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COMPARISON OF TOTAL SERUM MENINGOCOCCAL-SPECIFIC IGG LEVEL IN THE ELDERLY AND YOUNG ADULTS AFTER MENINGOCOCCAL VACCINATION RUNNING HEAD: MENINGOCOCCAL VACCINATION IN THE ELDERLY AND YOUNG ADULTS

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Abstract

Background: *In the elderly, the immune system undergoes age-associated decline in function known as immunosenescence, which produce a progressive deterioration in the ability to fight infections and to develop immunity after vaccination. The elderly who become umrah pilgrims have a high risk of meningococcal infection. We aimed to compare total serum level of meningococcal IgG changes in the elderly and young adults before and after meningococcal MenACWY-CRM197 vaccination.*

Methods: This study involved elderly (aged > 60) and young adult umra pilgrims in Surabaya Indonesia with a pre-post test design. MenACWY-CRM197 vaccination was done before umrah pilgrimage. Total serum meningococcal-specific IgG level was examined by ELISA before and 1 month after vaccination. The difference between groups was analyzed using independent t-test.

Results: *We recruited 68 subjects, consisted of 34 elderly and 34 young adult subjects. After MenACWY-CRM197 vaccination, the total serum meningococcal-specific IgG levels increased significantly in both groups (p <0.001), but changes in total serum meningococcal-specific IgG levels in the elderly was significantly lower than in young adults (p=0.001).*

Conclusion: *Compared to young adults, the increase in total serum meningococcal-specific IgG levels after meningococcal vaccination in the elderly group were significantly lower, confirming the effect of immunosenescence.*

Keywords: *MenACWY-CRM197; elderly; immunosenescence; serum meningococcal-specific IgG level*

Introduction

Elderly has its own health problems because of functional decline in the organs, including the immune system function known as immunosenescence. It is characterized by decreased natural and adaptive immune function, resulting in a high risk of infection and a decreased response to vaccination (1). The elderly who become hajj or umra pilgrims have a high risk of meningococcal infection because they will gather with other pilgrims from Sub-Sarahan African (the meningitis belt areas) at the same time in a specific place. The climates also supports the spread of meningococcal and Saudi Arabia is a meningococcal endemic country (2). There is some concern about the effectiveness of meningococcal vaccinations in elderly hajj or umrah pilgrims.

Vaccination that does not result in maximal response in the elderly will lead to high rates of infection. Infection will also trigger an exacerbation of the underlying illness which is a major cause of morbidity, mortality, as well as dependence and hospitalization, resulting in increased medical costs (1). Meningococcal outbreaks occurred several times in Saudi Arabia in 1987, 2000 and 2001, making the Saudi Arabian government mandate the meningococcal vaccine for all hajj and umrah pilgrims (3). Research done in Singapore and UK reported a significant increase in nasal

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colonization rates by meningococcus after returning from hajj and umrah (4). The number of meningococcal infection in the elderly is less than the general population, but the death toll rose to 32% compared to mortality at young age which is only at 5% (5).

Immunosenescence as a consequence of the aging process leads to changes of the natural and adaptive immune system that play a role in the response to vaccination. Decreased function of antigen presenting cells (APCs) is characterized by decreased antigen recognition capability, reduction of antigen processing, decreased ability of major histocompatibility complex (MHC) expression, intracellular signal changes and altered secretion of cytokines and chemokines (6). Decreased T cells in the elderly occur due to a decrease in the number of naive T cells produced, changes in T cell receptor (TCR), changes in signal transductions as well as decreased secretion of cytokines and chemokines (7). The decrease in the number of naive B cells in the elderly, changes in B cell receptor (BCR), decreased B cell proliferation ability, decreased ability of class switch recombination (CSR) and decreased ability of production of antibodies with high affinity will affect the amount and quality of antibodies produced (8). One way to assess the presence of immunosenescence is to measure the levels of antibodies produced after vaccine administration and compare it with young adult groups (9). The Saudi Arabian government requires all hajj and umrah pilgrims to obtain a cross reactive diphtheria material 197 - meningococcal conjugate vaccine (MenACWY-CRM197) as a condition for obtaining a hajj or umrah visa. The use of MenACWY-CRM197 was approved by the United States Food and Drug Administration (FDA) in 2005. There were only limited research on MenACWY-CRM197 vaccine use in the elderly (10).

In Indonesia, currently there is no study that assessed the effect of immunosenescence on the MenACWY-CRM197 vaccination response in the elderly, although this vaccine has been used for vaccination in hajj and umrah pilgrims. We therefore, aimed to compare total serum level of meningococcal IgG changes in the elderly and young adults before and after meningococcal MenACWY-CRM197 vaccination.

Material and Methods

We recruited 68 subjects to exceed the 50 minimum sample size requirement in this study, consisted of 34 elderly (aged > 60 year) and 34 young adult subjects, all were umrah pilgrims lived in Surabaya, Indonesia. The inclusion criteria were: male and female umrah pilgrims, agree to obtain MenACWY-CRM197 vaccination, and willing to give their written consent to be involved in this study. Subjects with a history of disease (diabetes mellitus, chronic obstructive pulmonary disease, hepatic cirrhosis, heart failure, renal failure, HIV infection, or malnutrition), active smokers, drug users, and individuals who have had previous meningococcal vaccinations were excluded from the study.

This study was a pre-post test design, conducted at Tanjung Perak Port Health Center in Surabaya, during May-September 2015. All of the subjects (the elderly and the young adults as a control) got MenACWY-CRM197 vaccine (Menveo®, Novartis Inc, Basel, Switzerland) intramuscularly on the deltoid muscle of the right arm. This vaccine contains a 10 mcg of serogroup A meningococcal cell wall polysaccharide conjugated with 16.7-33.3 mcg CRM197 protein, 5 mcg serogroup C meningococcal cell wall polysaccharide conjugated with 7.1-12.5 mcg CRM197 protein, 5 mcg serogroup W-135 meningococcal cell wall polysaccharide conjugated with 3.3-8.3 mcg CRM197 protein, and 5 mcg serogroup Y meningococcal cell wall polysaccharide conjugated with 5.6-10 mcg CRM197 protein (11). Total serum meningococcal-specific IgG levels were examined 30 minutes before and 1 month after meningococcal vaccination using ELISA method (Alpha Diagnostic Intl Inc, San Antonio Texas, USA). Subjects who were hospitalized with any cause within the 1 month period or cannot be followed up after they came back from Saudi Arabia were dropped from the analysis. This study protocol was aprroved by the Health Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia.

Normality of data distribution were analyzed using Kolmogorov-Smirnov test. Pre and post vaccination total serum meningococcal-specific IgG data with normal distribution were analyzed using paired t-test. Data with abnormal distribution were analyzed using Wilcoxon sign rank test. The changes in the antibody levels before and after vaccination in the elderly and young adult groups were also compared. Comparison data with normal distribution were analyzed using independent sample t-test, while data with abnormal distribution were analyzed using Mann Whitney test. All results with $p < 0.05$ were considered significant. The statistical analysis was done using SPSS software version 23.0 (SPSS, Inc., Chicago, IL).

Result

Subjects Characteristics: There were 68 subjects in this study. Most of the subject were females, being 55.89% in the elderly group and 52.94% in young adults group. The average age was 64.85 ± 3.46 years

(ranged 61 - 73 years) in the elderly group, and 45.12 ± 11.24 years (ranged 23- 59 years) in the young adults group (Table 1).

The were no significant difference in terms of the mean body mass index (BMI), mean hemoglobin (Hb), and mean leukocyte count between the elderly and young adult groups (p>0.05) (Table 2).

Total serum meningococcal-specific IgG levels: Before vaccination, the lowest total serum meningococcal-specific IgG level in the young adult group was 0.67 µg/mL. After vaccination, it was 13.51 µg/mL. The highest total serum meningococcal-specific IgG level was 12.65 µg/mL before vaccination and 18.57 µg/mL after vaccination. The mean total serum meningococcal-specific IgG level in the young adult group after MenACWY-CRM197 vaccination increased significantly from 3.79 ± 2.88 µg/mL to 16.71 ± 1.68 µg/mL (p <0.001, Wilcoxon Sign Rank Test).

In the elderly group, the total serum meningococcal-specific IgG levels ranged 0.61 - 11.73 µg/mL before vaccination and ranged 6.18 - 18.39 µg/mL after vaccination. The mean total serum meningococcal-specific IgG level also increased from 3.96 ± 2.87 µg/mL to 14.47 ± 2.58 µg/mL (p <0.001, Wilcoxon Sign Rank Test) (Figure 1).

Both the elderly and young adult group showed significant increase in meningococcal-specific IgG level after vaccination, but the size of the increase was still below the young adult group (p=0.001, independent sample t-test) (Figure 2). There were no side effects of vaccination reported by the study subject during this study period.

TABLE 1.

Subject Characteristics

Variables	Elderly n=34	Young adults n=34
Gender		
Male (%)	44.12	47.06
Female (%)	55.88	52.94
Age (years, mean ± SD)	64.85 ± 3.40	45.11 ± 11.23

TABLE 2.

Clinical Characteristics of Study Subjects

Variables	Elderly n=34	Young adults n=34	p
BMI (kg/m^2)	23.82 ± 2.92	24.90 ± 2.27	0.096
Hb (gr/dL)	13.98 ± 1.49	14.56 ± 1.51	0.118
Leukocytes count (µL)	6.97 ± 1.53	6.83 ± 1.73	0.757

NOTES: BMI - body mass index; Hb - hemoglobin; values were expressed as mean ± SD

DISCUSSION

Our study confirm the influence of immunosenescence on the meningococcal-specific IgG levels in the elderly after vaccination. Although both of the elderly and young adult groups in our study experienced a significant increase in the specific IgG level before and after the vaccination, the size of the antobody changes in the elderly was significantly lower compared to young adults, showing the decreased potential of antibody production in the elderly in response to vaccination.

We did not find any other study comparing the effectiveness of MenACWY-CRM197 in the elderly and young adult group. It might be because meningococcal vaccination is not routinely recommended for elderly population, except for persons who would travel to meningitis belt areas. Meningococcal vaccines for the elderly in America and Europe that have been licensed for use in the elderly are polysaccharide type (MPSV4) (12).

Immune functions deteriorate with age. One way to assess immunosenescence is to test the ability of the elderly to produce antibodies after vaccine administration. Vaccination is one of the most successful strategies to stimulate the immune system in an effort to reduce the number of morbidity and death from infectious diseases. The process of introducing antigens to induce the production of antibodies is an effective immunization process involving the immune and adaptive systems. Although every process and components of the adaptive immune response can be evaluated, antibodies are the final product from a vaccination that can be evaluated easily and inexpensively (13).

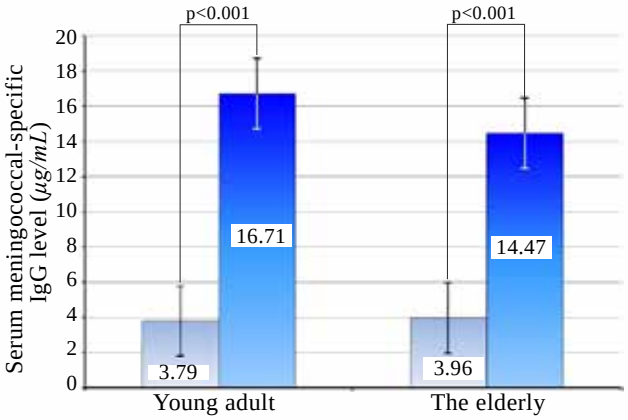

FIGURE 1. *Mean total serum meningococcal-specific IgG levels in young adults and the elderly before (left bars) and after (right bars) MenACWY-CRM197 vaccination. There were significant increase of total serum meningococcal-specific IgG level after MenACWY-CRM197 vaccination both in young adults and the elderly groups (p<0,001, Wilcoxon Sign Rank Test)*

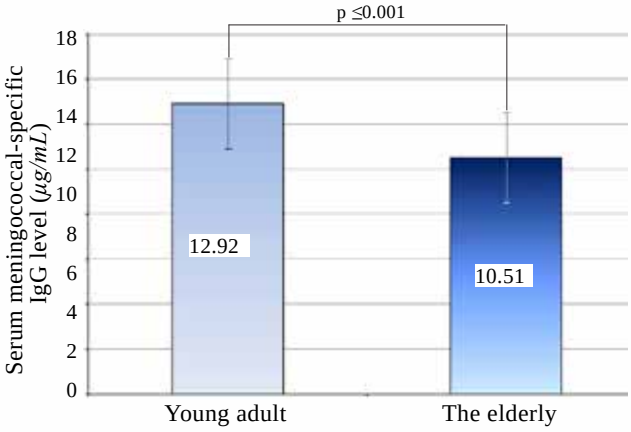

Figure 2. *Increase (Δ) in total serum meningococcal-specific IgG from basal levels after MenACWY-CRM197 vaccination in young adults and the elderly groups. Although both groups experienced an increase in total serum meningococcal-specific IgG level after MenACWY-CRM197 vaccination, the increase (delta) in the elderly group was significantly less than in young adults group (p≤0,001, Independent t-test)*

Research on the effect of age on the vaccination response is mostly conducted using vaccines that are routinely recommended in old age such as influenza and pneumococcus. In North America, Japan and Europe, the antibody response to influenza vaccination in the elderly had been compared to young adults. The results suggest that an increase in age has a significant effect on decreased vaccination response as measured by seroconversion, seroprotection and antibody levels for all H1N1, H3N2 and B influenza virus subtypes. Further analysis showed significant differences in seroconversion, seroprotection and antibody levels between individuals aged <75 and those who 75 years old for all influenza subtypes (14). In North America, Europe and Israel, the influenza vaccination responses in individuals of 18-59 year and >60-year age group were compared. The vaccination responses were measured as seroconversion, seroprotection and antibody levels for all subtypes of H1N1, H3N2 and B influenza. All of those parameters were significantly lower in the elderly compared to the young adult group (15). Hence, although there is an increase in antibody titers after vaccination in elderly and might be capable of providing protective effect, it is not as good as in young adults. These findings should inflict the question of whether the elderly will benefit from the vaccination or not.

Another study in Brazil enrolled 102 elderly people with average age of 71 years. Compared to young adult group, the elderly group experienced an increase in pneumococcal antibody titer up to protective level but not as good as in young adult group (16). There was a significant reduction of pneumococcal antibody titer after vaccination in people at age of >85 years (17). Other study also confirmed the significant reduction of pneumococcal antibody titer after vaccination in people at age of >77 years (18).

The evaluation of the vaccine effectiveness in the elderly, especially in the middle old age group (70-79 years old) and the very old group (>80 years old) were very rarely done (9). The aim of vaccination in the elderly is different from vaccination in children which aimed to eliminate the incidence of infection such as measles and polio. Vaccination in the elderly usually aimed to reduce the severity of infectious diseases, reduce the exacerbation of the underlying chronic illness, reduce functional decline and frailty, hospital care, and mortality (1). With the increasing age, the effects of the immunosenescense will also profound, requiring a separate strategy for vaccination to provide the expected response in the elderly. Efforts were undertaken such as using increased doses of vaccines, the use of more immunogenic antigen components, refinements in vaccine administration techniques, and the use of adjuvants and immunomodulators. The world's elderly population is increasing, and it will have an increasing impact on health problems including the infectious diseases burden (19).

Hajj and umrah pilgrims are required to have meningococcal vaccinations before departure to Saudi Arabia. There are growing numbers of Indonesian pilgrims departing for hajj or umrah, reaching to 817,000 individuals each year (20). With that huge number, Indonesia is a huge market share for meningococcal vaccine. It is certainly necessary to evaluate the effectiveness and side effects of meningococcal vaccine in the Indonesian population. Meningococcal MenACWY-CRM197 vaccines were used in Indonesia only based on the results of the research conducted in Western populations. Currently there are no studies that evaluate the effectiveness and side effects of this vaccine in Indonesian population. Our study confirmed that the vaccine is effective and there were no side effects reported by the subjects. More studies with bigger sample size and with other types of vaccination should be done to evaluate the influence of immunosenescence to the antibody response in our population. If there is a profound effect of immunosenescence, then a specific vaccination strategy should be implied.

Conclusion

Our study confirmed that after MenACWY-CRM197 vaccination there were a significant increase in total serum meningococcal-specific IgG level both in the elderly and young adult groups, but the changes in the elderly subjects were significantly less than in the young adult subjects, which likely due to immunosenescence process.

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