Original Article

Evaluation of Antibody Responses in Hemodialysis Patients, Peritoneal Dialysis, Kidney Transplant Recipients and Normal Subjects after Administration of 23-Valent Pneumococcal Polysaccharide Vaccine

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Received: 06 June, 2019; Accepted: 09 November, 2019

Abstract

Background: Pneumococcal vaccines are recommended in patients with immune deficiencies such as kidney transplant recipients and dialysis subjects. *Streptococcus pneumoniae* is an agent of pneumonia, meningitis, important morbidities and mortality in such patients. The purpose of this study was to evaluate and compare the antibody responses in hemodialysis patients, peritoneal dialysis, kidney transplant recipients and normal subjects after administration of 23-valent pneumococcal polysaccharide vaccine (PPV23).

Materials and Methods: The present randomized clinical trial was conducted on 162 subjects including 57 hemodialysis patients, 29 peritoneal dialysis patients, 48 kidney transplant recipients, and 28 healthy controls. The participants received a single-dose pneumococcal vaccine (Pneumovax 23) of 0.5 ml in the upper limb muscle. The efficacy of vaccination was evaluated by measuring the antibody response to the entire vaccine. Serum samples were collected before, one and six months after vaccination.

Results: The levels of IgG pneumococcal antibodies at pre-vaccination periods, one and six months after vaccination were 11.6±1.52 IU/ml, 14.98±1.98 IU/ml and 14.87±0.66 IU/ml in kidney transplant recipients, 12.03±1.93 IU/ml, 15.26±0.49 IU/ml and 14.3±0.72 IU/ml in hemodialysis patients, and 11.5±1.55 IU/ml, 15.2±1.81 IU/ml, and 14.2±1.7 IU/ml, respectively. The serum antibody level was significantly higher in kidney transplant recipients than in both dialysis groups after six months of vaccination (p=0.029).

Conclusion: We found that patients with renal failure respond to pneumococcal vaccination in hemodialysis and kidney transplantation. However, they lost their serum antibodies within six months of vaccination. Determining the protective level for serum IGG and IGG2 in these patients helps us to follow up on these patients more precisely in order to re-vaccinate when the protective level of serum antibody is broken.

Keywords: Pneumococcal vaccination, Immunogenicity, Kidney Transplant Recipients, Dialysis

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Please cite this article as: Argani H, Rostamiasl A. Evaluation of Antibody Responses in Hemodialysis Patients, Peritoneal Dialysis, Kidney Transplant Recipients and Normal Subjects after Administration of 23-Valent Pneumococcal Polysaccharide Vaccine. Novel Biomed. 2020;8(1):36-44.

Introduction

Pneumococcal infection is one of the major causes of morbidity and mortality in the world[1]. Pneumonia, bacteremia, sepsis, and meningitis are the most common manifestations of invasive pneumococcal disease; the hematogenous spreading of the bacteria causes a minimally-invasive middle ear infection,

sinusitis, and chronic bronchitis[2]. In contrast to invasive infections, non-invasive infections are less severe but more prevalent. Although all age groups are affected, there is a high prevalence of pneumococcal infection in adolescents and the elderly. In addition, people with various chronic illnesses and immune deficiencies are at risk[3]. The pneumonia is a common infection in dialysis patients and with an incidence rate of 21% per year in a study of 289,000 hemodialysis patients. More than 80% of dialysis patients with pneumonia have no known microbial agents, and approximately 50% of such patients will die within 12 months[4]. Although the proportion of pneumococcal pneumonia is unclear in the incidence and mortality of pneumonia in the dialysis patients, the administration of pneumococcal vaccine seems to be logical in reducing this high mortality rate[5]. As one knows, the uremic environment in dialysis patients and the use of immunosuppressive drugs in the transplant patients cause immune deficiency and contribute to reducing the antibody response and host serum changes to vaccination[6]. As a result, the level of adherence and willingness to vaccinate is reduced in these patients. For example, in a study on 683 hemodialysis patients, only 44% received the pneumococcal vaccine[7], which, of course, seems to be much less in our country, Iran. Therefore, this low tendency to vaccination appears to be due to the lack of information on the pneumococcal vaccine in these patients[8]. Although a decrease in the protective level of the antibody has been reported after pneumococcal vaccination in some studies[9-11], multiple studies have shown that vaccination is effective in this group of patients[12,13].

Therefore, given the high risk of infection in these patients and the probability of mortality, and since this topic has never been investigated in the country so far, the current study was conducted to evaluate the antibody response in hemodialysis patients, peritoneal dialysis, kidney transplant recipients and normal subjects after the administration of PPV23 (23-valent pneumococcal polysaccharide vaccine).

Methods

This clinical trial was performed on 105 hemodialysis patients, peritoneal dialysis subjects, kidney transplant recipients and normal people referred to the hemodialysis center of Modarres Hospital and Kidney Transplantation Clinic and Shafa Clinic in Tehran. The sample size in this study was calculated based on the study conducted by Monika Lindemann et al.[14], who only compared the antibody titer against pneumococci in kidney transplant recipients before and after the vaccination and used median and IQR (interquartile range) to obtain sample size. In this approach, the assumption was that the distribution of data was normal and the standard deviation was considered to be approximately 3.4 IQR. Considering the small sample size, 10% was added to the final sample size for highly skewed distributions. Accordingly, the sample size was calculated to be 105. In this study, the patients were divided into four groups including 20 peritoneal dialysis patients, 40 hemodialysis patients, 20 kidney transplant patients, and 25 healthy subjects. Exclusion criteria were the lack of cooperation of the patient in the timely attendance and unwillingness to participate in the study and taking samples. A blood sample was taken before the vaccination from all eligible subjects by observing ethical considerations, and then demographic information and follow-up profiles were recorded. A single-dose of PPV23 was injected at zero time and the next blood samples were taken one and six months later. The serum blood samples of the patients were analyzed for pneumococcal antibodies in the months 0, 1 and 6 months after vaccination with Human Anti-Pneumococcal CPS23 IgG ELISA Kit in a Pathobiology Laboratory in Tabriz city.

Attained data were analyzed by SPSS version 21 software using the Kolmogorov-Smirnov test to evaluate the normal distribution of data, Mann-Whitney and Log Transformation test to assess nonparametric variables, ANCOVA test to study the effect of confounding factors and the difference in the baseline values of metabolic parameters and others between the groups. In all stages, $P<0.05$ was considered as a significance level.

Results

In this study, 162 people were included in the study. The minimum age of the person entering the study was 21 years and the maximum age was 74 years. The study examined 28 healthy subjects (17.3%), 29 peritoneal dialysis patients (17.9%), 48 kidney transplant recipients (29.6%) and 57 hemodialysis subjects (35.2%). The mean age of the subjects in the study was

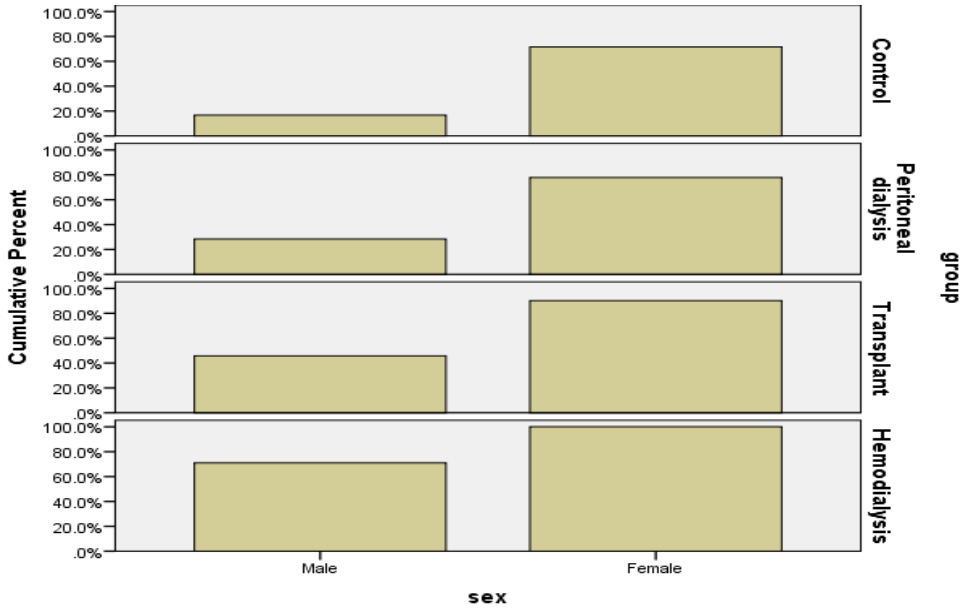

Figure 1. Gender distribution of the participants in different groups under study.

46.7±11.43 years. The ANOVA test showed a statistically significant difference in the mean age between the participants in the study (P=0.01).

The results of Tukey's post hoc analysis showed no significant difference between the control group and the peritoneal dialysis group (P=0.17), but the significant difference between the control group and the transplant group (P=0.013) and the hemodialysis group (P=0.012).

The study population consisted of 115 men (71%) and 47 women (29%). The results revealed no statistically significant difference in the mean age between women and men participating in the study.

In evaluating the concentration of PPV23-derived antibodies in the studied groups, the results showed that the distribution of this antibody in the sample was normal in the first measurement and sample distribution was non-normal in the remaining two doses (P<0.05). The mean, standard deviation, median, and Interquartile range of these variables are presented in Table 2.

Table 2 exhibits that one-way ANOVA showed no difference in antibody concentration between different

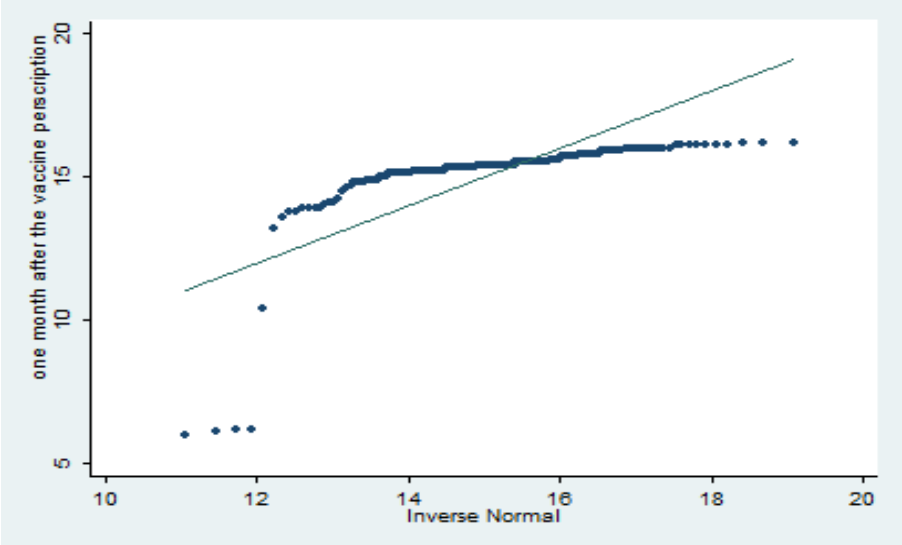

Figure 2. Distribution of antibody concentration variable in the second dose for all subjects.

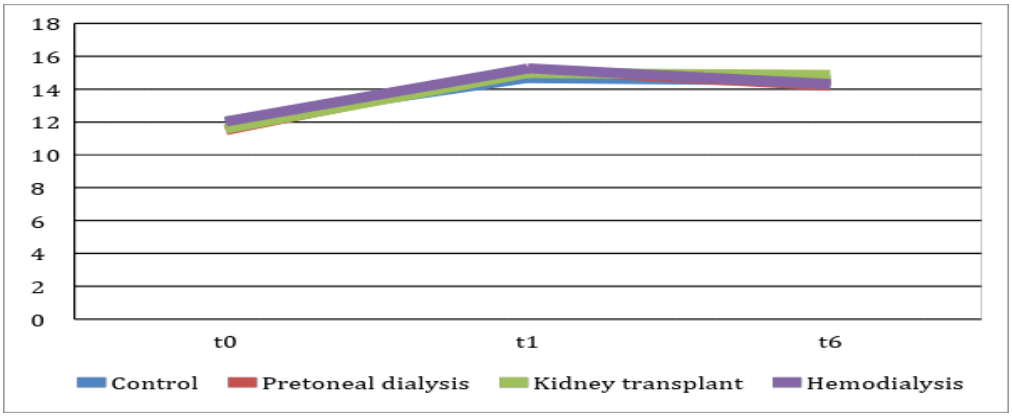

Figure 3. Changes in serum anti-streptococcal antibodies in subjects participating in the study.

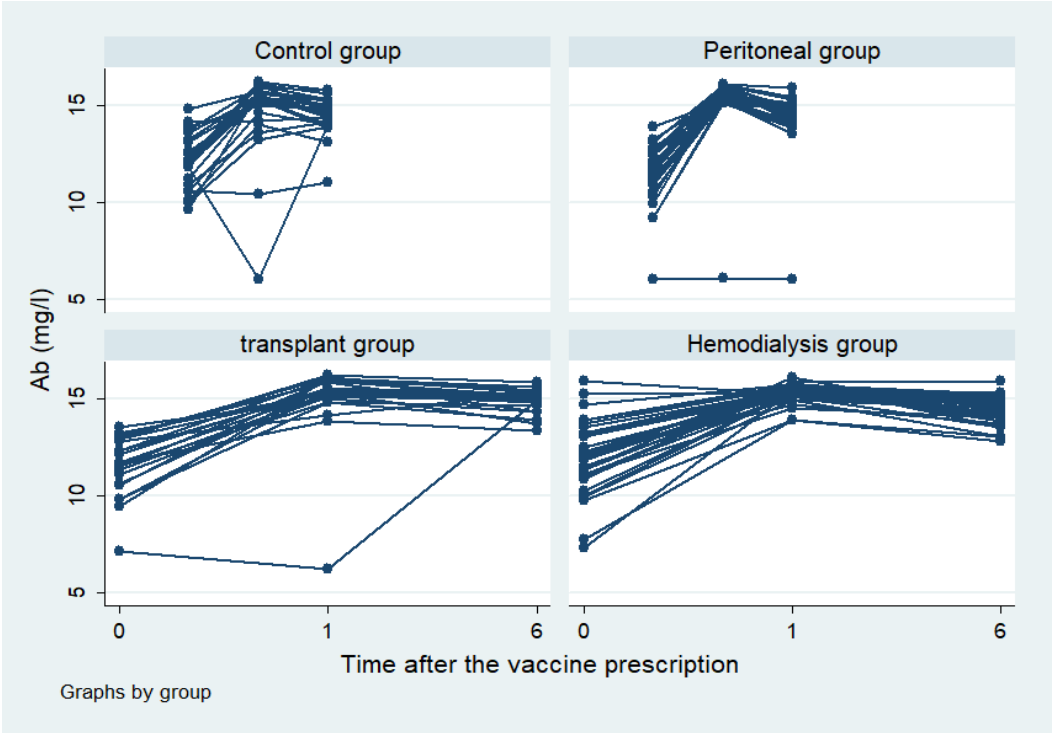

Figure 4. The trend of changes in the level of anti-pneumococcal antibodies 23 in different groups.

groups at zero time (P=0.3). Moreover, the results of the nonparametric Kruskal-Wallis test indicated that there was no difference between the mean concentrations of PPV23-derived antibodies after one month of vaccination.

In examining the difference in the antibody concentration after six months of vaccination, the results showed that there was a significant difference between the groups and this difference was between the peritoneal dialysis, kidney transplant and hemodialysis groups (P=0.029).

The repeated-measures ANOVA was used to evaluate the effect of vaccination on the serum antibody level in comparison with the control group in the first approach. Figure 4 displays the trend of changes in the serum antibody levels secreted in all four groups.

As shown in Figure 3, an increase in serum antibodies occurred after a month of vaccination, which was accompanied by a slight decrease in the next five months. Figure 4 displays the process of separate changes in each group.

Further, in examining the significant difference between the anti-PPV23 antibody concentrations over time, the results of repeated measures ANOVA by

Table 1: Statistical comparison of the age between the participants in the study.

Group	Frequency	Mean ± SD	P-value
Control	28	4.03±10.4	
Peritoneal Dialysis	29	46.4±10.5	0.01
Kidney transplant	48	48.5±9.7	
Blood dialysis	57	46.7±11.4	

Table 2: Mean, standard deviation, median and interquartile range of antibody concentration in different groups at zero, one month and six months after vaccination.

Time	Group	Mean ± SD	Median (IQR)	P-value
zero	Control	12±1.32	12.1 (11.2-13.1)	0.30
	Peritoneal Dialysis	11.5±1.55	11.8 (11-12.45)	
	Kidney transplant	11.6±1.52	11.7 (10.6-12.9)	
	Blood dialysis	12.3±1.93	12.1 (11.1-13.2)	
	Total	11.82±1.66	12 (11.1-13)	
one month	Control	14.68±2.14	15.35 (14.6-15.7)	0.36
	Peritoneal Dialysis	15.2±1.81	15.45 (15.2-15.9)	
	Kidney transplant	14.98±1.98	15.4(15-15.9)	
	Blood dialysis	15.26±0.49	15.4 (15.1-15.5)	
	Total	15.07±1.16	15.4 (15.1-15.7)	
six months	Control	14.5±0.97	14.7 (14-15.2)	0.015
	Peritoneal Dialysis	14.2±1.7	14.45 (14.05-14.9)	
	Kidney transplant	14.87±0.66	15 (14.6-15.3)	
	Blood dialysis	14.3±0.72	14.3 (14-14.8)	
	Total	14.5±1.01	14.7 (14.1-15.1)	

comparing the age of the participants in the study showed that the changes in the serum level of anti-pneumococcal antibodies in all four groups were associated with a significant decrease (P<0.001) and this change was the same for all studied groups and there was no significant difference in immunogenicity of the vaccine between different groups (P=0.82). In the fitted models, the interaction between the factor studied (serum antibody level) and the studied groups were significant, indicating a different immunogenicity effect of the vaccine at different times. In the second approach, the GEE analysis based on distribution-free was used to confirm the findings of repeated measures ANOVA. This analysis also showed no group effect on immunogenicity from the vaccine. Table 3 represents the results of this model.

The results of Table 3 show that the antibody titer in the peritoneal dialysis group was decreased by the coefficient of -0.16 in comparison with the control group, and the other two groups with the coefficients of 0.03 and 0.09 were more than the control group; however, not all of the above items were statistically significant.

In this study, the correlation between serum Tacrolimus level and antibody level before vaccination and six months after vaccination was investigated. The results of this study are shown in Table 4. According to the results of this table, there was no significant relationship between antibody level and drug level before and after the intervention.

Discussion

The patients with chronic renal failure are at high risk for infections caused by *Streptococcus pneumoniae*. This defect can be due to the reduction of antibody response to these polysaccharide antigens in such

patients[15-18]. Although immunization of these patients with pneumococcal polysaccharide vaccine has been suggested[19], there are rare reports of evaluating this vaccine in patients with chronic renal failure[20]. Similarly, the efficacy of the vaccine in these patients is not well defined[20,21]. The appropriate response to antibodies and pneumococcal antigens in patients with chronic renal failure can highlight the importance of vaccination in protecting against pneumococcal infections, and thus they may be protected against pneumococcal infections.

In evaluating the concentration of PPV23-derived antibodies in the studied groups, the results demonstrated that the distribution of this antibody in the sample was normal in the first measurement and non-normal in the other two doses. One month after vaccination, there is no difference between the mean concentrations of PPV23-derived antibodies, but the antibody level increased with respect to the first measurement, in line with the results of the study by Fuchschuber et al.[20]. The results showed that 83% of patients with chronic renal failure developed protective antibodies against pneumococcal antigens four weeks after immunization. This finding from the present study reveals that we can identify those with the poor responses that are more at risk for pneumococcal infections by measuring antibody dilution against pneumococcal antigens after vaccination. Concerning the difference in the antibody concentrations after six months of vaccination, there was a significant statistical difference between the two groups. This difference was between peritoneal dialysis with kidney transplant groups as well as hemodialysis with kidney transplant groups; so that it was higher in kidney transplant group than the other two groups but no significant difference exists between dialysis and kidney transplant groups with the control group.

After a month of vaccination, an increase in serum antibodies occurred, with a slight decrease over the next five months. The changes in the level of anti-pneumococcal antibodies in all four groups were associated with a significant reduction in the statistical significance and this change for all groups was similar and there was no significant difference in the immunogenicity of the vaccine between different groups. These data are consistent with the findings from the study of Ambrosiono et al.[22] that showed that children with recurrent infections after pneumococcal vaccination (containing 14 strains of bacteria) produced normal levels of IgG against pneumococcal antigens. In fact, the results of our study indicated the PPV23 immunization in patients with chronic renal failure. Additionally, the data of anti-pneumococcal IgG titers after vaccination in the patients with normal specific

Table 3: The results of the GEE model for investigating the effects of different groups on the immunogenicity of the anti-pneumococcal antibodies 23.

Variable	Class	Coefficient	P-value
Group	Control	-	-
	Peritoneal Dialysis	-0.16 (-0.84-0.52)	0.65
	Kidney transplant	0.03 (-0.55-0.6)	0.92
	Blood dialysis	0.09 (-0.41-0.59)	0.72
Age	Age	-0.006 (-0.015-0.014)	0.93
Sex	Male	-	-
	Female	0.07 (-0.37-0.51)	0.75

Table 4: The correlation between serum Tacrolimus level and antibody level before vaccination and 6 months after vaccination.

Variables			Serum Tacrolimus level	
			Base line	After 6 months
Antibody level	Base line	Pearson Correlation	0.130	-
		P-value	0.574	
	After 6 months	Pearson Correlation	-	-0.113
		P-value		0.626

antibody responses are in line with the findings of Dengler[23], which examined the immune response in the transplant recipient by the administration of the pneumococcal vaccine. The follow up exhibited that the patients with poor antibody response to the pneumococcal vaccine were infected with respiratory pneumococcal infections more than patients in Group 2 (patients with normal antibody response). These findings confirm previous studies, which showed that patients with chronic renal failure are more susceptible to recurrent respiratory infections[24-27]. According to the findings of this study, there was a significant relationship between the serum antibody level and the studied groups, highlighting the different immunogenicity of the vaccine at different times. The rate of increasing antibody level after vaccination and the rate of decreasing serum level after month 1 to month 6 in renal patients was higher than that in the control group. Limited studies exist about the efficacy of the pneumococcal vaccine in patients with renal failure. A study by Simberkoff on patients who were at higher risk for multiple infections, including those with renal failure, suggested that injections of pneumococcal polysaccharide vaccine in the patients with renal failure in the prevention of pneumonia or bronchitis have been associated with poor effects, or the effect of the vaccine on immune system induction has been too weak[28]. Case/control studies on patients with chronic infections indicated the preventive effect of the vaccine on the occurrence of pneumonia[29]. Other related studies have shown that hemodialysis patients, as well as kidney transplant recipients who produce antibodies at normal levels with pneumococcal vaccine, were advised to vaccinate and even booster to induce immunity[12]. On the other hand, the booster will be even ineffective in patients with poor response[30-31]. Studies have demonstrated that pure polysaccharide antigens induce type 2 antibodies (non-T cell-dependent), and these antigens do not stimulate memory B cells. However, the booster is unable to enhance the production of these antibodies in the secondary response. Therefore, the injection of a conjugate vaccine (a bacterial polysaccharide capsule conjugated with vector proteins) may improve the immune response in patients with poor response. Zielen et al. were able to enhance the antibody production rate in immunocompromised patients by administering the pneumococcal conjugate vaccine (containing seven bacterial strains) before injection of a pneumococcal vaccine containing 23 bacterial strains[32].

Conclusion

The results obtained from the present study indicated that the kidney failure patients undergoing hemodialysis and renal transplantation have a good response to pneumococcal immunization, but they have a rapid drop in serum antibodies within six months of vaccination. Knowledge of the protective levels of antibodies in these patients will help to make revaccinations more accurate and when necessary, and control infections and subsequent risks.
Protection code:IR.SBMU.MSP.REC.1396.505.

Acknowledgment

None.

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