Original Article

ISSN: 1735-0344 *Tanaffos 2023; 22(1): 143-151*

TANAFFOS

Effect of Pneumococcal Conjugate 13 Valent and Polysaccharide 23 Valent Vaccination on Anti-Pneumococcal Antibody Titer of Hemodialysis Patients: A Randomized Clinical Trial

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Received: 14 May 2022
Accepted: 1 November 2022

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Background: Pneumococcal infections are a life-threatening disease in hemodialysis patients and vaccination against pneumococcus is an effective prevention. The current study aims to evaluate the immune response and maintenance of the anti-pneumococcal antibody titer in hemodialysis patients to the 23 valent pneumococcal polysaccharide vaccine alone and 13 valent conjugated with 23 valent polysaccharide vaccine.

Materials and Methods: This study is a randomized clinical trial that was performed at Loghman Hakim Hospital in Tehran, Iran in 2017. A total of 70 patients undergoing hemodialysis were randomly assigned to intervention (22 patients) and control (23 patients). In the control group, only one dose of the PPSV23 vaccine while patients in the intervention group were injected initially with PCV13, and then after at least 8 weeks PPSV23 vaccine. The outcome of this study is first and sixth-month antibody titer after injection of the PPSV23 vaccine.

Results: The obtained result showed no significant difference between the two groups in the first month and sixth months. The results indicate that both the intervention group (treated with PCV13+PPSV23) and the control group (treated with PPSV23 only) experienced a significant impact from the first to the sixth month. Additionally, there was a noticeable effect on the levels of anti-pneumococcal antibodies during the first to sixth month between the intervention and control groups. In addition, the difference between the antibody titer of the first month and the sixth month was not significant in the two groups.

Conclusion: The anti-pneumococcal antibody titer in hemodialysis patients does not show a clear difference after two vaccine injections and one vaccination.

Keywords: Hemodialysis; PPSV23; PCV13; Antibodies; Vaccination

INTRODUCTION

Chronic kidney disease is a condition in which the function of kidneys is lost over time, and finally, it can lead to End-stage renal disease (ESRD). In this phase of the disease, the patients will need alternative therapies such as hemodialysis (1). ESRD patients undergoing hemodialysis (HD) are at risk of life-threatening infections due to uremic, malnutrition, and immunosuppression state (2-5). The immune system changes in this disease can expose the patients to infectious diseases (6). After cardiovascular

disease, infections are the second most life-threatening illness that can result in hospitalization and even death for patients (7).

Among all infectious diseases, pneumonia is one of the common reasons for patients' hospitalization and death. Reports indicate that the prevalence of this disease among these patients is 27.9/100 person/year, and the death rate from this disease is 10-16 times more than the usual population (8-10). This death rate is mainly due to the gram-positive bacteria (*Streptococcus pneumonia*), also known as pneumococcus (7). Pneumonia in these patients is so crucial in a way that the pneumococcus vaccine is recommended along with the hepatitis B and influenza vaccines. It can reduce the death rate of this disease (11).

Two categories of approved pneumococcal vaccines include pneumococcal 23 valent polysaccharides vaccine and pneumococcal 13 valent conjugate vaccine(7). In 2012, the US Immunization Committee recommended the use of PCV13 for high-risk patients. Furthermore, in 2014, PCV13 vaccine was recommended for all adults over the age of 65 years, as well as children older than 2 years of age who are at higher risk for pneumococcal infection. PPSV23 is also recommended in people between the ages of 19 and 64 who are at risk for pneumococcal infection and its complications (7, 12). Additionally, injection of these two vaccines is suggested in patients with chronic renal failure and nephrotic syndrome. It is recommended to receive the PCV13 vaccine first, followed by the PPSV23 vaccine, with a minimum interval of 8 weeks between each injection (12). PCV13 is injected both intramuscular and subcutaneous while PPSV23 is injected intramuscularly (13). Besides, the injection of pneumococcal vaccine is safe and can improve the outcome (14). A study of 36,966 HD patients indicated that pneumococcal vaccination has reduced mortality by 25%. Moreover, the vaccine has been well tolerated and its side effects were less than 2%, a month after vaccination (12). Due to the presence of the immune disorder in these patients, the response to the vaccine is weaker than in the normal population (6).

The studies mention that the effect of vaccine in the general population is higher than 90%, while in patients with kidney failure undergoing dialysis is only in 50 to 60% of cases (15). For example, studies have reported a weak immune response to the hepatitis B vaccine (16) and Td vaccine (17) in hemodialysis patients. Comparing the antibody titer after the PPV23 vaccine between a healthy population and hemodialysis patients showed that the antibody titer in hemodialysis patients is significantly lower than the healthy people (18). A case-control study compared the antibody response to the pneumococcus polysaccharide vaccine in healthy individuals and those with chronic kidney failure who had undergone kidney transplants. The study found that the amount of antibodies in the healthy group increased from 70 to 395 micrograms/milliliter before and four weeks after vaccination. While 21% of patients with chronic kidney failure had a weak response to the pneumococcus vaccine antigens, 79% of them had a typical response (19).

Another point to consider regarding these patients is that not only do HD patients have lower antibody titers than the healthy population, but over time, they are unable to maintain this level and it gradually decreases (15,16,20). For example, several studies have been conducted on the immune response of patients undergoing dialysis to hepatitis B and influenza. The results of these studies have shown the reduction of antibody levels over time. Furthermore, many researches indicated that a booster dose or increased dose of vaccine in these groups of patients can be recommended (20-23). It has been found that individuals with HD have a lower immune response to pneumococcal vaccination compared to the general population. Additionally, the antibody titer decreases rapidly in these patients (13, 15, 24). Studies have investigated the amount of antibody titer after the pneumococcus vaccine in periods of four weeks, two months, six months, and one year (13, 18, 24, 25). The gradual decrease of the antibody titer was apparent. However, the results also showed that the antibody titer in these patients decreases quickly in six months (15).

Studies recommend injecting the booster or changing the vaccine dose. Patients with end-stage kidney disease who receive revaccination show more than double the

increase in antibody levels compared to patients who have undergone renal transplants. Therefore, pneumococcal re-vaccination is required in patients undergoing HD and renal transplantation (26).

Accordingly, vaccination of these patients in the form of a single dose of PCV13 and PPSV23 after eight weeks is recommended. And even repeat after five years (27). However, further investigation is required for this particular case (28).

Based on the reports, about 30,000 patients are undergoing HD and peritoneal dialysis in Iran. Hence, research in these cases is necessary. Testing for antibody levels against pneumococcus after vaccination in HD patients can give insight into their immune response and guide the best vaccination strategy, including determining the optimal vaccine dosage. This study was conducted to assess the immune response and maintenance of anti-pneumococcal antibody titer in hemodialysis patients to the 23 valent pneumococcal polysaccharide vaccine alone and 13 valent conjugated with 23 valent polysaccharide vaccine.

MATERIALS AND METHODS

Trial design

This study is a randomized, double-blind, parallel-group clinical trial that comprises anti-pneumococcal antibody titer in pneumococcal conjugate 13 valent with polysaccharide 23 valent vaccination versus pneumococcal polysaccharide 23 valent vaccination alone in HD patients. The study was performed from March 2016 to March 2018.

Participants and setting

The total participants included 70 patients undergoing HD referred to Loghman Hakim Hospital. The inclusion criteria were at least 16 years of age, at least 3 months history of dialysis, receiving 3 times HD in a week and exclusion criteria were chronic or life-threatening illnesses (such as cancer), receiving immunosuppressive drugs, splenic dysfunction, positive HIV test, Bone marrow transplant, history of previous injection of pneumococcal vaccine or pneumonia, and injection of any other vaccine.

Intervention

The intervention in this study was vaccination. One group of patients under investigation injected only a 23 valent vaccine, and the other group at first injected a 13 valent of a conjugate vaccine. Then after eight weeks, they injected a 23 valent of polysaccharide vaccine.

One month after the second injection of the vaccine, 2 CC blood samples were taken in Clot Activator + Gel tubes and under specific conditions (in the first two hours after sampling) were centrifuged. Then, samples were frozen (until the second specimen was collected). Six months after injection of 23 polysaccharide vaccines, antibody titers were measured by kit Human Anti-S Pneumococcal vaccine (Pneumovax / CPS23) IgG ELISA Kit; (23rd Serotypes: 1, 2, 3, 4, 5, 6b, 7F, 8.9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F,19A, 20, 22F, 23F and 33F).

Depending on the type of vaccine, the minimum level required to respond to the pneumococcus vaccine has been suggested. In this study, the threshold was determined based on the laboratory kit and values above 1 IU / ml as a minimum.

Outcomes

The amount of antibody titer of anti-pneumococcus after a single 23 valent vaccine, 13 and 23 valent vaccines with two-week intervals, and the durability of antibody titer six months after the vaccination (Table 1), were considered as the outcomes in this study.

Table 1. Vaccine injection schedule and antibody titer measurement.

Month		1	2	3	4	5	6	7	8
Control	PPSV23 injection	Ab titer					AB titer		
Intervention	PCV13 injection		PPSV23 injection	Ab titer					AB titer

Data Collection Procedures

For each patient, demographic data including age, gender, history of diabetes, duration of initial dialysis, albumin level, serum hematocrit, urea level, dialyzer clearance of urea multiplied by dialysis time divided by the volume of distribution of urea (KT / V), and the history

of pneumococcal vaccine injection were obtained from the patient's records. The amount of antibody of each vaccine, one and six months after vaccination, was obtained from the lab and registered in the data collection list.

Sample Size

We used the effect size (ES) method with citation to the Whitehead et al. study for calculating the number of samples (29). The sample size for the current pilot study considering 0.2 for effect size, was conservatively calculated at 25 for each group.

Random Allocation

In the current study, patients were randomly allocated into two groups of intervention and control by balanced block randomization technique with 4 blocks. STATA software (version 10) generated random numbers from chains 1 to 6 until the desired sample size was achieved. Given that, the total number of cases to fit two people in 4-blocks is 6 modes. Preparation of sequences of random allocation of cases and putting them in sealed envelopes and numbered with a 5-5-digit serial number, were performed by a third person who was not involved in the study design. After the completion of basic information, individuals were assigned to an intervention or control group. The intervention group received PPSV23, at least 8 weeks after PCV13 and the control group received only PPSV23.

Statistical Methods

Due to the lack of normal distribution of data in the age, weight, urea, albumin, hematocrit, KT / V, and duration of dialysis, the Mann-Whitney test was used to determine the difference between intervention and control groups. Moreover, the Chi-square test was used to determine the relationship between the two groups in sex, marital status, employment status, education, diabetes, smoking, and cardiopulmonary disease with intervention and control groups. To determine the difference in antibody titers between the first and sixth months for the two groups, we used paired and independent sample t-tests assuming normal distribution. The p-value of 0.05 is considered a significant level.

The Mann-Whitney test was used to determine the difference between the two groups in terms of antibody titer in the first and sixth months of vaccination. Moreover, the Wilcoxon test was used to determine the statistical difference between the first and sixth months of vaccination in each group.

RESULTS

Participant flow

The participants included 70 patients undergoing HD from March 2016 to March 2018. According to exclusion criteria, 20 patients were not enrolled. Therefore, 25 samples with random allocation were assigned to each group. However, after starting the follow-up study, 3 patients from the intervention groups and 2 patients from the control group were lost to follow-up. Afterward, 23 patients in the control group and 22 patients in the intervention group were included in the final analysis (Figure 1).

Baseline data

There was no significant difference between the control and intervention groups in age, sex, marital and employment status, education, weight, hematocrit, KT / V, duration of dialysis, cardiopulmonary disease, and diabetes. Only in three variables of smoking, urea, and albumin, the difference was remarkable (Table 2).

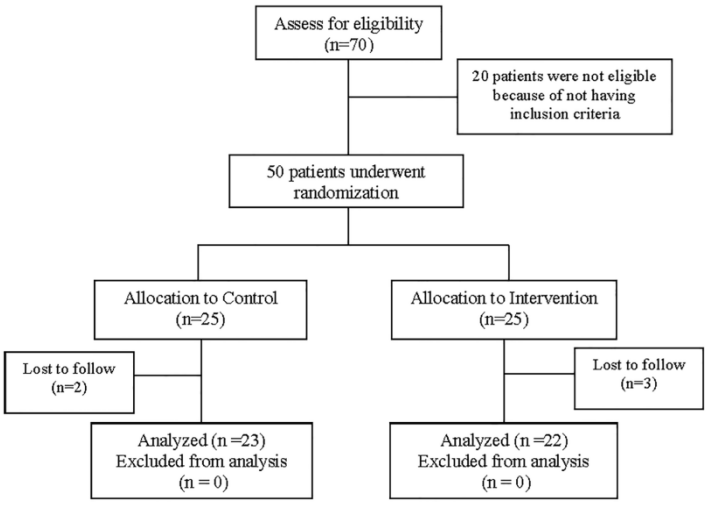

Figure 1. CONSORT flow diagram of eligibility

Table 2. Summary of qualitative and quantitative variables

Qualitative Variables		Control (N = 23)	Intervention (N = 22)	P-Value
		N (%)	N (%)	
Sex	Male	15 (65.2)	15 (68.2)	0.833 **
	Female	8 (34.8)	7 (31.8)	
Employment Status	Retired	3 (13.0)	8 (36.4)	0.119 **
	Employed	12 (52.2)	6 (27.3)	0.228 ***
	Unemployed/Housewife	8 (34.8)	8 (36.4)	
Education	Illiterate	10 (43.5)	4 (18.2)	0.143 **
	Diploma	12 (52.2)	15 (68.2)	0.089 ***
	Bachelor	1 (4.3)	3 (13.6)	
The cause of kidney failure	Diabetes	9 (39.1)	10 (45.5)	0.585 **
	Blood pressure	9 (39.1)	8 (36.4)	0.773 ***
	GN	2 (8.7)	0 (0)	
	ADPKD	1 (4.3)	2 (9.1)	
	uropathy	2 (8.7)	1 (4.5)	
	Cancer	0 (0)	1 (4.5)	
Diabetes	Yes	9 (39.1)	10 (45.5)	0.668 **
	No	14 (60.9)	12 (54.5)	
Heart disease	Yes	12 (52.2)	9 (40.9)	0.449 **
	No	11 (47.8)	13 (59.1)	
Lung disease	Yes	3 (13.0)	0 (0)	0.080 **
	No	20 (87.0)	22 (100)	0.125 ***
Smoking	Yes	4 (17.4)	0 (0)	0.040 **
	No	19 (82.6)	22 (100)	0.049 ***
Quantitative Variables		**Control (N = 23) Mean(SD)**	**Intervention (N = 22) Mean(SD)**	**P-Value**
Age		63.83 (13.15)	58.73 (14.87)	0.187 *
Urea		105.48 (21.31)	89.95 (21.34)	0.021 *
Hematocrit		33.89 (4.884)	31.63 (5.653)	0.328 *
KT/V		1.257 (0.282)	1.318 (0.382)	0.715 *
Albumin		3.84 (0.359)	4.136 (0.341)	0.003 *
History of dialysis (months)		44.09 (30.727)	36.55 (39.062)	0.159 *

* Mann- Whitney Test ** Chi-Square Test *** Fisher Exact Test

Outcomes

Comparison of the anti-pneumococcal antibody titer after PCV13+PPSV23 and PPSV23 valent after vaccination in HD patients indicated that there was no remarkable difference between the two groups in the first month and sixth month. In other words, the mean of antibodies in the two groups was approximately equal. However, the results show that vaccines in the intervention (PCV13+PPSV23) and control (PPSV23) groups have a significant effect from the first month to the sixth month. (Table 3). Considering, the difference of anti-pneumococcal antibody titer in the first month, there is a significant difference between the two groups of control and intervention. The results demonstrated that anti-pneumococcal antibody titer during the first to sixth month between intervention and control groups has a remarkable effect (Table 4).

Table 3. Comparison of the anti-pneumococcal antibody titer intervention and control groups.

	Control (N = 23)	Intervention (N = 22)	P-Value
	Mean(SD)	Mean(SD)	
Antibody (first month)	17.13 (2.07)	17.36 (2.34)	0.725 *
Antibody (6th month)	13.91 (2.07)	15.14 (2.48)	0.078 *
P-Value	0.001 **	0.001 **	-

* Independent Sample T-test ** Paired Sample T-test

Table 4. Difference of the anti-pneumococcal antibody titer first to the sixth month

	Control (N = 23)	Intervention (N = 22)	P-Value
	Mean(SD)	Mean(SD)	
Antibody (first month) - Antibody (6th month)	3.39 (1.41)	2.22 (1.02)	0.010 *

* Independent Sample T-test

DISCUSSION

Summary of findings

The results of this research that was performed by a clinical trial method to investigate the effect of PCV13 and PPSV23 in comparison with PPSV23 alone on antibody titer of anti-pneumococcus in hemodialysis patients demonstrated that the amount of antibody did not have any significant statistical difference after one month in two groups. Each antibody was produced as a result of the vaccine injection. However, after six months, the results showed that the amount of antibody in the two groups did not have any significant difference, but the amount of antibody reduction in the group that had received the PCV13 and then PPSV23 was significantly lower than the patients that received just a single 13 valent of the vaccine.

Limitations

This study was conducted with a limited sample size and an ES of around 0.2 which may affect the results. The investigations also measured the response of antibodies to serotypes (24, 30), which was not possible in this study. Furthermore, this study did not investigate the occurrence of pneumonia disease.

Comparison to existing literature

Studies have demonstrated that the antibody response after the injection of the pneumococcus polysaccharide vaccine in patients with chronic kidney failure, which had referred to the kidney transplant section, was weaker than the healthy people (19). So, the probability of getting this disease and subsequently the disability and death due to this infection is higher.

The current study showed that vaccine antibody titers were approximately the same in the groups and there was no significant difference at the first month. It also showed that injecting a single PPSV23 vaccine alone did not make any difference in producing antibodies with injection PCV13 vaccine and then the PPSV23 vaccine with an interval of eight weeks. So, it can be concluded that only 23 valent vaccinations may be enough to make immunization.

However, the studies in healthy people have demonstrated that the injection of the PCV-13 vaccine in people aged 70 years and older who received the 23 vaccines more than five years ago could lead to higher antibody production compared with the injection of the PPV-23 vaccine (31). Measurement of the antibody before the injection of the PPV-23 vaccine and after four weeks in patients before the transplant surgery showed that the immunogenicity of this vaccine in patients with kidney failure could protect many of them against pneumococcal infection. So, injection of this vaccine is recommended, but some patients cannot produce the antibodies against this vaccine (19).

After 6 months of vaccination, these patients had significantly decreased antibody levels in both groups. There was no outstanding difference between the two groups in the sixth-month antibody. However, the rate of antibody loss in the group that was injected only with the PPSV23 vaccine was higher than in the PCV13 and PPSV23 vaccines.

Studies similar to the current study were not found. However, a study evaluated the effect of the 13-valent pneumococcal conjugate vaccine (PCV13) in under-dialysis patients with end-stage renal disease and those over 50

years old. At first, the amount of antibodies against this vaccine was measured two and twelve months after vaccination. The amount of antibodies increased two months after vaccination in comparison with the beginning. However, the amount of antibodies decreased after one year (24). In another study, the amount of antibodies after the PPSV23 vaccine in patients with chronic kidney disease also gradually reduced after six months and one year (13).

In a study, four groups were compared for immune response to PCV-13 and PPV-23 vaccines in hemodialysis patients with/without prior PPV-23 vaccination. At first, the antibody was measured one month and one year after injection. According to the findings, patients who had not been given the PPV-23 vaccine previously and were injected with either the PPV-23 or PCV-13 vaccine exhibited an immune response. One month later, it was observed that the patients who received the PCV-13 vaccine had higher antibody levels as compared to those who received the PPV-23 vaccine. But after one year, there was no difference in the amount of antibodies in these two groups anymore. The immune response to the PCV-13 vaccine was weaker in patients who had received the PPV-23 vaccine before (25). Four-week antibody titers were higher in PCV-13-vaccinated patients than in PPV-23-vaccinated patients, but these differences grossly disappeared after 1 year.

It is essential to mention that patients with end-stage renal disease will be exposed to the infection due to the uremic syndrome, decreased activity of the complement system, neutrophils, monocytes/ macrophages, and T and B cells. This issue can even reduce their immune system response to the vaccine (32). Besides, a part of the blood antibody leaves the body during dialysis and blood circulation (24). This group of patients had a decreased response to the vaccine, and they will need more doses of the vaccine (24). However, the result of the current study showed that this reduced antibody between the two studied groups was not significant.

Considering the lack of difference between the antibody titers after 6 months between the two groups, the result of this study could be used to decrease dialysis patient-associated budget.

As regards a significant percentage of patients with end-stage renal disease undergoing peritoneal dialysis, a study on vaccination and the effect of some factors such as BMI, calcium and phosphorus, Urea Reduction Ratio (URR), and blood pressure on anti-pneumococcal antibody titer is suggested.

CONCLUSION

The study results demonstrated that the antibody was produced in both studied groups. Still, the antibody reduction rate during six months in the group that had been vaccinated twice, first with a 13-valent vaccine and then the 23-valent vaccines, was lower than the patients that had been vaccinated only once by the 13-valent vaccines. However, there was no significant difference in the amount of antibodies between the two groups after six months. It is recommended to do other studies about antibody reduction in longer intervals and investigate the factors that can affect it.

Acknowledgments

The authors would like to thank the Shahid Beheshti University of Medical Sciences for supporting this research, and to all research participants. This study is based on the specialist thesis of the first author.

Ethical Approval

This research was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR-SBMU.SMSP.IRC.1396.572). This randomized clinical trial was registered in 2017 at the Iranian Registry of Clinical Trials (Registration No. IRCT20171224038046N1; www.irct.ir).

Funding/Support

Shahid Beheshti University of Medical Sciences has sponsored this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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