

Joint Corticosteroid Injection Associated With Increased Influenza Risk

Terin T. Sytsma, MD; Lindsey K. Greenlund; and Laura S. Greenlund, MD, PhD

Abstract

Aging and immunocompromising conditions or medications may reduce influenza vaccine effectiveness. The high-dose vaccine has been used to improve vaccine response in patients 65 years and older. Because of systemic immunosuppressive effects, oral corticosteroids may reduce vaccine effectiveness; however, despite over half a century of use, no data are available regarding the effect of joint and bursa corticosteroid injection on influenza vaccine effectiveness. The aim of this retrospective study was to determine whether joint corticosteroid injection was associated with reduced influenza vaccine effectiveness. During the 5 influenza seasons between August 1, 2012, and March 31, 2017, a total of 15,068 major joint corticosteroid injections were given to patients residing in Olmsted County, Minnesota. Vaccinated patients receiving a major joint corticosteroid injection (n=4804) were at increased risk (relative risk, 1.52; 95% CI, 1.20-1.93) for developing influenza compared with vaccinated control patients. Women younger than 65 years were at the highest risk, suggesting that perhaps the high-dose vaccine should be considered for this group to enhance protection when possible.

© 2018 THE AUTHORS. Published by Elsevier Inc on behalf of Mayo Foundation for Medical Education and Research. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ *Mayo Clin Proc Inn Qual Out* 2018;2(2):194-198

From the Department of Medicine, Division of Primary Care Internal Medicine, Mayo Clinic, Rochester, MN (T.T.S., L.S.G.), and College of Science and Engineering, University of Minnesota, Minneapolis, MN (L.K.G.).

Influenza is a major global public health issue with significant risk for morbidity and mortality. Annual vaccination can provide important protection; however, the efficacy of influenza vaccination depends on the generation of protective antibodies by the host immune system. Because of poorer immune response to vaccination, patients 65 years and older are routinely administered the high-dose influenza vaccine to improve efficacy. In immunosuppressed individuals, the humoral immune response may be compromised, resulting in less effective immune response to vaccination. Intraarticular corticosteroid injection is known to cause transient suppression of endogenous cortisol production,¹ and corticosteroids (CSs) are known to cause immunosuppression by multiple mechanisms.² Despite well over a half century of use to treat inflammatory, crystalline, and degenerative arthritis,³ no data exist regarding the risk of intraarticular or bursa CS injections and susceptibility to influenza infection.

The aim of this retrospective study was to determine the rate of influenza in patients receiving a hip, knee, or shoulder CS injection just before or during 5 influenza seasons spanning

August 1, 2012, to March 31, 2017. Vaccinated and unvaccinated patients receiving CS injections and a control group of vaccinated patients not receiving a joint CS injection were evaluated.

METHODS

The influenza vaccine is administered between the months of October and March at our institution (Mayo Clinic in Rochester, Minnesota, Olmsted County); thus, these months were defined as “influenza season.” Patients who received an influenza vaccination at our institution during a given influenza season were defined as “vaccinated,” and those who did not were termed “unvaccinated.”

A retrospective chart review was conducted to identify all patients residing in Olmsted County who were vaccinated at our institution between October 1, 2012, and March 31, 2017. We also identified all patients who received a major joint CS injection (defined as hip, knee, shoulder joint, or bursa, *Current Procedural Terminology* codes 20610 and 20611) in the weeks before and during each influenza season spanning August 1, 2012, to March 31, 2017. August 1 was used for CS injection data collection to ensure that patients receiving a major joint CS injection a

few weeks before their influenza vaccination were included. Only those patients who were receiving CS injections between August 1 and March 31 of each year were included, whereas those between April 1 and July 31 were not. The location of the joint injected, the CS administered, and the CS doses were recorded for all injections.

The control group included patients 50 years or older receiving an influenza vaccination (but not a joint CS injection) at our institution between October 1, 2012, and March 31, 2017. Influenza diagnosis was based on clinical findings and recorded in the diagnosis section of the clinical visit note as “influenza,” “probable influenza,” or “influenza like illness.” Inclusion criteria included residence within Olmsted County, medical care at our institution, defined influenza vaccination status, and defined joint CS injection status. This study was approved by the Mayo Clinic institutional review board.

The CS dose equivalents were calculated in relation to methylprednisolone acetate using the following conversions: betamethasone 6 mg = methylprednisolone acetate 40 mg and triamcinolone acetonide 40 mg = methylprednisolone acetate 40 mg.

Statistics

For comparisons between multiple groups, χ^2 test was used for categorical data and ANOVA test was used for ordinal data; for within-group comparisons (baseline cohort vs patients with influenza), unpaired *t* test was used for ordinal data and χ^2 test was used for categorical data. *P* values of less than .05 were considered statistically significant. Multivariate logistic regression was performed for clinical and demographic variables. *P* values of less than .05 were considered statistically significant.

RESULTS

A total of 43,236 patients 50 years or older were vaccinated during the influenza seasons between August 1, 2012, and March 31, 2017. During these 5 influenza seasons, a total of 15,068 patients received a major joint CS injection (hip, knee, or shoulder): 10,264 were unvaccinated and 4804 were vaccinated. Table 1 presents baseline characteristics of the groups including comorbidities associated with immunosuppression or

immunosuppressive treatment. At baseline, the mean age of the control cohort was more than that of cohorts receiving joint CS injection ($P<.001$), and the percent of female patients was lower in the baseline control cohort than in patients receiving joint CS injection ($P<.001$). The most common comorbidity at baseline in all groups was diabetes mellitus. The overall percent of patients with rheumatoid arthritis in all groups was small, but statistically higher in the patients receiving joint CS injection ($P<.001$). This was expected given that joint CS injection has been a well-utilized treatment for painful rheumatoid arthritis.

Multivariate analysis of the groups together showed that joint CS injection was an important predictor for developing influenza ($P=.002$). Multivariate analysis of the control group alone showed that neither age ($P=.07$) nor sex ($P=.97$) was a significant factor for predicting influenza. In contrast, for patients receiving joint CS injections, multivariate analysis showed that both age less than 65 years ($P=.001$) and female sex ($P=.002$) were significant predictors of influenza. Looking at all vaccinated patients, including the control group and the vaccinated joint CS injection patients, multivariate analysis showed joint CS injection to be the most important predictor of influenza ($P=.002$).

To determine important risk factors for influenza within each group, baseline cohorts were compared with patients with influenza from their respective group. The control baseline cohort average age was not different from the average age of those who developed influenza ($P=.21$). Similarly, the percentage of females was not different between the control baseline cohort and the control patients with influenza. In contrast, for joint CS injection patients (vaccinated and unvaccinated), significantly more females developed influenza. In the joint CS injection baseline cohorts combined, 63.4% (weighted mean) were females and this rose to 73.1% (weighted mean) in patients with influenza receiving joint CS injection ($P<.001$). This finding suggests that for females, joint CS injection was a particular risk factor for the development of influenza.

Age was also an important factor for developing influenza in vaccinated patients receiving joint CS injection. There was a notable difference between vaccinated and

TABLE 1. Patient Demographic Information^a

Baseline cohorts	2012-2017 Influenza seasons		
	Control group: Vaccinated patients ≥ 50 y without joint injection	Major joint CS injection group	
		Unvaccinated	Vaccinated
n	43,236	10,264	4804
Age (y), mean \pm SD ^b	67.4 \pm 10.4	62.4 \pm 15.8	65.9 \pm 14.3
% under 65 y ^b	42.4	56.5	41.9
Sex			61.9
% female ^b	53.1	64.1	
BMI (kg/m ²), ^b mean \pm SD	27.6 \pm 7.5	31.5 \pm 8.1	31.4 \pm 7.3
Comorbidities, %			
Diabetes	12.50	9.30	12.82
COPD	4.96	4.74	5.47
Rheumatoid arthritis ^b	1.98	4.19	4.27
PMR/GA/Lupus/ScD ^b	1.10	1.57	1.72
Chemotherapy	0.97	0.57	0.54
Crohn's/UC	0.92	0.84	0.87
CLL	0.62	0.25	0.44
Myeloma	0.22	0.19	0.17
	Patients with influenza diagnosis, 2012-2017 influenza seasons		
Patients with influenza	Control group: Vaccinated patients ≥ 50 y without joint injection	Major joint CS injection group	
		Unvaccinated	Vaccinated
n (% baseline)	466 (1.08)	175 (1.70)	79 (1.64)
Age (y), mean \pm SD	66.8 \pm 10.7	61.0 \pm 17.8	61.3 \pm 16.4 ^c
% under 65 y	46.8%	62.8%	58.2%
Sex			67.1
% female	53.1	75.4	
BMI (kg/m ²), mean \pm SD	29.4 \pm 9.7	28.4 \pm 7.1	28.0 \pm 6.4
Comorbidities, n (%)			
Diabetes	91 (19.53) ^c	20 (11.42)	14 (17.72)
COPD	62 (20.24) ^c	16 (9.14) ^c	9 (11.39) ^c
Rheumatoid arthritis	9 (2.02)	6 (3.42)	2 (2.53)
PMR/GA/Lupus/ScD	11 (2.36)	2 (1.14)	3 (3.79)
Chemotherapy	8 (1.72)	1 (0.57)	0
Crohn/UC	7 (1.50)	6 (3.43)	2 (2.53)
CLL	7 (1.50)	2 (1.14)	1 (1.26)
Myeloma	0	3 (1.71)	0

^aCLL = chronic lymphocytic leukemia; COPD = chronic obstructive pulmonary disease; CS = corticosteroid; GA = giant cell arteritis; PMR = polymyalgia rheumatica; ScD = scleroderma; UC = ulcerative colitis.

^bP<.05 between-group differences.

^cP<.05 difference compared with respective baseline cohort.

unvaccinated patients. For unvaccinated joint CS injection patients, the average age of the baseline cohort was not statistically different from the average age of those who developed influenza ($P=.25$). In contrast, the vaccinated joint CS injection patients who developed influenza were significantly younger than their baseline cohort ($P=.005$). We hypothesized that perhaps this age difference could be

explained by the type of vaccine the patients of different ages received. Patients 65 years and older received the high-dose influenza vaccine, whereas those younger than 65 years did not. Thus, we sought to determine whether being younger than 65 years was associated with increased risk of influenza after joint CS injection, and indeed, comparison of the baseline cohort with patients with

TABLE 2. Joint CS Injection Details on the 79 Vaccinated Patients Diagnosed With Influenza^a

Total joint CS injections	n=129	
Average CS dose equivalent at visit ^b	65.9 mg (range, 40-120)	47 Patients (59.5%) had ≥80 mg
Multiple injections at single visit	n=29 (36.7%)	
Multiple visits for injections	n=20 (25.3%)	Cumulative dose average 156.5 mg
Corticosteroid received	Methylprednisolone acetate 78.9% Betamethasone 10.9% Triamcinolone acetonide 10.1%	
Location injected	26.0% Shoulder	74.0% Knee/hip

^aCS = corticosteroid.^bThe CS dose equivalent calculated as described in the [Methods](#) section.

influenza revealed a significant increase in the percent of patients younger than 65 years ($P=.003$). This suggests that likely the difference in vaccination type was important and that perhaps the high-dose vaccine was protective against the effect of CS injection.

The percentages of patients receiving a clinical diagnosis of influenza during the seasons between October 1, 2012, and March 31, 2017, are presented in [Table 1](#). The control vaccinated group had an overall influenza rate of 1.08% during the combined 5 influenza seasons studied. The rate of influenza was significantly greater in patients with a major joint CS injection ($P<.001$ vs control for both vaccinated and unvaccinated). The rate of influenza in vaccinated joint CS injection patients was 1.64% and the rate for unvaccinated joint CS injection patients was 1.70%. It is possible that a portion of the “unvaccinated” patients received an influenza vaccine elsewhere; thus, including these patients may have lowered the observed rate of influenza in this group. Further breakdown of the vaccinated joint CS injection group showed that in patients younger than 65 years, the rate of influenza was 2.28% ($n=46$ of 2015) vs 1.18% in patients 65 years or older ($n=33$ of 2789; $P<.001$). In contrast, among the control vaccinated group, there was no significant difference in the rate of influenza in patients younger than 65 years compared with patients 65 years and older ($P=.52$). The relative risk for influenza in vaccinated patients receiving a major joint CS injection compared with vaccinated controls was 1.52 (95% CI, 1.20-1.93).

[Table 2](#) presents details of joint CS injections among vaccinated patients diagnosed with influenza. Methylprednisolone acetate was the most commonly injected CS, and most patients received a single CS injection

with an average dose equivalent of 65.9 mg methylprednisolone acetate and 59.5% received 80 mg or higher at their visit. A total of 25% of patients had multiple visits for joint CS injections during the given influenza season and these patients received an average cumulative dose equivalent of 156.5 mg methylprednisolone acetate. Among the vaccinated patients with influenza who received a joint CS injection, most patients (53 of 79) received at least 1 joint CS injection between the months of September and December.

As a group, the baseline cohorts of joint CS injection patients and the subset that developed influenza predominantly received knee and hip CS injections (71.8% for baseline cohort and 74.0% for influenza; $P=.64$) as compared with shoulder CS injections (28.2% for baseline cohort and 26.0% for influenza; $P=.64$), suggesting that the increased risk of influenza is likely due to systemic CS effects rather than localized CS effects in the shoulder region, reducing vaccination efficacy ([Table 2](#)).

DISCUSSION

The risk for influenza is increased in patients receiving a major joint CS injection just before or during influenza season, even in vaccinated patients. The risk appears to be particularly high among women younger than 65 years who receive a major joint CS injection. Comorbid conditions that may be immunocompromising or require immunosuppressive treatment may contribute to risk; however, a similar percent of patients with these conditions was represented across all 3 groups. Based on this study, joint CS injection just before or during the influenza season appears

to confer an independent risk with a relative risk of 1.52.

Given the widespread practice of joint CS injection for pain due to arthritis or bursitis and the morbidity/mortality associated with influenza, understanding the associated risk has important public health implications. There may be a CS dose threshold over which risk is increased and a specific window of time during which risk is highest, but we were not able to determine these from our data. Given that vaccinated patients 65 years and older with a joint CS injection developed influenza at a lower rate than did those younger than 65 years suggests that perhaps the high-dose influenza vaccine may mitigate the risk associated with joint CS injection. A more detailed prospective, randomized study could confirm this finding, determine the effect of CS dosage, and determine the effect of timing of CS injection relative to vaccination. Perhaps indications for the high-dose influ-

enza vaccine should be expanded to include patients younger than 65 years, particularly women, receiving a major joint CS injection just before or during the influenza season when possible.

Abbreviations and Acronyms: CS = corticosteroid

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Laura S. Greenlund, MD, PhD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

REFERENCES

1. Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. *Clin Rheumatol*. 2014;33(1):99-103.
2. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol*. 2017;17(4):233-247.
3. Hollander JL, Brown EM Jr, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints: comparative effects of and use of hydrocortisone as a local antiarthritic agent. *J Am Med Assoc*. 1951;147(17):1629-1635.