

Effects of Glucocorticoids on Hospitalized Children With Anaphylaxis

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Background: The benefits of glucocorticoid treatment and recent trends of adjunctive treatments during episodes of anaphylaxis remain unclear.

Objectives: The aims of this study were to investigate the recent practice patterns and compare the effects of glucocorticoid for children hospitalized with anaphylaxis.

Methods: Using the Japanese Diagnosis Procedure Combination inpatient database, we compared the length of hospital stay, risk of 10-day readmission, and total hospitalization cost between the steroid and nonsteroid groups. We also evaluated recent trends of adjunctive treatments for anaphylaxis.

Results: From 2010 to 2014, the proportions of H₁-receptor antagonist use increased from 65.1% to 71.8% ($P_{\text{trend}} = 0.02$). The proportions of H₂-receptor antagonist use showed an upward trend, ranging from 12.8% to 16.7% ($P_{\text{trend}} = 0.01$). No significant change in glucocorticoid use was observed (from 86.7% to 82.6%; $P_{\text{trend}} = 0.08$). Stabilized inverse probability-weighting analyses showed that the total length of hospital stay was 0.39 days longer in the steroid group than in the nonsteroid group (95% confidence interval, 0.29–0.49 days). Total hospitalization cost was greater in the steroid group than in the nonsteroid group (difference, ¥3896; 95% confidence interval, ¥2464–¥5562). No significant difference in risk of 10-day readmission was observed between the groups. Instrumental variable analyses showed similar results to stabilized inverse probability-weighting analyses.

Conclusions: We observed increasing trends of H₁- and H₂-receptor antagonist use. Length of hospital stay and total hospitalization cost were greater in the steroid group than in the nonsteroid group, whereas readmission risks were similar between the 2 groups.

Key Words: anaphylaxis, Diagnosis Procedure Combination inpatient database, instrumental variable, inverse probability weighting, steroid

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Anaphylaxis is a serious and potentially fatal allergic reaction with a rapid onset.¹ There are many triggers of anaphylaxis, including food, insect venom, medication, latex, vaccination, and exercise.^{2,3} Regardless of the causative agents, anaphylaxis may be lethal through cardiovascular and/or respiratory compromise.^{4,5}

A biphasic reaction is defined as a recurrence of anaphylactic symptoms after improvement or resolution of initial symptoms and may result in a prolonged length of hospital stay, revisiting

the emergency department, and readmission to hospital.^{6–8} The first-line treatment of anaphylaxis is epinephrine, and recent studies have reported that adjunctive treatment with glucocorticoids is increasing.^{7–14} This upward trend of glucocorticoid use may be related to the current international guidelines recommending glucocorticoids as second-line agents for initial treatment of anaphylaxis after epinephrine administration.^{9–11} However, these guidelines are mostly based on expert opinions, and limited data support use of glucocorticoids for patients with anaphylaxis.¹⁵

Therefore, the present study investigated the effects of glucocorticoids on differences in length of hospital stay of children who were hospitalized with anaphylaxis using a Japanese national database. In addition, we ascertained the differences in total hospitalization costs and risks of readmission between children who received glucocorticoids and those who did not and also evaluated recent trends of adjunctive treatments (glucocorticoids, and H₁- and H₂-receptor antagonists).

METHODS

Study Population and Participation

We analyzed hospital discharge records of patients younger than 18 years with anaphylaxis using the Diagnosis Procedure Combination (DPC) inpatient database between July 1, 2010, and March 31, 2015. The details of this database were described elsewhere.¹⁶ Briefly, the discharge records in the DPC database were collected from more than 1000 hospitals. This database covers approximately 50% of all patients who were admitted to acute care hospitals in Japan. The database contains hospital discharge and administrative claims data for approximately 7 million inpatients per year. It contains the main diagnosis; preexisting comorbidities at admission; complications during hospitalization; patient's age, sex, body weight, and height; and the dates when procedures were performed. Study approval was obtained from the institutional review board at The University of Tokyo. The board waived the requirement for informed consent because of the anonymous nature of the data.

We identified patients who were hospitalized with anaphylaxis, allergic reactions, oral allergy syndrome, and urticaria using the *International Classification of Disease, 10th Revision (ICD-10)* codes (T78.x, K13.7, L50.x, L28.2) as the main diagnosis at admission. Among them, patients who received epinephrine at admission were considered to have the diagnoses of anaphylaxis and were included for the following analyses. We utilized data on patients with allergic reactions, oral allergy syndrome, and urticaria and use of adrenaline to avoid potential misclassification of diagnosis of anaphylaxis and maximize diagnostic accuracy. We excluded children who were admitted to the intensive care unit or those who had chronic medical conditions (congenital heart, kidney, pulmonary, endocrine, hematologic, gastrointestinal, and neurological diseases; cancer or leukemia; and autoimmune disease). Chronic medical conditions were defined by the pediatric complex chronic conditions classification system version 2.¹⁷

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Measurements of Variables

We defined children who received glucocorticoids at admission as the steroid group and those who did not as the nonsteroid group. Patient characteristics consisted of age, sex, preexisting allergic disorders, fiscal year and season of admission, and hospital type (academic or nonacademic). Preexisting allergic disorders were identified using *ICD-10* codes (asthma, J45.x and J46; atopic dermatitis, L208 and L30.x; allergic rhinitis, J30.x). Types of additional treatments included H₁- and H₂-receptor antagonists.

The outcomes of interests were the total length of hospital stay in days, total hospitalization costs in Japanese yen (¥), and 10-day readmission between the steroid and the nonsteroid groups. The currency exchange rate was approximately 100 to 120 Japanese yen per US dollar.

Statistical Analyses

To investigate the recent trends for adjunctive treatments of glucocorticoids and H₁- and H₂-receptor antagonists from the fiscal years 2010 to 2014, we constructed 2 logistic regression models. First, we developed an unadjusted model that included only the fiscal year of admission as the independent categorical variable. Second, to ascertain the independent relationships of fiscal year of admission with additional treatments of glucocorticoids and H₁- and H₂-receptor antagonists, we constructed multivariable logistic regression models, adjusting for patients' characteristics (age, sex, allergic disorders, seasonality, and hospital type).

Stabilized inverse probability of treatment weighting (IPTW) was conducted to compare the outcomes of interests between the steroid and nonsteroid groups. Inverse probability of treatment weighting methods aim to reduce bias by creating a pseudopopulation in which the treatment (glucocorticoids) is independent of the measured potential confounders (patients' characteristics listed above) so that the weighted treatment effect estimates would be less biased.¹⁸ We used stabilized inverse probability weights for the IPTW method because stabilized IPTW can preserve the sample size of the original data, produce appropriate estimation of the variance of the main effect, and control the type I error adequately, compared with nonstabilized IPTW.¹⁸ The propensity scores were calculated using a multivariable logistic regression model to estimate the probability of receiving glucocorticoids conditional on all the baseline characteristics.¹⁹ The observed differences in outcomes between the treated and the untreated were weighted with the marginal probability of receiving treatments and the inverse of the propensity scores to estimate the average treatment effects over the marginal distribution of observed covariates in the entire study population. The standardized difference was used to compare the baseline characteristics between the steroid and nonsteroid groups before and after stabilized IPTW. We considered an absolute standardized difference of greater than 10% as a significant imbalance in the baseline characteristics between the steroid and nonsteroid groups.²⁰

To assess the robustness of our results in stabilized IPTW analyses, we also conducted instrumental variable analyses to ascertain potential causal effects of treatment on the outcomes of interest. Instrumental variable analysis is a pseudorandomization method that can adjust for both measured and unmeasured potential confounders.²¹ For this method to be valid, it requires the following assumptions: the instrumental variable is related to the treatment assignments, it is independent of potential confounders, and it affects the outcomes of interests only indirectly through its effect on the treatment assignments. We defined the proportion of glucocorticoid use in each hospital as the instrumental variable. This proportion was calculated by dividing the total number of patients who were assigned glucocorticoids by the total number of inpatients at each hospital. Under these conditions, we assumed that

the hospital's preference for glucocorticoid use may act as an instrumental variable. This assumption allowed us to calculate unbiased estimates of the treatment effects on the outcomes of interest conditional on the baseline characteristics using a 2-stage least-squares method, even in the presence of unmeasured potential confounders.

Risk ratios and risk differences were estimated with 95% confidence intervals (CIs) for 10-day readmission. Student *t* tests were used to compare the total hospitalization costs and length of hospital stay between the 2 groups. Log transformations were necessary to ensure the error-term normality assumptions. Statistical significance was 2-sided *P* < 0.05 for all analyses. All data were analyzed using STATA software version 14.1 (StataCorp LP, College Station, Tex).

RESULTS

A total of 59,106 hospitalized patients were identified, including 56,168 patients with anaphylaxis, 85 with allergic reactions, 48 with oral allergy syndrome, and 2805 with urticaria. Among them, 6161 patients received epinephrine and were included in the following analyses.

Table 1 shows the recent trends of the patients' characteristics and adjunctive treatments in children who were treated with epinephrine. In the unadjusted analysis, the proportion of patients who were treated with glucocorticoids in addition to epinephrine decreased from 86.7% in 2010 to 82.6% in 2014 (*P* = 0.04). In contrast, the multivariable-adjusted model did not show a significant downward trend (adjusted odds ratio [OR], 0.76; 95% CI, 0.56–1.36; *P* = 0.08). The proportions of H₁-receptor antagonist use significantly increased from 65.1% in 2010 to 71.8% in 2014 in the crude analysis (*P* = 0.006). The adjusted analysis also demonstrated a significant upward trend of H₁-receptor antagonist use (adjusted OR, 1.32; 95% CI, 1.65–1.05; *P* = 0.018). The proportions of H₂-receptor antagonist use showed a significant increasing trend, ranging from 12.8% in 2010 to 16.7% in 2014 (*P* = 0.048). After adjusting for patients' characteristics, the upward trend was still statistically significant (adjusted OR, 1.55; 95% CI, 1.10–2.18; *P* = 0.01).

To compare the outcomes of interests, we divided the 6161 patients who received glucocorticoids into the steroid group (*n* = 5113) and those who did not receive steroids into the nonsteroid group (*n* = 1048). The baseline characteristics between the 2 groups are summarized in Table 2. Before stabilized IPTW was performed, patients treated with glucocorticoids were less likely to have atopic dermatitis, more likely to receive H₁- and H₂-receptor antagonists, and less likely to be hospitalized to academic hospitals in winter. The C statistic for the goodness of fit for the propensity score was 0.67. After the stabilized IPTW, the baseline characteristics were well balanced between the 2 groups.

Table 3 shows the outcomes of interest between the 2 groups after the stabilized IPTW. The total length of hospital stay was 0.39 days longer in the steroid group than in the nonsteroid group (95% CI, 0.29–0.49 days; *P* < 0.001). The total hospitalization cost was greater in the steroid group than in the nonsteroid group (difference, ¥3896; 95% CI, ¥2464–¥5562; *P* < 0.001). The risks of 10-day readmission were not significantly different between the steroid and nonsteroid groups (1.2% vs 1.0%; *P* = 0.71). The risk ratio of 10-day readmission, comparing the steroid group with the nonsteroid group, was 1.13 (95% CI, 0.60–2.16; *P* = 0.71).

In the instrumental variable analyses, a significant difference in length of hospital stay was observed between the 2 groups (difference, 1.01 days; 95% CI, 0.83–1.16 days; *P* < 0.001) (Table 4). The total hospitalization cost was significantly greater in the steroid group than in the nonsteroid group (difference, ¥6624; 95% CI, ¥5158–¥8397; *P* < 0.001). Risks of 10-day readmission

TABLE 1. Baseline Characteristics of Children Hospitalized With Anaphylaxis by Fiscal Year of Admission and Trend Analyses for Use of Glucocorticoids and H₁ and H₂ Blockers

	Fiscal Year of Admission					
	2010	2011	2012	2013	2014	
Total admission, n	413	748	1251	1406	2343	
Age, mean (SD), y	7.0 (5.0)	7.2 (5.4)	7.1 (4.9)	6.9 (5.0)	6.7 (5.0)	
Male, n (%)	276 (66.8)	489 (65.4)	816 (65.2)	887 (63.1)	1503 (64.1)	
Preexisting allergic disorder						
Asthma, n (%)	73 (17.7)	129 (17.2)	214 (17.1)	223 (15.9)	316 (13.5)	
Atopic dermatitis, n (%)	46 (11.1)	96 (12.8)	158 (12.6)	152 (10.8)	258 (11.0)	
Allergic rhinitis, n (%)	13 (3.5)	25 (3.3)	59 (4.7)	68 (4.8)	120 (5.1)	
Academic hospital	106 (25.7)	161 (21.5)	359 (28.7)	373 (26.5)	466 (19.9)	
Season of admission						
Spring, n (%)	62 (15.0)	203 (27.1)	322 (25.7)	364 (25.9)	597 (25.5)	
Summer, n (%)	118 (28.6)	199 (26.6)	366 (29.3)	424 (30.2)	711 (30.3)	
Fall, n (%)	123 (29.8)	162 (21.7)	266 (21.3)	322 (22.9)	549 (23.4)	
Winter, n (%)	110 (26.6)	184 (24.6)	297 (23.7)	296 (21.1)	486 (20.7)	
Type of Treatment	2010	2011	2012	2013	2014	P_{trend}
Glucocorticoid, n (%)	358 (86.7)	634 (84.8)	1032 (82.5)	1154 (82.1)	1935 (82.6)	0.08
H ₁ blocker, n (%)	269 (65.1)	538 (71.9)	839 (67.1)	1016 (72.3)	1683 (71.8)	0.02
H ₂ blocker, n (%)	53 (12.8)	135 (18.0)	203 (16.2)	253 (18.0)	392 (16.7)	0.01

TABLE 2. Baseline Characteristic of the Steroid and the Nonsteroid Groups Before and After Stabilized Inverse Probability Weighting (IPW)

	Before Stabilized IPW (n = 6161)			After Stabilized IPW (n = 6161)		
	Steroid (n = 5113)	Nonsteroid (n = 1048)	Standardized Difference	Steroid (n = 5113)	Nonsteroid (n = 1048)	Standardized Difference
Age, mean (SD), y	6.96 (0.07)	6.67 (0.14)	5.9	6.90 (5.0)	7.01 (5.2)	−1.6
Sex, n (%)						
Male	3278 (64.1)	693 (66.1)	−4.2	3297 (64.5)	678 (64.7)	−1.9
Allergic disorder, n (%)						
Atopic dermatitis	546 (10.7)	164 (15.7)	−14.7	794 (11.5)	167 (11.5)	1.4
Allergic rhinitis	230 (4.5)	55 (5.3)	−3.5	236 (4.6)	49 (4.6)	1.4
Asthma	796 (15.6)	159 (15.2)	1.1	699 (16.2)	141 (16.3)	−0.3
Year of admission, n (%)						
2010	358 (7.0)	55 (5.3)	2.6	342 (6.8)	71 (6.8)	−0.1
2011	634 (12.4)	114 (10.9)	4.7	619 (12.1)	122 (11.6)	−0.7
2012	1032 (20.2)	219 (20.9)	−1.7	1035 (20.3)	201 (19.2)	2.5
2013	1154 (22.6)	252 (24.1)	−3.4	1165 (22.8)	248 (23.6)	−0.2
2014	1935 (37.8)	408 (38.9)	−2.2	1942 (38.1)	406 (38.7)	−1.7
Season of admission, n (%)						
Spring	1282 (25.1)	266 (25.4)	−0.4	1282 (24.1)	252 (25.1)	2.5
Summer	1538 (30.1)	280 (26.7)	7.5	1509 (30.6)	321 (29.5)	−1.3
Fall	1194 (23.4)	228 (21.8)	3.8	1182 (23.7)	248 (23.1)	−2.7
Winter	1099 (21.5)	274 (26.2)	−10.9	1140 (21.6)	227 (22.3)	1.5
Type of hospital, n (%)						
Academic	1148 (22.5)	317 (30.3)	−17.8	1214 (23.7)	246 (23.5)	1.9
Treatment, n (%)						
H ₁ blocker	3752 (73.4)	593 (56.6)	35.8	3607 (70.5)	739 (70.5)	1.2
H ₂ blocker	964 (18.9)	72 (6.9)	36.4	861 (16.8)	196 (18.7)	−4.2

TABLE 3. Risk of Readmission Within 10 Days, Total Hospitalization Cost in Japanese Yen (¥), and Length of Hospital Stay in Days Between the Steroid Versus Nonsteroid Groups Using Stabilized IPTW

Total, n	Steroid (n = 5113)	Nonsteroid (n = 1048)	Stabilized IPTW Analyses		
			Difference	95% CI	P
Total length of stay (SD), d	2.22 (1.30)	1.84 (1.04)	0.39	0.29–0.49	<0.001
Total hospitalization costs (SD), ¥	10,230 (2367)	6334 (1013)	3896	2464–5562	<0.001
			Risk Ratio	95% CI	P
Readmission, n (%)	60 (1.2)	11 (1.0)	1.13	0.60–2.16	0.71

were similar between the 2 groups (risk difference, -0.011 ; 95% CI, -0.026 to 0.004).

DISCUSSION

In the present study, we observed that the length of hospital stay and total hospitalization costs were greater in the steroid group than in the nonsteroid group. No significant difference in 10-day readmission was observed between the 2 groups. We also found increasing trends of H₁- and H₂-receptor antagonist use from 2010 to 2014.

The efficacy of glucocorticoids in anaphylaxis has historically been debatable, and the international guidelines differ regarding glucocorticoid administration in anaphylaxis.^{10,11,22–24} Previously, use of glucocorticoids was reported to reduce the risk of a prolonged length of hospital stay in children hospitalized with anaphylaxis.¹⁵ In contrast, we observed a significantly longer length of hospital stay in the steroid group than in the nonsteroid group. Therefore, the effects of glucocorticoids on preventing a prolonged length of hospital stay appear to be controversial. Furthermore, elevated hospitalization costs were observed in the steroid group compared with the nonsteroid group. These differences of health care costs may have been due to a prolonged length of hospital stay, close monitoring and evaluations for patient, and conservative management by physicians in the steroid group.

Previous studies did not provide sufficient evidence to support the use of glucocorticoids for preventing a biphasic reaction, revisiting the emergency department, or readmission to hospital, whereas most published guidelines recommend glucocorticoids as second-line therapy after epinephrine administration.^{7,15,25} Similar to the previous findings, we found the risks of readmission were not different between the steroid and nonsteroid groups. Further studies would be warranted to support and validate glucocorticoid use for patients with anaphylaxis.

We observed no significant change in the trend of glucocorticoid use from 2010 to 2014. This finding may have reflected the high proportions of the glucocorticoid use in our study (83%) compared with those in previous studies with a US national

database (50%–76%).^{13,15} On the other hand, increasing trends in H₁- and H₂-receptor antagonist use were found in our study. Previous studies reported that approximately 62% to 70% of patients hospitalized with anaphylaxis received H₁-receptor antagonists, and 18% to 67% of them did H₂-receptor antagonists,^{13,15} whereas the proportions of H₁- and H₂-receptor antagonist use in our study were 71% and 17%, respectively. We believe that the reasons for the upward trends in histamine-receptor antagonist use could be multifactorial, such as changes in practice patterns and adherence to recent international clinical guidelines of anaphylaxis.^{10,11,23,24}

There are several limitations to our study. Although we determined patients hospitalized with anaphylaxis based on ICD-10 codes and use of adrenaline, the diagnostic accuracy was uncertain because of the restrictions of the database. Indeed, a large number of patients were excluded from the analyses, which may lead to limitations of external validity of the results. We believe that the main reasons for the exclusions were multifactorial such as high sensitivity and low specificity of the diagnosis of anaphylaxis based on ICD-10 code, conservative management of Japanese physicians against pediatric anaphylaxis, and prehospital treatment. The numbers of preexisting allergic disorders may have been underestimated because of possible underreporting, which may have led to bias toward the null. The detailed clinical presentation, severity of the illness, causative agents of allergic reactions, and laboratory data were unavailable in the DPC database. Development of a biphasic reaction and revisit to the emergency department after discharge could not be identified because of restrictions of the database. Although we applied epidemiological methods for causal inference, there may have been confounding by indication in our study. Therefore, a randomized controlled trial is warranted to determine the causal effects of glucocorticoids on clinical outcomes of anaphylaxis. A unique feature and strength of this study were the use of the DPC database, which is the only national inpatient database available to examine the effect of glucocorticoids on the clinical outcomes of pediatric anaphylaxis in Japan. Using the DPC database, we were able to calculate robust national estimates of the differences in clinical outcomes between the different treatment regimens.

TABLE 4. Risk of Readmission Within 10 Days, Total Hospitalization Cost in Japanese Yen (¥), and Length of Hospital Stay in Days Between the Steroid Versus Nonsteroid Groups Using Instrumental Variable Analyses

	Difference	95% CI	P
Total length of stay, d	1.01	0.83–1.16	<0.001
Total hospitalization costs, ¥	6624	5158–8397	<0.001
	Risk Difference	95% CI	P
Readmission	-0.011	-0.026 to 0.004	0.16

In summary, this study provides novel insights into treatment strategies by comparing outcomes between the steroid and nonsteroid groups. The use of glucocorticoids does not improve the risk of readmission and is associated with elevated health care costs and prolonged hospital stay. We believe that our findings provide valuable information for further large prospective cohort or randomized controlled studies of pediatric anaphylaxis.

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