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Effect of Androgens and Erythropoietin on Haemoglobin in Patients of End Stage Renal Disease on Hemodialysis

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SUMMARY

Adequate exogenous erythropoietin (EPO) is the treatment of choice for anemia in patients with end stage renal disease (ESRD). But high cost of EPO is one of the limitations. Addition of androgen may enhance the erythropoitic response by increasing the sensitivity of the erythroid progenitors to the exogenous EPO. 11 patients (6 male and 5 females) suffering from anemia of chronic renal failure were given 100 mg of nandrolone deconate intramuscularly, once a week for three months along with their previous dose of EPO. At the end of the three months hemoglobin increased from 9.2±0.8 gm/dl to 10.1±0.8 gm/dl (P .001) and serum albumin from 3.5±0.4 gm/dl to 4.1±0.3gm/dl (P<0.001). The dry weight of the patients did not changed significantly. No significant side effects like elevated liver enzymes or hypertension were seen during the study period. It is concluded that androgen therapy significantly augments the erythropoitic action of exogenous EPO at least for short period i.e. three months. Further studies to see the effects oprolonged use of androgens in combination with EPO are needed.

INTRODUCTION

Anemia is one of the common and early complications of renal failure. Many factors like iron deficiency[1-3], folate deficiency[4], hyperparathoirdism[5], aluminum bone disease[6], decreased red blood cell survival in uremic atmosphere[7], blood losses from gastrointestinal tract and during hemodialysis due to bleeding from fistula needles, hemolysis[8] or clotting of dialyzer or blood lines contribute to the pathogenesis of anemia. Lack of Erythropoetin (EPO) is the major cause of anemia in chronic renal failure[9,10]. Keeping in mind the diverse pathogenesis, different treatment modalities have been tried in the past like iron and folic acid supplementation[11], increasing the dose of dialysis[12], vitamin D3 for the treatment of hyperparathyroidism[13] and by blood transfusion. Androgen was the main non- transfusional treatment of anemia in hemodialysis patients for many years before the availability of EPO[14]. Androgens not only directly stimulate the erythropoisis by rapid stem cell differentiation, but also increase the release of EPO from the kidney and increase the sensitivity of erythroid progenitors to available EPO[15-17]. In addition androgens have anabolic effect. EPO mainly has effect upon the erythroid clone forming units (CFU - E) and increases the number of cells in cycle of erythropoeisis[18-19]. As androgens and EPO have effects at different levels, addition of androgen should enhance the effect of EPO on erythropoisis in patient of chronic renal failure who are already receiving EPO. Limited number of studies with combination therapy has shown variable results[20-23].

AIMS AND OBJECTIVES

This study was carried out to see the additional effects of Nandrolone Deconate (ND) on hemoglobin (Hb), albumin, and dry body weight in patients of end stage renal disease (ESRD) on hemodialysis .

PATIENTS AND METHODS

ESRD patients undergoing regular hemodialysis receiving EPO regularly and stable hemoglobin for at least three months were included in the study. Base line serum iron, ferritin and transferrin saturation were obtained to exclude iron deficiency. Stool examination was done for occult

blood for three consecutive days to rule out any gastrointestinal bleeding. Patients either positive for stool occult blood or having iron deficiency were excluded from the study. The patients suffering from chronic infections were also excluded from the study. Their Hb and albumin was checked on monthly basis for three months and also dry weight was evaluated monthly for three months. Mean of these were taken as pretreatment data. Base line liver functions, total bilirubin (T.Bil) alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline posphatase (ALP) were checked. Blood pressure was recorded on each hemodialysis and mean of last three readings was calculated. After taking informed consent, 100 mg of Nandrolone Deconate was given intramuscularly weekly for three months. During the study period the dose of the EPO, iron and folic acid suplimentations were not changed. Haemoglobin albumin, and liver functions were monitored monthly. The dry weight was adjusted every fortnightly. The values at three months after start of ND treatment were compared with pre treatment values.

RESULTS

Eleven patients (6 males and 5 females) completed the study. Out of these 11 patients, 4 were suffering from ESRD due to diabetic nephropathy, 2 due to hypertensive nephropathy, 3 due to chronic glomerulonephritis and one each due to Alport syndrome and autosomal dominant polycystic kidney disease. Their mean age was 35±10 years (ranging from 15 to 50 years) and the duration on dialysis was 41.5+38 months (ranging from 8 to 144 months). Their mean dose of EPO was 2363±809 units per week. Mean pretreatment systolic blood pressure was 154±12 mmHg and diastolic blood pressure was 90±8 mmHg. The mean values of the pre treatment and post treatment of Hb, albumin, ALT, AST ALP, and T. Bil are shown in the Table 1. There was significant rise in the Hb from 9.2±0.8gm/dl to 10.1±0.8 gm/dl (P.001) and in albumin from 3.5±0.4 gm/dl to 4.1±0.3 gm/dl (P<0.001) at the end of the study. The monthly increase in Hb and albumin is shown in the Figures 1 & 2. There was a continuous trend to rise in Hb and albumin until the end of the study. Although ALT and T.Bil slightly rose in 3 patients initially but later on came to the base line and as is evident from the Table 1 there was no significant difference in the pre and post treatment mean values of ALT, AST, T.Bil and ALP. The post treatment mean systolic and diastolic blood pressures were 156±10 mmHg and 90±7 mmHg respectively and

Table 1: Comparison of Pre and Post treatment parameters

	Mean pre-treatment value	*3rd month value*	*P value*
Hb. (gm/dl)	9.2±0.8	10.1±0.8	0.001
ALB. (gm/dl)	3.5±0.4	4.1±0.3	< 0.001
T.Bil. (mg/dl)	0.8±0.2	0.7±0.2	0.17
ALT (U/L)	66±21	58±14	0.08
AST (U/L)	43±12	45±7	0.56
ALP (U/L)	207±70	180±38	0.16
Dry Weight (Kg)	54±10	54.4±9.4	0.11

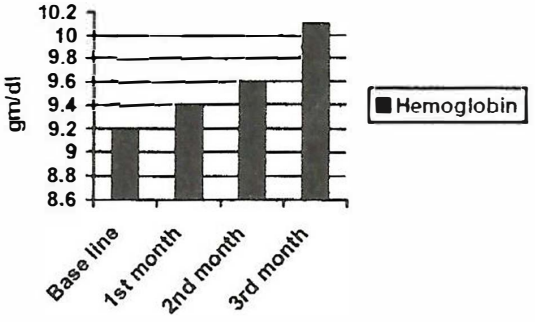

Fig. 1: Hemoglobin after treatment with androgen and EPO.

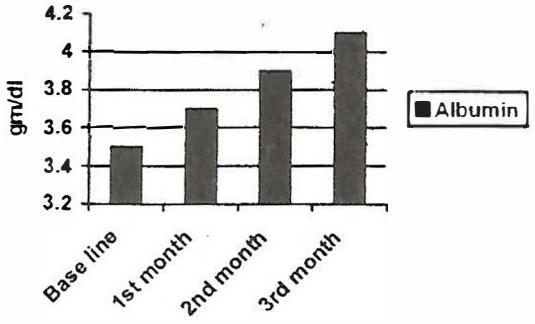

Fig. 2: Serum albumin values after treatment with androgen and EPO.

these values were not significantly different from their base line readings. There was no significant difference in pre and post treatment dry body weights (54±10 kg versus 54.4±9.4 Kg).

DISCUSSION

Anemia is one of the most common complications of chronic renal failure and may be responsible for several uremic symptoms.It has been well documented that the proper treatment of the anemia in ESRD patients relieve the problems of early fatigability, loss of appetite[24-26], reduced exercise tolerance[27], decreased quality and duration of sleep and cognition functions[28], left ventricular hypertrophy and increasing angina specially in elderly patients[29]. Correction of the hemoglobin also reduces the mortality and the rate of hospitalization[30-31]. Many therapies have been tried in the past for the treatment of anemia in chronic renal failure, such as iron and folic acid supplementation, improving the dose of dialysis, blood transfusion and androgens[11-14].

The introduction of EPO in late eighties of the last century by Amgen has totally changed the concept of the treatment anemia[32]. However, economic constraints led many clinician to work out various strategies to enhance the erythropoeitic respose to EPO thus resulting in lower dose of the drug. These various strategies include administration of intravenous iron[33], L-carnitine supplementation[34] and combination of EPO with androgen[20-23]. The erythropoitic effect of the androgens results, in part, from their ability to increase endogenous EPO production. Additionally they may increase the mass and sensitivity of the erythroid progenitors to available erythropoietin[15-17]. On the other hand EPO acts mainly by stimulating the erythryoid clone-forming unit[19]. As both of these drugs have effects at different levels, the combined use may have additive response. Ballal et al[21] compared 8 male patients on combination therapy with 7 patients on EPO alone for 12 weeks. Hematocrit was increased from 24.4±1.4% to 32.9±1.8% in patients on combination therapy as compared to 25.3±0.8% to 27.4±1.5% in patients only on EPO (P<0.001). Gaughan et al[20] compared 9 patients on nandrolone plus EPO with 10 patients only on EPO for 6 months. He concluded that in patient having combination therapy, the hematocrit increased by 8.2±4.4% versus 3.5±2.8% in patients on EPO alone (P= 0.012). Teruel et al[22] observed the effect of nandrolone with EPO in 84 patients for 6 months. Hemoglobin increased by 0.8 gm/dl in patients younger than 46 years, 1.8 gm/dl in patients between 46 and 55 years and by 2.7 gm/dl in patients aged more than 55 years. In contrast to these, Bern et al[23] failed to see any additional effect of androgen in 12 patients in 16 weeks study, probably due to the difference in study design. In this study the patients were not on regular EPO. It was started after 2 months treatment of nandrolone and patients remained on combination therapy only for 2 months during the study period. There is chance that if they would have followed for a prolonged period on combination therapy, the results might be different. In the present study the use of androgen in 11 patients significantly increased the hemoglobin from 9.2±0.8gm/dl to 10.1±0.8 gm/dl (P 0.001). Increment in Hb seen in this study was less than what has been reported by Gaughan et al and Teruel et al. This could also be explained on the basis of shorter period of this study.

Like anemia, hypoalbuminemia is also a bad prognostic sign in hemodialysis patients[35]. There was a significant rise in serum albumin from 3.5±0.4 gm/dl to 4.1±0.3 gm/dl (P<0.001). It was comparable to the Gaughan et al study where albumin increased from 3.8±0.54gm/dl to 4.1±0.2 gm/dl (P 0.20) in patients on EPO alone in contrast to the patients on combination therapy where it increased from 3.8±0.35gm/dl to 4.0±0.36 gm/dl (P 0.03). Teruel et al reported significant increase in dry weight in patients receiving androgens and EPO. But we, like Gaughan et al did not find a significant increase in dry weight. There was trend for progressive increase in hemoglobin, dry body weight and serum albumin, a longer follow up may result in further rise in serum albumin, haemoglobin and weight of these patients.

Rise in blood pressure has been reported with increase in Hct after treatment with EPO which is due to increase in hematocrit and also due to release of Endothelin from the blood vessels[36]. No significant change in blood pressure was seen in association with increase in HcT after androgen therapy. The rise in ALT was seen only in 3 cases in the 1st and 2nd month of the treatment, which later came down to the base line. Same was the observation by Teruel et al. But in the study by

Gaughan et al the ALT remained elevated.

In conclusion we found that combined use of EPO and androgen has better erythopoitic response without any significant side effects. There is also additional beneficial effect on serum albumin due to anabolic effects of androgens. Regular use of androgen may decrease the dose of the EPO and so may be cost effective. This study was only for three months, further long term trials are needed to see the effects of prolonged use of androgens.

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