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# Safety and tolerability of intradermal influenza vaccination in patients with cardiovascular disease

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**Abstract**

**Background** It is well-established that influenza vaccination reduces adverse cardiovascular outcomes in patients with cardiovascular diseases (CVD), however, the vaccine coverage rate in most countries remains low. The concern about the local adverse effects of intramuscular injection, particularly in CVD patients receiving antithrombotic therapy, is one of the important impediments. This study was conducted to assess the safety, side effects and tolerability of intradermal influenza vaccine in CVD patients. **Methods** This was an observational study in adult CVD patients who had undergone vaccination against seasonal influenza by intradermal vaccination between May 16th and May 30th, 2012 at Maharaj Nakorn Chiang Mai Hospital. The medical history, patients' acceptability and adverse effects were collected using a written questionnaire completed by the patient immediately following vaccination and by a telephone survey eight days later. **Results** Among 169 patients, 52.1% were women and the mean age was 63 ± 12 years. Coronary artery disease, valvular heart disease and dilated cardiomyopathy were present in 121 (71.6%), 40 (23.7%) and 8 (4.7%), respectively. Antithrombotics were used in 89.3%. After vaccination, the pain score was 0, 1 or 2 (out of 10) in 44.4%, 15.1%, and 27.6% of the patients, respectively. Eight days after vaccination, the common adverse reactions were itching 19 (11.9%), swelling 9 (5.7%) and fatigue (4.7%). No hematoma or bruising was reported. **Conclusions** The intradermal influenza vaccination is safe and well tolerates with high rates of satisfaction in CVD patients. This technique should be useful in expanding influenza vaccine coverage.

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## 1 Introduction

Cardiovascular disease (CVD) is a global health problem and one of the leading causes of hospitalization and death.[1] Influenza virus, types A and B, are the common causes of highly contagious acute respiratory illnesses.[2] For most people, the illness usually resolves after about one week, but severe illness can occasionally lead to death.[2–4] CVD patients are at higher risk than the general population for developing serious complications from influenza infection, which may also increase the risk of cardiovascular complications.[4–7] In addition, the association between influenza infection and acute myocardial infarction (AMI) has been documented in several studies.[6] There are several possible mechanisms that may underlie this association. Acute influenza infection may cause high fever, tachycardia or dehydration, increasing the myocardial oxygen demand and precipitating the AMI.[8] Additionally, there is evidence supporting the role of influenza virus in the initiation of atherosclerotic plaque transformation to the plaque causing acute coronary syndrome.[9–11] Furthermore, the benefits of influenza vaccination in the reduction of cardiovascular events have been shown in randomized, controlled trials.[12–15] International guidelines strongly recommend annual influenza vaccination in persons with coronary and other atherosclerotic vascular disease. However, influenza vaccination coverage remains low worldwide, especially in patients with CVD.[16,17] There are numerous barriers to influenza vaccination including the lack of awareness of its benefits by both patients and physicians, the common belief that vaccination is unnecessary, or that vaccination itself causes illness, and concerns about the possible adverse effects of vaccination in patients taking antiplatelet or anticoagulants.[17–20]

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Before the introduction of intradermal influenza vaccine, all influenza vaccines were administered through subcutaneous, or intramuscular routes.[21,22] After evidence showing strong immune response against influenza by intradermal vaccination,[23,24] the micro-needle injection system for intradermal influenza vaccine was developed. This technique may lead to less concerns of local adverse effects of intramuscular injection.[25,26] Furthermore, in the elderly population where the immune response to influenza vaccine is lower than in the younger one, 15 μg intradermal vaccine provided comparable, or superior immunogenicity to intramuscular vaccine.[27–29] However, there are no data regarding the safety and tolerability in CVD patients. Therefore, this study was conducted to assess the safety, side effect profile, and tolerability of influenza vaccine in these patients.

## 2 Methods

This was an observational study in patients who had undergone vaccination against seasonal influenza with intradermal vaccination. The study was approved by the Chiang Mai University Ethics Committee and was done in accordance with the Helsinki Declaration and Good Clinical Practice.

### 2.1 Population

The present study enrolled patients aged ≥ 18 years, who had been regularly followed at the Cardiology Clinic of Maharaj Nakorn Chiang Mai Hospital and received intradermal influenza vaccination. Subjects who had hypersensitivity to egg or chicken proteins, neomycin, formaldehyde or octoxinol-9, or had febrile illness, or acute infection were excluded. Intradermal influenza vaccine 9 μg and 15 μg were given to patients who were younger, and older, than 60 years, respectively. All eligible individuals were asked for participation sequentially as they presented for vaccination to reduce selection bias.

### 2.2 Data collection

Data were collected using a self-administered, written questionnaire completed by the patient just after seasonal influenza vaccination with intradermal influenza vaccine. The questionnaires captured the data of baseline characteristics, history of influenza vaccine injection, perceived risk of contracting influenza; motivation for seeking vaccination, the patients' acceptability of intradermal influenza vaccine and the willingness to receive the vaccine the following year. The pain rating scale (range from 0 to 10 for no pain to the most intense pain sensation) was used to assess the pain quality. Patients' medical history including CVD, co-morbidities and current medications were retrieved from medical records. Eight days after vaccination, patients were contacted by telephone to inquire about any medical safety issues, side effects of intradermal vaccination and the patients' intentions for the next influenza season. The patients were then followed up by telephone every month for the symptoms of upper respiratory tract infection, hospitalization for respiratory tract infection, unplanned hospitalization for CVD, including acute coronary syndrome or heart failure.

### 2.3 Statistical analysis

Data were presented as mean ± SD for continuous variables and as percentage for categorical data. All statistical analyses were performed using SPSS (SPSS Statistic 17.0, Chicago, SPSS Inc.).

## 3 Results

From 225 vaccinated patients in cardiology clinic, 169 patients were recruited into the study. Fifty-six patients were excluded due to the lack of established CVD.

The mean age of the study population was 63 ± 12 years and 52.1% were women. Established CVD comprised stable coronary artery disease in 88 (52.1%) patients; recent acute coronary syndrome 33 (19.5%); valvular heart disease 37 (21.9%) and dilated cardiomyopathy 8 (4.7%). Reported co-morbidities included hypertension 101 (59.8%), diabetes 49 (29.0%), dyslipidemia 99 (58.6%) and chronic kidney disease 21 (12.4%). Most of the patients received antithrombotic agents which included aspirin 79 (46.7%), clopidogrel 6 (3.6%), dual antiplatelets 23 (13.6%), warfarin 43 (25.4%) and warfarin with single antiplatelet agent 2 (1.1%).

### 3.1 Vaccination history and opinions

Most of the patients [159 (94.1%) patients] considered that they were at risk for influenza infection due to chronic illness (Table 1) and 141 (83.4%) patients were vaccinated upon the advice of their doctors. Two-thirds of the patients (107 patients, 63.3%) never received influenza vaccination, while 31 (18.3%) received influenza vaccination every year, 18 (10.7%) every two years and 13 (7.7%) less often than every two years. Reasons cited for not being vaccinated against influenza in the past year included not being encouraged 71 (71.9%), the perception that they were not at risk 4 (3.7%), the fear that they would contact influenza after vaccination 13 (12.1%) and the concern of local adverse effects of injection 13 (12.1%), (Table 1). To be vac-

cinated in the future, the main convincing factors for patients were the annual advice from the physician and the postcard, or e-mail from the hospital in 136 (80.5%) and 22 (13.0%), respectively (Table 2). Among 62 patients that had previously received intramuscular influenza vaccination, 59 (95.2%) preferred the intradermal vaccination in the following year.

### 3.2 Safety and tolerability

Immediately post vaccination, the pain score (range 0–10) was 0, 1 or 2 in 76 (45%), 25 (14.8%), and 48 (28.4%) patients, respectively (Figure 1). There was only one (0.6%) patient had a pain score more than five. At day 8$^{th}$ after vaccination, 159 patients (94.1%) were contacted by telephone; only 32 (20.1%) developed symptoms in the vaccinated area.

**Table 1. History of prior influenza vaccination.**

| Questions/answers | *n* (%) |
|---|---|
| Reasons for feeling at risk, *n* = 169 | |
| I suffer from a chronic disease | 159 (94.1) |
| I belong to an older age category | 2 (1.2) |
| I have a lot of personal contacts in my daily life | 5 (3.0) |
| I have already had influenza | 1 (0.6) |
| What/who prompted you to be vaccinated this time, *n* = 169 | |
| My doctor | 141 (83.4) |
| My pharmacist | 1 (0.6) |
| Me | 1 (0.6) |
| Nurse | 1 (0.6) |
| Family/friend/people in my environment | 17 (10.1) |
| A media/press campaign | 8 (4.7) |
| How often have you been vaccinated in recent years, *n* = 169 | |
| Every year | 31 (18.3) |
| Every 2 years | 18 (10.7) |
| Less often than every 2 years | 13 (7.7) |
| Never | 107 (63.3) |
| When were you last vaccinated, *n* = 169 | |
| Last year | 32 (18.9) |
| Two years ago | 12 (7.1) |
| Several years ago | 11 (6.5) |
| I do not remember | 7 (4.1) |
| Never | 107 (63.3) |
| What is the main reason why you missed vaccination in recent years, *n* = 107 | |
| I was not encouraged/motivated to be vaccinated | 71 (71.9) |
| I was afraid of the injection/needle size | 4 (3.7) |
| I was afraid of contracting influenza after vaccination | 13 (12.1) |
| I did not think I was at risk of influenza | 13 (12.1) |

The most common symptoms were itching 19 (11.9%), swelling 9 (5.7%), and hive 6 (3.8%) (Table 3). The common systemic symptoms were fatigue and subjective symptoms of fever in 9 (5.7%) and 6 (3.8%), respectively. None

**Table 2. Patients' opinion to be vaccinated against influenza in the future.**

| Questions/answers | *n* (%) |
|---|---|
| What would convince you to be vaccinated against influenza in the future, *n* = 169 | |
| The annual advice of your doctor | 137 (81.1) |
| A postcard or e-mail from hospital | 22 (13.0) |
| A reminder from your pharmacist | 0 (0) |
| Advice from a relative/friend/colleague | 0 (0) |
| A media/press campaign | 9 (5.3) |
| Do not remind | 1 (0.6) |
| Would you consider receiving the influenza vaccine with the micro-needle next year, *n* = 159 | |
| Yes | 156 (98.1) |
| No | 3 (1.9) |

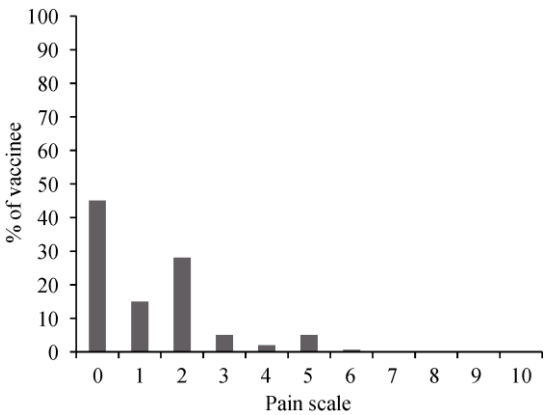


**Figure 1. Pain quality assessment rate (range 0–10).**

**Table 3. Medical safety and side effects post 8 days vaccination (*n* = 159).**

| Symptoms at vaccinated area | *n* (%) |
|---|---|
| Pain | 3 (1.9) |
| Swelling | 9 (5.7) |
| Erythema | 4 (2.5) |
| Hive | 6 (3.8) |
| Itch | 19 (11.9) |
| Other symptoms | |
| Fever | 6 (3.8) |
| Headache | 3 (1.9) |
| Fatigue | 9 (5.7) |
| Discomfort | 1 (0.6) |

of the patients developed hematoma or bruising. One hundred and fifty-six patients (98.1%) would prefer to have intradermal vaccination in the following year.

During 12 months, all of the patients were completely followed up. Of 169 patients, 17 (10.7%) patients experienced symptoms of upper respiratory tract infection, but none was hospitalized for respiratory tract infection. Four (2.4%) patients were hospitalized due to acute coronary syndrome and 12 (7.5%) patients were hospitalized due to heart failure. Six (3.8%) patients died during the follow- up. The causes of death included myocardial infarction (1), heart failure (1), sudden cardiac death (1), stroke (1), renal failure (1) and sepsis (1).

## 4 Discussion

This observational study was the first study of intradermal influenza vaccination acceptability in CVD patients. Sixty-three percent of subjects had never been vaccinated against influenza. Our findings highlighted the important role of physicians in recommending the vaccination. The intradermal influenza vaccination was safe and well tolerated in CVD patients, including patients taking antithrombotic agents.

The benefits of influenza vaccination have been established in patients with coronary artery disease leading to the recommendation as a secondary prevention.[12–14,30] Nevertheless, the vaccine coverage rate is still low.[16,17] There are several barriers cited by patients and physicians to vaccination.[17] In this study, the lack of encouragement from physician, lack of patients' awareness of being at risk and concern for contracting influenza after vaccination were the important objections, which are similar to the findings of other studies. The awareness of physician and health care team to educate the patients about the benefit and risk of vaccination, as well as encouraging patients to receive the vaccine, should be the main tools to expand vaccine coverage.

The safety of intramuscular injection has been demonstrated in patients with coagulopathy,[31] and patients taking oral anticoagulation.[32] Intramuscular influenza vaccination in patients taking warfarin has also been shown to be safe in a prospective cross-over study. The mean prothrombin times, expressed as the International Normalized Ratio (INR) warfarin weekly dose, and time in therapeutic range were similar after receiving the vaccine or placebo with no major bleeding events.[33] Nevertheless, concerns about bleeding complications from influenza vaccination in CVD patients taking antiplatelets and anticoagulants could be an important physicians' barrier to vaccination. In our study, there were no local or systemic bleeding events after intradermal influenza vaccination. Therefore, the micro-needle injection system for intradermal vaccination offers comparable immunogenicity to intramuscular influenza vaccine, but higher acceptability and greater preference especially in the elderly could be a useful tool to improve vaccine coverage.[26]

### 4.1 Study limitations

The present study has some limitations. First, this is an observational study, and therefore, characterized by less stringency as opposed to randomized, prospective, blinded research. Second, the size of the studied population was relatively small. However, this study provides the real life practice regarding safety of intradermal influenza vaccine.

### 4.2 Conclusions

The intradermal influenza vaccination was safe and well tolerated with high rates of satisfaction in CVD patients. This technique should be useful in expanding influenza vaccine coverage.

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