Immunogenicity and Reactogenicity of High Versus Standard Dose Trivalent Inactivated Influenza Vaccine in Healthcare Workers (HCWs)

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Abstract (revised)

Background: Significant influenza morbidity and mortality persists despite use of current vaccines. The most effective existing vaccine for healthy adults is standard dose split virus vaccine (SDTIV), which prevents only 60% of influenza infection. A high dose trivalent inactivated influenza vaccine (HDTIV) has shown greater immunogenicity and efficacy in older subjects. This trial was designed to assess immunogenicity and reactogenicity of HDTIV versus SDTIV in HCWs.
Methods: We conducted a prospective, randomized controlled, observer blind trial of HDTIV (60µg antigen/strain) versus SDTIV (15µg antigen/strain) in healthy HCWs 18-64yrs of age in November, 2014. The primary outcome was seroconversion to vaccine strains measured by change in HAI GMT from day 0 (pre-vaccine) to day 21 post-vaccination.
Results: 47 HCWs were enrolled; 37 were female; the median age was 40yrs (range 22-64yrs). 25 received HDTIV (24 with HAI results) and 22 SDTIV. There was no significant difference in pre-vaccination HAI GMTs. Post-vaccination HAI GMTs for vaccine strains were: for A(H3N2) 1092 HD v 405 SD, A(H1N1) 1337 HD V 601 SD, and B 2061 HD v 1165 SD (all $p<0.05$). Seroconversion rates for vaccine strains were: A(H3N2) 17/24 (71%) HD v 4/22 (18%) SD (p=0.0004); A(H1N1) 13/24 (54%) HD v 7/22 (32%) SD (p=0.15); B 8/24 (33%) HD v 3/22 (14%) SD (p=0.17). No subject missed work or sought medical attention in the 7 days after vaccination. HCWs receiving HDTIV reported more site pain one day following vaccination (mean 3.1 v 1.6 on numeric [0-10] pain scale, p=0.03). More HCWs receiving HDTIV reported a systemic reaction causing interference with activities in the 7 days post-vaccination. The most common systemic reactions were fatigue, malaise, muscle aches and headache. There was no difference in the rate of those who would accept vaccination with the same vaccine in the future (HD 22/25 v SD 20/22, p=1.0).
Conclusion: HCWs receiving HDTIV were more likely to seroconvert than those receiving SDTIV and day 21 HAI GMT were significantly higher. HDTIV was associated with an increased rate of injection site pain and systemic reactions, although this appeared not to influence acceptability. Further study of HDTIV efficacy in this group is warranted.

Introduction

- Significant morbidity and mortality secondary to influenza infection persists despite use of current vaccines
- The most effective existing vaccine for healthy adults, the standard dose split virus vaccine (SDTIV), prevents only 60% of influenza infection
- A high dose TIV (HDTIV) has shown greater immunogenicity and efficacy in people ≥ 65 years of age
- This trial was designed to assess immunogenicity and reactogenicity of HDTIV versus SDTIV in HCWs

Material and Methods

- Prospective, randomized controlled, observer blind trial of HDTIV (60µg antigen/strain) versus SDTIV (15µg antigen/strain) in non-immunocompromised HCWs 18-64 years of age
- Primary outcome was seroconversion: 4-fold rise in HAI GMT to vaccine strains from day 0 (pre-vaccine) to day 21 post-vaccine
- Data input in duplicate, cleaned, & analyzed in Excel, SPSS
- Fisher's exact and Student's t-test used in analysis. P values of ≤0.05 considered significant
- Mount Sinai Hospital & North York General Hospital research ethics board approval obtained

Outcome	HDTIV (N=24)	SDTIV (N=22)	P-value
Post-vaccine HAI GMT:			
A (H3N2)	1092	405	< 0.01
A (H1N1)	1337	601	< 0.01
B	2061	1165	0.04
Seroconversion:			
A (H3N2)	17/24 (71%)	4/22 (18%)	0.0004
A (H1N1)	13/24 (54%)	7/22 (32%)	0.15
B	8/24 (33%)	3/22 (14%)	0.17

Table 1. Immunogenicity outcomes in recipients of HDTIV v SDTIV in November, 2014.

Outcome	HDTIV (N=25)	SDTIV (N=22)	P-value
Subjects with local site reaction* within 7 days (any)	17 (68%)	11 (50%)	0.25
Mild only	13 (52%)	10 (45%)	0.77
Moderate	4 (16%)	1 (5%)	0.35
Extreme	0	0	-
Subjects with systemic reaction* within 7 days (any)	16 (64%)	11 (50%)	0.39
Mild only	7 (28%)	8 (36%)	0.76
Moderate	8 (32%)	3 (14%)	0.18
Extreme	1 (4%)	0	1.00
Would receive same vaccine again	22 (88%)	20 (91%)	1.00

Table 2. Reactogenicity outcomes in recipients of HDTIV v SDTIV in November, 2014. *mild = no interference with activities, moderate = some interference with activities, extreme = prevents activities

Results

- 47 HCWs were enrolled; 37 were female; median age 40yrs (range 22-64yrs)

Immunogenicity:

- No significant difference in pre-vaccination HAI GMTs
- 25 received HDTIV (24 with HAI results) and 22 SDTIV
- Post-vaccination HAI GMTs were significantly higher for all vaccine strains in HD recipients (see Table 1)
- Seroconversion rates were higher for all vaccine strains in HD recipients (see Table 1)
- 100% in both groups were seroprotected (HAI GMT ≥ 1:40)

Reactogenicity:

- One subject (HDTIV) missed a few hours of work; no subject sought medical attention in the 7 days after vaccination
- HCWs receiving HDTIV reported more site pain one day following vaccination (mean 3.1/10 for HDTIV v 1.6/10 for SDTIV on numeric 11 point [0-10] pain scale, p=0.01)
- HCWs receiving HDTIV reported a greater number and severity of systemic reactions
- 8 (32%) of HDTIV and 3 (14%) of SDTIV reported systemic reactions on day 1 somewhat or much worse than those experienced with seasonal influenza vaccine (p=0.18)
- No difference in the rate of those who would accept the same vaccine in the future (HD 22/25 v SD 20/22, p=1.0)

Summary and Conclusions

- HCWs receiving HDTIV were more likely to seroconvert than those receiving SDTIV and day 21 HAI GMT were significantly higher
- HDTIV was associated with increased injection site pain and moderate systemic reactions, though this appeared not to influence acceptability
- Further study of HDTIV efficacy in this group is warranted

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