

# Effect of Erythropoietin on Kidney Allograft Survival Early Use After Transplantation

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**Introduction.** Erythropoietin is administered for treatment of anemia in chronic kidney disease and kidney transplantation. Erythropoietin improves oxygenation of organs and prevents them against apoptosis. The aim of this study was evaluation of erythropoietin's effect on graft survival in the early phase after transplantation.

**Materials and Methods.** Forty kidney transplant candidates with a hemoglobin level of 8 g/dL to 10 g/dL were randomized to receive either erythropoietin (PD-Poietin) or placebo for the first posttransplant week. They were followed up for 6 months and serum creatinine levels, glomerular filtration rate (GFR), allograft rejection episodes, and graft loss were compared between the two groups.

**Results.** The mean creatinine level and GFR were  $1.16 \pm 0.03$  mg/mL and  $85.1 \pm 18.3$  mL/min in the erythropoietin group and  $1.2 \pm 0.2$  mg/dL and  $83.3 \pm 21.1$  mL/min in the control group at baseline. After 6 months of follow-up, the mean of creatinine level and GFR reached to  $1.11 \pm 0.23$  mg/dL and  $86.6 \pm 10.3$  mL/min in the erythropoietin group and  $1.31 \pm 0.35$  mg/dL and  $79.7 \pm 12.5$  mL/min in the control group, respectively ( $P = .04$  and  $P = .02$ ). None of the patients lost their grafts and no death was reported. There were no adverse effects in the erythropoietin group.

**Conclusions.** Our findings suggest that erythropoietin may have beneficial effects on graft function if administered early after transplantation. Erythropoietin can be used for all kidney transplant recipients for protecting the allograft due to its effects on tissue oxygenation.

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## INTRODUCTION

Erythropoietin is synthesized in the kidney and plays an important role in producing erythrocyte. Erythropoietin is administered for treatment of anemia in chronic kidney disease and end-stage renal disease patients. It is also used for anemic patients after kidney transplantation. In transplantation, the use of immunosuppressant-like

mycophenolate mofetil and sirolimus causes anemia with erythropoiesis blockade.<sup>1-3</sup> However, it is not clear whether erythropoietin is effective in the early phase after transplantation. In some studies on rat models, the remodeling effect of erythropoietin has been studied after myocardial infarction and cerebrovascular diseases such as cerebrovascular accident and vascular obstruction.<sup>3-11</sup> Their findings

demonstrated improvement of the impaired organ function and patients survival. Erythropoietin affects the target organ by stimulating cellular proliferation, mitogenesis, cytokinesis, and angiogenesis. Also, it prevents organs against cellular apoptosis. The final effect of erythropoietin is increasing the repair of damaged organ.<sup>12,13</sup>

Studies on remodeling effects of erythropoietin are limited to rat model. There are concerns that in the early phase after transplantation, erythropoietin may not have the same effect on kidney function and patient survival as it has in dialysis patients. Erythropoietin may increase blood pressure, as one of the known side effects of erythropoietin is hypertension, leading to deterioration of kidney function and acute rejection. There are a few studies of evaluating the remodeling effect of erythropoietin<sup>6,14-17</sup>; however, findings in transplantation are limited.<sup>18</sup> Therefore, we compared erythropoietin with placebo in kidney transplant patients to evaluate its effect on graft survival.

## MATERIALS AND METHODS

In a Randomized double-blinded controlled trial (registered at Iranian Registry of Clinical Trials, #IRCT138704222046N3), 40 kidney transplant patients signed the informed consent form and were enrolled in the study. The inclusion criteria were a hemoglobin level between 8 g/dL and 10 g/dL; age between 18 and 65 years old; immunosuppression with cyclosporine, mycophenolate mofetil, and prednisolone; a serum ferritin level between 100 ng/mL and 400 ng/mL; a parathyroid hormone level less than 800 pg/dL; blood pressure less than 140/90 mmHg or controlled hypertension by antihypertensive drugs; and a first kidney transplantation. Patients with the following conditions were excluded: history of cardiac disease

on medical records, malignancy, history of allergic reaction to erythropoietin, delayed graft function, complicated transplant operation by acute tubular necrosis, and panel reactive antibodies higher than 50%.

Participants were randomly divided into 2 groups to receive subcutaneous erythropoietin (PD-Poietin, Pooyesh Darou, Tehran, Iran), 2000 U, thrice per week, or placebo, after the first day of transplantation for 1 week after transplantation. The treatment was terminated if local or systemic infections were documented. All of the patients were followed up for 6 months and their baseline and follow-up clinical and laboratory data were recorded. Data on kidney function (serum creatinine and estimated glomerular filtration rate [GFR]), graft failure, adverse events, and death were collected during the follow-up. Patients with a serum creatinine rise underwent kidney allograft biopsy. Both groups received a same treatment protocol and main co-interventions included cotrimoxazole, folic acid, and carbonate calcium.

Data were analyzed by the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). The quantitative variables were demonstrated as mean standard deviation and were compared by the Student *t* test, and qualitative ones were compared using the chi-square test. *P* values less than .05 were considered significant.

## RESULTS

The mean age of the erythropoietin and control groups were  $45.4 \pm 12.2$  years and  $48.3 \pm 15.5$  years, respectively ( $P = .24$ ). 59% of patients in case group were man in contrast to 52% of control ones ( $P = .11$ ). Baseline parameters are outlined in the Table. The mean baseline serum creatinine

Baseline Data of Studied Groups

Variables	Erythropoietin Group	Placebo Group	<i>P</i>
Age, y	$45.4 \pm 12.2$	$48.3 \pm 15.5$	.24
Male gender, %	59	52	.11
Hemoglobin, g/dL	$9.0 \pm 0.8$	$8.8 \pm 0.5$	.29
Serum creatinine, mg/dL	$1.16 \pm 0.03$	$1.20 \pm 0.20$	.19
Glomerular filtration rate, mL/min	$85.1 \pm 18.3$	$83.3 \pm 21.1$	.46
Serum ferritin, ng/mL	$270 \pm 45$	$300 \pm 50$	.10
Serum parathyroid, pg/mL	$150 \pm 65$	$170 \pm 44$	.20
Systolic blood pressure, mm Hg	$115 \pm 25$	$110 \pm 20$	.35
Diastolic blood pressure, mm Hg	$85 \pm 15$	$85 \pm 10$	.55

level and estimated GFR, calculated according to the Cockcroft-Gault formula, were  $1.16 \pm 0.03$  mg/mL and  $85.1 \pm 18.3$  mL/min in the erythropoietin group and  $1.2 \pm 0.2$  mg/mL and  $83.3 \pm 21.1$  mL/min in the control group, respectively ( $P = .19$  and  $P = .46$ ). The underlying diseases related to end-stage renal disease were comparable between the two groups. All of the patients received a same immunosuppressive protocol.

After 6 months of follow-up, the mean of creatinine level and GFR reached to  $1.11 \pm .23$  mg/dL and  $86.6 \pm 10.3$  mL/min in the erythropoietin group and  $1.31 \pm 0.35$  mg/dL and  $79.7 \pm 12.5$  mL/min in the control group, respectively ( $P = .04$  and  $P = .02$ ). The mean hemoglobin levels were  $11.6 \pm 1.2$  g/dL and  $11.2 \pm 1.1$  g/dL in the erythropoietin and control groups, respectively ( $P = .44$ ). None of the patients experienced any adverse events and none had graft failure or the need for dialysis. No Mortality was reported in any of the groups.

## DISCUSSION

Our findings showed that erythropoietin had a beneficial effect on the kidney allograft after transplantation. We administered erythropoietin in the 1st week after transplantation in anemic patients. Although hemoglobin levels were not significantly different after 6 months, kidney allograft function was better in the patients who received erythropoietin as compared with placebo.

There are a few in vitro and in vivo studies of erythropoietin effect on organ remodeling for organs including the heart, the lung, and the nervous system. Ben-Dor and colleagues studied the effect of erythropoietin after myocardial infarction.<sup>4</sup> In a rat model, they administered erythropoietin in different doses and duration. They followed the rats for 6 weeks and showed that erythropoietin with a low dose resulted in better outcomes during the 6 weeks. The improvement of heart function after myocardial infarction was related to the effect of erythropoietin on decreasing tissue fibrosis and apoptosis.<sup>4</sup> Another study on rat model was published in 2007 that evaluated the effect of erythropoietin on pulmonary vessels and right ventricle function. The authors used erythropoietin for 3 weeks after pulmonary injury. They recommended that erythropoietin improved neurovascular function in heart failure and right ventricular dysfunction by moving the precursor endothelial cells.<sup>5</sup>

Schwenger and coworkers reported the effect of erythropoietin administration after solid organ transplantation.<sup>19</sup> Despite promising results of the first experiment regarding the organoprotective properties of erythropoietin, especially in ischemic animal models, little is known about the usefulness of erythropoietin administration after solid organ transplantation in human subjects. Erythropoietin has been shown to increase hemoglobin, but the optimal target level of hemoglobin is thus far unknown. Therefore, one may only speculate as to whether erythropoietin use furnishes any additional benefits with respect to organ and/or patient survival.<sup>19</sup>

In vivo studies are few or are related to other organs than the kidney.<sup>20-24</sup> Layon and colleagues studied the erythropoietin administration in early phase after kidney transplantation. They evaluated 100 patients in 2 groups.<sup>25</sup> One group received erythropoietin without steroid as immunosuppressant. The other group received erythropoietin in company with steroids. The findings showed in the second group, the incidence of hypertension was high. The authors found the difference was related to renovascular artery stenosis, which happened as cumulative effect of erythropoietin in company with other immunosuppressant.<sup>25</sup> This study did not show any significant differences between the two groups associated with erythropoietin use for a short time and minimum dosage.

The safety and efficacy of erythropoietin in chronic allograft nephropathy was studied in 2007 by Baltar and colleagues.<sup>26</sup> The erythropoietin treatment neither accelerated nor decelerated kidney allograft failure. The difference between patients in whom anemia was and was not corrected did not depend upon the previous level of hemoglobin and hematocrit, but upon worse kidney function. Finally, they concluded that erythropoietin in patients with chronic allograft nephropathy is safe and effective, and therefore, its administration should be initiated early to avoid adverse events deriving from anemia.<sup>26</sup> Molina and coworkers conducted another study about erythropoietin treatment in the 6th posttransplant month as a prognostic factor for kidney allograft survival.<sup>27</sup> They demonstrated that treatment with erythropoietin at 6 months was the only predictor of kidney function deterioration. Therefore, the need for erythropoietin at 6 months

posttransplant was a good predictor of later kidney allograft deterioration, more sensitive than serum creatinine or proteinuria.<sup>27</sup>

Lietz and colleagues evaluated the impact of pretransplant erythropoietin therapy on late outcomes of kidney transplantation.<sup>28</sup> Their findings showed the use of recombinant erythropoietin as de novo therapy or conversion from blood transfusion treatment to erythropoietin prior to transplantation was associated with a decline in late posttransplant alloreactivity and improved late kidney allograft survival.<sup>28</sup>

## CONCLUSIONS

Our data demonstrates that the erythropoietin can be effective on maintenance of kidney allograft function if it starts early after transplantation. It may be effective due to its role in organ remodeling. We suggest further study with larger samples in a longer follow-up duration to confirm these findings.

## FINANCIAL SUPPORT

Pooyesh Daru was the sponsor of this study and prepared the PD Poietin and placebo.

## CONFLICT OF INTEREST

The first and second authors are the editor-in-chief and editorial manager of the publishing journal of the article.

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