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한국의 건강한 소아청소년을 대상으로 한 인플루엔자 사백신의 면역원성과 안전성 연구

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Immunogenicity and Safety of Inactivated Influenza Vaccine in Healthy Korean Children and Adolescent

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Purpose: This study aimed to evaluate the immunogenicity and safety of a trivalent inactivated influenza vaccine (TIV) among healthy Korean children and adolescents.

Methods: From October to December 2008, 65 healthy patients aged 6 months to 18 years who visited Korea University Ansan Hospital for influenza vaccination were enrolled in this study. We measured the hemagglutinin inhibition antibody titers at baseline and 30 days after vaccinating enrollees with split influenza vaccine and calculated the seroprotection rates, geometric mean titers, and seroconversion rates. Local and systemic adverse events were assessed after vaccination.

Results: The seroprotection rates against all three viral strains (A/H1N1, A/H3N2, B) were 87.7%, 89.2%, and 89.2% (≥70%), respectively; seroconversion rates were 44.6%, 73.8%, and 63.1% (≥40%), respectively; and seroconversion factors were 4.5, 8.4, and 10.5 (>2.5), respectively. The TIV immunogenicity was acceptable according to the CPMP (Committee for Proprietary Medicinal Products) criteria. Although 48 patients (73.8%) reported one or more adverse events, no severe adverse events such as anaphylaxis and convulsion were observed. Forty-two patients (64.6%) reported a local skin reaction, including redness (29.2%), pain (43.1%), or swelling (41.5%) of the injected site, and 26 (40.0%) reported a systemic reaction: fatigue (23.1%), myalgia (20.0%), headache (10.8%), arthralgia (10.8%), chills (9.2%), or fever (7.7%).

Conclusions: This study shows that the immunogenicity of the TIV vaccine is acceptable. As there were no serious adverse events aside from local reactions and mild systemic reactions, this vaccine can be safely used among healthy Korean children and adolescents.

Key Words: Influenza vaccines; Immunogenicity, vaccine; Safety

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Introduction

Influenza infection causes an acute febrile illness mainly of the respiratory type. It can also increase hospitalization and mortality rates in high-risk groups[1-3].

The prevalence of influenza is the highest among children and adolescents, and these groups play an

important role as a mediator by shedding more viruses longer than adults and by making close contact with each other in the family or at school. Therefore, prevention of influenza in childhood is important socioeconomically[4,5].

According to the Organization for Economic Cooperation and Development (OECD) Health Data, in 2015[6], the influenza vaccination rate among people aged 65 and older was 81.7% in Korea, which is the highest among OECD countries. According to data from the Commissioner of Statistics Korea and the Centers for Disease Control and Prevention, in 2015[7], the rate of influenza vaccination among children and adolescents aged 1 to 18 years was 49.3%, indicating that about half of all children and adolescents get the influenza vaccine every year.

However, there are limited immunogenicity and safety data on Korean children and adolescents. This study was aimed at evaluating the immunogenicity and safety of an inactivated split influenza vaccine, which is widely used in Korea, among healthy Korean children and adolescents[8-11].

Materials and Methods

1. Study population

From October to December 2008, healthy children and adolescents, aged 6 months to 18 years, who visited the Department of Pediatrics, Korea University Ansan Hospital, for influenza vaccination were included in the study. Of the 68 patients who agreed to participate in the study with informed consents, three withdrew and 65 completed the study. We collected demographic information and data on the medical history and immunization history from the subjects. Height, weight, and body temperature were measured, and physical examination was conducted. This study was reviewed and approved by the Institutional Review Board of Korea University Ansan Hospital (IRB number: AS0857).

2. Vaccination and blood sampling

The split vaccine used in this study was Vaxigrip® (SPL influenza vaccine; Aventis Pasteur MSD, Lyon, France). Vaxigrip contained three inactivated viral strains: (1) A/Brisbane/59/2007 (H1N1) strain (IVR-148), (2) A/Uruguay/716/2007 (H3N2) strain (NYMCX-175C), and (3) B/Florida/4/2006 strain. After the baseline blood sampling (5 mL), the vaccine was injected, and the adverse effects were monitored at the hospital for 30 minutes. The second blood sampling was performed 30 days after the first shot in each primed subject and 30 days after the second shot in the unprimed group. The vaccine was injected intramuscularly (deltoid or upper lateral thigh) in 0.25-mL volume. Usually, one dose was given, and in the case of no influenza vaccination history, two doses were injected at a 1-month interval.

3. Antibody assays

Anti-hemagglutinin antibody titers were determined by the hemagglutinin inhibition (HI) test. Anti-hemagglutinin titers toward H1N1 were measured by means of A/Brisbane/59/2007 (H1N1) strain (IVR-148), titers to H3N2 were measured by means of A/Uruguay/716/2007 (H3N2) strain (NYMCX-175C), and titers to influenza B were measured using B/Florida/4/2006 strain.

4. Immunogenicity

The seroprotection rate, seroconversion rate, geometric mean titer (GMT), and seroconversion factor were calculated from the antibody titers for the three viruses (A/H1N1, A/H3N2, and B) whose antigens were contained in the vaccine. Afterwards, immunogenicity was assessed based on the CPMP (Committee for Proprietary Medicinal Products) standards[12,13]. According to these standards, in case of healthy adults aged 18 to 60, if at least one of the following three conditions is met, then the vaccine is immunogenic: (1) the seroprotection rate of 70% or higher; (2) the seroconversion rate is 40% or higher; (3) the seroconversion factor (GMT ratio, which is the ratio of GMT values of HI pre- and post-vaccination) is greater than 2.5-fold.

The seroprotection rate was defined as the percentage of people with the HI antibody titer of 1:40 or better. The seroconversion rate was defined as: the percentage of participants whose post-vaccination HI

antibody titer reached 1:40 or better among those with the baseline titer 1:10 or weaker; or increased fourfold or more among those with the baseline titer 1:10 or stronger. The seroconversion factor is the GMT fold increase after vaccination relative to GMT before vaccination.

5. Adverse events

Immediately after the vaccination, the examiner monitored possible emergence of immediate and serious adverse events such as anaphylaxis, allergic asthma, and angioedema for 30 minutes at the hospital. A diary was kept by each guardian until the 7th day, and adverse events were subdivided into systemic reactions and local reactions. Redness, pain, swelling, and ecchymosis were recorded as four types of local reaction, whereas fever, chills, fatigue, headache, myalgia, and arthralgia were recorded as six types of systemic reaction. The participants were instructed to report convulsions and serious adverse events immediately to the examiners. The recorded adverse-event diaries were collected 30 days after the injection. In case of the second injection, the adverse events were monitored in the same manner as after the first injection, and the diaries were collected 30 days after the second injection.

6. Statistical analysis

These analyses were performed in the SPSS version 20.0 (IBM Co., Armonk, NY, USA). The statistical methods for age-specific comparisons of immunogenicity, seroconversion rates, and serum protection rates were as follows: the chi-square test, one-way analysis of variance for discontinuous variables, and the t-test for continuous variables. Differences with $P<0.05$ were considered statistically significant.

Results

1. Characteristics of subjects

Of the 68 patients who agreed to participate in the clinical trial, three withdrew, and 65 completed the study. The 65 subjects were subdivided into two groups by age: (1) 6- to 59-month-olds, 31 subjects (47.7%); and (2) 5- to 18-year-olds, 34 subjects (52.3%). The mean age±standard deviation was 5.9±4.1 and the sex ratio was 33 (50.8%) to 32 (59.2%). Fifty-seven subjects were influenza vaccine primed, and eight subjects were influenza vaccine unprimed (Table 1).

2. Immunogenicity of influenza vaccine

Trivalent inactivated influenza vaccine (TIV) was successfully induced immunogenicity in most subjects. Seroprotection rate for H1N1, H3N2, B were 87.8%, 89.2%, and 89.2%, respectively. Seroconversion rate were 44.6%, 73.8%, and 63.1%. GMT ratio were 4.5, 8.4, and 10.5 (Table 2).

1) Immunogenicity comparison by age

We compared immunogenicity of TIV by age (Table 3). The seroprotection rate toward the inactivated H1N1 virus was 80.6% in the 6- to 59-month-old group and 94.1% in the 5- to 18-year-old group (P=0.021). The seroprotection rates toward the H3N2 virus were 83.9% and 94.1%, respectively (P=0.042). The seroprotection rates for influenza B virus were 83.9% and 94.1%

Table 1. Demographic Characteristics

Characteristic	Total subjects (n=65)
Age	
6–59 mo	31 (47.7)
5–18 yr	34 (52.3)
Mean age (yr)	5.9±4.1
Sex	
Male	33 (50.8)
Female	32 (59.2)
Pre-vaccination history	
Primed	57 (87.7)
Unprimed	8 (12.3)

Values are presented as number (%) or mean±standard deviation.

Table 2. Immunogenicity of Subjects

	A/H1N1	A/H3N2	B	CPMP standards
Seroprotection rate (%)	87.7	89.2	89.2	≥70%
Seroconversion rate (%)	44.6	73.8	63.1	≥40%
GMT ratio	4.5	8.4	10.5	>2.5-fold

Abbreviation: CPMP, committee for proprietary medicinal products; GMT, geometric mean titer.

(*P*=0.042).

The seroconversion rate toward the H1N1 virus was 51.6% in the 6- to 59-month-old group and 38.2% in the 5- to 18-year-old group (*P*=0.398). The seroconversion rate for the H3N2 virus was 80.6% and 67.6%, respectively (*P*=0.620). The seroconversion rates for the influenza B virus were 74.2% and 52.9% (*P*=0.152).

The GMT ratio for H1N1 virus was 6.7 in the 6- to 59-month-old group and 3.0 in the 5- to 18-year-old group (*P*=0.026). The GMT ratios for H3N2 virus were 8.5 and 8.7, respectively (*P*=0.284). The GMT ratios for influenza B were 6.4 and 7.5, respectively (*P*=0.024).

2) Immunogenicity comparison by vaccination history

We compared the immunogenicity of TIV by vaccination history (Table 4). The seroprotection rate toward the H1N1 virus was 91.2% in the primed group and 62.5% in the unprimed group (*P*=0.021). The seroprotection rates for the H3N2 virus were 87.7% and 100% (*P*=0.294), whereas the seroprotection rates for influenza B were 89.5% and 87.2%, respectively (*P*=0.866).

The seroconversion rate for the H1N1 virus was 42.1% in the primed group and 62.5% in the unprimed group (*P*=0.284). The seroconversion rates for the H3N2 virus were 71.9% and 100% (*P*=0.084), whereas the seroconversion rates for influenza B were 59.6% and 87.5%, respectively (*P*=0.126).

The GMT ratio for the H1N1 virus was 4.1 in the primed group and 8.0 in the unprimed group (*P*=0.405). The GMT ratios for the H3N2 virus were 8.1 and 26.9 (*P*=0.033), and for influenza B virus 9.0 and 29.4, respectively (*P*=0.059).

3. Adverse drug events for influenza vaccine

There were no severe adverse events, and the most

Table 3. Comparison of Immunogenicity of Influenza Vaccine According to Age Groups

	6–59 mo (n=31)	5–18 yr (n=34)	Total (n=65)	*P*-value
H1N1				
Pre-vaccination HI Ab ≥1:40 (%)	11 (35.5)	25 (73.5)	36 (55.4)	<0.001
Post-vaccination HI Ab ≥1:40 (%)	25 (80.6)	32 (94.1)	57 (87.7)	0.021
Seroconversion (%)	16 (51.6)	13 (38.2)	29 (44.6)	0.398
Pre-vaccination GMT	20.0	72.0	38.3	0.015
Post-vaccination GMT	134.5	219.3	172.4	0.329
GMT ratio	6.7	3.0	4.5	0.026
H3N2				
Pre-vaccination HI Ab ≥1:40 (%)	10 (32.3)	20 (58.8)	30 (46.1)	0.017
Post-vaccination HI Ab ≥1:40 (%)	26 (83.9)	32 (94.1)	58 (89.2)	0.042
Seroconversion (%)	25 (80.6)	23 (67.6)	48 (73.8)	0.620
Pre-vaccination GMT	16.8	36.0	27.8	0.194
Post-vaccination GMT	170.7	313.3	232.4	0.107
GMT ratio	8.5	8.7	8.4	0.284
B				
Pre-vaccination HI Ab ≥1:40 (%)	5 (16.1)	18 (52.9)	23 (35.4)	<0.001
Post-vaccination HI Ab ≥1:40 (%)	26 (83.9)	32 (94.1)	58 (89.2)	0.042
Seroconversion (%)	23 (74.2)	18 (52.9)	41 (63.1)	0.152
Pre-vaccination GMT	8.8	33.1	17.2	0.004
Post-vaccination GMT	128.8	248.7	179.9	0.126
GMT ratio	6.4	7.5	10.5	0.024

Values are presented as number (%).
GMT ratio is defined as division of post-GMT by pre-GMT.
Abbreviations: HI, hemagglutinin inhibition; GMT, geometric mean titer.

Table 4. Comparison of Immunogenicity of Influenza Vaccine between Primed and Unprimed Group

	Primed (n=57)	Unprimed (n=8)	*P*-value
H1N1			
Pre-vaccination HI Ab ≥1:40 (%)	34 (59.6)	2 (25.0)	0.065
Post-vaccination HI Ab ≥1:40 (%)	52 (91.2)	5 (62.5)	0.021
Seroconversion (%)	24 (42.1)	5 (62.5)	0.284
Pre-vaccination GMT	43.6	15.4	0.305
Post-vaccination GMT	180.7	123.4	0.370
GMT ratio	4.1	8.0	0.405
H3N2			
Pre-vaccination HI Ab ≥1:40 (%)	28(49.1)	2 (25.0)	0.200
Post-vaccination HI Ab ≥1:40 (%)	50 (87.7)	8 (100.0)	0.294
Seroconversion (%)	41 (71.9)	8 (100.0)	0.084
Pre-vaccination GMT	27.8	10.9	0.153
Post-vaccination GMT	224.9	293.4	0.588
GMT ratio	8.1	26.9	0.033
B			
Pre-vaccination HI Ab ≥1:40 (%)	22 (38.6)	1 (12.5)	0.148
Post-vaccination HI Ab ≥1:40 (%)	51 (89.5)	7 (87.5)	0.866
Seroconversion (%)	34 (59.6)	7 (87.5)	0.126
Pre-vaccination GMT	19.3	7.7	0.140
Post-vaccination GMT	174.2	226.3	0.610
GMT ratio	9.0	29.4	0.059

Values are presented as number (%).
GMT ratio is defined as division of post-GMT by pre-GMT.
Abbreviations: HI, hemagglutinin inhibition; GMT, geometric mean titer.

frequent one was a local skin reaction. The total number of subjects who reported one or more local and/or systemic reaction was 48 (73.8%). Forty-two subjects (64.6%) reported a local skin reaction such as redness (29.2%), pain (43.1%), and/or swelling (41.5%) of the injected site, and 26 subjects (40.0%) reported a systemic reaction: fatigue (23.1%), myalgia (20.0%), headache (10.8%), arthralgia (10.8%), chills (9.2%), and/or fever (6.2%) (Table 5).

In the comparison by age groups, 17 out of 31 subjects (54.8%) in the 6- to 59-month-old group and 31 out of 34 subjects (91.2%) in the 5- to 18-year-old group reported one or more adverse events (P<0.001). A local reaction was reported by 14 subjects (45.1%) and 28 subjects (82.3%), respectively (P<0.001). Eight subjects (25.8%) and 18 subjects (52.9%) reported a systemic reaction, respectively (P=0.007).

In the comparison by vaccination history, 48 out of 57 subjects (84.2%) in the primed group and four out of eight subjects (50.0%) in the unprimed group reported one or more adverse events. A local reaction was reported by 41 subjects (71.9%) and two subjects (25.0%), whereas 24 subjects (42.1%) and four subjects (50.0%) reported a systemic reaction, respectively.

Discussion

This study was conducted to investigate the immunogenicity and safety of an inactivated split influenza vaccine that is widely used in Korea, among healthy children and adolescents.

The European Medicines Evaluation Agency decides that an influenza vaccine (that is administered every year) is immunogenic when it meets at least one of the three criteria for adults aged 18 to 60 years. These CPMP criteria were applied to our subjects who were aged 6 months to 18 years in this study[12,13]. Among all the subjects, seroprotection rates toward viruses H1N1, H3N2, and B were >70%; seroconversion rates for the three inactivated viruses in the vaccine were >40%; and the serum conversion factor for the three viral strains were >2.5. Based on these results, it was confirmed that the immunogenicity was acceptable according to the CPMP standards (Table 2).

In Korea, nationwide free inactivated split influenza vaccination of 6- to 59-month-old children was started in September 2017. Therefore, in this study, we tried to compare immunogenicity by subdividing the subjects into two age groups: the 6- to 59-month-old group and 5- to 18-year-old group (Table 3). There are not many studies on the efficacy and effectiveness of

Table 5. Local and Systemic Adverse Events

	Total (n=65)	Age			Pre-vaccination status		
		6–59 mo (n=31)	5–18 yr (n=34)	*P*-value	Primed (n=57)	Unprimed (n=8)	*P*-value
Subjects experiencing local reactions (%)	42 (64.6)	14 (45.1)	28 (82.3)	<0.001	41 (71.9)	2 (25.0)	0.008
Redness	32 (49.2)	6	17	0.268	31	1	0.026
Pain	28 (43.1)	3	13	<0.001	27	1	0.042
Swelling	27 (41.5)	2	15	0.026	27	0	0.013
Subjects experiencing systemic reactions (%)	26 (40.0)	8 (25.8)	18 (52.9)	0.007	24 (42.1)	4 (50.0)	0.679
Fever	5 (7.7)	3	2	0.573	4	1	0.593
Chill	6 (9.2)	1	5	0.114	6	0	0.343
Fatigue	15 (23.1)	3	12	0.014	13	2	0.892
Headache	7 (10.8)	0	7	0.003	7	0	0.265
Myalgia	13 (20.0)	3	10	0.026	12	1	0.809
Arthralgia	7 (10.8)	0	7	0.007	7	0	0.301
Subjects experiencing ADE (%)	48 (73.8)	17 (54.8)	31 (91.2)	<0.001	48 (84.2)	4 (50.0)	0.077

Values are presented as number (%).
Abbreviation: ADE, adverse drug event.

the inactivated influenza vaccine in children, and some studies have shown that immunogenicity of the vaccine is lower in infants than in adolescents and adults[14-17]. According to one study, the rate of conversion of the antibody to a titer of 1:40 or better after vaccination is approximately 40% to 80% among children younger than 6 years, and 70% to 100% among children older than 6 years[18]. There are some studies presenting differences in immunogenicity by age as described above. However, recent studies showed that influenza vaccines are effective enough for children under 2 or 3 years of age[19-21]. Therefore, we wanted to evaluate the age differences in immunogenicity of an influenza vaccine.

In this study, the seroprotection rates toward viruses H1N1, H3N2, and B in the two age groups were in compliance with the CPMP standards (≥70%). This study shows statistically significantly higher seroprotection rates in the 5- to 18-year-old group than in the 6- to 59-month-old group, and this finding is consistent with other studies, indicating that the immunogenicity of the inactivated vaccine increases with age[22]. These results can be discussed in terms of HI antibody levels prior to influenza vaccination. In this study, the proportion of subjects with HI antibody of 1:40 or better before the vaccination was determined in each age group, 6- to 59-month-olds versus 5- to 18-year-olds (Table 3): 35.5% versus 73.5% (P=0.001) for the H1N1 virus; 32.3% versus 58.8% (P=0.017) for the H3N2 virus; and 16.1% versus 52.9% (P<0.001) for influenza B. These data suggest that there is a contribution to the pre-existing immunity by the current vaccination. This finding is similar to the results of a study on hospital workers between the ages of 18 and 60, namely, that they already have high levels of the HI antibody before influenza vaccination[20].

Although the difference was not statistically significant, the seroconversion rate tended to be higher in the younger age group. The reason for the low seroconversion rate in the 5- to 18-year-old group may be that the HI antibody was already upregulated prior to vaccination, and accordingly, the number of subjects whose antibody level increased 4-fold or more after the vaccination was relatively low. The seroconversion rate toward the H1N1 virus in the 5- to 18-year-old group was less than 40%, which is insufficient according to the CPMP standards. Because the seroprotection rate was 94.1%, overall immunogenicity was good.

The GMT ratios (i.e., the seroconversion factor) for viruses H1N1, H3N2, and B met the CPMP standards (>2.5) in both age groups. In the analysis of pre- and post-vaccination GMT of each viral strain by age of the participants, the H1N1 virus' pre-vaccination GMTs were 20.0 and 72.0 (P=0.015), and post-vaccination GMTs were 134.5 and 219.3 (P=0.329), respectively. The H3N2 virus's pre-vaccination GMTs were 16.8 and 36.0 (P=0.194), and post-vaccination GMTs were 170.7 and 313.3 (P=0.107). Influenza B virus' pre-vaccination GMTs were 8.8 and 33.1 (P=0.004), and post-vaccination GMTs were 128.8 and 248.7 (P=0.126). Viruses H1N1 and B showed a statistically significant difference in pre-vaccination GMT between the two age groups, but post-vaccination GMT showed no statistically significant difference between the two age groups.

According to the comprehensive analysis of the results by age, this study shows statistically significantly higher seroprotection rates in the 5- to 18-year-old group than in the 6- to 59-month-old group for all three viral strains, and the seroconversion rate tended to be higher in the younger age group albeit statistically not significantly. These age differences may be closely related to differences in the immunity already obtained before vaccination.

Eight of the 65 subjects (12.3%) were first-time vaccine recipients, all under 5 years of age. In this study, two vaccinations were administered to unprimed subjects with a 1-month interval (Table 4).

The seroprotection rate toward the H1N1 virus showed a statistically significant difference between the primed and unprimed group. The numbers of subjects with the HI antibody titer 1:40 or better before vaccination against influenza viruses H1N1, H3N2, and B were two (25.0%), two (25.0%), and one (12.5%) among the eight unprimed subjects, and 34 (59.5%), 28 (49.1%), and 22 (38.6%) among the 57 primed subjects. These results suggest that there is a difference in immunogeni-

city between unprimed and primed groups before influenza vaccination. This is because the percentages of subjects with the HI antibody titer 1:40 or better before vaccination were 35.5%, 32.3%, and 16.1% in the 6- to 59-month-old group, and 73.5%, 58.8%, and 52.9% in the 5- to 18-year-old group. The percentage of primed subjects is higher in the older group, meaning the pre-existing immunity against influenza was stronger in older group.

As for the seroconversion rate, there was no statistically significant difference between the unprimed group and primed group. However, when the *P*-value for the seroconversion rate comparison for the H3N2 virus is 0.084, it is likely that there will be a significant difference between the two groups when the number of subjects is increased. The seroconversion rates toward viruses H3N2 and B were high, at 100% and 87.5%, respectively, whereas this rate for the H1N1 virus was low, 62.5%. In the case of the primed group, the results are similar. Thus, the seroconversion rate toward the H1N1 virus was relatively low regardless of the vaccination history. In the case of the H3N2 virus, the seroconversion rate was relatively high: 100% in the unprimed group and 71.9% in the primed group, indicating excellent immunogenicity because of its age-independent pattern.

The GMT ratio (i.e., the seroconversion factor) for the H1N1 virus was 4.1 in the primed group and 8.0 in the unprimed group (*P*=0.405). The GMT ratios for the H3N2 virus were 8.1 and 26.9 (*P*=0.033), and for influenza B virus 9.0 and 29.4, respectively (*P*=0.059). Among the subjects whose antibody titers increased more than 4-fold after the influenza vaccination, the proportion of subjects with a final antibody titer of 1:40 or better tended to be lower among the primed subjects than among the unprimed subjects. The GMT ratios for viruses H3N2 and B were significantly higher in the unprimed group than in the primed group; this result may be related to the higher pre-existing HI antibody titer.

In general, the most commonly reported adverse events after influenza vaccination are local reactions and fever[23]. Neuzil and Edwards[24] reported no serious adverse events in trials of an inactivated TIV among children between 1 and 16 years of age and stated that local reactions occurred in 6% to 14% of the subjects. And other studies have documented local reactions such as vaccinated site pain, redness, and swelling in 25% of the subjects[25,26]. The local reaction rates varied widely because in most of the studies, adverse events were self-reported by participants. However, in this study, local adverse event rate was particularly high as 64.6%. This may be due to that adolescents have a high level of awareness of adverse events and they constituted a relatively large portion of the total population[27]. In our study, the local adverse event reporting rate was significantly higher in the 5- to 18-year-old group than 6- to 59-month-old group (82.3% vs. 45.1%, *P*<0.001). As evidence to support this, in other two studies on healthy adults[28,29], local adverse events were reported at high rates as 56.3% and 78.0%, respectively. However, the objective index, fever, was 9.0% and <5%, respectively, similar to 7.7% of this study. Although the rates of objective adverse events are similar, rates of subjective adverse events can vary depending on the age and the degree of awareness of the target groups. According to a non-randomized cohorts study in 106 pediatric participants under 36 months, there was no significant difference between the subunit vaccine and the split vaccine, suggesting that local adverse reaction rates do not differ depending on the vaccine formulation[30].

Masurel et al.[31] reported that adverse reactions are more frequent in the unprimed group. However, in the present study, the older group, which had a higher vaccination rate, reported a greater number of systemic adverse reactions. This is probably because the systemic reactions almost all consisted of subjective symptoms self-reported by the subjects, e.g., fatigue, myalgia, headache, and arthralgia. Therefore, when comparing only the fever, which is an objective indicator, there was no significant difference in two groups (*P*=0.593).

Starting from September 2017, KCDC has begun free nationwide influenza vaccination for children in 6 to 59 months age group. Thus, our study can be meaningful

in that we have added basic data on immunogenicity and safety in the target age group of the policy. This study also included data comparing the unprimed and primed group.

The limitation of this study is that the study was performed in a single center; thus, the number of subject was small. Sixty-five subjects are difficult to generalize, and especially the unprimed subjects were only eight. In addition, studies on the comparison with the placebo group will be necessary to verify the safety of influenza vaccine itself. Therefore, multicenter randomized trial is needed in future studies. Also, it is necessary to develop objective indicators that can evaluate the adverse events. In addition, multi-year data should be constructed because influenza vaccine strains change every year.

In conclusion, this study shows that the seroprotection rate, seroconversion rate, and GMT—of the vaccine under study toward influenza viruses H1N1, H3N2, and B—meet the CPMP criteria. There were no serious adverse events aside from local reactions and mild systemic reactions such as fatigue and myalgia. Therefore, this vaccine can be considered relatively safe.

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PEDIATRIC INFECTION & VACCINE PIV

요약

목적: 인플루엔자 유행 예방에 대한 가장 효과적인 방법은 인플루엔자 백신이나 한국의 소아청소년을 대상으로 한 면역원성 및 안전성에 대한 자료가 많지 않다. 이에 본 연구는 국내에서 많이 사용되는 불활성화 3가 백신의 면역원성과 안전성을 확인하고자 하였다.

방법: 2008년 10월부터 12월까지 고려대학교 의료원 안산병원 소아청소년과에 인플루엔자 예방접종을 위해 내원한 건강한 소아청소년 중 임상시험 지원자 65명을 대상으로 하여 접종 전과 접종 후 30일째 혈구응집억제(hemagglutinin inhibition) 항체검사를 시행하고 접종 직후부터 접종 후 7일까지 국소반응과 전신반응을 포함한 이상반응을 관찰하여 기록하도록 하였다.

결과: 분할 인플루엔자 백신의 세 항원(H1N1, H3N2, B) 각각에 대한 접종 후 혈청보호율은 87.7%, 89.2%, 89.2% (≥70%)였으며 혈청전환율은 44.6%, 73.8%, 63.1% (≥40%), 혈청전환인자는 3.35, 7.18, 5.13 (>2.5)으로 Committee for Proprietary Medicinal Products (CPMP) 기준을 만족하였다. 전체 피험자 65명 중 48명(73.8%)이 백신 접종 후 이상반응을 보고하였으나 아나필락시스나 경련과 같은 심각한 이상반응은 없었다. 발적(29.2%), 동통(43.1%), 종창(41.5%)과 같은 국소반응을 보고한 피험자는 42명(64.6%)이었고, 권태(23.1%), 근육통(20.0%), 두통(10.8%), 관절통(10.8%), 오한(9.2%), 발열(7.7%) 등과 같은 전신반응을 보고한 피험자는 26명(40.0%)이었다.

결론: 6개월에서 18세까지의 소아청소년을 대상으로 한 불활성화 3가 백신의 면역원성과 안전성에 대한 연구 결과 H1N1, H3N2, B 항원 모두 CPMP 기준에 부합하여 적합한 면역원성이 있는 것으로 나타났으며, 국소반응 및 경미한 전신반응 이외에 심각한 이상반응은 보이지 않아 비교적 안전하다고 판단된다.