The effect of anemia management on chronic renal failure progression

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Abstract  Background: Treatment of anemia in children with predialysis chronic kidney disease (CKD) has been facilitated by the administration of recombinant human erythropoietin (rHuEpo). The aim of this study was to evaluate the effect of rHuEpo on the correction of anemia and to study its effect on the progression of CKD in predialysis patients.

Methods: This study was done at the New Children’s Hospital, Cairo University, included 40 patients with CKD and renal anemia on conservative management. The patients were divided into two groups; group I (received rHuEpo) and group II (did not receive rHuEpo). For all patients, clinical assessment and routine laboratory investigation were recorded every 2 weeks, in addition to iron indices and ultrasonography. Glomerular filtration rate (GFR) was calculated every 2 weeks and the rate of decline of GFR (ΔGFR) was determined over 6 months preceding starting follow up. GFR was also determined over a follow up period of 12 months.

Results: There was a statistically significant difference between the initial and final levels of hemoglobin (Hb) and hematocrit (Hct) in group I. Also, there was a statistically significant difference between the two groups as regards Hb and Hct levels at the end of the study. The progression of CKD is already slower before T0 (the time of starting rHuEpo administration) in group I and also decreased after T0, with highly statistically significant difference.

Conclusion: The study concluded that rHuEpo therapy is beneficial for correction of renal anemia and its early treatment is a useful intervention for slowing the progression in patients with CKD.

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diseased kidneys are unable to produce sufficient quantities of erythropoietin. Successful treatment of renal anemia with recombinant human erythropoietin (rHuEpo) confirms inadequate erythropoietin production as the main cause.

Among the therapeutic interventions that could possibly slow the progression of CKD is the correction of anemia through the administration of rHuEpo. Partial correction of anemia with rHuEpo has been shown to markedly improve the general condition and quality of life of predialysis patients, but the effects of rHuEpo therapy on blood pressure and the rate of progression of CRF are still disputed.

Intravenous iron has been shown to improve responsiveness to rHuEpo in selected patients with CKD patients. In the absence of iron replacement, development of iron deficiency during rHuEpo therapy is common and deficient available iron is the most common cause of initial poor response to erythropoietin.

Subjects and methods

This study was done from December 2007 to May 2009 at the nephrology clinic, New Children’s Hospital, Cairo University. The study included 40 randomly selected patients, 1–15 years old, with CKD on conservative management. All patients have anemia with hematocrit (Hct) level from 30% to 36%. This study was approved by the ethical scientific committee in the Cairo University hospital and was conducted in accordance with the University bylaws for human research. All caretakers have given their informed consent. Cases of acute renal failure or hematological disease other than anemia were excluded from the study.

The patients were randomly divided into two groups (The patients’ files numbers are arranged serially, files were randomly selected electronically using Microsoft office Excel 2007):

Group I (received rHuEpo subcutaneously [SC] once weekly) and group II (did not receive rHuEpo), each composed of 20 patients. In both groups the GFR was calculated every 2 weeks and the rate of decline of GFR (ΔGFR) was determined over 6 months preceding the start of follow up, which was the time of starting rHuEpo administration in group I and was mentioned as T0. GFR was also determined over the follow up period.

For all patients, clinical assessment and investigation were recorded

Clinical data included: age, gender, etiology of nephropathy, measurement of blood pressure, weight, height, dose of rHuEpo and use of antihypertensive treatment and were recorded every 2 weeks.

Investigation: blood urea nitrogen (BUN), serum creatinine, serum calcium, phosphate, alkaline phosphatase, albumin, complete blood picture (CBC), serum iron, ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT) and arterial blood gases (ABG) and also abdomino-pelvic ultrasonography were done for all patients.

Statistical analysis

All patient information was tabulated and processed using SPSS 14.0. For quantitative variables, means and medians (as a measure of central tendency), standard deviation, range and minimum and maximum (as measures of variability) were used. Frequency and percentage are presented for qualitative variables. Chi-square test and Fisher’s exact test were used to estimate differences in qualitative variables.

Results

Our study included 40 patients, following up at the nephrology clinic, with CKD on conservative management, with anemia (Hct level from 30% to 36%). The patients were divided into two groups; group I (received rHuEpo SC once weekly) and group II (did not received rHuEpo), each composed of 20 patients. Their age ranged from 2 to 14 years (mean ± SD = 8.93 ± 3.67). The etiologies of CKD are shown in Fig. 1.

There was no statistically significant difference with respect to the distribution of original renal disease between the two groups. Table 1 shows sex distribution, weight and height of the studied groups.

Ten patients (25%) (seven patients in group I and three patients in group II) were hypertensive, with systolic or diastolic blood pressure greater than the 95th percentile. The proportion of patients receiving angiotensin-converting enzyme (ACE) inhibitors was similar in both groups. Table 2 shows the duration of conservative treatment, blood pressure of the studied patients at the start (T0) and at the end of the study and laboratory investigations in the two studied groups.

By ultrasound examination, the size of the kidneys was small in 28 patients (70%) and small and atrophic in nine patients (22.5%). Twenty patients (50%) had back pressure changes and three patients (7.5%) had renal stones. There was no statistically significant difference between the two groups.

Fig. 2 shows types of anemia in all studied patients. Microcytic hypochromic anemia was prevalent in group I while functional iron deficiency was prevalent in group II, with statistically significant difference between the two groups.

All patients received iron supplement; 12 (30%) patients received IV iron (four in group I and eight in group II) and 28 (70%) received oral iron (16 in group I and 12 in group II) with no statistically significant difference between the two groups.

There was statistically significant difference between the two groups as regards transferrin saturation (TSAT) which
was more in group II (36.46 ± 6.53), compared to group I (33.87 ± 6.21).

In group I, there was statistically significant difference between the initial and final hemoglobin (Hb) and Hct levels, as shown in Figs. 3 and 4.

Also, there was a highly statistically significant difference between the two groups as regards Hb and Hct levels at the end of the study, with \( p \)-value <0.001, as shown in Table 3.

The rate of decline of the glomerular filtration rate (\( \Delta \text{GFR} \)) did not change in group II; with a mean \( \Delta \text{GFR} \) value of 0.55 ± 0.48 before versus 0.57 ± 0.44 after T0 (difference is not significant). In contrast, the progression of CRF is already slower before T0 in group I with a mean \( \Delta \text{GFR} \) value of 0.36 ± 0.16 and decreased to 0.26 ± 0.15 after T0, with highly statistically significant difference as shown in Table 4.

The slope of \( \Delta \text{GFR} \) change in rHuEpo-treated group was reduced by more than 50% in 10 patients (decreased from 0.39 ± 0.06 to 0.18 ± 0.03) whereas \( \Delta \text{GFR} \) did not significantly change in the other 10 rHuEpo-treated patients. Similarly, the initial and final value of GFR did not significantly differ between the two groups. When comparing the 10 patients whose progression was slowed with the other 10 patients, the only difference is the distribution of original renal disease between the two subgroups; five of the patients with slowed progression had obstructive uropathy (difference is statistically significant), whereas chronic glomerulonephritis and inherited renal disease were present in seven of the 10 patients with unchanged progression.

### Discussion

Chronic kidney disease (CKD) patients with anemia need higher health care costs compared with patients without anemia and compared with other diseases known to have a high prevalence of associated anemia (such as cancer).²

Concerning the etiology of CRF in our studied patients, 15 out of 40 patients (37.5%) had obstructive uropathy, another 15 (37.5%) had unknown etiology, seven patients (17.5%) had chronic glomerulonephritis and three patients (7.5%) had inherited diseases (two oxalosis and cystinosis in one).

Collins et al. (2003),⁸ reported that the unknown nephropathy was 17.95% and Seikaly et al.(2003),⁹ reported it as...
Hb and Hct of group I and group II at the end of the study.

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb at the end (g/dl)</td>
<td>11.13 ± 1.4</td>
<td>9.5 ± 0.92</td>
<td>&lt;0.001*</td>
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<tr>
<td>Hct at the end (%)</td>
<td>33.24 ± 4.0</td>
<td>28.56 ± 2.41</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; Hct, hematocrit. *p < 0.05 is significant, p > 0.05 is not significant.

Variation of the rate of decline of GFR (ΔGFR) in the studied patients.

<table>
<thead>
<tr>
<th></th>
<th>ΔGFR before T0 (ml/min/1.73m2/month)</th>
<th>ΔGFR after T0 (ml/min/1.73m2/month)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.36 ± 0.16</td>
<td>0.26 ± 0.15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Group II</td>
<td>0.55 ± 0.48</td>
<td>0.57 ± 0.44</td>
<td>&gt;0.05</td>
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T0, the start of rHuEpo administration in group I; GFR, glomerular filtration rate; ΔGFR, variation of the rate of decline of glomerular filtration rate. *p < 0.05 is significant, p > 0.05 is not significant.

In our study, there was highly statistically significant difference between the initial and final Hb levels and between the initial and final level of Hct in group I.

In agreement, Sinnen (2008), stated that iron deficiency is common in predialysis patients and replenishing iron stores in anemic patients with CKD significantly increases Hb levels and should be considered as an integral part of the therapy for treating anemia in the predialysis population.

In our study, the incidence of microcytic hypochromic anemia was 35% of the whole study group i.e. 14 patients (nine patients in group I and five patients in group II), while the incidence of normocytic normochromic anemia with high iron stores (functional iron deficiency) was 40% of the whole study group i.e. 16 patients (five patients in group I and 11 patients in group II), with statistically significant difference between the two groups, with functional iron deficiency more in group II.

Johnson et al. (2007), stated that both absolute and functional iron deficiency have been associated with sub-optimal response to rHuEpo.

In our study, there was highly statistically significant difference between the initial and final Hb and Hct levels in rHuEpo-treated patients.

In our study, there was highly statistically significant difference between the two groups as regards Hb and Hct levels at the end of the study. Also, there was statistically significant difference between the two groups as regards transferrin saturation (TSAT), being more in group II.

The rate of decline of GFR (ΔGFR) did not change in group II. In contrast, the progression of CRF is already slower before T0 in group I and decreased significantly.

The slope of ΔGFR change in rHuEpo-treated group was reduced by more than 50% in 10 patients whereas ΔGFR did not significantly change in the other 10 patients. Similarly, the initial and final values of GFR did not significantly differ between the two groups. When comparing the 10 patients whose progression was slowed with the other 10 patients, the only difference is the distribution of original renal disease between the two subgroups.

Several retrospective studies comparing renal function before and after rHuEpo treatment have found no evidence that rHuEpo therapy accelerates the progression of renal failure (Kato et al., 2010) and (Gouva et al., 2004).

Dean et al. 2005, compared patients treated with rHuEpo with patients not treated with rHuEpo. The slope of the inverse of serum creatinine was lower in the rHuEpo-treated group.

Our study concluded that rHuEpo therapy is beneficial for the correction of renal anemia without worsening of blood pressure or adverse effects on renal function.
Conflict of interest

There are no conflicts of interest.

Acknowledgment

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References