Glucocorticoids and rates of biphasic reactions in patients with adrenaline-treated anaphylaxis

Shimpei Nagata[1], Hiroyuki Ohbe[1], Taisuke Jo[1], Hiroki Matsui[1], Kiyohide Fushimi[2], and Hideo Yasunaga[1]

[1]The University of Tokyo
[2]Tokyo Medical and Dental University Graduate School of Medicine

April 05, 2024

Abstract

Background: The effectiveness of glucocorticoids in preventing biphasic reactions in patients with anaphylaxis is still controversial. We evaluated the effects of glucocorticoids on rates of biphasic reactions in patients with anaphylaxis treated with adrenaline. Methods: In this retrospective observational study using a national inpatient database in Japan, we identified 31,570 patients with anaphylaxis treated with adrenaline on the day of admission. We divided them into two groups: those who were treated with adrenaline plus glucocorticoids and those who received adrenaline only on the day of admission. We performed a one-to-four propensity score matching analysis between the two groups. The primary outcome was occurrence of a biphasic reaction and the secondary outcome was 7-day all-cause mortality. Results: Of the 31,570 eligible patients, 28,145 (89.2%) were treated with glucocorticoids. After propensity score matching, there were no significant differences in rates of biphasic reactions (odds ratio, 1.03; 95% confidence interval, 0.86–1.24; p=0.14) or 7-day all-cause mortality (odds ratio, 0.68; 95% confidence interval, 0.40–1.17; p=0.16) between patients with anaphylaxis treated with and without glucocorticoids. Conclusion: Our findings do not support the use of glucocorticoids to prevent biphasic reactions in patients with severe anaphylaxis requiring adrenaline.

Introduction

Anaphylaxis, a form of hypersensitive reaction, can be life-threatening at any age and in either sex. A biphasic reaction is defined as the recurrence of anaphylactic symptoms without re-exposure to the allergen within 72 hours of resolution of the initial reaction.[1] Biphasic reactions reportedly occur in 4.6% of patients with anaphylaxis.[1]Current anaphylaxis guidelines therefore recommend continuous observation for several hours or longer after resolution of the initial reaction.[2–5] In these guidelines, intramuscular injection of adrenaline is the recommended first-line treatment, glucocorticoids, histamine-1 receptor blockers, and beta 2-adrenergic receptor stimulants being second-line treatments.[2–5] However, there is limited available evidence for the effects of second-line treatments on symptoms and rates of biphasic reactions in patients with anaphylaxis.

Glucocorticoids inhibit inflammatory responses by suppressing the function of mast cells and are thought to prevent biphasic reactions in patients with anaphylaxis.[6] Recent retrospective cohort studies have failed to show any preventive effects of glucocorticoids on biphasic reactions.[7,8]However, the cohorts of these studies included patients with various types of allergy, including mild to moderate anaphylaxis. Given that glucocorticoids can ameliorate allergic inflammatory responses, it is possible that they prevent biphasic reactions, especially in patients with severe anaphylaxis.

Therefore, in this retrospective observational study using a national inpatient database in Japan, we aimed to examine the effect of glucocorticoids on rates of biphasic reactions in patients with severe anaphylaxis treated with adrenaline.

Methods

Data source

In this nationwide retrospective cohort study, we used data from the Japanese Diagnosis Procedure Combination database, the details of which have been described elsewhere.[9] Briefly, this database includes data of approximately 7 million inpatients per year, which represent more than half of all inpatient admissions to acute care hospitals in Japan. The database includes the following characteristics for each patient: age, sex, body height, weight, Japan Coma Scale score, smoking status, diagnoses, pre-admission comorbidities, post-admission complications, medications, and discharge status. Diagnoses are recorded using the International Classification of Disease 10th revision (ICD-10) codes. The Institutional Review Board of The University of Tokyo approved this study (Approval Number, 3501-3; 25 December 2017). Because the data were anonymized, the requirement for informed consent was waived.

Patients, intervention, and outcomes

Using data from July 2010 to March 2018, we identified patients who were diagnosed with anaphylaxis and treated with intramuscular adrenaline on the day of admission. Patients with anaphylaxis were identified on the basis of the following ICD-10 codes: T78.0 (Anaphylactic shock due to adverse food reaction), T78.2 (Anaphylactic shock, unspecified), and T88.6 (Anaphylactic shock due to adverse effect of correct drug or medicament properly administered). We only assessed the initial hospitalization for patients who were hospitalized twice or more during the study period. We defined the glucocorticoids group as patients who received oral or intravenous glucocorticoids on the day of admission, the remaining patients comprising the control group.

The primary outcome was a biphasic reaction within 7 days of admission. We defined biphasic reaction as adrenaline re-use within 7 days from the date of admission. The secondary outcome was 7-day all-cause mortality.

Statistical analyses

We conducted propensity score matching analysis to compare outcomes between the two groups. A multivariable logistic regression model with the following variables as covariates was used to estimate propensity scores for receiving glucocorticoids on the day of admission: age, sex; body mass index category, Japan Coma Scale score (alert, drowsy, somnolent, and comatose)[10]; smoking status (never, past and current smoker, and missing); diagnoses (T78.0, T78.2, T88.6); Charlson Comorbidity Index score (0, 1, 2, and [?]3); history of asthma, atopic dermatitis, and atopic rhinitis; use of histamine 1 blockers, histamine 2 blockers and beta 2-adrenergic receptor stimulants; hospital volume (very low, low, high, and very high); and teaching hospital. We performed one-to-four nearest-neighbor matching with replacement for estimated propensity scores, using a caliper width set at one fifth of the standard deviation of the estimated propensity scores. To assess the accuracy of the matching, we compared the covariates before and after propensity-score matching using absolute standardized differences, absolute standardized differences [?] 10% being considered to denote negligible imbalances between the two groups.[11] After propensity score matching, we assessed the outcomes through generalized linear models, accompanied by cluster-robust standard errors with hospitals as the clusters. We calculated odds ratios and their 95% confidence intervals (CIs) with generalized linear models using the logit link function.

Sensitivity analyses

We used the following statistical methods to conduct sensitivity analyses to check the robustness of our findings. First, we performed traditional multivariable regression analysis using a generalized linear model. In this analysis, we created a generalized linear model using outcomes as dependent variable and glucocorticoids on the day of admission and all covariates as independent variables. Second, we performed a propensity score adjustment analysis. In this analysis, we created a generalized linear model using outcomes as dependent variables and estimated propensity score in the main analysis as independent variables. Third, we conducted an inverse probability of treatment weighting analysis.[12] For this, we used a weighted generalized linear

model with stabilized average treatment effect weight calculated from the estimated propensity scores in the main analysis.

Continuous variables are presented as mean and standard deviation (SD), and categorical variables as number and percentage. $p<0.05$ was defined as denoting statistical significance. We used Stata version 16.0 (StataCorp, College Station, TX, USA) to perform all statistical analyses.

Results

We identified 31,570 eligible patients during the study period. Of these, 28,145 (89.2%) were treated with glucocorticoids on the day of admission (Fig. 1).

Table 1 shows the patients' baseline characteristics before and after propensity score matching. Before propensity score matching, significantly higher proportions of patients were using histamine-1 receptor blockers, histamine-2 receptor blockers, and beta 2-adrenergic receptor stimulants in the glucocorticoids group than in the control group.

The overall percentage of biphasic reactions within 7 days of admission was 11.2% and 7-day all-cause mortality was 0.4% (Table 2). The percentages of biphasic reactions that occurred on days 1, 2, and 3–7 of the initial reaction were 88.8%, 9.1%, and 2.1%, respectively.

One-to-four propensity-score matching created matched cohorts of 3,425 patients in the control group and 13,700 patients in the glucocorticoid group. After propensity score matching, the distribution of patient characteristics was well-balanced between the matched groups and there were no statistically significant differences in rates of biphasic reactions (odds ratio 1.03; 95% CI 0.86–1.24; p=0.14) or 7-day all-cause mortality (odds ratio 0.68; 95% CI 0.40–1.17; p=0.16) between the two groups (Table 2).

The results of three sensitivity analyses of traditional multivariable regression analyses, propensity score adjustment, and inverse probability of treatment weighting were similar to those using propensity score matching for biphasic reactions (Table 3).

Discussion

In this study, about 90% of the 31,570 patients with anaphylaxis treated with adrenaline were also treated with glucocorticoids. The overall proportion of biphasic reactions was 11.2%. There were no significant differences in rates of biphasic reactions or 7-day all-cause mortality between those treated with and without glucocorticoids.

Previous studies have failed to show that glucocorticoids reduce the rate of biphasic reactions in patients with anaphylaxis of varying severity.[7,8] In the present study, which included only patients with severe anaphylaxis, we also found no evidence that glucocorticoids reduce the rate of biphasic reactions.

Biphasic reactions occurred on the day of the initial anaphylactic reaction in about 90% of the patients in our study. A previous study reported a median time between initial symptom resolution and onset of biphasic reaction of 11 hours (range 0.2–72 hours.[1]The anti-allergic effects of glucocorticoids, which are thought to be responsible for any effect on biphasic reactions, occur within 4 to 6 hours.[6] Therefore, the failure of glucocorticoids to reduce the rate of biphasic reactions may be attributable to the difference between the time required for glucocorticoids to take effect and the time of onset of biphasic reactions.

Long-term steroid administration is associated with adverse effects, including infection, osteoporosis, hypertension, mood disorder, peptic ulcer, and adrenal insufficiency. Even short-term administration may result in avascular necrosis.[13,14] Short-term steroid use can also be associated with development of hyperglycemia within a few hours.[15] Given that this study showed no significant association between glucocorticoid use and rate of biphasic reaction, routine use of glucocorticoids to prevent biphasic reaction may not be indicated, not even in patients with severe anaphylaxis requiring intramuscular adrenaline.

This study has several limitations. First, it was a retrospective observational study. Although we used propensity score matching to adjust for confounding factors, our results may have been affected by unmea-

sured confounding factors, including symptoms of anaphylaxis, time from onset of anaphylaxis to treatment, use of epinephrine autoinjectors, and the results of laboratory tests. Future research is expected to be prospective or to use registries that include detailed clinical data. Second, in this study, severe anaphylaxis was defined as anaphylaxis requiring admission to hospital and treatment with adrenaline. However, some patients without severe clinical symptoms receive adrenaline, potentially resulting in misclassification and underestimation of the effects of glucocorticoids.

Conclusion

Our nationwide database study of patients with severe anaphylaxis showed no significant reduction in rates of biphasic reactions by glucocorticoids. Our findings do not justify routine administration of glucocorticoids to prevent biphasic reaction in patients with severe anaphylaxis.

References

1. Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL. Time of onset and predictors of biphasic anaphylactic reactions: A systematic review and meta-analysis. J Allergy Clin Immunol Pract 2015;3(3):408-416.
2. Japanese Society of Allergology. Anaphylaxis guideline 2014.*https://anaphylaxis-guideline.jp/pdf/anaphylaxis_guideline.* pdf Accessed March 11, 2021
3. Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis–a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145(4):1082-1123.
4. Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015 Oct 28;8(1):32.
5. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69(8):1026-1045.
6. Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; a systematic review of evidence. Eur Ann Allergy Clin Immunol 2017;49(5):196-207.
7. Grunau BE, Wiens MO, Rowe BH, et al. Emergency department corticosteroid use for allergy or anaphylaxis is not associated with decreased relapses. Ann Emerg Med 2015;66(4):381-389.
8. Lee S, Bellolio MF, Hess EP, Campbell RL. Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. J Allergy Clin Immunol Pract 2014;2(3):281-287.
9. Yasunaga H. Real World Data in Japan: Chapter II The Diagnosis Procedure Combination Database. Ann Clin Epidemiol 2019;1(3):76-79.
10. Ono K, Wada K, Takahara T, Shirotani T. Indications for computed tomography in patients with mild head injury. Neurol Med Chir (Tokyo). 2007;47(7):291-297.
11. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28(25):3083-3107.
12. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168(6):656-664.
13. Dilisio MF. Osteonecrosis following short-term, low-dose oral corticosteroids: a population-based study of 24 million patients. Orthopedics 2014;37(7):e631-636.
14. Kennedy P, Bassiouni A, Psaltis A, Antisdel J, Brunworth J. Avascular necrosis after oral corticosteroids in otolaryngology: Case report and review of the literature. Allergy Rhinol (Providence) 2016;7(1):50-54.

15. Roberts A, James J, Dhatariya K; Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med 2018;35(8):1011-1017.

16.

Table 1 . Baseline characteristics of patients treated with and without glucocorticoids according to unmatched and propensity score-matched groups

		Unmatched	Unmatched	Unmatched
Characteristics		Control (n=3425)	Glucocorticoids (n=28145)	ASD (%)
Age, mean (SD) (y)		37.1 (27.4)	38.6 (26.5)	5.4
Male		1829 (53.4)	15125 (53.7)	0.7
Body Mass Index (kg/m^2)	Body Mass Index (kg/m^2)			
	<18.5	861 (25.1)	6291 (22.4)	6.6
	18.5<= <25.0	1379 (40.3)	11765 (41.8)	3.1
	25.0<= <30.0	443 (12.9)	3973 (14.1)	3.5
	>=30.0	132 (3.9)	1064 (3.8)	0.4
	missing	610 (17.8)	5052 (17.9)	0.4
Japan Coma Scale	Japan Coma Scale			
	Alert	2941 (85.9)	24175 (85.9)	0.1
	Drowsy	332 (9.7)	2750 (9.8)	0.3
	Somnolence	104 (3.0)	852 (3.0)	0.1
	Coma	48 (1.4)	368 (1.3)	0.8
Smoking status	Smoking status			
	never	2341 (68.4)	18605 (66.1)	4.8
	past and current	717 (20.9)	6262 (22.2)	3.2
	missing	367 (10.7)	3278 (11.6)	3.0
Diagnosis	Diagnosis			
	T78.0$^+$	730 (21.3)	5284 (18.8)	6.3
	T78.2^{++}	2343 (68.4)	20039 (71.2)	6.1
	T88.6§	352 (10.3)	2822 (10.0)	0.8
Charlson Comorbidity Index	Charlson Comorbidity Index			
	0	2771 (80.9)	21834 (77.6)	8.2
	1	441 (12.9)	4160 (14.8)	5.5
	2	135 (3.9)	1288 (4.6)	3.1
	[?]3	78 (2.3)	863 (3.1)	4.9
Medical history	Medical history			
	Asthma	197 (5.8)	2139 (7.6)	7.4
	Atopic dermatitis	80 (2.3)	634 (2.3)	0.6
	Atopic rhinitis	50 (1.5)	686 (2.4)	7.1
Use of drugs	Use of drugs			
	H1 blocker	2385 (69.6)	24227 (86.1)	40.4
	H2 blocker	1398 (40.8)	15167 (53.9)	26.4
	β2 agonist	392 (11.4)	4531 (16.1)	13.5
Hospital volume	Hospital volume			
	Very low	756 (22.1)	7268 (25.8)	8.8
	Low	868 (25.3)	7014 (24.9)	1.0
	High	852 (24.9)	6982 (24.8)	0.2
	Very high	949 (27.7)	6881 (24.4)	7.4
Clinical training hospital	Clinical training hospital	3167 (92.5)	26027 (92.5)	0.0

Abbreviations: ASD, absolute standardized difference; H1 blocker, histamine-1 receptor blockers; H2 blocker, histamine-2 receptor blockers; SD, standardized difference; β2 agonist, beta 2-adrenergic receptor stimulants.

+: T78.0, Anaphylactic shock due to adverse food reaction

++: T78.2, Anaphylactic shock, unspecified

§: T88.6, Anaphylactic shock due to adverse effect of correct drug or medicament properly administered

Table 2 . Proportions of biphasic reactions and 7-days all-cause mortality in unmatched and propensity score-matched groups

	Unmatched	Unmatched	Unmatched	After 1:4 matching	After 1:4 mat
	Control (n=3425)	Glucocorticoids (n=28145)	Total (n=31570)	Control (n=3425)	Glucocorticoi
Biphasic reaction	358 (10.5)	3172 (11.3)	3530 (11.2)	358 (10.5)	1474 (10.8)
Death	19 (0.6)	93 (0.3)	112 (0.4)	19 (0.6)	52 (0.4)

Table 3 . Results using other analytic methods

	Biphasic reaction	Biphasic reaction	Death
	Odds Ratio (95% Confidence Interval)	P-value	Odds Ratio (95
Traditional multivariable regression analyses	1.07 (0.95-1.21)	0.25	0.72 (0.41-1.29)
Propensity score adjustment	1.07 (0.95-1.20)	0.26	0.76 (0.45-1.26)
Inverse probability of treatment weighting	1.11 (0.98-1.26)	0.10	0.94 (0.53-1.66)

Figure legend

Figure 1. Flowchart showing the stratification and selection of patients with severe anaphylaxis.