Novel Aspects of Vitamin C in Epoetin Response

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Provision of sufficient available iron is a prerequisite to ensure the body's optimal response to recombinant human erythropoietin (epoetin). Functional iron deficiency (a state when iron supply is reduced to meet the demands for increased erythropoiesis) is a common cause of poor response to epoetin in dialysis patients who have normal iron status, even when they are iron-overloaded. Iron supplementation is not justified for this hyporesponsiveness in patients with iron overload due to the potential hazards of iron overload aggravated by intravenous iron therapy. Furthermore, *in vivo* studies have indicated that the promising effect of intravenous iron medication to overcome iron-deficient erythropoiesis is not observed in iron-overloaded hemodialysis (HD) patients. Vitamin C, a water-soluble antioxidant as well as a reducing agent, has a number of associations with iron metabolism. Recent research highlights that vitamin C can potentiate the mobilization of iron from inert tissue stores and facilitates the incorporation of iron into protoporphyrin in HD patients being treated with epoetin. Interest has turned towards the use of vitamin C as an adjuvant therapy in this field. This review focuses on the improvement of epoetin response by administration of vitamin C and discusses its clinical implications and potential issues for internal medicine doctors. [*J Chin Med Assoc* 2007;70(9):357–360]

Key Words: erythropoietin, hemodialysis, vitamin C

Introduction

The potential role of adjuvant therapies in enhancing the efficacy of recombinant human erythropoietin (epoetin) in patients receiving regular dialysis has received increasing attention in recent years.[1,2] The important reason for adjuvant therapies is that they may help to reduce epoetin requirements or allow dialysis patients to achieve increased hemoglobin concentrations, and derive more cost-effectiveness and greater clinical benefits from epoetin treatment. Recent research highlights how the use of such epoetin adjuvants as vitamin C (ascorbic acid, ascorbate), iron, androgens and L-carnitine has the potential to improve the efficiency of anemia therapy in patients with kidney diseases.[3] Vitamin C could act as a temporary iron chaperone through its chelating characteristic. Sixteen published studies during the past decade have addressed this issue.[4–19] Administration of intravenous (IV) vitamin C to hemodialysis patients with functional iron deficiency may promote better anemia control and iron utilization. This promising effect for ameliorating poor response to epoetin can be observed not only for hemodialysis patients having a high ferritin level of > 500 to 800 μg/L,[4–13] but also for those with normal iron status.[7]

Intravenous Vitamin C Improves Epoetin Responsiveness

In the first report about hemodialysis patients on epoetin therapy,[4] IV vitamin C improved hemoglobin response to epoetin in 4 patients with iron overload. Subsequently, several clinical studies by Tarng et al[8–10] and other investigators[5–7,11] reported an apparent beneficial effect of high-dose IV vitamin C in terms of a 13–24% increase in hemoglobin concentrations or a 10–32% increase in hematocrit levels and/or a 0–24% reduction in epoetin doses (Figure 1). Doses of 300 mg and 500 mg IV vitamin C 3 times a week have been used with similar efficacy,[4–11] although most were small, short-term studies that were not appropriately controlled or randomized. Nevertheless, the recent studies

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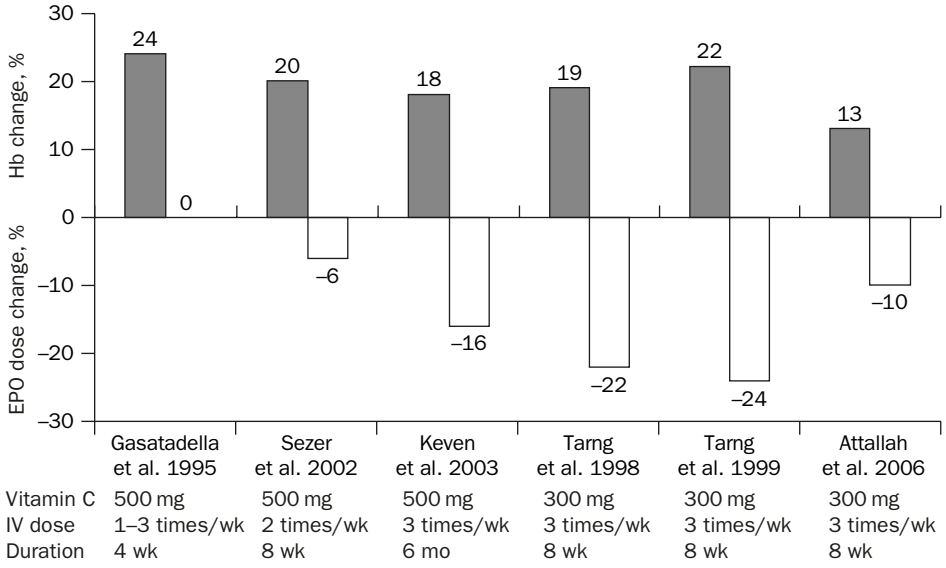

Figure 1. Intravenous vitamin C effects on hemoglobin (Hb) response (gray bars) and epoetin (EPO) dose (white bars) in patients receiving hemodialysis.

by Keven et al[7] and Attallah et al[11] seem to have been well designed and substantiate the findings of earlier investigations and the less rigorously controlled trials. IV vitamin C is not suggested as a cure for all hemodialysis patients, and Tarng et al[10] and other investigators[6,7] reported that about 49–83% of the patients were responsive to IV vitamin C. Keven et al[7] further observed that hemoglobin responses to vitamin C were the same in patients with iron overload and those with normal iron status, but the response rate (83%) tended to be greater in the former (59%).

Mechanisms of Vitamin C to Combat Epoetin Hyporesponsiveness

Vitamin C, a reducing agent, is able to release iron from ferritin and mobilize iron from the reticuloendothelial system to transferrin.[20,21] This leads to an increase of iron utilization in the erythrons. Tarng et al[19] demonstrated a decrease in serum levels of soluble transferrin receptor with a parallel rise in transferrin saturation (TSAT) within 7 days in patients receiving 2,000 mg IV vitamin C, indicating it was probably through alterations in intracellular iron metabolism. Although there is no concrete evidence to support this contention, 10 observations are at least compatible with it.[4–13] Most studies have shown a 6–15% rise in TSAT[4–13] and a 5–31% reduction in serum ferritin concentrations[5,6,10,12,13] following administration of IV vitamin C to hemodialysis patients (Figure 2). Other explanations for the positive effect of vitamin C on epoetin responsiveness include amelioration of oxidative stress and inflammation. Cumulative data show that vitamin C treatment is effective in palliating hemodialysis-induced oxidative stress, as indicated by lipid peroxidation,[22,23] and by hemolysis and overexpression of proinflammatory cytokines.[22] There are concerns that vitamin C promotes electron exchanges and it can be shown *in vitro* to enhance iron toxicity to cellular constituents. However, our study showed no compelling evidence for a pro-oxidant effect of vitamin C supplementation on DNA oxidative damage in hemodialysis patients.[24] The most recently reported study by Attallah et al[11] also showed that improvement in erythropoiesis was associated with a significant decrease in C-reactive protein levels in patients treated with IV vitamin C. Since vitamin C is a well-known antioxidant, its effect on erythropoiesis may have arisen from this property.

Potential Problems of Vitamin C Treatment in Dialysis Subjects

Major concern regarding safety of vitamin C supplementation arises from its metabolism to oxalate, which may lead to tissue deposition of calcium oxalate crystals by exceeding the threshold of its solubility, and eventually increase cardiovascular risks in uremic patients. As in most of the previous works on epoetin adjuvant therapy, vitamin C at dosages many times higher than that suggested for the general population became recommended in dialysis patients, without

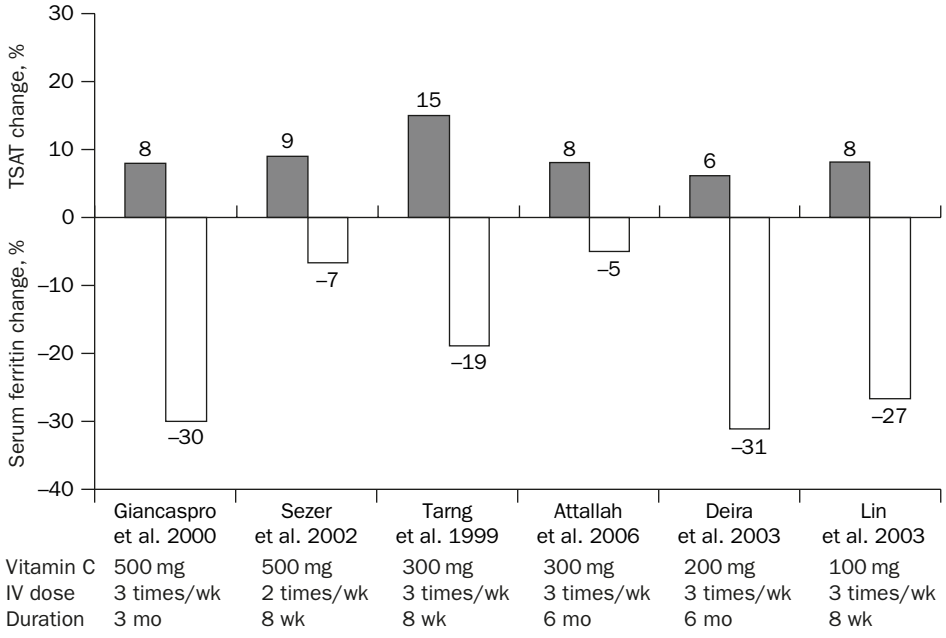

Figure 2. Intravenous vitamin C effects on transferrin saturation (TSAT) changes (gray bars) and serum ferritin changes (white bars) in patients receiving hemodialysis.

putting evidence forward to demonstrate the safety in terms of oxalate metabolism.[4–7,11–17] In the studies by Tarng et al,[8,10] there was a modest increase in plasma oxalate levels after 8 weeks of IV (900 mg per week) vitamin C treatment. A small uncontrolled study further showed an increase in serum oxalate levels by 12% or 18% from baseline in patients treated with IV (750 mg per week) and oral (1,750 mg per week) vitamin C for 8 weeks, but no significant changes in LV function or renal calculi formation.[16] The long-term risks for vitamin C-induced oxalosis remains to be determined, since these generally short-term studies[8,10,16] were too small to detect infrequent adverse events.

Low-dose IV or Oral Vitamin C Treatment

To reduce the risks of oxalosis induced by high-dose vitamin C, treatment options with low-dose IV or oral vitamin C may be considered if both could be proved safe and effective. The efficacy of IV vitamin C at doses of < 900 mg weekly has been evaluated in 3 small, non-randomized studies. A dose of 100 mg or 200 mg IV 3 times a week has shown some promise in reduction in epoetin doses or a rise in hematocrit levels in 2 clinical trials,[12,13] but the effect was not demonstrated in another one.[14] Canavese et al further showed a significant increase in plasma oxalate levels, from 35.6 μmol/L to 39.5 μmol/L and 50.3 μmol/L, with IV vitamin C 250 mg and 500 mg weekly, respectively.[25] Calcium oxalate supersaturation occurred in 40% of patients during 6 months' therapy with 500 mg weekly. Oral vitamin C can augment absorption of iron from the gastrointestinal tract. Theoretically, functional iron deficiency might be overcome by oral vitamin C substitution in patients with iron overload as it was by IV vitamin C. However, most of the clinical studies using oral vitamin C formulas failed to increase iron utilization or improve epoetin responsiveness in hemodialysis patients.[15–17] Exceptionally, a small uncontrolled study found that oral use of vitamin C with iron could increase hematocrit and serum iron levels in hemodialysis patients, but the data on epoetin dose change were not mentioned.[8] Collectively, the literature implies possible efficacy for low-dose IV vitamin C as an adjuvant therapy, but the body of evidence is not definitely conclusive.

Recommendations

Vitamin C has not been evaluated in peritoneal dialysis or chronic kidney disease patients. The optimal dose frequency and duration of vitamin C therapy remain to be established. So far, there are still gaps between theoretical knowledge and actual demonstration of benefits of vitamin C as an epoetin adjuvant in major outcomes, i.e. improvement in erythropoiesis,[4–19,26] reduction in cardiovascular mortality,[27] amelioration

of endothelial dysfunction,[28] and complications associated with secondary oxalosis. The ratio between unknown benefits and known side effects should be carefully evaluated to maintain the imperative of *primum, non nocere*. Unfortunately, many opinions about the utility of this agent in hemodialysis patients are often based on either small, short-term uncontrolled studies or cross-sectional observations. To obtain evidence for future guidelines, we clearly need additional long-term, adequately sized, randomized controlled studies evaluating the efficacy and safety of vitamin C to better define the appropriate clinical role, if any, of this therapy. However, in hemodialysis patients with poor response to epoetin if other factors have been corrected or excluded, it is reasonable to start these patients on 100 mg vitamin C IV administered at the end of hemodialysis 3 times a week for 2–6 months. If no response is seen, the dose should be titrated up to a dose of 300 mg or 500 mg IV 3 times a week for 2–6 months with careful monitoring of potential toxicity. Once serum ferritin falls to 300 μg/L, vitamin C therapy should be stopped and IV iron administration begun.[9]

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