

Blood Pressure Increase After Erythropoietin Injection in Hemodialysis and Predialysis Patients

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Introduction. Anemia is among the most important complications of chronic kidney disease (CKD) and a lot of symptoms and signs are due to this problem. Erythropoietin injection may improve anemia, but it may cause hypertension in these patients. The aim of this study is to evaluate erythropoietin injection effects on blood pressure of hemodialysis and predialysis patients.

Materials and Methods. Forty hemodialysis patients and 40 predialysis patients with end-stage renal disease were enrolled in the study. The studied patients were comparable in terms of age, sex, hemoglobin, serum calcium, and baseline blood pressure. Erythropoietin was injected for all of the patients with anemia (4000 U, twice weekly). The effect of erythropoietin on their blood pressure was evaluated for each group by comparison of systolic, diastolic, and mean arterial blood pressure values before and 1 hour after the injection.

Results. After erythropoietin injection, systolic, diastolic, and mean arterial blood pressure values increased significantly in the hemodialysis group, and the increases were significantly greater in this group than the predialysis group ($P = .02$, $P = .01$, and $P = .02$, respectively). Blood pressure increase was significant only for the systolic component in the predialysis group.

Conclusions. Erythropoietin injection increases blood pressure levels in both groups. However, this is more significant in the hemodialysis patients as compared with patients with end-stage renal disease who have not started dialysis. Monitoring of blood pressure after erythropoietin injection is recommended.

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INTRODUCTION

Anemia is one of the most important complications of end-stage renal disease (ESRD), and a lot of symptoms and signs in dialysis patients are related to this problem.^{1,2} Anemia predicts mortality of patients with ESRD. It has many pathophysiologic effects on these patients.³ Tissue oxygenation impairment, left ventricular hypertrophy, angina pectoris, heart failure, and so many immunological problems may be induced by anemia.⁴ When kidney function drops below 30%, erythropoietin secretion reduces and it finally cause anemia. Iron, folic acid, and other supplements cannot solve this problem,

until erythropoietin administration. Anemia will be corrected remarkably by accurate administration of synthetic erythropoietin in hemodialysis patients.⁵

Erythropoietin injection may induce or exacerbate hypertension. This is an unwanted side effect in patients with chronic kidney damage, because it is hard to treat and may lead to excessive heart damage, especially cardiomyopathy.⁶ The mechanisms of these cardiovascular effects are not clearly understood and hypertension induced by erythropoietin may have a role.⁷ In normal persons, erythropoietin increases hematocrit and mean arterial pressure is increased thereafter. It is reported that increased

blood pressure is not due to increased blood volume.⁸ Some animal studies revealed that blood pressure increasing may be due to vasoconstriction, but in human subjects, vasoconstriction in the arteries is not fully characterized. On the other hand, vasoconstriction is prevented in vitro by angiotensin I antagonists.⁹ Even after removal of endothelium, erythropoietin still constricts the renal artery of rat. It may be due to circulatory and direct effects of endothelin, prostanoids, or nitric oxide.¹⁰

Treatment of anemia in predialysis patients is sometime associated with hypertension. The mechanism is not completely known, but many different factors are considered. It is reported that increasing of blood viscosity due to increased erythrocytes mass or direct endothelial promotion with erythropoietin injection may be the reason.¹¹⁻¹³ Endothelium is affected directly and indirectly by erythropoietin.¹⁴ In animal studies when erythropoietin is co-administered with anti-erythropoietin antibody, hypertension is prevented, but the erythropoietic effect is preserved so it has been concluded that hypertension is not due to erythrocyte mass increasing. This suggests that it has independent erythropoietic and hemodynamic effects.¹⁵

Erythropoietin increases endothelin-1, thromboxane, and mitogenic response in endothelial cells; on the other hand, prostacyclin is decreased. These results may be the reason of vasoconstriction and hypertension.¹⁶ Some other reports did not support the direct effect of endothelin-1.¹⁷ In experimental models, increased erythrocytes mass by erythropoietin increased renal nitric oxide production,¹⁸ but erythropoietin decreased endothelial nitric oxide synthase expression rates in human subjects; thus, nitric oxide production may be decreased.¹⁹ Endothelial nitric oxide may be decreased due to reactive oxygen species and asymmetric dimethylarginine production.²⁰

It is reported that erythropoietin exacerbates angiotensin II effects, norepinephrine effects, and endothelin-1 activity.²¹ Recently, it has been reported that increased transient receptor potential canonical channels may be the reason of increased blood pressure due to erythropoietin injection in patients with ESRD.²²

Hypertension is the most important side effect of erythropoietin injection in hemodialysis patients. Increasing of blood pressure is seen in two-thirds

of the patients and sometimes antihypertensive therapy is recommended. Hypertension is not closely related to dosage of erythropoietin.²³ Abraham and Macres, in a case-control study of erythropoietin effects on blood pressure changes in hemodialysis patients, showed that hemoglobin level in the case group increased significantly and also systolic and diastolic blood pressure was higher than those in the control group.^{24,25} However, there are some studies which have not shown any significant increasing in blood pressure after erythropoietin injection.²⁶

It is reported that erythropoietin injection in predialysis patients also increases blood pressure.²⁷ There are so many studies about erythropoietin-induced hypertension in hemodialysis patients, but the effects of erythropoietin on predialysis patients are not fully clarified. So we designed a study for comparison of erythropoietin injection effects on blood pressure of hemodialysis and predialysis groups. We compared systolic, diastolic, and mean blood pressure levels between the studied groups.

MATERIALS AND METHODS

Forty hemodialysis and 40 predialysis patients were enrolled in this study. This study was done in Sina Teaching Hospital, in Tabriz, Iran, from January 2010 until September 2011. The two groups were comparable in terms of age, sex, hemoglobin level, and serum levels of calcium, iron, ferritin, and total iron-binding capacity levels. Erythropoietin was injected for all of the patients with anemia (4000 U, twice weekly). The initial erythropoietin dose was approximately 50 U/kg to 100 U/kg per week in the predialysis patients.²⁸ The initial dose of erythropoietin varied based upon the baseline hemoglobin level, overall clinical setting, mode of administration, and the target hemoglobin level in hemodialysis patients. A large number of studies have found that there is wide inter-patient variability, as the dose of erythropoietin required to reach hemoglobin levels above 11 g/dL among hemodialysis patients ranges from less than 50 U/kg to greater than 300 U/kg per week²⁹; thus, we used an average dose of 8000 U/w in our studied patients. If the patient needed more or less than this amount due to higher or lower weight or other clinical conditions, he or she was excluded.

Systolic and diastolic blood pressure was measured before injection and 1 hour thereafter.

We measured blood pressure according to the American Heart Association Council.³⁰ According to the 7th report of the Joint National Committee, isolated systolic hypertension was considered to be present when the systolic blood pressure was 140 mm Hg and greater, while the diastolic pressure was less than 90 mmHg and isolated diastolic hypertension was considered to be the present when the systolic blood pressure was less than 140 mm Hg, but the diastolic blood pressure was 90 mm Hg and higher.³¹ On the other hand, we studied blood pressure increase in studied patients. Some of them became hypertension according to the Joint National Committee, and some of them, in spite of blood pressure increasing, were still not classified as hypertensive patients. We reported blood pressure increasing regardless of hypertensive or non-hypertensive state in the studied patients. The mean arterial blood pressure was also measured. We measured blood pressure after 20-minute resting times, with one sphygmomanometer. Blood pressure was measured by one person.

The SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA) was used for statistical analysis. Descriptive and analytic studies were done and quantitative parameters were reported as mean ± standard deviation. The Student *t* test was used for comparisons between groups. A *P* value less than .05 was considered significant.

RESULTS

Eighty patients with chronic kidney disease were enrolled in this study (40 on hemodialysis and 40 ESRD patients not on dialysis yet). Demographic and laboratory characteristic of patients are shown in the Table. Serum creatinine level was significantly higher in the hemodialysis group than in the predialysis group (*P* = .03).

The mean systolic blood pressure of the predialysis group was 133.01 ± 29.80 mm Hg before erythropoietin injection and 154.75 ± 23.96 mm Hg after injection (*P* = .01). The mean diastolic blood pressure of the predialysis group was 82.25 ± 9.99 mm Hg before erythropoietin injection and 84.75 ± 9.76 mm Hg after injection (*P* = .11). The mean arterial blood pressure in this group was comparable before (99.16 ± 16.59 mm Hg) and after (108.8 ± 14.56 mm Hg) erythropoietin injection (*P* = .09).

Demographic and Laboratory Characteristics

Characteristic	Hemodialysis	Predialysis	<i>P</i>
Age, y	46.31 ± 11.02	41.20 ± 8.11	.08
Sex			
Male	21	20	.11
Female	19	20	
Serum creatinine, mg/dL	7.12 ± 2.81	5.31 ± 3.13	.03
Hemoglobin, g/dL	8.02 ± 2.12	9.01 ± 2.13	.07
Serum calcium, mg/dL	8.51 ± 2.31	8.72 ± 2.71	.12
Serum phosphate, mg/dL	5.65 ± 0.79	5.11 ± 1.02	.03
Serum Iron, µg/dL	61.2 ± 82.3	69.3 ± 91.4	.08
Serum ferritin, ng/mL	21.6 ± 180.1	32.1 ± 179.6	.09
Total iron-binding capacity, µg/dL	310.2 ± 401.3	289.8 ± 411.9	.11

The mean systolic blood pressure of the hemodialysis group was 139.01 ± 27.34 mm Hg before erythropoietin injection and 165.50 ± 17.35 mm Hg after injection (*P* = .01). The mean diastolic blood pressure of the hemodialysis group was 84.75 ± 9.86 mm Hg before erythropoietin injection and 92.75 ± 7.33 mm Hg after injection (*P* = .01). The mean arterial blood pressure in increased from 90.10 ± 11.01 mm Hg before erythropoietin injection to 119.60 ± 7.38 mm Hg after the injection (*P* = .02).

Comparison of the systolic blood pressure increase after erythropoietin injection between the hemodialysis and predialysis groups showed that it was more prominent in the hemodialysis group (*P* = .02; Figure 1). Diastolic blood pressure changes were also more significant in the hemodialysis group (*P* = .01; Figure 2). The mean arterial blood pressure in the hemodialysis group was significantly higher than that in the predialysis group (*P* = .02; Figure 3).

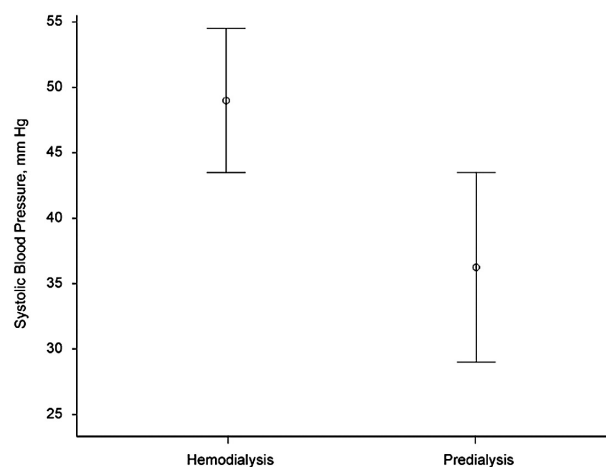


Figure 1. Comparison of systolic blood pressure increasing after erythropoietin injection between hemodialysis and predialysis patients.

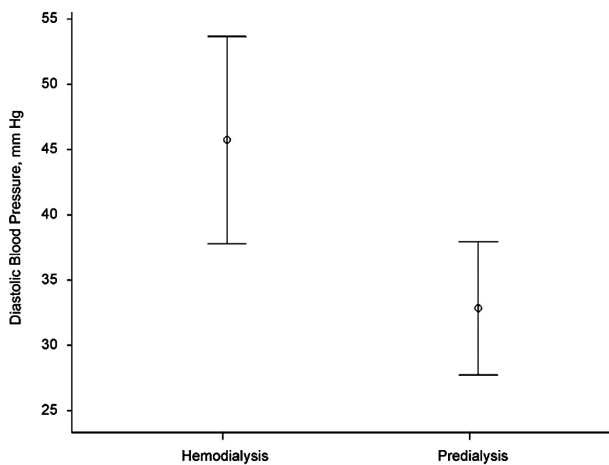


Figure 2. Comparison of diastolic blood pressure increasing after erythropoietin injection between hemodialysis and predialysis patients.

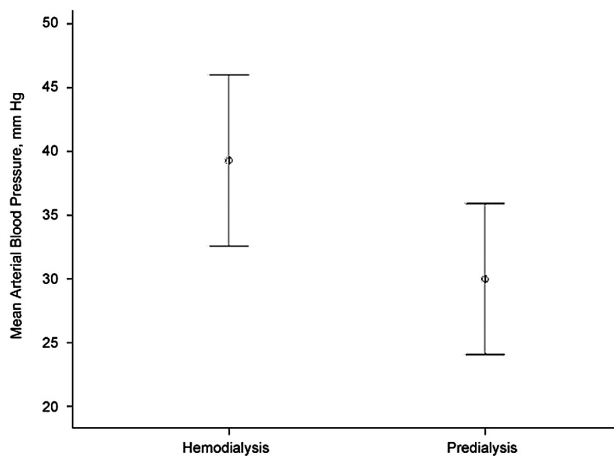


Figure 3. Comparison of mean arterial blood pressure increasing after erythropoietin injection between hemodialysis and predialysis patients.

DISCUSSION

Erythropoietin injection is an essential therapy in anemia of chronic kidney disease.² Erythropoietin, however, may increase blood pressure of the patients, and control of blood pressure is sometimes difficult in these patients.¹¹ We measured blood pressure according to the American Heart Association Council,³⁰ and found that erythropoietin injection increased systolic, diastolic, and mean arterial blood pressure in hemodialysis and only systolic blood pressure in predialysis patients.

It has been shown that about one-third of patients who receive erythropoietin intravenously for anemia of chronic kidney disease may develop an elevated blood pressure, but this is less likely after subcutaneous administration.³² Thus, we

used erythropoietin subcutaneously. Increased blood pressure has been the most commonly reported side effect in trials of treatment of the anemia of chronic kidney failure with recombinant human erythropoietin. Previous studies showed that an increase in blood pressure developed in one-third of patients, necessitating in most cases initiation or increase of antihypertensive therapy. Elevated blood pressure was not related to dose of erythropoietin, nor to the final hematocrit level achieved or the rate of increase of hematocrit.³³ Recombinant human erythropoietin therapy does not appear to affect blood pressure in patients with normal kidney function.²⁸ The mechanism of hypertension related to recombinant human erythropoietin remains uncertain.²⁴

There are so many reports which confirm increasing of blood pressure due to erythropoietin injection, but there are no studies for comparing hypertensive effect of erythropoietin injection in hemodialysis and predialysis patients.^{12,23} Comparison of our studied groups showed that increasing of systolic, diastolic, and mean arterial blood pressure were more significant in hemodialysis than predialysis patients. Navarro studied 23 dialysis and predialysis pediatric patients, and reported a mean serum creatinine level of 9.9 ± 0.9 mg/dL.³⁴ In our patients, however, serum creatinine levels was lower (7.97 ± 0.60 mg/dL). In their study, 5 of 23 patients had increased blood pressure, but in our study it was seen more frequently in adults.³⁴ Linde and coworkers studied correlation between anemia therapy with erythropoietin and some hemodynamic factors in 18 hemodialysis patients. Erythropoietin injection induced hypertension in all of the patients.³⁵ These results were similar to ours. Furthermore, Miyashita and colleagues studied the effects of erythropoietin injection on exacerbation of hypertension in hemodialysis patients. They showed that a single-dose injection of erythropoietin could increase systolic, diastolic, and mean arterial blood pressure in hemodialysis patients.² This results have been supported by other studies as well.³⁶

Tomczak-Watras and colleagues studied erythropoietin injecting effects on blood pressure of 13 patients with chronic kidney disease. The mean age of the patients was 64.8 ± 8.9 years, and the mean serum creatinine level of patients was 3.82 ± 1.30 mg/dL. They concluded that erythropoietin injection had no significant effect on blood pressure of the

studied patients. The mean age of our patients was 46.31 ± 11.02 years and serum creatinine level was 4.64 ± 1.68 mg/dL. According to our results, erythropoietin injection increased systolic blood pressure in predialysis patients which is not similar to Tomczak-Watras and colleagues' study results.³⁷

Abraham and colleagues reported the effects of erythropoietin injection on blood pressure of hemodialysis patients in a case-control study.³⁸ Blood pressure increases after erythropoietin injection, but this effect is not persistent and hypertensive effect will disappear after discontinuing of erythropoietin.³³ We studied its hypertensive effect 1 hour after injection (before presenting of erythropoietic or hyperviscosity effects). We have designed and performed another study for long-term effects of erythropoietin on blood pressure of hemodialysis and prehemodialysis patients (ongoing study). Some other reports showed that hyperviscosity is not the reason of blood pressure rising in hemodialysis and nonhemodialysis patients treated with erythropoietin.³³

Some animal experimental studies showed that increasing of erythrocytes mass and hyperviscosity is not responsible for blood pressure rising, because simultaneous administration of erythropoietin with an anti-erythropoietin antibody prevented erythropoietin-induced hypertension while erythropoietic response remained intact. They suggest that hypertensive effect of erythropoietin injection is an independent effect.¹¹ The best studied and most likely mechanisms by which erythropoietin induces hypertension in hemodialysis patients comprise changes in hemodynamics and activation of vasoactive hormone axes, namely enhanced adrenergic sensitivity and increased circulating endothelin-1 levels.³³

Hemoglobin rises after erythropoietin injection and suitable follow-up, but changes of hemoglobin will happen in longer time. Our study was done on a short-term period (before and 1 hour after erythropoietin injection). For this reason, interestingly, our results showed that erythropoietin-induced hypertension is not dependent on hyperviscosity (before inducing of hyperviscosity effects, hypertensive effect was detected). Kaupke studied 23 patients with ESRD treated with erythropoietin and after 4 weeks there was no significant increasing in their systolic and diastolic blood pressure.¹¹

CONCLUSIONS

According to the findings of our study, erythropoietin injection increases systolic, diastolic, and mean arterial blood pressure in hemodialysis and only systolic blood pressure in predialysis patients. Thus, increasing of blood pressure was more prominent in hemodialysis patients. Clinicians should be aware of blood pressure increasing and have to control it accurately. Erythropoietin-induced hypertension is not dependent on hyperviscosity. We suggest other studies with larger sample sizes. Also, this study may be performed in patients without chronic kidney disease (like hematologic patients) and results may be compared with hemodialysis or predialysis patients.

CONFLICT OF INTEREST

None declared.

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