Intravenous ascorbic acid in haemodialysis patients with functional iron deficiency

Sir,

We read with interest the articles by Tarng and Huang [1] and Tarng et al. [2] that demonstrated the adjuvant effect of intravenous ascorbic acid (IVAA) on the treatment of iron-overload anaemia with recombinant erythropoietin (rHuEpo).

Iron therapy is important to achieve an adequate iron status defined as transferrin saturation (TS) greater than 20%, serum ferritin greater than 100 μg/l, and serum iron greater than 80 mg/dl [3]. Some haemodialysis patients with increased iron deposits exhibit rHuEpo hyporesponsiveness due to an inadequate iron mobilization and defective iron utilization [4].

Functional iron deficiency is characterized by both low TS% and serum iron despite normal or elevated iron stores [5,6]. TS% shows circadian variations caused by wide fluctuations in reticuloendothelial iron release [7]. Nevertheless, TS% remains a reliable parameter of iron availability. In recent studies, it has been demonstrated that TS% < 20 correlates with new markers of functional iron deficiency, erythropoiesis (percentage of hypochromic red cells [%Hypo] > 3.7; reticulocyte haemoglobin (Hb) content < 26 pg and soluble transferrin receptor > 5 mg/l) [8–10].

Iron therapy in functional iron deficiency patients may represent a potential hazard leading to iron overload and consequently to haemosiderosis. Therefore, the efficacy of IVAA to circumvent rHuEpo resistance in patients with functional iron deficiency was evaluated. Vitamin C seems to favour iron mobilization from tissue stores and to increase iron utilization in the erythron [11–13].

IVAA was administered to a large number of chronic haemodialysis patients at a dosage of 500 mg thrice weekly in an attempt to obtain in patients with iron functional deficiency a similar correction of anaemia as that demonstrated by Gastaldello et al. in only four iron-overload patients [14].

Twenty-seven patients, aged 18–75 years, who were on bicarbonate haemodialysis for at least 6 months, were enrolled. Inclusion criteria were: (i) treatment with unchanged dosage of subcutaneous rHuEpo; (ii) Hb level < 10 g/dl, serum ferritin level > 300 μg/l and TS < 20%, for at least 3 months. Exclusion criteria were: (i) iron therapy or blood transfusion; (ii) active gastrointestinal blood loss or gastrointestinal malabsorption syndromes; (iii) acute inflammatory or infectious processes, (iv) hepatic disease, haemosiderosis, malignancy, uncontrolled hyperparathyroidism, inadequate dialysis dose, haemoglobinopathy and treatment with theophylline or angiotensin-converting enzyme.

The patients were randomly divided in two groups (14 vs 13 patients) to enter a cross-over trial with IVAA. I.v. vitamin C (500 mg) was administered in group I three times per week for 3 months and discontinued in the next 3 months of the study. Vitamin C was not administered during the first 3 months in group II (control group, first 3 months of the study) and was then started at 500 mg i.v. three times per week for the next 3 months. Three patients left the protocol before the end of the study, therefore 12 patients in group I and 12 patients in group II could finally be analysed.

At baseline and monthly thereafter, serum iron, total iron binding capacity (TIBC), transferrin, ferritin, blood Hb and haematocrit (Hct) were measured. Serum iron was evaluated by a colorimetric method while an immunoturbidimetric
A method was used for transferrin detection. TIBC was studied by TIBC Microtest and ferritin by a chemiluminescent immunoassay and TS was calculated.

Values of Hb, serum ferritin and TS% at the start of the study are expressed in Table 1 as means ± SEM.

Hb level and TS% increased significantly in group I after 3 months, while ferritin level decreased significantly. IVAA was discontinued in the following 3 months and at the end of the study Hb level and TS% decreased significantly while mean ferritin value did not show significant changes.

Mean Hb, ferritin and TS% values remained unchanged in group II after 3 months; mean Hb and TS% values increased significantly and ferritin decreased markedly at the end of the study. rHuEpo dose was kept unchanged during the entire study period.

Thus, our randomized and cross-over study support previous reports by Tarng and Gastaldello et al. Although our results confirm the previously reported significant increase of Hb and TS% we must underline that target Hb (12 g/dl) and TS% (50%) was not achieved. We obtained only a partial correction of anaemia and functional iron deficiency together with a reduction of serum ferritin levels within the treatment period of 3 months. The question of the efficacy of IVAA is still an unsettled issue and future studies are necessary to evaluate the adequate dose for maximum results with minimum risks. It is well known that vitamin C overdoses may cause secondary oxalosis via an increase of plasma oxalate levels and the deposition of calcium oxalate in various tissues [15,16]. Costello et al. suggested that the daily dose of AA should not exceed 150 mg. However, the standard ‘safe’ dose and the optimal duration of such a treatment have as yet to be defined [17].

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