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ORIGINAL ARTICLE

Change in Hemoglobin with Androgen and Low Dose Erythropoietin Versus Erythropoietin Alone in Patients of Anemia of Chronic Kidney Disease

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ABSTRACT

Objectives: To determine the mean rise in hemoglobin with androgen and low dose erythropoietin versus erythropoietin alone in patients of anemia of chronic kidney disease.

Methodology: A randomized control trial was conducted at a tertiary care hospital between October 2019 to April 2020. Both male and female from age >17years to 70 years with anemia of CKD as per operational definition were included. Patients with a history of blood transfusion in the last three months. Patients already on Erythropoietin therapy or those with uncontrolled hypertension BP >190/105 mm Hg at the time of study were excluded. Relevant data including demographic details, baseline hemoglobin was noted. Patients were randomly assigned to group A or group B by lottery method. Patients in group A were given 100mg of androgen (Nandrolone Decanoate) intramuscularly once weekly plus low dose of erythropoietin (2000 units twice weekly) subcutaneously for 6 months and patients in group B were given standard dose of erythropoietin (4000 units twice weekly) subcutaneously for 6 months. Rise in hemoglobin was recorded as per operational definition. Follow up was ensured by taking telephone contact. Data was recorded on pre-designed proforma.

Results: Mean Hb levels after treatment were calculated as 12.48+1.20 in Group-A and 11.12+1.32 in Group-B, p value was calculated as 0.0001 showing a significant difference between the two groups, comparison of mean increase in Hb levels after treatment were calculated as 3.0+0.09 in Group-A and 1.72+0.67 in Group-B, p value was calculated as 0.0001 showing a significant difference between the two groups.

Conclusion: We concluded that there was significantly greater rise in the mean hemoglobin with androgen plus low dose erythropoietin as compared to erythropoietin alone in treatment of anemia of chronic kidney disease. Nevertheless, further large-scale and multi-center studies will be needed to further explore the long-term efficacy and adverse effects of androgens among patients of anemia of chronic kidney disease.

Keywords: Chronic kidney disease, anemia, androgen and low dose erythropoietin versus erythropoietin alone, mean increase

INTRODUCTION

Anemia is defined as hemoglobin (Hb) concentrations of less than 13.5g/dl in adult males and less than 12.0g/dl in adult females.[1] Anemia is a very common complication of chronic kidney disease (CKD). [2] It is primarily the result of inadequate production of erythropoietin by the kidneys in response to decreasing hemoglobin (Hb) concentration. Anemia affects the quality of life and is an important factor in morbidity and mortality of CKD patients.[3,4] It can occur even at early stages of disease.3 However anemia further worsens with the progressive deterioration of renal functions. Almost 3/4th of patients needing dialysis are suffering from anemia.

According to a British study its prevalence is 1% in CKD stage III, 9% in stage IV and 33% in CKD stage V.[5] Erythropoietin (EPO) is currently used for treatment of anemia of CKD.[6] It is a glycoprotein hormone synthesized by the kidneys in response to decreased oxygen supply. It regulates the proliferation, differentiation, and survival of erythroid progenitor cells. Thus it controls the level of erythrocytes in blood. [7]

However, the main limitation of its use is that patients of poor socioeconomic status with anemia of CKD could not afford it.[8] Thus it is unavailable to most of the patients of developing countries. So the use of EPO in combination to reduce its dose and a cheaper alternative regimen needs to be evaluated.[9]

Androgens which are cheaper than EPO were used for anemia of CKD patients before the introduction of erythropoietin.[10] Studies show that use of adjuvant agents like androgen along with erythropoietin can reduce cost and expenditure in treating anemia of CKD.[11-12]

Previous studies included only a small number of patients which were not adequate to draw any conclusion so further studies need to be done with more patients in each group.[13-14] There is no local literature available at the moment. Most patients in Pakistan with CKD cannot afford erythropoietin which is 10 times more expensive than androgen. The rationale of the study is that if anemia can be corrected with androgen and low dose erythropoietin then this will provide a cheaper solution for CKD patients. The aim of this study was to determine the mean increase in hemoglobin with androgen and low dose erythropoietin

versus standard dose of erythropoietin alone in patients of anemia of chronic kidney disease.

MATERIAL AND METHODS

A randomized control trial was conducted at a tertiary care hospital between October 2019 to April 2020. Using a non-probability consecutive sampling technique patients were recruited in the study. It is estimated as 100 cases (50 each) using 95% confidence level, 80% power of test taking an expected mean increase in Hb level as 2.22+0.21 in erythropoietin alone group versus 3.59+0.31 in androgen plus low dose erythropoietin group.

Both male and female from age > 17years to 70years with anemia of CKD as per operational definition were included. Patients with a history of blood transfusion in the last three months.

Patients already on Erythropoietin therapy or those with uncontrolled hypertension BP >190/105 mm Hg at the time of study were excluded. Other causes of anemia diagnosed from blood peripheral film, serum iron, total iron binding capacity, Hb electrophoresis etc.(on previous history/medical record) were also excluded from the study.

Data collection was started after approval of synopsis. Informed written consent from patient/guardian was taken. Relevant data including demographic details, baseline hemoglobin was noted. Patients were randomly assigned to group A or group B by lottery method. Patients in group A were given 100mg of androgen (Nandrolone Decanoate) intramuscularly once weekly plus low dose of erythropoietin (2000 units twice weekly) subcutaneously for 6 months and patients in group B were given standard dose of erythropoietin (4000 units twice weekly) subcutaneously for 6 months. Rise in hemoglobin was recorded as per operational definition. Follow up was ensured by taking telephone contact. Data was recorded on pre-designed proforma.

Data was analyzed in (SPSS) version 23.0. Mean and standard deviation was calculated for variables like age, Hb levels at baseline and post treatment. For categorical variables e.g., gender, frequency and percentages were calculated. The mean increase was calculated by subtracting post treatment Hb levels from baseline in both the groups. P value <0.05 was considered as significant. Independent sample t test was applied for significant differences between groups. Effect modifiers like age, gender, stage of CKD (attached as annexure) and economic status. Post stratification test was applied.

RESULTS

A total of 100 cases (50 in each group) fulfilling the inclusion/exclusion criteria were enrolled to determine mean rise in hemoglobin with androgen and low dose erythropoietin versus erythropoietin alone in patients of anemia of chronic kidney disease (Table 1).

Mean Hb levels at baseline were calculated as 9.48+1.29 in Group-A and 9.4+1.21 in Group-B, p value was calculated as 0.750 showing insignificant difference between the two groups. Mean Hb levels after treatment were calculated as 12.48+1.20 in Group-A and 11.12+1.32 in Group-B, p value was calculated as 0.0001 showing a significant difference between the two groups.

Table 1. Baseline Characteristics of Study Participants

Age (in years)	Group-A (n=50)		Group-B(n=50)	
	No. of patients	%	No. of patients	%
18-50	27	54	22	44
51-70	23	46	28	56
Mean ± SD	46.49 ± 12.54		51.46 ± 12.63	
Male	28	56	31	62
Female	22	44	19	38

Comparison of mean increase in Hb levels after treatment were calculated as 3.0+0.09 in Group-A and 1.72+0.67 in Group-B, p value was calculated as 0.0001 showing a significant difference between the two groups (Table 2).

Table 2. AEfficacy of Androgen plus Erythropoietin versus Erythropoietin alone

	Group-A (n=50)		Group-B (n=50)		P-value
	No. of patients	%	No. of patients	%	
Hb level (Baseline)	9.48	1.29	9.4	1.21	0.750
Hb level (After Baseline)	12.48	1.2	11.12	1.32	0.0001
Comparison of Mean Increase in Hb Level After Treatment	3	0.09	1.72	0.67	0.0001

DISCUSSION

Androgens are relatively cheaper and have been used for the management of anaemia in dialysis patients before the Erythropoietin (EPO) advent.[15] This study was aimed to determine the mean increase in hemoglobin with androgen and low dose erythropoietin versus standard dose of erythropoietin alone in patients of anemia of chronic kidney disease.

In a study conducted on rats, it was found that administration of high doses of Nandrolone decanoate resulted in significant increases in cell blood count, hemoglobin, and hematocrit.[16] The mean Hb levels after treatment were significantly higher in group A than the control group indicating higher efficacy of androgens than erythropoietin as treatment of anemia in our patients. The findings of our study are in agreement with a previous study by Aggarwal et al who showed that there was a statistically significant rise in mean haemoglobin concentration in a group with low dose erythropoietin plus androgen.[17] The mean increase in Hb was 6.27 ± 0.37 to 9.86 ± 0.6 gm/dl (3.59 ± 0.31) versus erythropoietin alone 6.48 ± 0.39 to 8.70 ± 0.60 gm/dl (2.22 ± 0.21) at the end of three months with P value <0.05.9 In another study hemoglobin at end in groups with erythropoietin alone versus low dose erythropoietin plus androgen was (7.75 +/- 0.9 vs 8.99 +/- 1.39g/dl, p< 0.01)[18] Using androgens as adjuvant therapy has been effective and found to reduce the recommended dosage of rHuEPO in patients with HD.

A study conducted by Ballal et al. found high levels of haematocrit in patients who were given rHuEPO including nandrolone decanoate (NAND) in contrast to patients who were given rHu EPO only.[19] Similar findings were found by Gaughan et al. that giving low dosages of rHuEPO along with NAND led to higher increase in hematocrit in contrast to using rHuEPO alone.[20]

Recent research on animals has indicated that androgens promote erythropoiesis by stimulating EPO expression and this action is mediated by DNA binding-dependent actions of the androgen receptor (AR) in the non-hematopoietic cells. [21]

Considering our findings and other studies showing agreement with our hypothesis that "there is difference in mean rise in hemoglobin with androgen plus low dose erythropoietin as compared to erythropoietin alone in treatment of anemia of CKD", however, our results may be considered as primary in our population as controversy still exists, which needs multi-center trials to establish a clear results. Large scale studies are needed to explore the long-term efficacy and adverse effects of androgens among patients of anemia of chronic kidney disease.

CONCLUSION

We concluded that there was significantly greater rise in the mean hemoglobin with androgen plus low dose erythropoietin as compared to erythropoietin alone in treatment of anemia of chronic kidney disease. Nevertheless, further large-scale and multi-center studies will be needed to further explore the long-term efficacy and adverse effects of androgens among patients of anemia of chronic kidney disease.

REFERENCES

1. Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC heart failure. 2020 Oct;7(5):2007-11.
2. Patel EU, White JL, Bloch EM, Grabowski MK, Gehrie EA, Lokhandwala PM, Brunker PA, Goel R, Shaz BH, Ness PM, Tobian AA. Association of blood donation with iron deficiency among adolescent and adult females in the United States: a nationally representative study. Transfusion. 2019 May;59(5):1723-33.
3. van Haalen H, Jackson J, Spinowitz B, Milligan G, Moon R. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: Analysis of multinational real-world data. BMC nephrology. 2020 Dec;21(1):1-5.
4. Akizawa T, Okumura H, Alexandre AF, Fukushima A, Kiyabu G, Dorey J. Burden of anemia in chronic kidney disease patients in Japan: a literature review. Therapeutic Apheresis and Dialysis. 2018 Oct;22(5):444-56.
5. Dmitrieva1O, Lusignan S, Macdougall I, Gallagher H, Tomson C, Harris K. Association of anaemia in primary care patients with chronic kidney disease: cross sectional study of quality improvement in chronic kidney disease (QICKD) trial data. BMC Nephrol 2013;14:24.
6. Abdu A, Arogundade F, Adamu B, Dutse A, Sanusi A, Sani M.. Anaemia and its Response to Treatment with Recombinant Human Erythropoietin in Chronic Kidney Disease Patients. WAJM 2009;28(5):295–99.
7. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient preference and adherence. 2008;2:195.
8. Paul AK, Latif ZA, Iqbal S, Amin F, Shefin SM, Ashrafuzzaman SM. Androgen versus erythropoietin for the treatment of anaemia of pre-dialysis chronic kidney disease. Dhaka, Bangladesh. Med J. 2012 ;21(1):125-8.
9. Adamu B, Ma'aji S, Erwin P, and Tleyjeh I. Meta-Analysis of Randomized Controlled Trials on Androgens versus Erythropoietin for Anaemia of Chronic Kidney Disease: Implications for Developing Countries. Int J Nephrol. 2012;2 Sept
10. Ballal SH, Dornoto DT, Polack DC, Marciulonis P, Martin KJ. Androgens potentiate the effects of erythropoietin in the treatment of anemia of end-stage renal disease. American Journal of Kidney Diseases. 1991 Jan 1;17(1):29-33.
11. Adamu B, Ma'aji SM, Erwin PJ, Tleyjeh IM. Meta-analysis of randomized controlled trials on androgens versus erythropoietin for anaemia of chronic kidney disease: implications for developing countries. International journal of Nephrology. 2012 Oct 16;2012.
12. Gaughan WJ, Liss KA, Dunn SR, Mangold AM, Buhsmer JP, Michael B, Burke JF. A 6-month study of low-dose recombinant human erythropoietin alone and in combination with androgens for the treatment of anemia in chronic hemodialysis patients. American journal of kidney diseases. 1997 Oct 1;30(4):495-500.
13. Berns JS, Rudnick MR, Cohen RM. A controlled trial of recombinant human erythropoietin and nandrolone decanoate in the treatment of anemia in patients on chronic hemodialysis. Clinical nephrology. 1992 May 1;37(5):264-7.
14. Teruel JL, Marcen R, Navarro-Antolin J, Aguilera A, Fernandez-Juarez G, Ortuno J. Androgen versus erythropoietin for the treatment of anemia in hemodialyzed patients: a prospective study. Journal of the American Society of Nephrology. 1996 Jan 1;7(1):140-4.
15. Yuen MV, Gianturco SL, Pavlech LL, Storm KD, Yoon S, Mattingly AN. Nandrolone decanoate: Summary Report. Available from: http://hdl.handle.net/10713/14876
16. SHAHRAKI MOHAMMAD REZA, MIRSHEKARI HAMIDEH, SHAHRAKI AHMAD REZA. CHRONIC HIGH DOSES OF NANDROLONE DECANOATE ON BLOOD CELL, LIPOPROTEIN PROFILE, AND LIVER ENZYMES IN MALE RATS. ZAHEDAN JOURNAL OF RESEARCH IN MEDICAL SCIENCES (TABIB-E-SHARGH). 2016 [cited 2021November13];18(6):0-0.
17. Aggarwal H, Sehgal R, Singh S, Nand N,Bharti K, Chakrabarti D. Evaluation of Efficacy of Low Dose Recombinant Human Erythropoietin in Combination with Androgen Therapy in Anaemia of Chronic Renal Failure. JIACM 2005;6(3): 208-15.
18. Lee M. Ahn S. Song J. Effects of adjuvant androgen on anemia and nutritional parameters in chronic hemodialysis patients using low dose recombinant human erythropoietin. Korean J Intern Med.2002 Sep vol 17, no 3.
19. Ballal SH, Domoto DT, Polack DC, Marciulonis P, Martin KJ. Androgens potentiate the effects of erythropoietin in the treatment of anemia of end-stage renal disease. Am J Kidney Dis 1991;17:29–33.
20. Gaughan WJ, Liss KA, Dunn SR. A 6-month study of low-dose recombinant human erythropoietin alone and in combination with androgens for the treatment of anemia in chronic hemodialysis patients. Am J Kidney Dis 1997;30:495–500.
21. McManus JF, Nguyen NY, Davey RA, MacLean HE, Pomilio G, McCormack MP, Chiu WS, Wei AH, Zajac JD, Curtis DJ. Androgens stimulate erythropoiesis through the DNA-binding activity of the androgen receptor in non-hematopoietic cells. European journal of haematology. 2020 Sep;105(3):247-54.