 20. Boyle S, Berns J. Erythropoietin and Resistant Hypertension in CKD. *Seminars Nephrol* 2014; 34(5): 540-49.
 21. Palmer S, Saglimbene V, Mavridis D, Salanti G, Craig J, Tonelli M, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Datab Systemat Rev* 2014; 2014(12): CD010590.
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