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Original Article

Levamisole as an adjuvant to hepatitis B vaccination in patients with chronic kidney disease

Mohammad Hossein Somi[1], Mohammad Reza Ardalan[2], Majid Moghadaszadeh*[3], Masoud Shirmohamadi[1], Reza Piri[4], Mohammad Naghavi-Behzad[5]

[1] *Professor, Liver and Gastrointestinal Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[2] *Professor, Chronic Renal Failure Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[3] *Resident, Department of Internal Medicine, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[4] *Student of Medicine, Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[5] *Student of Medicine, Students Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract

Introduction: High risk of blood-borne infections is one of the problems of patients with chronic kidney disease (CKD), above which, there is hepatitis B. One of the ways to prevent this disease is vaccination against hepatitis B besides observing standard precautions. Lack of response to vaccine in uremic patients has been reported up to 33.0%. The aim of this study was to investigate the effect of levamisole as an adjuvant in improving vaccination response in patients suffering from CKD.

Methods: In this cohort study, 30 patients suffering from the chronic renal disease who had undergone levamisole plus hepatitis B vaccine were included in the study as exposed group (Group A). Then 30 equivalent patients who had just underwent hepatitis B vaccination were in the study as a unexposed group (Group B). Antibody titer against hepatitis B virus (HBV) was compared between two groups monthly, then data was analyzed.

Results: Mean age of all investigated patients was 58.1 ± 14.9 years old, and it ranged from 26 to 82. 23 patients (38.3%) were female, and 37 patients (61.7%) were male. None of the patients in both groups had a history of previous hepatitis B vaccination. Mean antibody titer was higher in group A than that of the group B after the first and second stages of hepatitis B vaccination. However, the difference between two groups was not statistically significant (P = 0.14 and P = 0.46 respectively). Also, the mean antibody titer after the third stage was 98.8 ± 61 u/l in group A and 86.2 ± 49 u/l in group B where the difference between two groups was not statistically significant (P = 0.38). Side effects resulted from levamisole was not observed in any of patients in group A.

Conclusion: According to the results it is possible to express that levamisole pill could be used as a proper adjuvant in improving the response of hepatitis B vaccination in patients suffering from CKD. However, further studies in this field are recommended according to the lack of significant difference between two groups for confirming above mentioned point.

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Introduction

Chronic kidney disease (CKD) is a progressive and irreversible disorder in renal function beside which, the ability of the body to balance liquids and electrolytes is being damaged and finally results in uremia. This disease is recognized with a progressive decrease in function of kidney tissue in a way that kidney tissue is not able to keep the internal environment of the body in long-term.[1] CKD has a high prevalence. Only in the United States of America now there are

*** Corresponding Author:** Majid Moghadaszadeh, Email: m_moghadaszadeh@hotmail.com

approximately 300000 suffering people and this population increases by about 8.0% annually.[2] This disease is considered as a health problem in terms of care and more than 60000 death cases per year happens as a consequence of renal failure. In order to decrease death rate and to increase lifetime of these patients using alternative methods of renal function is suggested among which the role of dialysis is more prominent than other methods.[3]

Patients with CKD are immunocompromised, and patients who undergo hemodialysis are highly vulnerable to several infections, due to exposure to blood products. Patients with CKD present with impaired cell-mediated and humoral immunity, reduced activities of the immune system cells (B-cell, T-cell, monocytes, macrophages…) leading to a lower seroconversion rate, a lower peak of antibody titers and an earlier decline of antibody.[4] Hepatitis B virus (HBV) infection is a serious worldwide health problem with more than 150 million chronic carriers. The frequency of hepatitis B infection has been higher in patients who undergo dialysis than in the general population because of their potential persistent exposure to blood and frequent transfusions.[5-7]

One of the preventive ways of this disease is a vaccination against hepatitis B besides observing standard precautions.[8,9] Vaccine satisfaction conducted on normal people in various studies in Iran and other countries is in favorable level, but in some groups such as uremic people up to 33.0% of lack of response to vaccine has been reported. Yet immune stability caused by vaccine is also low in these people, which could have various reasons.[10-12] Main factors for lack of proper response is aging and creatinine level. General causes of lack of proper response to vaccine (malnutrition, intravenous drug abuse, blood transfusions, genetic background) are also important in uremic patients like ordinary people.[13-15]

For people who don't properly respond to vaccine, injecting another 3-dose period is in intramuscular form, but for those who have not respond to two periods (6 doses) of vaccine, a standard method has not been suggested; in such a condition in order to overcome to this issue various methods have been suggested among which it is possible to mention to increase in vaccine dose, simultaneous prescription of zinc supplementation, levamisole, gamma interferon, interleukin-2, and intradermal injection of vaccine. Some also suggest vaccination in primary stages of development of kidney disease.[16-20]

In a study, Sanadgol et al. investigated levamisole as adjuvant for improvement of response to hepatitis B vaccination in hemodialysis patients and conclude that levamisole did not lead to significant increase in antibody titer in the second and 4th month and only anti-HBV antibody level was significantly lower immediately after HBV vaccination when it was accompanied by levamisole administration.[21]

According to published literature, it seems that there is no study conducted on effect of levamisole as adjuvant to improve response rate to hepatitis B vaccination in patients suffering from CKD in stage before starting hemodialysis.[22-24] Therefore considering above mentioned issues on effect or lack of effect of adjuvant as supplementation alongside with hepatitis B vaccination in CKD patients in one hand, and considering dangers and complications caused by resulted infections in hemodialysis patients on the other hand, in order to improve seroprotection we tried to study and investigate the effect of levamisole as an adjuvant on chronic kidney failure patients before starting hemodialysis stage.

Methods

In this cohort study, 30 patients suffering from chronic renal disease (glomerular filtration rate < 60 ml/min per 1.73 m^2) who had undergone levamisole administration plus hepatitis B vaccination and did not undergo hemodialysis, with negative HBV antigen were included in study as exposed group (Group A) after writing a written consent. All of these patients had undergone

levamisole administration due to their physicians' prescription. Then 30 equivalent patients suffering from the chronic renal disease (glomerular filtration rate < 60 ml/min per 1.73 m^2) who had undergone only hepatitis B vaccination were included in the study as unexposed (Group B). Place of study was Nephrology Clinic and Gastroenterology Research Center of Imam Reza Educational-Medical in Tabriz University of Medical Sciences, Iran. Duration of study was 15 months and data collection, evaluation of patients, and data analysis started from June 2012 to August 2014.

Both groups A and B were included in the study. After acquiring consent in 15 months-time duration after plan approval, all of the patients were followed-up intensively. In order to determine sample size results of a study of Demir et al.[25] was used. Considering 90% power and $\alpha = 0.05$ and acceptable clinical changes in rate of primary outcome (improvement of antibody titer against HBV) a 54 sample size was calculated and in order to increase study validity a size of 60 patients (30 patients for each group) was considered. It should be mentioned that patients of two groups were similar in terms of age, sex, and other involved factors so there were no statistically significant differences. Selection of studied people among patients suffering from CKD with all inclusion criteria was randomized (method of randomized numbers table). Random assignment of subjects into one of the study groups was done using the rand list software.

Group A were prescribed 100 mg of levamisole pill daily as an adjuvant for 12 days as oral (6 days before and 6 days after each vaccination), besides vaccination. Levamisole pills used in this study were 50 mg pills of Tehran Poursina Pharmaceutical Company, Iran. In all patients, we investigated hepatitis C virus (HCV) antibody, hepatitis B core antibody (HBC Ab), hepatitis B surface (HBs) antigen, HBs Ab, and human immunodeficiency virus antibody (HIV Ab) at the start of study. After triple injection of 40 µg of recombinant HBV vaccine at 0, 1, and 6 months antibody titer was investigated again in 1-month intervals after each vaccination in both groups. We compared results between two groups of patients. In this study, primary outcome was defined as an increase in antibody titer more than 10 u/l (responder). Patients with positive antigen for HBV, symptoms of other systemic diseases and autoimmune diseases, history of using immunosuppressive and steroid drugs, and immunodeficiency cases such as HIV were excluded from the study.

Obtained results were presented as mean ± standard deviation (SD) and also as frequency and percentage. Employed statistical software was SPSS (version 16, SPSS Inc., Chicago, IL, USA). To compare quantitative variables Student's t-test was used and for qualitative variables chi-square and Fisher's exact test (if needed) was used. In all study cases, results were considered statistically significant if $P < 0.05$.

Results

All participants were present in the investigation up to the end of the study. Mean age of all participants was 58.1 ± 14.9 years old and age ranged from 26 to 82 years old. Also as separate groups, mean age of group A was 61 ± 14 years (ranged from 30 to 82) and that of group B was 55.1 ± 15.3 years (ranged from 26 to 80) which had no statistically significant difference ($P = 0.12$). Totally, 37 people (61.7%) of patients were men and 23 people (38.3%) were women, in group A there were 17 men (56.7%) and 13 women (43.3%). Also in group B, there were 20 men (66.7%) and 10 women (33.3%). Again there was not statistically significant difference between two groups ($P = 0.59$).

None of the patients of two groups in A and B groups had vaccination history against hepatitis B. Cause of CKD in most of patients of two groups was diabetes and hypertension. Only in 2 cases (6.7%) of patients of group A, the cause of CKD was kidney stone and consequent recurrent urinary tract infections, and also in three cases (10.0%) of patients of group B the causes of CKD were urinary reflux, kidney stone, and unknown reason. The cause of

CKD in patients of both groups has been investigated and compared the description of which, has been presented in table 1 with details and numerical value of P.

Among total 60 patients investigated in two groups. 10 cases (16.7%) had not referred in the first round of antibody titer check and 9 cases (15.0%) had not referred in the second round of antibody titer check. The third round of antibody titer check was conducted for all patients of both groups. Totally after the first and second stages of vaccination, only 4 cases (16.7%) of patients of group A and 6 cases (23.1%) of patients of group B were non-responder (had antibody titer < 10 u/l) and difference between two groups was not statistically significant (P = 0.41). In the third round of vaccination (completion of hepatitis B vaccination course), 55 patients had criterion of antibody more than 10 u/l, so it is possible to express that 91.6% of patients were responder to vaccine. Description of antibody titer has been presented in table 2 with details and the numerical value of P.

In patients of group A, changes in values of liver enzymes were compared before and then and description of its details and their comparison in group A are presented in table 3 with numerical value of P. Adverse effects and drug side-effects such as diarrhea, nausea, swelling and pain in joints, anxiety, dizziness and headaches, insomnia, itching and inflammation of the skin, and nervous disorders was observed in none of levamisole pill users of group A.

At the end of the study none of patients in two groups reached end stage renal disease (ESRD) level and there was not need to renal replacement therapies such as hemodialysis.

Discussion

As it was mentioned, studies have shown that CKD patients and hemodialysis patients do not represent a proper response to hepatitis B vaccine due to humoral and cellular immunodeficiency.[25] In this study like most of the studies, the acceptable response to hepatitis B vaccine has been considered as hepatitis B anti-surface antigen-antibody titer higher than 10 u/l. In a similar study, levamisole effects on improving the response to hepatitis B vaccination in hemodialysis patients were studied.[10]

Table 1. Comparison of CKD causes between two groups

Investigated value	Exposed group (n = 30)	Unexposed group (n = 30)	P
	n (%)	n (%)	
Diabetes	10 (33)	9 (30.0)	0.38
Hypertension	6 (20)	11 (36.7)	
Hypertension + diabetes	12 (40)	7 (23.3)	
Other mentioned causes	2 (6.7)	3 (10.0)	

CKD: Chronic kidney disease

Table 2. Comparison of antibody titer after vaccination between two groups

HBs Ag	Exposed group (n = 30)	Unexposed group (n = 30)	P
	mean ± SD (minimum-maximum)	mean ± SD (minimum-maximum)	
After the first round of vaccination	22.9 ± 16.9 (0-57)	16.6 ± 12.6 (0-45)	0.14
After the second round of vaccination	51.3 ± 34.2 (12-147)	45.2 ± 23.0 (12-98)	0.46
After the third round of vaccination	98.8 ± 61.0 (28-213)	86.2 ± 49.0 (15-198)	0.38

SD: Standard deviation; HBs Ag: Hepatitis B surface antigen

Table 3. Comparison of changes in values of liver enzymes in intervention group A

Studied variable	Before intervention	After intervention	P
	mean ± SD (minimum-maximum)	mean ± SD (minimum-maximum)	
AST value	27.8 ± 10.7 (12-48)	23.8 ± 8.7 (14-54)	0.15
ALT value	27.2 ± 8.6 (12-43)	26.2 ± 6.8 (12-41)	0.82
ALKP value	202.5 ± 39.4 (145-335)	191.3 ± 22.1 (146-235)	0.43

AST: Aspartate transaminase; ALT: Alanine transaminase; ALKP: Alkaline phosphatase

In 12 months, period HBs Ab negative and HBC Ab negative hemodialysis patients from four dialysis centers were investigated in two groups. In this study, besides vaccination of two groups in group A, 100 mg levamisole pill was administered to patients after each dialysis session. In this study, 81.6% of patients of levamisole group and 81.3% of placebo group had responded to vaccination and there was no statistically significant difference between two groups.[10]

In another study patients of two groups had no statistically significant difference in terms of hemodialysis duration and weight indexes.[10] The disadvantage of this study was the fact that the effect of levamisole had been investigated in hemodialysis patients' group and that patients of two groups had not been compared in terms of resulted antibody titer. In the present study, against study of Sali et al.,[10] the effect of levamisole on CKD patients who had not reach ESRD level were investigated and it is possible to say that humoral and cellular responses in these patients have been maintained partly. Also, the used levamisole in our group A, was daily 100 mg oral for 12 days as 6 days before and 6 days after each vaccination session. In our study, antibody titer level at the end of the study was 98.8 ± 61 u/l for levamisole group and 86.2±49 u/l for group B, whose difference was not statistically significant. In our study like the study of Sali et al.,[10] patients had not significant statistically difference in terms of weight indexes, history of disease, and smoking, and they were similar.

In another study by Somi and Hajipour, the role of various adjuvants in improving the response of hepatitis B vaccination has been investigated and it was concluded that levamisole has an important role in improving the response of hepatitis B vaccination of patients.[3] Therefore according to the background,[26] levamisole adjuvant has been used in the current study as supplementation in CKD patients. In another study on effect of adding levamisole on seroconversion response to HBV vaccination in hemodialysis patients and it was concluded that antibody titer level against HBV in patients receiving levamisole was even lower than that of group B but has not had statistically significant difference.[21]

Results of the study of Sanadgol et al.[21] is against of the results of studies of Sali et al.,[10] Somi and Hajipour[3] and Alavian and Tabatabaei.[26] In the study of Sanadgol et al. levamisole pill has only been suggested for patients who had no response to hepatitis B vaccination (non-responder).[21] Argani and Akhtarishojaie investigated the effects of oral levamisole on improving immunologic responses of hepatitis B vaccination in chronic hemodialysis patients and concluded that adding levamisole to intramuscular hepatitis B vaccine in chronic hemodialysis patients leads to 30.0% increase of response in the 1st month (the first round of vaccination) and 60.0% increase of response in the 6th month (the third round of vaccination).[27] In the current study also 83.3% of patients of levamisole group and 76.9% of patients of group B had proper response to the first round of vaccination, which is approximately in accordance with the results of studies by Sali et al.[10] and Argani and Akhtarishojaie.[27]

In a study of levamisole treatment effect on protective antibody response to hepatitis B vaccination in hemodialysis patients it was concluded that levamisole treatment increases the response rate to the first hepatitis B vaccination and that of the previously unresponsive cases by modifying possible cellular immune response.[28]

About side-effects of hepatitis B vaccination and levamisole pill in different investigations, ignorable issues have been reported.[29] Of these side-effects, it is possible to mention to itching, hyperpigmentation, myalgia, headache, and nausea which in none of the studies were in a level causing to stop injecting the vaccine or levamisole pill.[30-32] Furthermore in our study, vaccination was stopped in none of the cases due to possible side-effects. No specific side-effect of using levamisole pill was observed in group A. Also, patients were monitored during follow-up period for hepatic drug metabolism in terms of changes in live enzymes and no disorder

was observed in patients of group A.

Conclusion

According to the obtained results it is possible to express that levamisole pill could be used as one of the appropriate adjuvants in improving response to hepatitis B vaccination in chronic renal disease patients, but considering the lack of significant difference between two groups to verify this claim, further studies are suggested in this field.

Conflict of Interests

Authors have no conflict of interest.

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