Efficacy of the Trivalent Influenza Vaccination in Thai Patients with Hemodialysis or Kidney Transplant Compared with Healthy Volunteers

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Objective: *To evaluate the immune response to trivalent influenza vaccination in Thai patients with hemodialysis (HD) or kidney transplant (KT) compared with healthy volunteers.*
Material and Method: *This was a cross-sectional study in Thai healthy volunteers and patients with HD and KT who received the trivalent influenza vaccine provided by the Ministry of Public Health of Thailand from 1 November 2011 to 31 December 2011. Each subject was injected intramuscularly with one dose (0.5 milliliter) of trivalent influenza vaccine containing viral strains recommended by the WHO for the 2011 influenza season (southern hemisphere). Blood samples before and 6 weeks after the vaccination were measured for immune response using a hemagglutination-inhibition antibody assay.*
Results: *Subjects consisted of 30 healthy volunteers, 30 patients with HD and 30 patients with KT. Prevalence of pre-vaccination seroprotective (SP) immunity in each group (healthy volunteers, HD, KT) was as follows: against H1N1 (33.3%: 23.3%: 10.0%), H3N2 (80.0%: 26.7%: 23.3%) and B (60.0%: 20.0%: 3.3%) viral strains, respectively. Those who were seronegative (SN) before testing positive after one dose of this vaccine were as follows: H1N1 (100.0%: 73.9%: 74.1%), H3N2 (66.7%: 86.4%: 34.8%) or B (58.3%: 66.7%: 48.3%) viral strains, respectively. The healthy group showed significantly higher SP immune response for H1N1 than the HD and KT groups (p = 0.023). The HD group had significantly higher SP immune response for H3N2 than the KT groups (p = 0.001). Immune responses for the B vaccine in all groups were not different. No major adverse event was found in any group.*
Conclusion: *Immune response for H1N1 vaccine in the HD and KT groups was slightly less than that of the healthy group. Immune response for H3N2 vaccine in the KT groups was less than in the healthy and HD groups. Immune responses for B vaccine in all groups were not different.*

Keywords: *H1N1 influenza A virus infection, Influenza vaccine*

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Influenza is an acute respiratory illness caused by infection with the influenza A or B viruses. It is usually self-limiting and occurs in epidemics worldwide every year. Three subtypes of hemagglutinins (H1, H2, and H3) and two subtypes of neuraminidases (N1 and N2) are usually reported from patients with influenza A infection. In March 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico. During 2009 and 2010, a pandemic of H1N1 influenza A infection was detected on several continents[1]. The influenza vaccination was proved to be effective in preventing seasonal influenza and H1N1 influenza A. During the 2009-2010 pandemic, a monovalent vaccine against pandemic H1N1 influenza A was used, and it was found to be safe and well tolerated. Serious complications, such as anaphylaxis[2] or Guillain-Barre syndrome[3], were rare. A new trivalent influenza vaccine has now been developed for worldwide use[4]. It includes antigens from the 2009 pandemic H1N1 influenza A, seasonal Influenza A and Influenza B. It has been recommended for people with increased risk of influenza complications such

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as pregnant women; patients with hematologic malignancies; immunocompromised host; HIV infection; chronic kidney disease (CKD); end-stage renal disease (ESRD) including hemodialysis (HD) and peritoneal dialysis; and solid organ transplant including kidney transplant (KT)[5]. Since 2010 the Ministry of Public Health of Thailand has offered the new trivalent influenza vaccine to the above high-risk groups as a priority free of charge before offering the vaccine to the rest of the country. However, the efficacy of the vaccine in patients with HD or KT has been uncertain, with inconsistent reports on immune response. The purpose of the present study was to evaluate the immune response to trivalent influenza vaccination in Thai patients with HD or KT compared with healthy volunteers.

Material and Method

This was a cross-sectional study in Thai healthy volunteers, and patients with HD and KT who received the trivalent influenza vaccine provided by the Ministry of Public Health of Thailand from 1 November 2011 to 31 December 2011. The present study was approved by The Institutional Ethical Committee of Rajavithi Hospital.

The authors recruited 30 healthy volunteers from hospital staff who had normal annual health check-up, 30 patients with HD, and 30 with KT from the out-patient department of Rajavithi Hospital. All of the patients' clinical and laboratory states had been stable for at least 12 months. The inclusion criteria were: Thai persons over 18 years of age, having no definite history of influenza and not having received influenza vaccination for at least 12 months. Exclusion criteria were: pregnancy, current infection, malnutrition, history of anaphylaxis to the vaccine, or egg allergy. Signed informed consents were obtained. The period of study was from 1 November 2011 to 31 December 2011.

Medical history and complete physical examination was carried out on all subjects. If there was no contraindication, the subjects were given the trivalent influenza vaccine (Fluarix™) provided by the Ministry of Public Health of Thailand. Fluarix™ is manufactured by GlaxoSmithKline Biologics Branch of SmithKline Beecham Pharma GmbH & Co. KG, Zirkusstrasse 40, D-01069, Dresden, Germany. Fluarix™ is an inactivated influenza vaccine (split virion) propagated in embryonated eggs. The vaccine contains the following antigens: A/California/7/2009 (H1N1)-like viral strain [variant A/California/7/2009 (NYMC X-181)], A/Perth/16/2009 (H3N2)-like viral strain [variant A/Victoria/210/2009 (NYMC X-187)], B/Brisbane/60/2008, which are viral strains recommended by the WHO for the 2011 influenza season (southern hemisphere)[6]. Each recommended dose of 0.5 milliliter contains 15 micrograms of hemagglutinin of each viral strain in accordance with WHO and the European Pharmacopoeia requirements for influenza vaccine. Each subject was injected intramuscularly with one single dose of 0.5 milliliter of the vaccine.

Blood samples were obtained before the vaccination (baseline samples) and 6 weeks after (convalescent samples). Clinical symptoms and any adverse events were recorded at six-weeks follow-up. All samples were stored at -80°C until analysis. Antibody titers against established strains of influenza virus were measured by hemagglutination-inhibition antibody assay.

Immune responses at baseline and convalescent periods were expressed as seronegative (SN) and seroprotective (SP)[7]. The authors assigned an antibody titer of 1:40 or above as SP, and antibody titer below 1:40 as SN immunity. Antibody titers of 1:40 or more have been shown to correlate with evidence of vaccine immunogenicity[8,9].

Data were presented as mean $\pm$ standard deviation (SD) for continuous data and number (%) for categorical data. Differences in the frequencies of events between patient groups were analyzed using a Chi-square or Fisher exact test. One way ANOVA was used for comparison of the mean between patient groups and the Tukey method was used for multiple comparisons. A p-value of < 0.05 was considered to be statistically significant. All analyses were performed with the statistical program SPSS version 17.0.

Results

The present study investigated immune response in Thai healthy volunteers and patients with HD and KT who had received the trivalent influenza vaccine provided by the Ministry of Public Health of Thailand. A total of 30 healthy volunteers, 30 patients with HD and 30 patients with KT were recruited. Their clinical and laboratory data are summarized in Table 1. Basic characteristics of all groups were not different except that serum creatinine was significantly higher in the HD group. Duration of HD and KT were 5.1 ± 3.2 years and 5.7 ± 4.1 years, respectively. KT patients were taking two or three immunosuppressive drugs (46.7%: 53.3%, respectively).

Before vaccination, the prevalence of SP immunity in healthy volunteers, patients with HD, and

Table 1. Baseline characteristics of healthy volunteers, patients with HD and KT

Characteristics	Healthy (n = 30)	HD (n = 30)	KT (n = 30)	Total (n = 90)	p-value
Gender					0.561
Male	13 (43.3)	14 (46.7)	17 (56.7)	44 (48.9)	
Female	17 (56.7)	16 (53.3)	13 (43.3)	46 (51.1)	
Age					
Mean ± SD	36.70 ± 9.09	40.83 ± 10.49	43.73 ± 12.20	40.42 ± 10.94	
Occupation					0.067
Worker	15 (50.0)	16 (53.3)	14 (46.7)	45 (50.0)	
White collar	15 (50.0)	9 (30.0)	10 (33.3)	34 (37.8)	
Other	0 (0.0)	5 (16.7)	6 (20.0)	11 (12.2)	
BMI (Kg/M^2)					0.377
Under weight (< 18.5)	1 (3.3)	3 (10.0)	3 (10.0)	7 (7.8)	
Normal (18.5-24.9)	15 (50.0)	17 (56.7)	20 (66.7)	52 (57.8)	
Over weight and obesity (≥ 25.0)	14 (46.7)	10 (33.3)	7 (23.3)	31 (34.4)	
Mean ± SD	24.71 ± 4.30	23.10 ± 3.67	23.30 ± 4.15	23.70 ± 4.07	0.250
Min-max	18.4-35.5	17.3-31.9	15.6-34.9	15.6-35.5	
Serum creatinine (mg/dl)	0.63 ± 0.09[A]	10.59 ± 3.83[B]	1.27 ± 0.42[A]	5.31 ± 5.37	< 0.001*
Body surface area (m^2)	24.71 ± 4.30	23.10 ± 3.67	23.30 ± 4.15	23.70 ± 4.07	0.248

Value were represented as number (percent), Mean ± SD
Letter (A, B) shown multiple comparison. The same letters are not statistically different
* Significant at $p < 0.05$

Table 2. Number and percent of immune response among healthy persons and patients with HD or KT before vaccination

Immunity before vaccination	Normal (n = 30)	HD (n = 30)	KT (n = 30)	Total (n = 90)	p-value
H1N1	10 (33.3)	7 (23.3)	3 (10.0)	20 (22.2)	0.093
H3N2	24 (80.0)[A]	8 (26.7)[B]	7 (23.3)[B]	39 (43.3)	< 0.001*
B	18 (60.0)[A]	6 (20.0)[B]	1 (3.3)[B]	25 (27.8)	< 0.001*

Value were represented as number (percent)
Letter (A, B) shown multiple comparison. The same letters are not statistically different
*significant at $p < 0.05$

KT for viral strains H1N1 were (33.3%: 23.3%: 10.0%), H3N2 (80.0%: 26.7%: 23.3%) and B (60.0%: 20.0%: 3.3%), respectively (Table 2). SP immunity for H1N1 in all groups was not significantly different. However, the healthy group had significantly more SP immunity for H3N2 and B than the HD and KT groups.

Responses to the trivalent influenza vaccination in those who had SN immunity before vaccination are shown in Table 3. This showed that healthy volunteers, and patients with HD and KT had seroconverted from SN to SP for viral strains H1N1 (100.0%: 73.9%: 74.1%), H3N2 (66.7%: 86.4%: 34.8%) or B (58.3%: 66.7%: 48.3%), respectively. The healthy group had significantly more SP immune response for H1N1 than the HD and KT group ($p = 0.023$). The HD group had significantly more SP immune response for H3N2 than the KT groups ($p = 0.001$). Immune responses for B were not significantly different between groups.

No major adverse event was found in any subject. Minor adverse events were reported insignificantly in all groups. The common minor adverse effects were mild local soreness and erythema at the injection site, and some patients reported mild febrile illness for 24 hours after the immunization. The adverse events were not significantly different between

Table 3. Number and percent of immune response after vaccination among healthy persons and patients with HD or KT who had SN immune response before vaccination

Immunity after vaccination	Normal	HD	KT	p-value
H1N1	20/20 (100.0)[A]	17/23 (73.9)[B]	20/27 (74.1)[B]	0.023*
H2N3	4/6 (66.7)[AB]	19/22 (86.4)[A]	8/23 (34.8)[B]	0.001*
B	7/12 (58.3)	16/24 (66.7)	14/29 (48.3)	0.402

Value were represented as number/total (percent)
Letter (A, B) shown multiple comparison. The same letters are not statistically different, significant at $p < 0.05$

subjects with and without SP immunity before the vaccination. Patients with KT had no vaccine triggered acute rejection.

Discussion

Acute respiratory illness caused by influenza A or B viruses is a common infectious disease in Thailand and worldwide. An outbreak of influenza A especially the H1N1 viral strain caused high morbidity and mortality in several countries. The treatment of H1N1 influenza is very difficult and expensive. There are guidelines for the use of antivirals for suspected or confirmed cases but many patients have still died[11,12]. A new trivalent influenza vaccine has been developed which has proved to be effective, safe and well tolerated. A systematic review of the inactivated vaccines in healthy adults found that the vaccine was 80% (95%CI 56% to 91%) efficacious against influenza when the vaccine matched the circulating strain and circulation was high[13]. The present study showed that after one recommended dose of the trivalent influenza vaccine, the rate of seroconversion from SN to SP in healthy volunteers was 100% for H1N1, 66.7% for H3N2, and 58.3% for B. This trivalent influenza vaccine that is provided by the Ministry of Public Health of Thailand should be used in healthy persons during an outbreak of H1N1 influenza A viral infection.

End-stage renal disease patients and KT patients are susceptible to influenza infection and run the risk of influenza-related complications[14]. Influenza vaccination in patients with ESRD can decrease the rate of hospitalization and death[15]. KT recipients were responsible for the majority of the reports of influenza in solid organ transplant recipients[16]. Influenza infection is associated with graft rejection, graft loss and mortality in kidney transplant recipients[17,18]. The trivalent influenza vaccine has been recommended for persons with high risk of influenza complications, and this influenza vaccine should be used in patients with HD and KT.

The efficacy of the trivalent influenza vaccination provided by Ministry of Public Health of Thailand has been evaluated in Thai healthy volunteers, and patients with HD and KT. The present study showed that after one recommended dose of the trivalent influenza vaccine, the HD group had significantly less SP immune response for H1N1 than the healthy group but SP immune response for H3N2 and B was not different. The present study supported the findings of previous reports. After 2009 pandemic influenza A H1N1 vaccination in patients with HD, SP immune response of H1N1 was significantly lower than in the healthy volunteers[19]. After trivalent influenza vaccination in patients with HD, SP immune response of H1N1 was significantly lower than in the healthy volunteers but SP immune response of H3N2 and B were not different[20]. Generally patients with CKD and ESRD have a poor response to routine vaccination because their immune system may be suppressed by uremic toxins. T-lymphocytes and antigen-presenting cells in dialysis patients may be disturbed and alter immune response[21-23]. Compared with healthy persons, patients with renal disease have a lower antibody titer and cannot maintain adequate antibody titer after routine vaccination[24]. However, the present study showed that one recommended dose of the trivalent influenza vaccine was able to protect most of the HD patients (70.0%) from H1N1 infection without major adverse event. This vaccine is effective and cost-efficient for patients with HD[25]. Yearly influenza vaccination is recommended for all dialysis patients, especially vaccination with H1N1 strain. Whether a higher dose or two doses of the H1N1 influenza vaccine will yield a higher protection rate for HD patients may be worth investigating in future studies.

Immune response to influenza vaccination in patients with KT remains controversial. Some studies have described adequate immune response[26,27], while others have shown decreased immune response[28]. The present study showed that after one dose of the

trivalent influenza vaccine, antibody responses to H1N1 influenza vaccine decreased in the KT group in comparison with the healthy group. Immunosuppressive treatment and impaired renal function after KT affect antibody production[29,30]. Studies have shown that organ transplant recipients who received two doses of an influenza A H1N1 vaccine had no significant improvement in vaccine response[31] and less immune response than healthy persons who received only one dose[32]. Further study may be able to clarify the best regimen of H1N1 vaccine for the KT group.

Influenza vaccine has to be produced each year because the influenza virus has a high rate of mutation, resulting in new variants every year. The immunity to previous years' viruses cannot protect against new variants of future years[33]. Patients with HD or KT should be injected every year with an appropriate vaccine recommended by the WHO. The present study showed that some people who had no history of influenza and had not received an influenza vaccination for at least 12 months already had SP immunity for H1N1, H3N2 or B viral strains. However this inactivated vaccine was well tolerated in persons with or without SP immune response before vaccination. No major adverse event was found. The trivalent influenza vaccination in healthy, HD and KT groups is effective, safe, and cost-effective. Current guidelines have recommended vaccinating patients with HD and KT[34,35] but the proper regimen of the H1N1 influenza vaccine should be further evaluated.

Limitation of this present study were its small sample size and the fact that some subjects already had SP immune response before vaccination.

Conclusion

Immune response for H1N1 vaccine in the HD and KT groups was slightly less than in the healthy group. Immune response for H3N2 vaccine in the KT group was less than in the healthy and HD groups. Immune responses for B vaccine in all groups were not different. Further study may evaluate the proper regimen of the H1N1 influenza vaccine in patients with HD and KT.

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Potential conflicts of interest

None.

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ประสิทธิภาพของวัคซีนไข้หวัดใหญ่สามชนิดในผู้ป่วยไทยที่ได้รับการฟอกเลือดหรือปลูกถ่ายไต เปรียบเทียบกับคนปกติ

อุดม ไกรฤทธิชัย, มาลินี จิตตกานต์พิชย์

วัตถุประสงค์*: เพื่อประเมินภูมิคุ้มกันที่เกิดจากวัคซีนไข้หวัดใหญ่สามชนิดในผู้ป่วยที่ได้รับการฟอกเลือดหรือปลูกถ่ายไต เปรียบเทียบกับคนปกติ*

วัสดุและวิธีการ*: การศึกษาภาคตัดขวางในคนปกติ ผู้ป่วยที่ได้รับการฟอกเลือดหรือปลูกถ่ายไตที่ได้รับวัคซีนไข้หวัดใหญ่สามชนิดของกระทรวงสาธารณสุขในระหว่างวันที่ 1 พฤศจิกายน พ.ศ. 2554 ถึง 31 ธันวาคม พ.ศ. 2554 ทุกคนจะได้รับวัคซีนไข้หวัดใหญ่สามชนิดฉีดเข้ากล้ามเนื้อตามขนาดมาตรฐาน (0.5 มิลลิลิตร) ตามชนิดของไข้หวัดใหญ่ที่องค์การอนามัยโลกแนะนำสำหรับปี พ.ศ. 2554 ก่อนและหลังได้รับวัคซีน 6 สัปดาห์ จะได้รับการตรวจเลือดหาภูมิคุ้มกันที่เกิดจากวัคซีนไข้หวัดใหญ่ด้วยวิธี hemagglutination-inhibition antibody assay*

ผลการศึกษา*: มีคนปกติ 30 ราย ผู้ป่วยที่ได้รับการฟอกเลือด 30 ราย และผู้ป่วยปลูกถ่ายไต 30 ราย เข้าร่วมการศึกษา ก่อนได้รับวัคซีนพบว่า คนปกติผู้ป่วยที่ได้รับการฟอกเลือดและปลูกถ่ายไตมีภูมิคุ้มกันไข้หวัดใหญ่ชนิด H1N1 (33.3%: 23.3%: 10.0%), H3N2 (80.0%: 26.7%: 23.3%) หรือ B (60.0%: 20.0%: 3.3%) ตามลำดับ ภายหลังได้รับวัคซีนไข้หวัดใหญ่แล้วพบว่าคนปกติ ผู้ป่วยที่ได้รับการฟอกเลือดและปลูกถ่ายไตที่ยังไม่มีภูมิคุ้มกันไข้หวัดใหญ่จะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด H1N1 (100.0%: 73.9%: 74.1%), H3N2 (66.7%: 86.4%: 34.8%) หรือ B (58.3%: 66.7%: 48.3%) ตามลำดับในคนปกติจะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด H1N1 มากกว่าผู้ป่วยที่ได้รับการฟอกเลือดและปลูกถ่ายไต (p = 0.023) ผู้ป่วยที่ได้รับการฟอกเลือดจะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด H3N2 มากกว่าผู้ป่วยที่ได้รับการปลูกถ่ายไต (p = 0.001) ทั้งสามกลุ่มเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด B ไม่แตกต่างกัน ไม่พบภาวะแทรกซ้อนรุนแรงจากการฉีดวัคซีนไข้หวัดใหญ่*

สรุป*: ผู้ป่วยที่ได้รับการฟอกเลือดและผู้ป่วยที่ได้รับปลูกถ่ายไตจะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด H1N1 น้อยกว่าคนปกติ ผู้ป่วยที่ได้รับปลูกถ่ายไตจะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด H3N2 น้อยกว่าคนปกติและผู้ป่วยที่ได้รับการฟอกเลือดทั้งสามกลุ่มจะเกิดภูมิคุ้มกันไข้หวัดใหญ่ชนิด B ไม่แตกต่างกัน*