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Research Article

Effect of pentoxifylline on the dose of erythropoietin among hemodialysis patients: A double-blind randomized clinical trial

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Abstract

Introduction: It was suggested that pentoxifylline (PTX) might improve the response to recombinant human erythropoietin (rhEPO) in anemic hemodialysis (HD) patients. However, there is no considerable evidence for it. We aimed to evaluate the effect of PTX on anemia and prescription of rhEPO dose in HD patients.

Methods: This double-blind randomized clinical trial study was conducted on 57 HD patients (54.1 ± 13.8 years old and 52.6% of them were women). Patients were randomly categorized into 2 groups (27 PTX cases and control group with 30 cases). Hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin (Alb) were measured before and after the study. Data were analyzed using SPSS, and p-value <0.05 was considered significant.

Results: Hb levels increased significantly after treatment in both groups (p<0.002). Although the mean Hb change in the PTX group was more but not significant (p=0.195). rhEPO dose decreased significantly after treatment in the PTX groups (11000.0 ± 3140.0 IU vs. 9100.0 ± 3400.0 IU, p=0.018) compared to the control (11130.0 ± 3180.0 IU vs. 10870.0 ± 3900.0 IU, p= 0.690). CRP levels significantly reduced only in the PTX group (22.8 ± 15.3 vs. 16.5 ± 9.5, p=0.005). Also, a significant increase in Alb was observed only in the PTX (3.9 ± 0.4 vs. 4.1 ± 0.3, p=0.031).

Conclusion: Using the PTX may reduce the required rhEPO dose, so it could be used in the anemia treatment in HD patients. Although, as a therapeutic strategy in HD patients with anemia it is controversial. Due to the limitations of the studies in this field, further studies with more sample size are recommended.

Keywords: Chronic kidney disease, Erythropoietin, Hemodialysis, Hemoglobin, Pentoxifylline

Introduction

Renal anemia is a major complication in chronic kidney disease (CKD), and is a problem that has yet to be overcome. This problem had been improved by the recombinant human erythropoietin (rhEPO), but some patients are relatively resistant to it and require higher doses, which is associated with increased adverse outcomes and mortality [1]. Furthermore, the consequence of higher demand for rhEPO to achieve target Hb level is costly. Some factors can be considered as the reasons of rhEPO resistance; blood loss, impaired hematopoiesis and inadequate dialysis. Moreover, there is a hypothesis that enhancement of the immune system activity in CKD patients is one of the important causes of resistance to EPO [2], and the use of anti-inflammatory drugs like pentoxifylline (PTX) may be useful as a methylxanthine derivate used for the management of chronic peripheral arterial disease that increases the blood flow to the microcirculation because of its potent hemorheological properties, which include preservation of the erythrocyte water and cation content and enhanced tissue oxygenation [3]. Also, anti-inflammatory effects, anti-apoptotic, anti-oxidant, and anti-TNF-α/anti-IFN-γ actions are important properties of PTX [4,5].

Although some non-randomized clinical trials [6,7] showed that PTX was able to increase the hemoglobin (Hb) levels in CKD patients significantly, there is no substantial evidence supporting the effectiveness of PTX for improving anemia control in hemodialysis (HD) patients [8].

an anti–TNF-α antibody provided a significant rise in hemoglobin levels [18]. Anti–TNF therapy should be administered parenterally and has been associated with severe adverse consequences. PTX is administered orally and has a low incidence of serious side effects which makes it a more reasonable adjuvant therapy for treatment of renal anemia compared to anti-TNF antibody [19].

During the current study, 3 patients of the PTX group were excluded due to adverse events. The most common side effects of the drug are gastrointestinal ones as nausea and vomiting [20] Advanced research in this area is warranted.

The PTX effect on CRP and ESR in **HD patients**

It is established that inflammatory factors, such as CRP rise in ESRD patients [21]. In the current study, all parameters related to Hb procedure, like dialysis solution, type of membrane, vascular access, and KT/V which affect inflammation [22] were the same in both groups. However, the patients were evaluated throughout the study for signs and symptoms of infection to eliminate the confounding factors in evaluation of CRP. According to our results, PTX could significantly decrease the CRP level compared to the control group which was the same as previous studies in HD patients [9,15].

PTX inhibits phosphodiesterase, causing an increase in intracellular cyclic adenosine monophosphate activity and down-regulation of pro-inflammatory cytokine synthesis. This drug inhibits the synthesis of the inflammation markers at a transcriptional level. In addition, PTX prevents proliferation of the peripheral blood mononuclear cell, adherence to the cell matrix and endothelium and T and natural killer cell cytotoxicity [23-25].

The PTX effect on Alb as a nutritional index in **HD patients**

Serum Alb levels increased significantly after treatment in the PTX group compared to the control group like other studies. Malnutrition followed by decreased serum Alb and inflammation, which is often observed in HD, which can cause the activation of oxidative stress and inflammatory response and also cause renal anemia [1,12,15,16]. PTX increase the serum Alb levels by its anti-inflammatory effect. Also, the correlation of low serum Alb with mortality in CKD patients is partly linked to its association with systemic inflammation [13,14].

Enhancement of proinflammatory cytokines such as TNF-α and IL-6 in HD patients may suppress the appetite and induce catabolism, [26,27] contributing to a wasting illness. Bologa *et al.* [28] found a significant correlation between plasma TNF-α and IL-6, and the degree of hypoalbuminemia and dyslipoproteinemia in this population.

Vaidyanathapuram *et al.* [29] indicated that single nucleotide polymorphisms in the promoter region of the proinflammatory cytokines IL-6, TNF-α and the regulatory monokine IL-10 are strongly associated with indices of comorbidity and function, as well as serum albumin in ESRD patients on long-term HD. Several immune function mechanisms are involved in this condition, including activation of oxidative stress, inflammatory response and the dialysis measure itself. As a result, PTX by prohibiting inflammatory markers may lead to improvement in the serum albumin and nutritional state of patients.

Study limitations

The most important limitations of this study were short research duration and single center accomplishment. Therefore, larger and longer studies are recommended.

Conclusions

According to the results of the present study and other researches in this field, it has been seen that the use of PTX causes a reduction in the required dose of EPO and could be helpful in treatment of renal anemia. However, it is controversial as a therapeutic strategy in CKD anemia. In addition, CRP levels as an inflammatory index were significantly decreased in the PTX group. We recommend that more trials with larger sample size should be done to clarify the PTX role in improvement of CKD anemia.

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Disclosure Statement

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Authors' Contribution

MP: Contributed to design and analysis, drafted the manuscript, finally approved it, revised the manuscript, and accepts accountability for the overall work. PA and MR: Contributed to design and analysis, revised the manuscript, finally approved it, and accepts accountability for the overall work. LM Contributed to data collection, revised the manuscript, finally approved it, and accepts accountability for the overall work.

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