Research Paper

The Effect of Discontinuation of Angiotensin-II Receptor Blocker on Therapeutic Effect of Synthetic Erythropoietin on Anemia Modification in Hemodialysis Patients

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ABSTRACT

Aims The aim of this study was to evaluate the effect of discontinuation of losartan in response to synthetic erythropoietin therapy on hemoglobin level in patients on maintenance hemodialysis.

Methods & Materials This study was a pre-and post-interventional clinical trial. The population of the study was hemodialysis patients with chronic renal failure. In the beginning of the study, and three months after removal of losartan, the patients' hemoglobin changes were compared.

Findings Hemoglobin was significantly increased at the end of the study in all patients (from 10.90±1.66 at the beginning of the study to 11.37±1.42g/dl at the end of 3 months, P=0.046). No significant changes were seen in the hemoglobin level before and after intervention between patients according age, sex, and duration of the disease.

Conclusion There was a significant increase in hemoglobin level at the end of study after losartan discontinuation. But this increase did not have a significant relationship with patient's age, sex as well as the duration of the disease.

Extended Abstract

1. Introduction

Chronic renal failure is a permanent and progressive disease which finally leads to End-Stage Renal Disease (ESRD). In addition, these patients suffer from anemia due to endogenic erythropoietin deficiency, requiring regular administration of synthetic erythropoietin. Many of these patients also have hypertension and receive various types of antihypertensive medications including Angiotensin Converting Enzyme Inhibitor (ACEI) and the Angiotensin II Receptor Blocker (ARB). There are numerous and controversial reports on the interference of these drugs with the efficacy of recombinant erythropoietin.

2. Methods

Qureshi et al. studied the effect of ACEIs and ARBs on recombinant human Erythropoietin (EPO) in patients with

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chronic renal failure (n=100, 55 males and 45 females with age range 13-78 years). who were divided into two groups [10]; one received EPO and ACEI/ARBs while other received EPO with other antihypertensive drugs. Their monthly increment in hematocrit (HCT%) was monitored for 4 months. Results showed that HCT% was significantly higher in the group received EPO with other antihypertensive drugs than ACEI/ARBs. They concluded that treatment with ACEIs/ARBs interfere with recombinant human EPO therapy for treatment of anemia even if EPO dose be high. Hence, their simultaneous use should be carried out with caution.

Saudan et al. in a study on 155 patients treated with chronic hemodialysis in Switzerland, evaluated the effect of ACEIs and ARBs on recombinant human EPO used to treat anemia in these patients [22] (Table 1). By dividing patients into five groups according to their antihypertensive treatment, prevalence of EPO resistance among groups was measured where all groups received tse same dosage. Their results showed that prevalence of EPO resistance were similar in patients treated with ACEIs (EPO resistance 12%), ARBs (EPO resistance 7%), ACEIs + ARBs (EPO resistance 10%), other antihypertensive drugs (EPO resistance 10%) and no antihypertensive treatment (EPO resistance 9%). They concluded that the use of ACEIs and ARBs has no association with the EPO resistance among hemodialyzed patients (Table 2).

Samavat et al. in a multicenter cross-sectional study, Erythropoiesis-Stimulating Agent (ESA) Hyporesponsiveness Index (EHRI) among hemodialysis patients (n=1224) and its related factors [30]. Results reported that 25% had EHRI≥16.49 with mean hemoglobin level of 9.8±1.4 g/dL. This group received higher ACEIs or ARBs compared to those had lower EHRI value (P<0.01). they recommend the discontinuation of these drugs as a therapeutic strategy to overcome ESA resistance.

Aim

The aim of this study was to evaluate the effect of discontinuation of losartan in response to synthetic erythropoietin therapy on hemoglobin level in hemodialysis patients

Study design

This study is a pre-and post-test non-randomized clinical trial.

Study population and sample

Study population consists of all patients with ESRD treated with hemodialysis in two hospitals located in Mashhad, Iran in 2018. Of this, 30 patients undergoing regular hemodialysis who had hypertension and were treated with Losartan were recruited using convenience sampling technique. No changes in the dose of EPO, iron supplements and carnitine were made for any patient one month before and during the three-month period. In addition, any serious infections (leading to hospitalization), visible bleeding, or a history of blood transfusions and its products in these 4 months, as well as any surgery and active bleeding were resulted in exclusion from the study.

Patients were monitored monthly for C-Reactive Protein (CRP) during 3 months of study and those with CRP >10 mg/L were excluded from the study. Furthermore, their serum ferritin levels were measured before the beginning of the study and those with serum ferritin level >100 ng/ml were excluded. The type and amount of the used drugs did not change and the frequency of hemodialysis and the interval between them were constant.

Measures

At the beginning of the study, venous blood samples were taken from patients for necessary tests. Moreover, losartan use was discontinued and oral antihypertensive drugs except ACEIs or ARBs was administered to control hypertension according to clinical status and therapeutic response. In all patients, CinnaPoietin® (Cinnagen, Iran) as exogenous EPO was administered intravenously at a dose of with a dose of 4000 IU immediately after completion of each hemodialysis phase. After three months, blood samples of 5 cc were taken again from vascular access line immediately before hemodialysis. Blood hemoglobin level was measured using Cell Counter Mindray BC 3000 analyzer.

3. Results

Blood hemoglobin levels were measured and compared before and 3 months after losartan discontinuation. A significant increase in hemoglobin concentration followed by Losartan discontinuation was observed in all subjects. However, in men and women, there was no significant difference in hemoglobin level at baseline and at the end of study (after discontinuation of losartan) (Table 3). Regarding the duration of hemodialysis in two groups of ≤2 years and >2 years, no significant statistical difference in hemoglobin levels was observed in any groups at baseline and at the end of study (P> 0.05) (Table 4). The effect of gender and duration of disease were also evaluated and no significant effect was observed on hemoglobin level after losartan discontinuation (p>0.05) (Table 5).

Table 1. Primary causes of renal failure in hemodialysis patients

Disease	N0. (%)
Diabetes mellitus	24(43)
Hypertension	11(19.6)
Chronic urinary tract infection and Vesicoureteral reflux	5(9)
Polycystic kidney disease	3(5.45)
Nephrolithiasis	3(5.45)
Prostatic hyperplasia	2(3.5)
Membranoproliferative glomerulonephritis	2(3.5)
Metastatic cancer	1(1.75)
Hyperoxaluria	1(1.75)
Lupus nephritis	1(1.75)
Alport syndrome	1(1.75)
Unknown	2(3.5)
Total	56(100)

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Table 2. Primary causes of renal failure in hemodialysis patients with hypertension

Disease	No. (%)
Diabetes mellitus	14(46.7)
Primary hypertension	6(20)
Chronic urinary tract infection	2(6.66)
Nephrolithiasis and high blood pressure	2(6.66)
Polycystic kidney disease	1(3.33)
Membranoproliferative glomerulonephritis	1(3.33)
Hyperoxaluria	1(3.33)
Alport syndrome	1(3.33)
Unknown	2(6.66)
Total	30(100)

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Table 3. Comparing hemoglobin levels before and after discontinuation of losartan use based on gender

Group	Phase	Mean±SD	T	P
All patients (n=30)	Before	10.90±1.56	2.089	0.046
	After	11.37±1.42		
Female patients (n=16)	Before	10.85±1.69	-1.475	0.166
	After	11.41±1.28		
Male patients (n=14)	Before	10.95±1.46	-1.636	126/0
	After	11.33±1.62		

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Table 4. Comparing hemoglobin levels before and after discontinuation of losartan use based on duration of hemodialysis

Duration	Phase	Mean±SD	t	P
≤2 years (n=13)	Before	11.02±1.71	-0.876	0.403
	After	11.33±1.55		
>2 years (n=17)	Before	10.80±1.48	-2.017	0.061
	After	11.40±1.37		

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4. Discussion

Our study showed a significant increase in hemoglobin level in all participants with the discontinuation of losartan after three months. This is consistent with the results of other studies which showed the relationship between Losartan use and hemoglobin levels in ESRD and hemodialysis patients [10, 20]. Another study showed that Losartan use in hemodialysis patients increases their need for EPO requirement [21]. However, Saudan et al. [22] showed that the use of ACEIs and ARBs had no effect on EPO resistance among hemodialyzed patients. Which is against our results.

In our study, increase in hemoglobin level had no significant association with patient's age. Aging is generally associated with oxidative stress and most chronic diseases in-

Table 5. Results of regression analysis for examining the effect of hemoglobin level

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	β		
Constant	4.723	1.612		2.930	0.007
Hemoglobin level at baseline	0.623	0.149	0.683	4.172	0.000
Age	-0.010	0.013	-0.128	-0.770	0.448
Gender	0.079	0.413	0.028	0.192	0.850
Duration of hemodialysis	0.085	0.069	0.184	1.231	0.230

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cluding kidney disease caused by an imbalance between the production of free radicals and antioxidant defense mechanisms, are linked to this phenomenon [23, 24]. Bunke et al. 's study showed that at older ages the response to treatment with recombinant human EPO is lower [25] which also shown in two studies conducted in previous years [26, 27]. However, in some studies, elderly patients were less in need of EPO use [18, 28]. In the present study, no relationship was found which can be because of low sample size.

After discontinuation of treatment with Losartan, the mean level of hemoglobin in female patients was higher than in total patients, but this increase was no significant which is probably because of the decline in the female population. In some studies, male gender and the concomitant use of ACEIs have been identified as EPO resistance factors [29]; However, Samavat et al. showed that gender has no role in preventing EPO adverse effects [30].

It is suggested that for the treatment of anemia resistant to EPO, losartan be excluded from the treatment regimen of patients and hypertension should be controlled by antihypertensive drugs based on the patient's hemodynamics. Moreover, A further study is recommended using larger sample size and randomized, double-blinded and crossover design clinical trial. Low sample size, short follow-up period, and non-random sampling

5. Conclusion

Higher levels of hemoglobin can be achieved by discontinuing Losartan in patients undergoing hemodialysis, which is not related to their age, sex, or duration of disease.

Ethical Considerations

Compliance with ethical guidelines

This study is a registered clinical trial (registration code: IRCT20190127042516N1) with an ethical approval obtained from National Committee for Ethics in Biomedical Research of Iran Ministry of Health & Medical Education (ethical code: IR.IAU.MSHD.REC.1397.028). All ethical principles were respected and nessesary permissions were obtained includig written consent.

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Authors' contributions

Preparation of initial draft, investigation, resources, and sampling by Farid Reza Ejlali (contribution rate= 30%); methodology, resources, sampling, supervision, editing and review by Mahmood Reza Khazaei (contribution rate= 30%); methodology, editing, review, and formal analysis by Zahra Mostafavian (contribution rate= 25%); methodology, editing and review by Jalil Moshari (contribution rate= 15%).

Conflicts of interest

The authors declare no conflict of interest.

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