Subcutaneous versus Intravenous Recombinant Human Erythropoietin Administration in Hemodialysis Patients

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Dear Sir,

Recombinant human erythropoietin (r-Hu-EPO, Cilag, Switzerland) has been shown in clinical trials to be safe and effective in treating anemia of chronic renal failure patients on hemodialysis [1]. The efficacy of intravenous r-Hu-EPO to correct anemia of uremic patients on regular hemodialysis treatment has been demonstrated in several studies [2]. Administration of r-Hu-EPO by the subcutaneous route may be equally effective [5]. However, the optimal route of administration and dosage of r-Hu-EPO has yet to be determined.

Following intravenous injection of r-Hu-EPO, high levels were reached in the serum followed by mono- or biexponential decline. An approximate half-life of 4.0 ± 0.5 h was calculated [6]. According to Cotes [7], the half-life of r-Hu-EPO in dialysis patients ranged between 2.3 and 7.34 h. Egrie et al. [8] described a half-life for r-Hu-EPO of 9.3 ± 3.2 h in hemodialysis patients after the first administration. Following subcutaneous administration, the concentration maximum was reached after 8-12 h and maintained for another 12-16 h. Subcutaneous r-Hu-EPO allowed for dose reduction as compared to intravenous therapy [5]. Thirty-six patients whose hemoglobin levels were less than 9 mg/dl and who were on regular hemodialysis three times a week for not less than 6 months at the hemodialysis unit of the Turkiye Yüksek Ihtisas Hospital were eligible for the study. The patients were randomized to either subcutaneous or intravenous administration groups. Patients with uncontrolled hypertension were excluded from the study. r-Hu-EPO was supplied by Cilag as a sterile buffered solution in vials containing 0.25% human albumin with a specific activity of 160,000 U r-Hu-EPO pro-tein/mg. Each milliliter contains 4,000 U r-Hu-EPO.

Eighteen patients in the intravenous administration group were given 50-90 U/kg r-Hu-EPO according to Hb, and 18 patients in the subcutaneous group were given 25-30 U/kg r-Hu-EPO into the thigh three times a week at the end of hemodialysis. Vital signs, such as blood pressure, pulse rate, body weight and temperature, were monitored regularly during the study. Hematological indices including red blood cells, white blood cells, platelets, hemoglobin, hematocrit, reticulocyte count, mean corpuscular volume, mean corpuscular hemoglobin concentration and also serum sodium, potassium, urea, creatinine, calcium, phosphate, albumin, bilirubin transaminase, alkaline phosphate, iron and iron-binding capacity were...
measured. Oral iron supplements (ferrous sulfate 200 mg twice daily), B12, folic acid vitamins were given routinely to all patients.
The demographic and baseline clinical parameters of the study in the two groups were similar. All patients responded to subcutaneous r-Hu-EPO injections. The hemoglobin level raised from 6.5 to 11.8 g/dl (p < 0.001), and the hematocrit level from 20.5 to 31.7% (p < 0.001) at the end of 12 weeks. In the intravenous group, the hemoglobin level increased from 6.7 to 10.7 g/dl (p < 0.001) and

Table 1. Hemoglobin levels and complications in patients on r-Hu-EPO therapy given intravenously (50-90 U/kg) or subcutaneously (25-40 U/kg) thrice a week

<table>
<thead>
<tr>
<th>BT (Before therapy)</th>
<th>AT (after therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>6.5 g/dl</td>
<td>20.5%</td>
</tr>
<tr>
<td>11.8 g/dl</td>
<td>31.7%</td>
</tr>
<tr>
<td>6.7 g/dl</td>
<td>20.8%</td>
</tr>
<tr>
<td>10.7 g/dl</td>
<td>30.9%</td>
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</tbody>
</table>

Table 1 shows the hemoglobin levels and complications in patients on r-Hu-EPO therapy given intravenously (50-90 U/kg) or subcutaneously (25-40 U/kg) thrice a week. The hemoglobin level increased from 6.5 g/dl (p < 0.001) at the end of 12 weeks. The hematocrit level from 20.5 to 31.7% (p < 0.001) at the same period. Although the dose in the subcutaneous group was half that of the intravenous group, there was no difference in antianemic effects.

In the intravenous group, we observed accelerated hypertension in 4, A-V fistula thrombosis in 1 and a transient increment in transaminase levels in 1 patient. In the subcutaneous group, there was not any of these complications. There was no significant difference in plasma urea, creatinine and electrolyte levels between the two groups. Subcutaneous r-Hu-EPO was well tolerated in our patients, and local reaction to the subcutaneous injection was minimal.

Although the bioavailability of r-Hu-EPO given by the subcutaneous route was only 22% [9], our data show that, when given thrice weekly, it induces significant erythropoiesis. Even with the half dose, the rise in hemoglobin was highly satisfactory. It was possible to achieve a rise in hemoglobin of 4.3 g/dl over a period of 12 weeks with a mean r-Hu-EPO dosage of 86 ± 7 U/kg/week. Therefore, the subcutaneous route of administration thrice a week at a low dose is a convenient, economical, safe and effective means of treating anemia in patients with end-stage renal failure on regular hemodialysis. This will be more convenient than the intravenous route, because it is cost-effective and also will allow to administer r-Hu-EPO at home and alleviate the need for repeated venipunctures.

References

114
Boran/Dalva/Yazicioglu/Cetin
Subcutaneous versus Intravenous r-Hu-EPO