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Factors Influencing Effectiveness of Renal Anaemia Treatment with Epoetin in Dialysis Patients

E. Vazelov, S. Antonov , I. Stanchev
Department of Nephrology, Sofia, Bulgaria

Introduction

Renal anemia (RA) is a major complication in patients with Chronic Kidney Disease (CKD). RA treatment became more efficient after the clinical implementation of erythropoiesis stimulating agents (ESA) in the late eighties. The high cost of this therapy stimulated scientific research to ascertain the factors influencing the effectiveness of ESA treatment. On the basis of the experience gathered and the scientific evidence collected in USA (National Kidney Foundation Kidney Disease Outcome Quality Initiative - NKF K/DOQI) and Europe (European Best Practice Guidelines - EBPG), guidelines for anaemia treatment were formulated and published (1, 2). Clinical practice issues in RA therapy were assessed in large scale, cross sectional surveys – Dialysis Outcomes and Practice Patterns Study (DOPPS) and European Survey on Anaemia Management (ESAM 98/99, ESAM 2003) (3, 4).

In Bulgaria, several investigations on factors influencing effectiveness of anaemia treatment with ESA were performed recently (5, 6). The following study examines the role of variables such as protein levels, iron status and supplementation and dialysis adequacy and their influence on hemoglobin levels and epoetin doses applied.

Material and Methods

61 adult (43 M and 18 F) dialysis patients – (Group A) on RA treatment with a mean age of 54 (18 to 80 years) were included in the study. There were no selection criteria – the investigation encompassed practically all adapted (without serious intercurrent diseases) patients in the haemodialysis program on renal anemia therapy. Reported primary cause of ESRD were as follows: 30 cases (49.2%) with pyelo- and interstitial nephritis; 14 (23.0%) – glomerulonephritis; 7 (11.5%) – polycystic kidney disease; 5 (8.2%) hypertensive nephrosclerosis; 1 (1.6%) – diabetes mellitus and 4 (6.6%) cases – other.

The following parameters were examined: serum albumin and total protein concentration, hemoglobin, iron, iron binding capacity (IBC), transferrin saturation (TSAT) value and urea reduction ratio (URR). Technically, blood was drawn from the arterio-venous fistula, catheter or prosthesis prior to the start of a dialysis session in vacutainers (Becton-Dickinson Vacutainer Systems, New Jersey, USA). Blood samples for the calculation of URR were taken by the method of "slow flow" in order the vascular access and cardio-pulmonary recirculation effect to be eliminated.

The ESA were epoetin-α (EPREX®, Janssen-Cilag, Belgium) and epoetin-β (Neo Recormon®, Roche, Switzerland) applied intravenously postdialysis in doses according to a protocol (calculated in U/kg BW/week). Intravenous iron as Iron (III)-hydroxide sucrose complex (5ml – 0.100) - Venofer® (Vifor) was used as adjuvant treatment.

The results were compared with those achieved in our previous similar investigation carried out nine months ago. In the latter 70 patients (principally almost same individuals) were included - Group B.

All measurements were expressed as mean values for Groups A and B +/- standard deviation. Differences between groups were examined using Student t-test and in the groups between factors with correlation analysis. A two-tailed P-value of <0.05 denoted the presence of statistically significant difference.

Results and Discussion

The data for both groups is presented on Tables 1 and 2.

Table 1. Characteristics and biochemical results of Group A – mean values +/- SD.

ALB LEVEL (g/l)	< 35	35-40	>40	TOTAL
ALB VALUE (g/l)	30.6+/-3.6	37.3+/-1.2	42.2+/-1.9	35.3+/-5.2
PATEINTS (n)	26	24	11	61
T.P. (g/l)	67.6+/-5.3	70.6+/-5.9	75.0+/-4.3	70.1+/-5.9
HAEMOGLOBIN (g/l)	94.1+/-20.1	102.7+/-13.0	104.2+/-11.6	99.3+/-16.6
EPO (U/kg BW/week)	67.7+/-30.3	75.2+/-31.9	59.2+/-20.1	69.2+/-29.6
IRON (μmol/l)	12.5+/-13.9	11.4+/-4.6	10.0+/-2.8	11.6+/-9.5
IBC (μmol/l)	50.5+/-12.0	52.9+/-7.5	52.3+/-10.8	51.8+/-10.1
TSAT (%)	20.8+/-13.4	22.3+/-10.1	19.4+/-4.4	21.1+/-10.9
VENOFER (mg Fe^{++}) mo.	190+/-60	180+/-40	190+/-60	190+/-50
URR (%)	60.7+/-9.5	58.2+/-9.2	59.1+/-6.5	59.4+/-8.9

Correspondence to: E. Vazelov, Department of Nephrology, Sofia, Bulgaria

Table 2. Characteristics and biochemical results of Group B – mean values +/- SD.

ALB LEVEL (g/l)	< 35	35-40	>40	TOTAL
ALB VALUE (g/l)	33.7+/-1.0	37.8+/-1.4	41.7+/-1.5	39.0+/-2.7
PATEINTS (n)	5	39	26	70
T.P. (g/l)	66.3+/-3.6	71.8+/-5.0	74.8+/-6.8	72.5+/-6.0
HAEMOGLOBIN (g/l)	92.4+/-18.6	104.7+/-19.0	100.2+/-16.4	102.2+/-18.2
EPO (U/kg BW/week)	73.8+/-27.4	57.4+/-34.5	72.3+/-39.2	64.1+/-36.2
IRON (μmol/l)	9.7+/-1.8	12.2+/-4.9	12.1+/-4.9	12.0+/-4.7
IBC (μmol/l)	47.8+/-10.6	56.9+/-13.5	56.0+/-10.1	55.8+/-12.3
TSAT (%)	21.3+/-6.5	22.6+/-10.1	22.5+/-9.6	22.5+/-9.6
VENOFER (mg Fe^{+++})mo.	0.80 +/- 40	0.70 +/- 30	0.80 +/- 30	75 +/- 30
URR (%)	61.4+/-3.6	59.9+/-8.8	61.3+/-6.6	60.6+/-7.7

Statistically significant differences between Group A and Group B are ascertained for serum levels of albumin (35.3+/-5.2 vs. 39.0+/-2.7 g/l; P<0.001) and total protein (70.1+/-5.9 vs. 72.5 +/- 6.0; P<0.05). Mean hemoglobin level in Group A was 99.3 +/- 16.6 g/l and the mean epoetin dose was 69.2 +/- 29.6 U/kg BW/week. The comparison of the results for these parameters with the achieved in Group B show insignificant decrease in hemoglobin level (Hb – 102.2 +/- 18.2; P=0.4,NS) and insignificant elevation of the erythropoietin dose (64.1 +/- 36.2 U/kg BW/week; P=0.4,NS).

The unfavorable trends in hemoglobin level and erythropoietin dose were analyzed in relation to the factors influencing the effectiveness of renal anemia treatment. Serum albumin (35.3+/-5.2 vs. 39.0+/-2.7 g/l; P<0.001) and total protein levels (70.1+/-5.9 vs. 72.5 +/- 6.0; P<0.05) were significantly lower in Group A. Albumin insignificantly/moderately correlates with hemoglobin (r = 0.3728), and insignificantly with Epo dose (r = -0.1563) and age (r = -0.2893). Total protein exhibited same pattern of correlations with hemoglobin (r = 0.2762) and Epo dose (r = - 0.2123).

Iron level was in lower normal range and diminished insignificantly in Group A compared to Group B (11.6 +/- 9.5 vs 12.0 +/- 4.7; P=0.8 NS). Same tendency was noted for IBC, which dropped significantly in Group A compared to Group B (51.8 +/- 10.1 vs. 55.8 +/- 12.3 µmol/l; P>0.05). This finding does not correspond with the normalized iron supplementation – increase in iron dose as Iron (III)-hydroxide sucrose complex (5ml – 0.100) - Venofer® (Vifor) from 0.75 +/- 30 to 190 +/- 50 mg/month. TSAT also decreased insignificantly from 21.1 +/- 10.9 % in Group A vs. 22.5 +/- 9.6 % in Group B (P=0.47 NS). Our explanation for these findings is that the increase in iron supplementation started one month prior the investigation of Group A and the results for iron, IBC and TSAT were not affected by the change in therapy so far.

Epoetin dose increased in Group A compared to Group B (69.2 +/- 29.6 vs 64.1 +/- 36.2 U/kg BW/week; P= 0.38, NS) and insignificantly correlated with hemoglobin levels.

Urea reduction ratio as a parameter of dialysis adequacy is a factor influencing effectiveness of RA treatment. URR in Group A decreased insignificantly to 59.4 +/- 8.9 % vs 60.6 +/- 7.7 in Group B (P= 0.4, NS). URR insignificantly correlated with hemoglobin level (r = 0.1848)

Decreased albumin level > 35 g/l (as a marker of malnutrition) was found in 26 (43%) patients in Group A, while in previous investigations only 5 (7%) patients (Group B) exhibited this abnormality. The number of patients with hypoalbuminemia had increased more than six times in Group A.

Conclusion

Effective renal anemia treatment is multi factorial dependant. Some of the important factors either are not easily reproducible in each dialysis session – URR for example or have complex metabolism – iron. Other important factors influencing anemia treatment were not in the scope of this investigation – blood loss, inflammation, PTH levels and hence were not discussed but affected the overall results.

We establish significant decrease in protein levels (albumin and total protein) and insignificant decrease in iron, TSAT, IBC and URR. Overall decrease in these factors is connected with the elevation of epoetin dose, but with less effect achieved. Presumably, optimization of treatment should be directed to correction of each individual factor to stop the inefficient use of higher epoetin doses.

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