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Original Article

The effect of selenium on immunogenicity of influenza vaccine in the elderly: A case-control double-blinded clinical trial

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Abstract

Introduction: Influenza can cause more severe diseases and higher rate of morbidity and mortality in the elderly population. Therefore, they should receive influenza vaccine annually. However, the host response to vaccine is less in older individuals. On the other hand, selenium can act as a stimulator of the immune system and cause increased immunity and response to vaccine. This study was carried out to determine the effect of selenium on antibody production against influenza vaccine. By verifying this effect, selenium can be recommended as an adjuvant therapy in the elderly.

Methods: A total of 110 subjects were selected at Infectious Diseases Research Center of Imam Reza Hospital in Kermanshah. They were divided into two groups of adjuvant (N=56) and placebo (N=54). The adjuvant group received influenza vaccine and selenium tablet. The placebo group received influenza vaccine and placebo tablet. Venous blood samples were taken before and four weeks after vaccination and the results were compared between the two groups.

Results: Seroconversion, seroprotection, and geometric mean titer (GMT) for three strains (H1N1, H3N2, and B) were assessed. The seroconversion and GMT rates against influenza B vaccine component were significantly higher in adjuvant group than placebo group.

Conclusion: Considering the ability of selenium in induction of a better response to influenza vaccine in older people as well as its low cost and accessibility, selenium can be used to increase antibody level in such cases.

Introduction

It is important to note that correlates of protection against influenza are not well-defined, and several studies have also shown influenza vaccine protection in years with poor match. For such reasons, effectiveness studies should be considered the gold standard for evaluating the potential impact of influenza vaccines (1). Elderly and those with pre-existing medical conditions are susceptible to influenza complications, called high risk groups. These patients should receive influenza vaccine annually to decrease the severity of influenza complications and its morbidity and mortality (2). Studies have shown that vaccination in the elderly causes decreased mortality and coronary events (heart attack) during influenza season (3). Vaccination also decreases the transmission of disease in community, and secondary cases of disease, due to contact with patient, will be fewer and will decrease the complications of the disease (4). In a meta-analysis which reviewed 20 cohort studies, influenza vaccination resulted in 56% decrease in respiratory diseases, 53% in hospital admission, and 50% in mortality (5). Selenium is a potential anti-oxidant which exerts its effects on the immune system through participation in selenoprotein structure. This protein affects inflammation and immune system responses. Selenium causes exacerbated immune responses against definite pathogens (6). In previous studies, it has been shown that selenium causes lymphocyte proliferation as well as increased IL-2 receptor expression and macrophage activity. These effects are at their maximum levels with a daily dose of 200 micrograms of selenium (7). Selenium, through participation in selenoprotein and selenocystein structure, affects the immune response. These effects of selenium are produced in the setting of lymphocyte activity, proliferation, and differentiation (8). As mentioned earlier, the rate of influenza complications is higher in older people. The amount of antibody produced against vaccine is low in older people. Selenium can be used as a stimulator of immune system and stimulate antibody production.

In this study, selenium was applied as an adjuvant in order to find out its effect as stimulator of the body's response to influenza vaccine. In the case of observed appropriate immune response, it can be suggested to be administered in the elderly to increase the effect of influenza vaccine.

Materials and Methods

Patients

In this double-blinded clinical trial, 116 people who were older than 50 years and presented to the Infectious Diseases Research Center of Imam Reza Hospital, Kermanshah were selected. This study was approved by Ethics Committee of Kermanshah University of Medical Sciences. The patients were divided into two groups of adjuvant and placebo using random number table. The study was explained to them, and written informed consent was obtained prior to the study.

First, before vaccination 5cc of venous blood was taken and influenza vaccine was then administered. Then, based on the study groups, the subjects received selenium tablet or placebo tablet. After this, the possible complications of influenza vaccine were explained to them and the time of next visit, which was one month after vaccination, was set.

The study samples presented once more after one month. Six patients did not return and finally 110 cases remained in the study.

Serum of the collected samples was separated after centrifugation and maintained at – 20°C at the laboratory of Imam Reza hospital. Serum samples of the subjects before and after vaccination were sent to the National Reference Laboratory for Influenza in the Health School of Tehran University of Medical Sciences to measure the related antibodies. Humeral immune response was assessed using hemagglutination inhibition (HI) and standard microtiter assays. This assay measures the antibody titers against hemagglutinin antigens of the vaccine strains (A/H3N2 and BH3N2). In this assay, the progression of serum dilution, which inhibits agglutination, is assumed as HI antibody titer.

Vaccine injections were done by the healthcare staff. The injection was intramuscular using the syringe within vaccine package.

The vaccine used here was a trivalent vaccine (Vaxigrip®, France) confirmed to be used in 2010/2011. This vaccine contains 15 micrograms hemagglutinin (HA) related to the following strains:

A/California/7/2009 (H1N1)

A/Perth/16/2009 (H3N2)

B/Brisbane/60/2008

The selenium we used was a product of Canada (Webber Naturals) in the form of 200 micrograms tablets. The placebo used was similar in color and shape to the selenium tablets and contained sugar. The placebo tablet was manufactured in a pharmaceutical company.

The vaccine immunogenicity was measured according to the following definitions:

A) Seroconversion: raised antibody level from negative (less than 1:40) to positive (≥ 1:40) or a 4-fold, or more increase in antibody titer after vaccination

B) Seroprotection: presence or production of antibody with titers ≥ 1: 40, which can have protective effects against influenza

C) Geometric mean titers (GMTs): significant increase in GMT following vaccination

To calculate the GMTs, we used 1:5 titer as the minimum titer.

Statistical analysis

The statistical analyses were performed using SPSS software (ver. 16.0). The variables were compared between the case and control groups by chi-square and Mann-Whitney tests.

Results

In adjuvant group (56 cases), there were 30 males (53.6%) and 26 females (46.4%). In placebo group (54 cases), there were 31 males (57.4%) and 23 females (42.6%). No significant difference existed between the two groups regarding gender (P= 0.995). The mean age of patients was 56.2 years in adjuvant group and 54.8 years in placebo group (P= 0.686). The mean body mass index (BMI) was 27.1±1.96 in adjuvant group and 26.9±1.08 in placebo group (P= 0.545). In this study, immunogenicity measurement was done using seroconversion, seroprotection, and GMTs.

Seroconversion

Seroconversion rate in adjuvant group was 51 (91.1%) for A/H1N1, 36 (64.3%) for A/H3N2, 46 (82.1%) for B strain, and overall, it was 64.3% to 91.7% (Table 1).

Seroconversion rate in placebo group was 46 (85.2%) for A/H1N1, 36 (66.7%) for A/H3N2, 40 (74%) for B strain, and overall, it was 66.7% to 85.2% (Table 1).

Table 1. Seroconversion level in case and control groups in response to three serotypes of influenza vaccine

Seroconversion	Group 1 (adjuvant) (N=56)	Group 2 (placebo) (N=54)	P-value
A/H_1N_1	51(91.1%)	46(85.2%)	0.339
A/H_3N_2	36(64.3%)	36(66.3%)	0.793
B	46(82.1%)	40(74%)	0.306

Seroprotection (percentage)

This rate in adjuvant group before vaccination was 34(60.7%) for A/H1N1, 38 (67.9%) for A/H3N2, and 26 (46.4%) for B strain. After vaccination and receiving selenium, these figures increased to 54 (96.4%), 49(87.5%), and 51(91.1%), respectively (Table 2).

In placebo group, seroprotection level before vaccination was 44(81.5%) for A/H1N1, 30(55.6%) for A/H3N2, and 48(88.9%) for B strain. After vaccination, these figures increased to 52(96.3%), 48(88.9%), and 53(98.1%), respectively (Table 2).

GMTs

GMTs rate in adjuvant group before vaccination was 55.1 microtiters for A/H1N1, 62.5 microtiters for A/H3N2, and 121.6 microtiters for B strain. After vaccination and receiving selenium, these figures increased to 199.7, 171.6, and 354.6, respectively (Table 4).

Table 2. Seroprotection level in case and control groups in response to three serotypes of influenza vaccine

Seroprotection	Group1 (N=56)			Group2 (N=54)			P- Value[b]
	Pre	Post	P-Value[a]	Pre	Post	P- Value[a]	
A/H_1N_1	34(60.7%)	54(96.4%)	<0.001	44(81.5%)	52(96.3%)	0.008	0.11
A/H_3N_2	38(67.9%)	49(87.5%)	<0.001	30(55.6%)	48(88.9%)	<0.001	0.589
B	26(46.4%)	51(91.1%)	<0.001	48(88.9%)	53(98.1%)	0.62	<0.001

P-value [b]: Intergroup P-value [a]: Before and after in each group

Table 3. The pre- and post GMTs in case and control groups in response to three serotypes of influenza vaccine

GMT (increase)	Group 1, adjuvant (N=56)			Group 2, placebo (N=54)			
	Pre	Post	P value a	Pre	Post	P value a	P value b
A/H1N1	55.1±2	199.7±1.6	< 0.001	51.6±2.6	188.9±1.9	< 0.001	0.67
A/H3N2	62.5±2.4	171.6±1.9	< 0.001	39.8±2.6	127±2.1	< 0.001	0.67
B	121.6±2.1	354.6±1.7	< 0.001	60.3±2.2	195.6±2.3	<0.001	0.002

P-value b: Inter group P-value a: Before and after in each group

GMTs rate in placebo group before vaccination was 51.6 microtiters for A/H1N1, 39.8 microtiters for A/H3N2, and 60.3 microtiters for B strain. After vaccination and receiving placebo, these figures increased to 188.9, 127, and 195.9, respectively (Table 3).

Discussion

The effect of trivalent vaccine (TIV) on influenza in healthy people aged less than 65 years and when antigenic match is good is about 70-90%. But when antigenic match is not appropriate, its efficacy may decrease 50-77%. But this rate in older people who are susceptible to serious complications and mortality of influenza is lower and estimated to be about 30-70% (6). In a study performed in a nursing center, the efficacy of influenza vaccine was lower, about 30-40%. However, its efficacy was considerable in prevention of complications, hospitalization (50-60%) and mortality (80%) (9).

In another study, the efficacy of influenza trivalent inactivated vaccine (TIV) in adults was 76% for H1N1 (95% confidence interval: 52-86%) (10). In a placebo-control study which was done among older patients, the efficacy of vaccine was 58% (11). High et al. (12) reported that despite normal diet, supplementation with selenium (200 micrograms per day) can improve the function of the immune system. Hurwitz et al. (13) showed that selenium as 200 micrograms per day has no serious side effects. In a study performed in Medicine Department of Liverpool University, the effect of selenium on immune system improvement was assessed. Selenium (100 micrograms as sodium selenite) was administered to 98 subjects and the cases were evaluated after three weeks. It was noted that selenium increased the production of IFN-gamma and other cytokines, raised T-cell proliferation and increased the number of T-helper cells (14). In a study conducted in Kermanshah, it was shown that levamisole-selenium supplementation along with anti-retroviral treatment (ART) prevented CD4 decrease in HIV/AIDS patients (15).

Nutritional elements such as lysine, proline, ascorbic acid, green tea extract, N-acetyl cysteine, and selenium have extensive biochemical and pharmacologic effects, among which are anti-cancer and anti-atherogenic properties. In former studies, it has been noted that these substances can prohibit influenza virus via the activity of neuraminidase (16). In a study from Liverpool University, it was reported that micronutrient supplements such as vitamins A, C, D3, E, folate, and selenium had no effect in eight weeks on antibody response against influenza vaccine in older people (17). In a study from China, it was shown that selenium, zinc, and magnesium had anti-influenza effects, which could be due to stimulation of immune system response (18).

In a basic study in China on mice, it was shown that the mortality rate was 75% in the mice with selenium deficiency, decreased INF-alpha, and INF-gamma, but in the mice that received selenium (0.5 mg/Kg) this rate decreased to 25% (19).

According to an American study, (20) selenoprotein prohibits pulmonary injury during influenza. In this study seroconversion rate in adjuvant group was 82.1 to 91.7%. This figure, though not significantly different from placebo group, is higher in comparison to similar studies. Seroprotection rate for all vaccine strains was significant in adjuvant group, but it was only significant for A/H1N1 and A/H3N2 strains in placebo group. When comparing the two groups, this difference was only statistically significant for B strain. GMTs rate was significant for A/H1N1, A/H3N2, and B strains in each group, and when the two groups were compared, this difference was only seen for B strain. According to the above mentioned issues, it is evident that selenium increases the antibody production in the body against influenza vaccine in comparison to placebo. This increase was obviously seen for B strain which produced higher seroprotection and higher GMTs than placebo group. However, the point to keep in mind is that during the study we did not have any information about the serum selenium level of the studied subjects. It is likely that the studied subjects had selenium deficiency and the administered selenium just alleviated the deficiency and did not help in antibody production.

Conclusion

Selenium can be effective in increasing the immune response of the elderly against influenza vaccine. Given the low cost and accessibility of selenium, it can be used as an adjuvant to influenza vaccine in older patients. We thank all the personnel of infectious diseases department of Imam Reza Hospital, Kermanshah University of Medical Science for their utmost help in conducting this study.

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