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Original Article

Adverse Events of Trivalent Influenza Vaccine among Health Care Workers in Iran

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Abstract

Background: To assess the frequency and type of adverse events after influenza vaccination in Iranian adults.
Methods: Health care workers in 7 medical centers received the influenza vaccine from October 2006 to February 2007 and followed by phone regarding symptoms experienced after vaccination.
Results: Of 897 adults who participated in the study, local and systemic reactions were reported by 187 (20.8%) and 198 (22.1%) persons, respectively. The most common local reaction was pain (20.2%), while myalgia (15.8%) was the most common systemic reaction. One case of Guillain-barre syndrome was reported.
Conclusion: Inactivated influenza vaccine administration did not result in potential adverse events in healthy adults.

Keywords: *Influenza, Vaccination, Adverse events, Healthy adults*

Introduction

Influenza is an acute respiratory illness caused by various influenza viruses. The illness affects the upper or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia and weakness (1). Influenza is a highly contagious, globally spread viral disease. The high degree of viral antigenic variability (antigenic drift) is responsible for seasonal recurring epidemics and less frequent pandemics (2-5). Outbreaks of variable extents and severity of the illness occur nearly every winter. Such outbreaks result in significant morbidity and mortality in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications (1).

Vaccination of people categorized as high-risk for developing complications (i.e. elderly, infants, debilitated individuals, and patients with respiratory, cardiovascular and immunodeficiency diseases including those infected with HIV) or vaccination of persons who can transmit the disease to such high-risk individuals is the most effective measure for reducing the influenza impact, both in terms of cost-effectiveness and cost-benefit ratio (6-8).

Although intranasal vaccines are under development (9), all currently licensed influenza vaccines are inactivated and injecting intramuscular. The composition of the subvirion influenza vaccine includes two types of a antigens and one type of B antigen of the influenza virus (10). These vaccines are all produced from viruses that are propagated in embryonated hen's eggs (11). The U.S. Public Health Service recommends the influenza vaccination for any children between 6 to 59 months and any individual older than 65 yr, those who are at an increased risk for complications of influenza and persons who can transmit influenza to high risk patients like health care workers (HCW). Since commercially available vaccines are inactivated ('killed'), they may be administered safely to immunocompromised patients. The vaccine should be administered early in autumn

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before any influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains (1). Although most individuals will experience no side effects from injected influenza vaccine, one of the major barriers to influenza vaccination and especially in HCW is fear of vaccine side effects. Side effects and adverse reactions associated with vaccination are both local and systemic but rarely very severe. The most frequent local reaction which is soreness at the site of vaccination is typically mild and rarely interferes with person's ability to conduct daily activity. Systemic reactions are fever, malaise, myalgia and other symptom that most often affect persons with no previous exposure to influenza virus antigens in the vaccine. Severe adverse events are usually immediate and presumably allergic reactions that rarely occur after influenza vaccination (12).
In this study, we tried to assess the adverse events to influenza vaccination in a group of healthy adult health care workers (HCW), in Iran. We also examined whether the occurrence of adverse events were influenced by the patient's age, sex, previous history of influenza vaccination and other factor

Material and Methods

Study design

This study was a prospective multicentre study to assess the frequency of adverse reactions to the influenza vaccination in a group of healthy adults in Iran. The study was conducted in 7 university affiliated medical centers in Iran ("Medical Universities of Tehran, Mashhad, Tabriz, Gilan, Mazandaran, Zahedan, and Birjand.), from October 2006 to February 2007.

Study population

The targeted population was healthy HCW who were directly and indirectly in charge of caring patients. Subjects with hypersensitivity to egg products, a history of Guillain-Barre syndrome, previous serious reaction to influenza vaccine, an influenza vaccination within the preceding six months, febrile illness (temperature ≥38.0° C) within 24 h before enrollment, or any other condition which may put a person at risk or interfere with his or her participation, were excluded from the study. Health care workers with underlying chronic diseases, immunodeficiency and use of immunosuppressive medication, vaccinated according to indications for vaccination but excluded from the study.
Demographic data along with information related to history of smoking, allergy, type of allergy, previous influenza vaccination, and previous adverse reactions to the vaccination were collected for all participants.
The study protocol was reviewed and approved by the local Institutional Review Board.

Vaccination regimen

The influenza virus subunit vaccine, inactivated with formaldehyde and produced by Solvay Pharmaceuticals (Netherlands), contained A and B strains from the component strains A/New caledonia/20/99(H1N1)-like strain, A/Wisconsin/67/2005/(H3N2)-like strain and B/Malaysia /2506/2004-like strain propagated in embryonated hen's eggs, was used during the study period. The vaccination was administered once to each participant. The dosage per inoculation was 0.5 ml for each subject which was given as a deep subcutaneous or intramuscular injection into deltoid muscle.

Safety assessment

Participants were instructed to measure their oral temperature in the morning and evening for 2 consecutive post-immunization days; assess the site of injection for adverse reactions (redness, swelling, tenderness, limited arm movement and etc.) and report any systemic adverse events (e.g. headache, muscle aches, nausea, vomiting and etc.).
All enrolled participants were followed for adverse events 48 h to 10 d after vaccination by trained investigators. An adverse reaction was defined as local (pain, erythema, or induration at the site of vaccination) and systemic (fever, nausea, vomiting, weakness, myalgia, flashing, pruritus, hypotension, oral cavity edema, headache, drowsiness, face edema, face numbness, paraplegia, vis-

ual disturbance, palpitation, dyspnea, urine incontinency, extremity movement defect, defecation disability and paresthesia).

Statistical analysis

The statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). We used the χ^2 test for independent proportions or Fisher's exact test if the number of expected observations was below six in one or more cells. Multiple logistic regression analysis was used to analyze the joint effect of the independent variables (gender, age, smoking, history of allergy, past medical history, drug history in past 3 months and previous vaccination side effects) on all systemic and local adverse events.

Results

Demographic status

A total of 897 healthy HCW were recruited. Base-line characteristics of the 897 subjects are listed in Table 1. Fifty-seven percent of vaccinated subjects (513 persons) were male. The mean age of the subjects was 35.9±8 (Range 19-58 yr). The mean ages of male and female subjects were 37.4±7.8 and 33.9±8.0 yr, respectively. Three hundred and eighty (42.3%) cases had previous history of influenza vaccination, among them 41(10.7%) had a previous history of at least one mild adverse event.

Adverse events

Table 2 shows the adverse events observed in the subjects who received inactivated influenza vaccine from October 2006 to February 2007. Among 897 subjects, 269 (30%) described an adverse event. Local and systemic reactions were reported by 187 (20.8%) and 198 (22%) individuals, respectively. The most common local adverse reactions to the influenza vaccine were pain (20.1%), whereas the most common systemic reactions were myalgia (15.8%). In participants who experienced pain at the site of injection the duration of pain alleviation was less than 2 d in 115(63.5%). Seventeen (1.9%) and 28(3.1%) participants had erythema and induration at the site of injection for more than 2 d, respectively. Thirteen (1.4%) participants had a fever over 38.5º C. Paraplegia was observed in one patient who managed according to diagnosis of Guillain-Barre Syndrome.

Table 3 gives the results of the multiple logistic regression analysis. Gender had a significant effect on local adverse events (odds ratio= 2.89). Adverse events were more common in women than men after adjustment for other factors. Occurrence of systemic events were influenced by previous history of vaccination side effects (odds ratio= 4.01) and smoking (odds ratio= 3.52). Age did not have an effect on the occurrence of adverse reactions.

One case of Guillain-Barre Syndrome was reported following vaccination. He was a 59 yr old man complained of paresthesia in his lower limbs 9 d after vaccination. He also reported weakness and respiratory failure which developed within hours that followed the paresthesia. He was a smoker. He did not have any history of allergy and no previous influenza vaccination. He was admitted to local hospital, managed according to diagnosis of Guillain-Barre Syndrome and was discharged in good condition one month later. In his hospital admission he also diagnosed as NIDDM and managed accordingly.

Table 1: Characteristics of the study participants in 7 Medical Centers in Iran, October 2006 to February 2007

Characteristic	No. of participants (%)
Gender	
Male	513 (57.1)
Female	384 (42.8)
Occupation	
Clerk	777 (86.6)
Worker	78 (8.6)
Others	24 (2.6)
History of smoking	85 (9.4)
History of allergy	89 (9.9)
Previous influenza vaccination	380 (42.3)
Previous vaccination side effects	41 (10.7)

Table 2: Frequency of adverse events of the study participants who received influenza vaccine in 7 Medical Centers in Iran, October 2006 to February 2007

Characteristic	No. of participants (%)
Local Reaction	
Pain	181 (20.1)
Induration	77 (8.5)
Erythema	39 (4.3)
Pruritus	23 (2.5)
Systemic Reaction	
Myalgia	142 (15.8)
Weakness	123 (13.7)
Headache	94 (10.4)
Fever	84 (9.3)
Nausea	27 (3.0)
Oral cavity edema	21 (2.3)
Paresthesia	18 (2.1)
Palpitation	11 (1.2)
Vomiting	8 (0.8)
Hypotension	7 (0.7)
Flashing	5 (0.5)
Drowsiness	1 (0.1)*
Face edema	1 (0.1)*
Paraplegia	1 (0.1)*
Dyspnea	1 (0.1)*

* Diagnosed later with GBS

Table 3: Results of multiple regression analysis of the effect of independent variables on local and systemic adverse reactions. Values are odds ratios (95% confidence intervals)

Variables	Odds ratio (95% CI)		
	Local reaction	**Systemic reaction**	**Total**
Gender	2.89 (1.54-5.42)*	1.62 (0.86-3.06)	1.97 (1.13-3.46)*
Age	1.01 (0.97-1.05)	1.02 (0.98-1.06)	1.03 (0.99-1.07)
Smoking	1.09 (0.41-2.93)	3.52 (1.58-7.87)*	2.1 (0.97-4.53)
History of allergy	1.27 (0.54-2.86)	0.94 (0.39-2.24)	1.16 (0.54-2.51)
Positive drug history	1.27 (0.64-2.48)	1.42 (0.73-2.77)	1.42 (0.77-2.64)
Previous influenza vaccination side effect	1.92 (0.88-4.17)	4.01 (1.89-8.49)*	3.03 (1.45-6.34)*

* $P<0.01$

Discussion

Recurrent worldwide epidemics of influenza are a major health problem. The illness affects hundreds of millions of people each year, resulting in a high morbidity in people of all ages and a high mortality in high-risk populations (13, 14). Immunization is recognized as one of the most effective strategies for preventing and reducing the risk of influenza infection and its secondary complications, such as pneumonia and death, especially in high-risk population, when there is a good match between the circulating and vaccine influenza strains (15, 16).

Most studies have found a low incidence of local (up to 20%) and systemic (up to 5%) adverse events to influenza vaccination (17-21). However, a Canadian survey showed local side effects in 87% of patients and systemic effects in 49% (22). In our study we found systemic reactions more frequent (22%) than local reactions (20.82%) in the study population.

The most frequent adverse events of the vaccine among adults included soreness at the site of vaccination, affecting 10% to 64% of vaccinated subjects, usually lasting less than 2 d (19, 23, 24). Our results were also consistent with these earlier results. Twenty percent of the participants had pain as a local reaction which in most of them, lasted less than 2 d. Systemic adverse events including fever, malaise, and myalgia, can also occur. These reactions may begin within 6 to 12 h following the vaccination and can last for 1 to 2 d (25). Sixteen percent of our participants had myalgia as a systemic reaction.

Like other studies which suggested that the adverse events are more common in women than in men (26-28), our study also showed that women reported more adverse events than men. Regression analysis also showed that female sex was the main co variable in suffering adverse reactions. We did not find any correlation between age and adverse events as our subjects were all adults (age over 18 yr old). However, two studies have indicated that the age of recipients is important in the development of systemic reactions (26, 29).

Our findings confirmed the results of an earlier study performed by American lung association asthma clinical research center on the safety of inactivated influenza vaccine in adults and children with asthma in 2001 (30). The length of observation in our study was 10 d, which enabled us to detect potentially delayed reactions to the vaccine.

We conclude that the inactivated influenza vaccine administered in healthy HCW did not result in potential adverse events in this study population. However, it remains important to assess the clinical efficacy of the influenza vaccine administration early in the influenza season. Once there is evidence that vaccine efficacy in a given year is zero or very low, it is important to reassess outbreak control policies and reinforce infection control practices. It is also important to consider influenza antiviral prophylaxis regardless of immunization status in high risk populations. Further studies involving greater number of participants are also required to assess the effectiveness of the influenza vaccine in reducing influenza like illness, pneumonia, and death related to pneumonia.

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