Role of Pentoxifylline in Treatment of Anemic Patients Suffering Chronic Hemodialysis: a Randomized Clinical Trial

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Background: Anemia is a major problem in patients with end-stage renal disease on chronic hemodialysis. rh-EPO is used mostly to elevate serum hemoglobin level and improve complaints caused by anemia, although in some patients it may not be totally effective for treating the disease. In this study, we aimed to evaluate pentoxifylline as a drug for treating anemia.

Methods and Material: Fifty patients were enrolled in the study and divided into 2 groups. The case group took 400 mg of pentoxifylline daily for 6 months, while the control group took placebo for the same time. The levels of hemoglobin and serum albumin, TIBC, ferritin, and PTH, and use of rh-EPO were estimated. The data were analyzed using SPSS-18 software.

Results: Of the 50 patients, 33 (66%) were male and 17 (34%) were female. Student paired t tests showed no significant difference in hemoglobin and serum albumin, TIBC, ferritin, and PTH levels, or use of rh-EPO between the case and control groups. However, iron level was significantly different in the 2 groups.

Conclusion: In contrast to previous studies, our data do not support the concept that pentoxifylline elevates hemoglobin level and improves anemia. Further studies on a larger number of patients are required to assess whether or not pentoxifylline is useful in these patients.

Key words: Anemia, pentoxifylline, hemodialysis.

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1. INTRODUCTION
Anemia is a complication in patients with end-stage renal diseases (ESRD) resulting from lack of erythropoietin (EPO) caused by renal insufficiency (1). In addition, dialysis may be accompanied by loss of blood and increased need for erythropoiesis. Factors such as reduced EPO activity, decreased lifespan of RBCs, and elevation of factors that decrease the response of the bone marrow to EPO also contribute to the development of anemia in ESRD patients on dialysis (2). Untreated anemia in patients with chronic kidney disease leads to physiological disorders such as congestive heart failure, ischemic heart disease, cardiomegaly, ventricular hypertrophy, insufficient immune response, exhaustion, dyspnea, sleep disorders, sexual dysfunction, and menstrual problems, which influence the patients’ quality of life and life expectancy (3, 4).

Recombinant human EPO (rh-EPO) is used to treat these patients and has a substantial effect of improving anemia (5). Although rh-EPO improves anemia in the majority of cases, it has no benefit in some patients, who may develop permanent anemia (6). Previous studies have shown an elevation of inflammatory factors such as interleukin 6 and tumor necrosis factor-alpha (TNF-α) in chronic kidney diseases. These factors reduce iron release from macrophages, resulting in reduced amount of iron available for erythropoiesis (7). Chronic inflammation and immune system activity may also lead to resistance to rh-EPO treatment for anemia (7). Accordingly, some patients may develop anemia even following administration of sufficient doses of rh-EPO. Finding a new drug that improves anemia is therefore necessary. Pentoxifylline is an anti-inflammatory drug that inhibits non-specific phosphodiesterase (8).

In experimental models, pentoxifylline has been shown to inhibit production of TNF-α by monocytes and gamma interferon by T-cells, (9, 10). It is therefore possible that pentoxifylline plays a role in the treatment of anemia with rh-EPO because of its anti-inflammatory effects. This randomized clinical trial was designed to assess whether pentoxifylline improved anemia in ESRD patients on chronic hemodialysis.

2. METHODS AND MATERIALS
This study was carried out at Isfahan University of Medical Sciences as project number 287029. Patients satisfying the following conditions were enrolled in the study: complete acquiescence,
hemoglobin <10.7 g/l at least 2 times during hemodialysis, no history of bleeding within the previous month, and no history of infection leading to hospitalization within the previous month.

Drug intolerance, bleeding during the study, and infections that led to hospitalization formed the exclusion criteria for the study.

Fifty patients at either Alzahra hospital (the referral hospital for the Isfahan center in Iran), or hemodialysis centers at Zahra-e Marzieh and Saei hospitals were selected to participate in the study. Patients were informed about the study protocol and then divided into 2 groups (case and control), with each group containing 25 patients. The case group took 400 mg of pentoxifylline (Amin factory, Iran) daily for 6 months and the control group took placebo (Amin factory, Iran) daily for 6 months. All patients were evaluated every month for adverse effects associated with the drug such as dyspepsia, nausea, vomiting, dizziness, headache, and insomnia (11). rh-EPO used by the patients was also recorded monthly. Hemoglobin, albumin, iron, TIBC, ferritin, and PTH were checked at the beginning and end of the study.

The data were analyzed using SPSS-18 (version 18, SPSS Inc., Chicago, IL, USA), with Student’s t-test being used to compare independent quantitative data and the paired t-test to compare dependent quantitative data. The level of significance was set at p < 0.05.

3. RESULTS

Of the 50 patients, 33 (66%) were male and 17 (34%) were female. There was no significant difference in gender distribution between the case and control groups (Table 1).

Mean age of the patients was 56.5±14.3 years in the control group and 57.9±17.6 years in the case group. This difference was not significantly different (p = 0.76).

The etiology of renal failure in the patients was hypertension (24%), diabetic nephropathy (60%), polycystic kidney disease (2%), reflux (2%), nephrolithiasis (2%), and no specific cause (10%). The mean duration of hemodialysis was 28±18.4 months in the case group and 27.4±19 months in the control group, with no statistical difference between the two groups.

As seen in Table 2, there was no difference in changes in hemoglobin level between the case and control groups.

Serum albumin was 3.8±0.46 g/l in the case group and 3.9±0.46 g/l in the control group at the onset of the study, with no significant difference between the two groups (p = 0.73). After treatment, serum albumin rose to 4.2±0.43 g/l in the case group and to 4.3±0.38 g/l in the control group. No evidence of changes in serum albumin due to pentoxifylline intake was observed (p = 0.87). Changes in serum iron level during the study were -62±56.8 in the case group and -13.2±47.1 in the control group. Student’s t-test showed this difference in iron level between the two groups was significant (p = 0.005).

TIBC was measured before and after the study with changes of -37±63.4 in the case group and -34±55.5 in the control group. No influence of pentoxifylline on TIBC levels was observed (p = 0.87). PTH also did not change significantly during the study (p = 0.4) with changes of -168±200 in the case group and -312±464 in the control group. Changes in ferritin level were -20±223 and -17.5±314 in the case and control groups, respectively. There was no statistical difference between the two groups (p = 0.13).

Table 3 shows the use of rh-EPO by the patients. Comparison of the data of the two groups showed pentoxifylline had no beneficial influence on changes in rh-EPO dose.

4. DISCUSSION

This study was designed to improve anemia in patients on chronic hemodialysis. A previous study showed the effect of pentoxifylline on EPO-resistant anemia and suggested that it may reduce the serum level of interleukin-6, leading to an increase in hemoglobin level (10). Cooper et al. also demonstrated that administration of pentoxifylline and rh-EPO improved anemia in hemodialysis patients (12), while Navarro et al. showed pentoxifylline increased hemoglobin level in 7 patients with rh-EPO anemia compared to a control group (13). Another clinical trial by Johnson et al. divided 110 anemic patients on dialysis into 2 groups, with one group being administered pentoxifylline. This group showed an increase in hemoglobin level after 4 months, in addition to a decreased need for blood transfusions (14). In contrast to previous studies, we did not show significant differences in changes in hemoglobin level in the study between the case and control groups. Our data therefore suggest that pentoxifylline has no beneficial effects of elevating hemoglobin levels in anemic patients on chronic hemodialysis. The levels of serum albumin, TIBC, PTH, and ferritin also did not change significantly following administration of pentoxifylline, although serum iron level was increased in the case group. This indicates pentoxifylline may have a beneficial influence on serum iron level. Due to the differences between the findings of our study and previous studies, further investigations on a greater number of patients is required to clarify whether or not pentoxifylline has a therapeutic effect on anemia.

Conflict of interest: none declared.

REFERENCE

1. Azhir A, Nastari J, Gheisari A. Prevalence and severity of anemia in pediatric hemo-

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TABLE 2. Comparison of changes in hemoglobin levels in the case and control groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Change in hemoglobin during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>9±1.4</td>
<td>10.1±1.1</td>
<td>-1.33±1.5</td>
</tr>
<tr>
<td>Control</td>
<td>9±1.4</td>
<td>10.1±1.1</td>
<td>-0.99±1.1</td>
</tr>
</tbody>
</table>

p value 0.7 0.29 0.49

TABLE 3. EPO usage during the study

<table>
<thead>
<tr>
<th>Timing Group</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Hemoglobin changes during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>12±1</td>
<td>7.5±4.4</td>
<td>4.5±4.4</td>
</tr>
<tr>
<td>Control</td>
<td>12±1</td>
<td>8.3±3.4</td>
<td>3.7±3.4</td>
</tr>
</tbody>
</table>

p value 1 0.54 0.54

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