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Research Article

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Treatment of Chronic Kidney Diseases with Darpeboetin can Ameliorate Kidney Functions: A Possible Clinical Relevance

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Abstract

Background: *Erythropoietin (EPO) has been used clinically for the treatment of anemia as it was the first characterized hematopoietic factor. Erythropoietin is produced primarily by the kidneys (renal cortical fibroblasts) which induces proliferation and differentiation of erythroid progenitor cells. Previous studies suggested that erythropoietin may directly stimulates the regeneration of damaged tubular cells due to presence of erythropoietin receptors on renal tubular epithelial, mesangial and endothelial cells. EPO directly prevent glomerulosclerosis as a consequence of amelioration of podocyte injury. Therefore, to improve kidney function in chronic kidney disease (CKD), it is of critical importance to investigate clinically the beneficial reno-protective effects of EPO in patients with CKD.*

Methodology: *The study was conducted at King Abdulaziz Medical City and included patients with chronic kidney diseases. Patients were under medical treatment with Darpeboetin for the first time. The administration frequency of Darpeboetin was single dose weekly. Kidney function tests including serum creatinine, serum urea, alkaline phosphatase, serum calcium, serum phosphorus, serum albumin and albuminuria were collected from the hospital electronic medical record system (BestCareR). Test values before and after treatment were compared. of the patients before starting treatment and at the end of treatment. The week before starting treatment was considered week 0 (baseline)*

Results: *The results indicated that, treatment with a weekly single dose of Darpeboetin reduces blood urea nitrogen (BUN $p=0.002$) and serum uric acid level ($p=0.009$). The effect of treatment on serum calcium and potassium, showed a significant elevation of serum potassium ($P<0.001$), serum calcium ($P<0.001$) and adjusted calcium ($P<0.001$) levels parallel with significant decrease in serum phosphorus ($p=0.004$). Also treatment of chronic kidney disease patients significantly ameliorates serum albumin ($P<0.001$).*

Conclusion: *Treatment with Darpeboetin may confirm the reno-protective potency. Darpeboetin is a promising drug to prevent or attenuate tissues kidney damage especially in chronic kidney disease*

Keywords: Darpeboetin, Erythropoietin, Chronic Kidney disease and Renal failure

Introduction

A rapid decline in glomerular filtration rate over hours to several days, and the elevation of plasma non-proteins nitrogenous waste products are the symptoms of acute renal failure (ARF) [1,2]. Despite the use of various pharmacological agents, mortality rate of patients with ARF remains unacceptably high; amounting to 25-70% [2-5]. The great challenge in intensive care is the prevention of kidney injury as specific nephron-protective therapies are still lacking [6-8]. Amelioration of renal tubular damage or promoting tubular regeneration in patients with acute tubular necrosis remain

the major investigations to mitigate the outcome of this disease. However, to date, we did not reach level to introduce new modalities that has made appreciable clinical trend on the high mortality and morbidity rates associated with this condition [9]. Unfortunately, in the clinical setting, after the insult has already occurred, most cases of ARF can be identified. Therefore, any therapeutic agent used for ARF or renal damage would be greatly enhanced if it is still proved to be effective as reno-protective agent. Several studies have investigated the effect of several growth factors as reno-protective therapy and concluded that all have been identified as regulator of regeneration and repair of renal cells [9,10].

Erythropoietin has been used clinically for the treatment of anemia as it was first characterized hematopoietic factor [10-12]. Erythropoietin is produced primarily by the kidneys (renal cortical fibroblasts) [10,11], induces proliferation and differentiation of erythroid progenitor cells. However, in-vitro studies declared that erythropoietin effects may not be limited to bone marrow cells but it stimulates endothelial cell proliferation [10-12] and angiogenesis [10,13,14]. Also, it has been shown to exert pleiotropic properties, such as anti-inflammatory effect, anti-apoptosis and cyto-protection in liver, kidney and the central nervous system [12-15]. Studies also suggested that erythropoietin may directly stimulates the regeneration of damaged tubular cells due to presence of erythropoietin receptors on renal tubular epithelial, mesangial and endothelial cells [9,15]. This effect may activate signaling pathways which prevent apoptosis and/ or stimulate reparative proliferation of the injured cells [9,14,15]. Furthermore, erythropoietin reduces high glucose-induced oxidative stress in renal tubular cells [16]. Moreover, erythropoietin prohibited high glucose-induced renal tubular cell apoptosis. The mechanism of renal protection induced by erythropoietin has been investigated in several studies and concluded that this protective effect was dependent on the down-regulation of Bax/caspase-3 expression and elevation of Bcl-2 expression. They suggested that erythropoietin can inhibit renal tubular cell apoptosis induced by high glucose-level by direct effect on anti-oxidative stress through erythropoietin receptor [17]. Therefore, erythropoietin attenuate kidney dysfunction by decreasing apoptosis, down-regulation of pro-inflammatory mediators, TNF-alpha and IL-2, in renal injury [15].

Erythropoietin is an extremely potent stimulator of endothelial progenitor cells, so it elevates nitric oxide bioavailability, which may be critical for its renal protective effect. Therefore, erythropoietin limits acute kidney injury in part by increasing tubular cell proliferation and stimulating vascular repair [18,19]. In an experimental study, the modest reduction in tubular cast formation in erythropoietin -treated rats following renal injury is due to the cytoprotective and mitogenic effects of erythropoietin on proximal and distal tubular epithelial cells and amelioration of renal functional impairment [18]. The mitogenic and anti-apoptotic actions in non-renal and non-erythroid cells, including endothelial and gastric mucosal cells and similarly in myoblasts and Leydig cells have been previously investigated [18,19].

Park et al., [20] demonstrated that erythropoietin inhibiting TGF-beta which is the main cause behind the protective effects of erythropoietin on tubulointerstitial fibrosis and decreased renal fibrosis in mice. While Schiffer et al., [21] showed that EPO directly prevent of glomerulosclerosis as a consequence of amelioration of podocyte injury. In experimental study Hassan et al., [22] suggested that the beneficial reno-protective effects of EPO are related to increasing the levels of hypoxia inducible factor-1a.

Therefore, to improve kidney function in all other kidney diseases especially chronic kidney disease (CKD) and also for improving post-transplant graft survival, it is of critical importance to investigate the beneficial reno-protective effects of EPO in chronic kidney diseases clinically.

Methodology

Study Design

This retrospective cohort study was conducted at King Abdul-Aziz Medical City and included patients with CKD and kidney transplant patients who were subsequently diagnosed with CKD. Patients were under medical treatment with Darpeboetin for the first time. The week before starting treatment was considered week 0 (baseline). The administration frequency of Darpeboetin was a weekly single dose. The kidney function test parameters including serum creatinine, serum urea, serum calcium, serum phosphorus, serum albumin and alkaline phosphatase, and albuminuria were collected from medical record of the patients before starting treatment and at the end of treatment.

Population and Study Sample

In our present retrospective study, we have included 66 of Saudi nationals aged 20-72 years with CKD managed at King Abdul-Aziz Medical City (KAMC), National Guard.

The demographic data concerned recipients were age, gender, height, weight and body mass index and other variables follow-up for 6 months.

Data collection

Data were collected from the hospital electronic medical record system (BestCare®). Medical record review was performed according to clinical data confidentiality protection. Each patient was assigned an anonymous study number in order to take confidentiality into consideration. Kidney function test parameters including serum creatinine, serum urea, serum calcium, serum phosphorus, serum albumin and alkaline phosphatase, and albuminuria were collected from the hospital electronic medical records system (BestCare) before starting treatment and at the end of treatment. Demographic data included age, gender, height, weight and body mass index.

Statistical Methods

Quantitative variables were expressed as median (IRQ) and categorical variables as frequency and proportions. Quantitative data were compared using the non-parametric Wilcoxon paired test. A longitudinal mixed-effect analysis was conducted to identify

factors associated with Kidney function test parameters measured prior and after treatment. Variables found significant in univariate analysis were used to build the final multivariate model. All tests were two-sided and a p value <0.05 was considered significant. Data were entered in Microsoft Excel 2010 and all statistical analyses were done by using IBM SPSS (version 21.0 (OK,USA).

Results

Of the 66 chronic kidney disease patients included in this study, 30 (45.5%) male and 36 (54.5%) female, 46 (69.7%) had diabetes, and 55 (83.3%) were hypertensive. Most of the patients were in CKD stage V, 8 patients underwent renal transplant. The characteristics of the patients are shown in Table 1.

Variable	N (%)
Age, years	
>60	28(42.4)
30-60	30(45.5)
<30	8(12.1)
Sex	
Male	30(45.5)
Female	36(54.5)
Diabetes	
Yes	46(69.7)
No	20(30.3)
Hypertension	
Yes	55(83.3)
No	11(16.7)
Hyperlipidemia	
Yes	16(24.2)
No	50(75.8)
Chronic kidney disease	
Yes	65(98.5)
No	1(1.5)
Chronic kidney disease stage	
1	1(1.5)
2	
3	6(9.1)
4	14(21.2)
5	45(68.2)
Transplant	
Yes	8(12.1)
No	58(87.9)
Dialysis	
Yes	50(75.8)
No	16(24.2)
Hypertension medication	
Yes	55(83.3)
No	11(16.7)
Steroids	
Yes	38(57.6)
No	28(42.4)

Dose	
≥40	46(69.7)
<40	20(30.3)
Route of Administration	
IV	8(17.1)
SC	58(87.9)

Table 1: Baseline demographic and clinical characteristics of patients (n=66).

Assessment of renal function tests before and after Darpeboetin administration. Treatment demonstrates that there was a remarkable higher level of serum creatinine, urea, uric acid and anion gap parallel with a highly reduced level of eGFR and serum albumin (Table 2). In contrast unexpectedly, treatment with higher or lower dose of Darpeboetin-induced a significant reduction in serum blood urea nitrogen (BUN) and serum uric acid, parallel with significant increase in serum albumin and amelioration of serum calcium (Table 2, Figure 1 & 2).

Variable	n	Percentile			p
		First quartile	Median	Third quartile	
eGFR					
Before	66	6.75	12	19.25	0.457
After	65	6	11	20.5	
Creatinine					
Before	65	253.5	441	687.5	0.761
After	65	273	421	734	
Calcium					
Before	64	1.9	2	2.2	<0.001
After	59	2.1	2.2	2.3	
Potassium					
Before	65	3.7	4.3	4.8	<0.001
After	62	4.1	4.6	5.1	
Phosphorus					
Before	65	1.2	1.60	2.3	0.004
After	61	1.1	1.5	1.7	
Sodium					
Before	65	133	136	139	0.122
After	64	131	135	138	
BUN					
Before	64	14.9	23.2	30.7	0.002
After	64	11.1	17.7	24	
Albumin					
Before	63	26	30	34	<0.001
After	62	28	33.5	38.3	
Adjusted calcium					
Before	64	2.10	2.21	2.31	<0.001
After	61	2.17	2.29	2.40	
Anion GAP					
Before	62	15	18	21	0.781

After	59	15	18	20	
Serum total protein					
Before	17	49.5	56	66.5	0.123
After	18	58.8	66	74.5	
Uric acid					
Before	62	327	456.5	603.5	0.009
After	52	265	360	450	
Alkaline phosphatase					
Before	36	75.5	121.5	138.5	0.898
After	43	82	104	151	

p: Wilcoxon paired test

Table 2: Comparison of laboratory parameters before and after treatment.

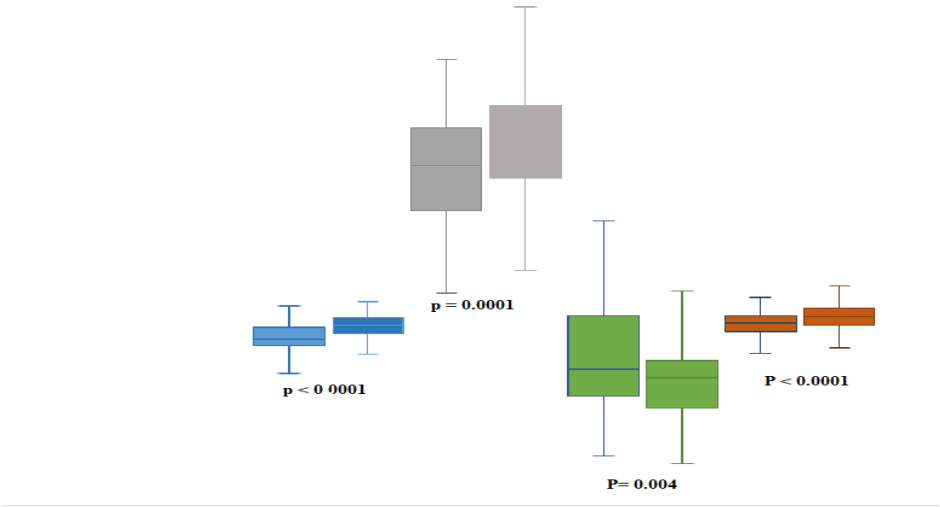

Figure 1: Comparison of before and after treatment measurements for Calcium (blue color panel), Potassium (Grey color panel), Phosphorus (Green color panel) and Adjusted calcium (Red color panel).

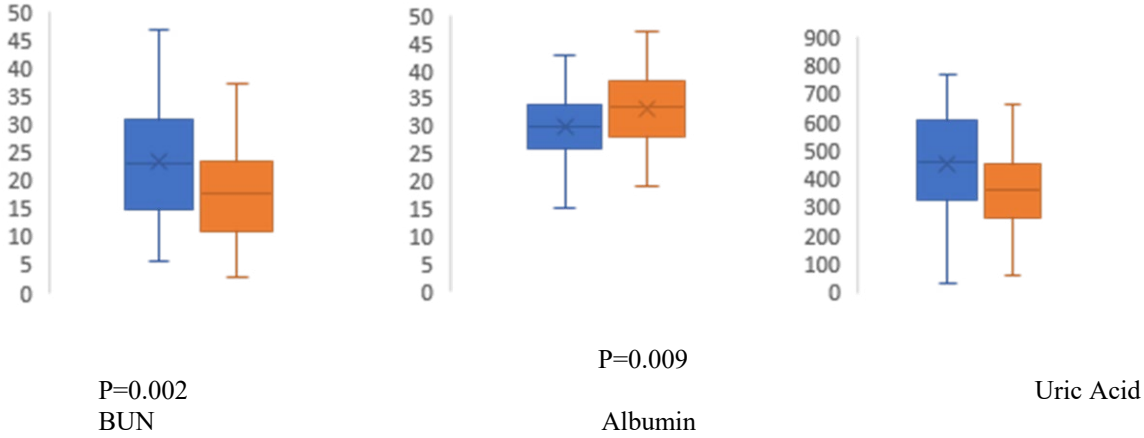

Figure 2: Comparison of before (Blue color pane) and after (Red color panel) treatment measurements for BUN, Albumin, and P>0.001 with uric acid

In longitudinal mixed-effect multivariate models, older age (>60vs<30 years; β=0.14; 95%CI -0.011, 0.29, p=0.06) was associated with increased calcium level, and a larger treatment dose (≥40vs<40 dose; β=-0.10; 95%CI -0.18,-0.012, p=0.025) was associated with decreased calcium level. In another multivariate model, patients on dialysis had increased potassium level (β=0.38; 95%CI 0.09,0.68, =0.012) compared with those who were not on dialysis. Lastly, middle age (30-60vs<30 years) was associate with increased adjusted calcium level (β=0.50; 95%CI 0.01,0.29, p=0042); Table 3.

	Calcium		Potassium		Adjusted Calcium	
Variable	**β(95%CI)**	**p**	**β(95%CI)**	**p**	**β(95%CI)**	**p**
Age, years						
>60	0.14(-0.011,0.29)	0.06	-0.04(-0.50,0.42)	0.85	0.14(-01,0.29)	0.068
30-60	0.12(-0.03,0.26)	0.11		-	0.50(0.01,0.29)	0.042
<30	1		1	-	1	-
DM						
Yes	-0.05(-0.15,0.53)	0.35	0.25(-0.06,0.55)	0.109	-0.01(-0.11,0.09)	0.920
No	1	-	1	-	1	-
Dialysis						
Yes	-0.08(-0.17.0.017)	0.12	0.38(0.09,0.68)	0.012	-0.04(-0.14,0.06)	0.384
No	1	-	1	-	1	-
Initial dose						
≥40	-0.10(-0.18,-0.012)	0.025	-0.27(-0.54,0.01)	0.054	0.02(-0.06.0.099)	0.675
<40	1	-	1	-	1	-

Table 3: Longitudinal mixed-effect multivariate models for factors associated with calcium, potassium and adjusted calcium levels.

Discussion

The results of the present study clearly demonstrate that treatment of CKD patients with human recombinant erythropoietin, single dose of Darpeboetin is associated with significantly improvement in kidney function test. As expected, impaired kidney function was confirmed by the highest level of serum creatinine and BUN. Furthermore, deterioration in renal functions were reflected by, a significant decrease in eGFR, serum albumin and serum calcium. After administration of single dose of Darpeboetin, a remarkably reduction in serum BUN together with elevated level of serum albumin, eGFR and calcium were reported. From the current study, follow-up of the kidney functions during erythropoietin treatment as serum creatinine and estimated eGFR from first month emerges as an important variable, which influences long term graft survival.

Based on current analysis of our study, a progressive increment of serum creatinine (two to three fold) together with remarkable decline (50%) in eGFR and alteration of serum electrolytes have been reported in chronic kidney diseases patients. Elevated level of serum creatinine, urea and decline in estimated eGFR are an indicator of renal damage and subsequent decline in renal survival. Results of our study, indicated that there was a significant amelioration in serum BUN and serum albumin and restored of serum electrolytes after treatment with Darpeboetin.

Renal cortical fibroblasts of the kidney can produce growth factor; erythropoietin which is cytokine regulates the differentiation and proliferation of erythroid progenitor cells [23,24]. The results of the present study are parallel with, in-vitro studies showed that erythropoietin effects may not be limited to bone marrow cells but human recombinant erythropoietin stimulates endothelial cell proliferation [23-25] and angiogenesis [23,26,27]. In addition, pleiotropic properties, such as cyto-protection, anti-inflammation and anti-apoptosis, in the central nervous, kidney and liver has been reported in different studies [25-28]. Our results confirm previous studies suggested that erythropoietin prevent tubular cells damage through stimulation of their regeneration [28,29]. As it has been reported that erythropoietin receptors are expressed on renal tubular epithelial, mesangial and endothelial cells. The mechanism explain the protective effect of erythropoietin may be through activation signaling pathways prohibit necrosis, apoptosis and/or stimulate reparative proliferation and generation of the injured cells [28-30]. Therefore, role of expression of erythropoietin receptors on renal tubular epithelial cells [28,30], may be extended the therapeutic efficacy of erythropoietin to protect kidney cell from several kidney damages mediators. Moreover, it is possible that the treatment of severe anemia associated with chronic kidney disease by erythropoietin (Eprex or Darpeboetin) can attenuate kidney damage and can be used against acute renal damage [28, 30]. The results of the present study together with previous reported pharmacological effects as Darpeboetin reduce high

glucose-induced oxidative stress in renal tubular cells [31] and prohibits high glucose-induced renal tubular cell apoptosis [32].

The molecular mechanism of this protective effect was dependent on the down-regulation of pro-apoptotic protein Bax/ caspase-3 expression and elevation of Bcl-2 expression. The anti-inflammatory effect of erythropoietin has been reported. Erythropoietin has been shown to suppress the expression of pro-inflammatory mediators, TNF-alpha and IL-2, in acute renal injury and prevent the effect of endotoxin on the antioxidant as renal superoxide dismutase. These anti-inflammatory properties of erythropoietin also may suggest the possibility of implication of the NF-kB pathway in its kidney protection [28]. While, erythropoietin potent enhancers of nitric oxide bioavailability which explain the mechanism of how erythropoietin is an extremely potent stimulator of endothelial progenitor cells. Therefore, Erythropoietin activates endothelial nitric oxide synthase, and this effect on the endothelium may be critical for its renal protective effect.

In an experimental study, it has been reported that erythropoietin attenuate toxic renal injury induced by administration of Cisplatin [30,33]. Similarly, reno-protective effect of erythropoietin was also reported in ischemia–reperfusion renal injury which is the most common cause of ARF in the community [28,30]. Due to stimulating vascular repair and increasing tubular cell proliferation, erythropoietin limits acute kidney injury [30,34, 35]. These findings suggested that protective effect induced by erythropoietin may be exerted via an interaction with the microvasculature and enhance renal perfusion, too [28,30,34,35,36].

Rjiba-Touati et al. [37] added new explanation about the mechanisms of how erythropoietin can ameliorate renal function against nephrotoxicity induced by cisplatin. She found that Cisplatin-induced oxidative stress and nephrotoxicity in rat kidney and the protective effect of erythropoietin may be mediated through decreased oxidative damage induced by Cisplatin. This hypothesis was confirmed by reduction in malondialdehyde and protein carbonyl levels and also prevention of glutathione depletion and elevation of catalase activity induced by Cisplatin treatment [37]. The inhibition of oxidative stress by recombinant human erythropoietin was confirmed by restored elevated plasma creatinine and blood urea nitrogen levels induced by Cisplatin treatment. They concluded that recombinant human erythropoietin administration especially in pretreatment condition protected rats against Cisplatin-induced renal oxidative stress and nephrotoxicity [37]. In another study Rjiba-Touati et al. [38] showed that protective effect of erythropoietin against Cisplatin-induced apoptosis in rat kidney, based on up regulation of anti-apoptotic protein expressions, down regulation of pro apoptotic protein levels, and reduction of caspase-3 activity in male Wistar rats [38]. Hence it seems that the protective action of erythropoietin on the kidney probably is not directly related to its hematopoietic effects [27,39,40]. It has been reported that in case of resistance to EPO treatment, the risk of negative outcomes in patients with CKD can be increased. The authors recommend that it is important to individualize management of anemia in these patients to identify the potential causes of resistance and implement the proper intervention for each patient before proposing an increased ESA dosage [41].

Further studies are highly warranted to investigate the molecular mechanism of reno-protective effect induced by EPO administration.

Conclusion

Treatment with Darpeboetin may confirm the reno-protective effect. Darpeboetin is a promising drug to prevent or attenuate tissues kidney damage especially in chronic kidney disease. Further studies are highly warranted to elucidate molecular mechanism of the reno-protective effect induced by Darpeboetin

Recommendations

Careful monitoring the kidney function test as serum creatinine, urea and albumin monthly among patients undergoing Darpeboetin treatment. The effect of different doses and other factors should be included.

Declaration of Conflicting Interest

The authors declare that there are no conflicts of interest.

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