Original Article

Comparison of the effect of two different intravenous methylprednisolone doses on the occurrence time of biphasic reaction

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Abstract

Aim: The aim of this study is to determine the effect of two different doses of methylprednisolone administered in our emergency department (ED) on the elapsed time in biphasic or recurrent anaphylaxis cases.

Materials and Methods: The patients with anaphylaxis admitted to the ED were retrospectively analyzed. A total of 82 patients who received methylprednisolone in combination with epinephrine in the ED due to anaphylaxis and who developed biphasic reaction within 48 h after discharge were included in the study. The patients were classified into two groups according to the dose of methylprednisolone administered: 80 mg (Group 1, low-dose) and 120 mg (Group 2, high-dose). The effect of different doses of methylprednisolone on the development time of biphasic reaction was evaluated.

Results: Two different doses of IV methylprednisolone administered in the ED did not affect the development time of biphasic reaction (p = 0.24). The biphasic reaction development times were 335 (IQR, 212−950) min in the low-dose group and 520 (IQR, 265−1150) min in the high-dose group. The earliest development time of biphasic reaction was 125 min (low-dose group) and the latest development time was 2270 min (high-dose group). The relationship between dose and biphasic reaction development times was evaluated using Kaplan−Meier curve. No significant difference was observed between the two groups (p = 0.28). Upon comparing the symptoms in patients' second admission to the ED due to biphasic reaction, no statistically significant difference was observed in patient symptoms with respect to the dose administered (p > 0.05).

Conclusions: Corticosteroids are often used in ED, although there is no definitive evidence that they prevent biphasic reactions. The administration of two different doses of methylprednisolone has no effect on biphasic reaction development time.

Keywords: Anaphylaxis; biphasic reactions; emergency department; methylprednisolone

INTRODUCTION

Anaphylaxis is an acute, systemic reaction with potential mortality risk, and its prevalence has been significantly increasing in the recent years in parallel with the increase in other allergic diseases (1,2). Anaphylaxis classically occurs via mediators secreted by the degranulation of mast cells and basophils mediated by IgE (3,4). Biphasic reaction is defined as the reappearance of symptoms without re-exposure to the triggering agent after the initial symptoms have completely recovered (5). In approximately 0.5%−20% cases with anaphylaxis, a new attack may develop 2−24 h after the patient completely recovers from the initial episode (biphasic or recurrent anaphylaxis) (6,7).

Although there is insufficient evidence to support the use of corticosteroids (CS) in anaphylaxis, they are often used

to reduce the symptoms and prevent recurrent reactions (8). For many years, it has been thought that CSs did not have a proven role in treating acute reactions because they acted via nuclear receptors by modulating gene expression and therefore worked with a slow onset of action (9,1 0). However, recent studies have found that CSs also act via cytosolic or membrane-bound receptors and show non-genomic rapid effects (11,12). Although adding CSs to the initial treatment to prevent biphasic reactions is recommended in all guidelines, there is insufficient evidence on whether CSs prevent the development of biphasic or recurrent reactions (8). The use of CSs in this context is thought to be beneficial due to their effectiveness in other allergic diseases such as asthma. The use and dosage of CSs in allergic diseases are similar to those used in acute asthma treatment (13). Therefore, the ideal effective dose of CSs used as the second-line

treatment is unknown. Different sources recommend that in anaphylaxis, methylprednisolone can be intravenously (iv) administered at doses of 80–125 mg (14,15).

Based on the literature review, we found no study evaluating the effect of methylprednisolone dose administered in the emergency department (ED) on the time elapsed in cases of biphasic or recurrent anaphylaxis. The aim of this study is to determine the effect of two different doses of methylprednisolone (80 or 120 mg) on the development time of biphasic or recurrent reactions.

MATERIALS and METHODS

Study design and setting
This retrospective cohort study was performed in the ED of a tertiary hospital affiliated to a university, which is the only hospital in the region and is a tertiary admission center for adult patients. The average number of patient admissions per year is 300,000 and 80% of this figure comprises patients aged ≥18 years. Local ethics committee approval was obtained for the present study (Ethics committee number: 2019/12-21).

Clinical and demographic characteristics, application time, follow-up notes, medications, consultations, epicrisis notes, outpatient prescriptions, and all procedures performed in the ED were accessed from the hospital's medical electronic records. (Probel, Hospital Information Management System).

Patient selection
The data of patients who were diagnosed with anaphylaxis in the ED between January 2015 and December 2019 who received methylprednisolone in combination with epinephrine were reviewed. A total of 82 patients aged ≥18 years who had biphasic reaction within 48 h after the initial symptoms had completely resolved were included in the study. The patients were classified into two groups according to the methylprednisolone dose administered: 80 mg (low-dose) and 120 mg (high-dose).

Patients aged <18 years, hereditary angioedema, who had undergone continuous epinephrine infusion in the ED, those with treatment resistance whose anaphylaxis condition had not completely disappeared despite the treatment, who had received epinephrine prior to ED admission, who did not receive methylprednisolone treatment, those discharged with oral methylprednisolone prescription after anaphylaxis, those with missing records, and those leaving before completing the necessary treatment in the ED and follow-up period were excluded from the study. In addition, those in whom the biphasic reaction occurred within the first hour after anaphylaxis attack were also excluded from the study to better evaluate the effects of methylprednisolone due to the late onset of CSs' in vivo effects (11,12).

Data collection and processing
Patient data was obtained from the hospital electronic database. Patient admissions were retrieved from the electronic medical database using "anaphylactic reaction" and "allergic reaction" diagnostic codes in the International Classification of Disease-10 (ICD-10) coding system. Patient data were recorded according to the diagnosis/diagnoses they received and the matching ICD-10 code/codes.

All ED documents were reviewed using commonly accepted clinical criteria for diagnosing anaphylaxis (16). Whether the patient fulfilled the definition of anaphylaxis at the time of admission was systematically examined by the researchers. Biphasic reaction was defined as the recurrence of allergic symptoms or findings without re-exposure to the triggering agent. Patients admitted to the ED due to anaphylaxis were followed-up for 5–10 hours depending on the clinical condition of the patient. Patients discharged after anaphylaxis were evaluated for the development of biphasic reaction within 48 h.

The patients were classified into two groups based on the dose administered. Group 1 comprised patients who received 80 mg of methylprednisolone (low-dose) and Group 2 comprised those who received 120 mg of methylprednisolone (high-dose). We scanned the complete list of patients admitted to the ED during the study period to obtain all the patients in the high-dose group. Then, an equal number of patients were sequentially included in the low-dose group. All patients were administered 0.5 mg of epinephrine intramuscularly (IM) to the thigh anterolateral region as a standard procedure in the ED. Patients were observed for the development of biphasic reactions during their follow-up in the ED and in the 48-h follow-up period after discharge. In patients who developed biphasic reaction, the initial dose of methylprednisolone administered, patient symptoms at second admission to the ED, time elapsed until the recurrence of symptoms, and the treatment administered were recorded. The effects of different doses of methylprednisolone on biphasic reaction development time were compared.

Outcomes and definitions
The primary outcome measurement was the time elapsed until the detection of the biphasic reaction after methylprednisolone administration in the ED. This was used to determine the effect of different doses of methylprednisolone on biphasic reaction development time. The secondary outcome was the effectiveness of different doses of methylprednisolone on recurrent symptoms in those with biphasic reaction.

Data analysis
According to previous studies (6,7) the rate of biphasic reaction development was estimated as 6%, and power analysis was performed to estimate the development of biphasic reaction with 95% reliability so that the estimated rate was 5% lower/5% higher than the actual population rate. At a power of 80% (β = 0.20), confidence interval of 95%, and error margin of α = 0.05, the number of individuals to be included in the study was determined to be at least 74 (at least 37 individuals in each group). The data was analyzed using Statistical Package Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive

statistical methods (percentage, median, mean, and standard deviation) were used when evaluating the study data. Kolmogorov–Smirnov test was used to evaluate the distribution of data. For inter-group comparison, Chi-square test was used for categorical variables, Student's t-test was used for normally distributed continuous variables, and Mann–Whitney's U test was used for non-normally distributed continuous variables and ordinal variables. The primary outcome variable of time elapsed until biphasic reaction after methylprednisolone dose was right censored because some patients developed biphasic reaction during the first hour after methylprednisolone administration. Kaplan–Meier curves were created and compared between groups using the log-rank test. Cox-proportional hazards regression analysis was not performed because the groups were well balanced and we could not identify the known confounders for our primary outcome. A P value of <0.05 was considered to be statistically significant in all analyses.

RESULTS

Medical records of 407 patients were retrospectively analyzed. A total of 82 patients who developed biphasic reaction during 48 h after anaphylaxis were included in the study. Of these, 41 were included in each group. Of the patients included, 52 were male and 30 were female (63.4% and 36.6%, respectively), and the mean age of the patients was 39.7 ± 8.9 years. The demographic characteristics of patients were similar between the groups (Table 1). No significant difference was observed between the groups in terms of age and gender (p > 0.05).

| Table 1. General characteristics of study population			
Subject characteristics and outcomes	Biphasic Reaction		
	Low-Dose (n=41)	High-Dose (n=41)	p value
Age (years)	40.2±9.6	39.1±8.2	0.56
Sex (male), %	27 (%65.9)	25 (%61)	0.64
Respiratory rate, breaths/min	20.0±2	21.7±2	<0.001
Oxygen saturation, %	97 (2)	96 (2)	0.10
Systolic blood pressure, mm Hg	116 (20)	110 (15)	0.009
History of allergies %	4 (%9.8)	10 (%24.4)	0.78
Epinephrine use>1in ED	1(%2.4)	4 (%9.8)	0.35
Biphasic time,minute(IQR)	335 (212-950)	520 (265-1150)	0.24
Biphasic in ED	24 (%58.5)	22 (%53.7)	0.65
Observation time in ED, minute	386±35	492±45	<0.001
Death in 48 hours	0	0	
ED: Emergency department, IQR:interquartile range in 25−75 percentiles			
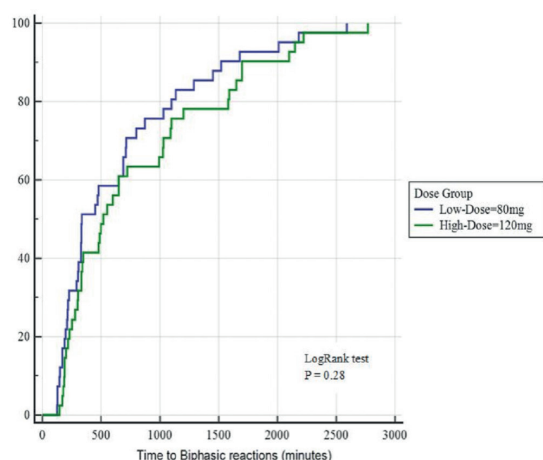
Figure 1. Kaplan-Meier curve for biphasic reaction time of high-dose and low-dose methylprednisolone

The mean follow-up time of patients in the ED was 420 (IQR, 389−499) min. No difference was observed between the low- and high-dose methylprednisolone groups in terms of follow-up time (p > 0.05). Over all 24 (58.5%) and 22 (53.7%) patients in the low- and high-dose groups, respectively, developed biphasic reaction during follow-up in the ED. When biphasic reaction development times were evaluated, no significant difference was observed between the low-dose [335 (IQR, 212−950) min] and high-dose [520 (IQR, 265−1150) min] groups (p = 0.24).

The relationship between dose and biphasic reaction development times was evaluated using Kaplan−Meier curve. No significant difference was observed between the groups (Figure 1). P value for the log rank test was 0.28. During follow-up, we observed that four (9.8%) and one (2.4%) patient in the high- and low-dose groups, respectively, required a second epinephrine administration. No patient died due to anaphylaxis.

To compare the symptoms at second admission to the ED after discharge, skin findings were detected in 76.8% (63) of all cases. This was followed by findings of the respiratory system (34.1%; Table 2). No significant difference was observed between the groups in terms of patient symptoms (p > 0.05).

Table 2. Signs and symptoms of biphasic reaction in patients			
Signs or symptoms in biphasic reaction	Low-Dose (n=41)	High-Dose (n=41)	p value
Skin involvement	34 (%82.9)	29 (%70.7)	0.19
Mucosal tissue involvement	11 (%26.8)	10 (%24.4)	0.80
Dispnea /wheeze/stridor	15 (%36.6)	13 (%31.7)	0.64
Gastrointestinal symptoms	10 (%24.4)	8 (%19.5)	0.59
Syncope	3 (%7.3)	1 (%2.4)	0.30

DISCUSSION

Because anaphylaxis is a life-threatening emergency clinical condition, it should be promptly and immediately treated after diagnosis (17). Given the pathogenesis of anaphylaxis and the mechanism of action of CSs, there is theoretical ground that CSs are beneficial in treating anaphylaxis. Although there is no strong recommendation for their use for treating anaphylaxis, 45%–97% patients are administered CSs during emergency treatment of anaphylaxis (18,19). It is thought that CSs can prevent relapses in biphasic anaphylaxis. However, there is no definitive evidence that CSs prevent biphasic reactions after anaphylaxis treatment (20). Because CSs are routinely used in anaphylaxis management and their ideal effective dose is unknown, the present study is therefore intended to determine the effect of two different doses of methylprednisolone on biphasic reaction development time.

Alqurashi et al. (21) systematically reviewed 31 studies and did not recommend routine use of CSs in anaphylaxis due to the potential harmful side effects and lack of definitive evidence on whether CSs reduce the severity of anaphylaxis or prevent biphasic reactions. Grunau et al. (22) evaluated CS use in anaphylaxis and allergy associated ED visits within 7 days and found that CS use in anaphylaxis was not associated with decreased relapses. In a recent study, they found that no definitive conclusions about the role of corticosteroids in preventing biphasic reactions (23). Another systematic review, they conclude that there is no compelling evidence to support or oppose the use of corticosteroid in emergency treatment of anaphylaxis (24). In the present study, we found that different doses of iv methylprednisolone administered in the ED did not affect the development time of biphasic reactions (p=0.24). Although there was no significant difference between the groups in terms of biphasic reaction development times, we detected a longer biphasic reaction development time in the high-dose group [520 (IQR, 265–1150) min]. Biphasic reaction developed in 22 (53.7%) and 24 (58.5%) patients in the high- and low-dose groups, respectively, during follow-up in the ED. There was no significant difference in terms of dose and biphasic reaction development during hospital follow-up (p = 0.65).

In three studies examining the incidence of biphasic reaction in ED, Brady et al. (25) retrospectively evaluated visits of 67 anaphylaxis cases to their own hospitals and neighboring hospitals within 7 days. Biphasic reactions were defined as recurrence of allergic symptoms or findings, and the authors reported two biphasic reactions that occurred 26 and 40 h after discharge from ED (3%). CSs were initially administered to the patient who developed biphasic reaction after 40 h. In both cases, the reactions were limited to urticaria. Smit et al. (26) examined 282 cases of anaphylaxis and reported 15 biphasic reactions (5%). Seven patients developed a biphasic reaction within 8 h of the first admission and eight developed a biphasic reaction 8 h after the first admission. All biphasic reactions occurred within 23 h of the onset of symptoms. A total of 13 patients initially received CSs; 12 patients mild symptoms, two patients hypotension, and one patient hypoxemia with the same clinical features as the initial reaction were defined in these patients. Ellis et al. (27) evaluated 134 cases of anaphylaxis for biphasic reaction within 72 hand reported that 20 patients with an onset of 2–38 h developed a biphasic reaction. CSs were administered to seven of these patients during initial admission. The authors found that in eight patients, the biphasic reaction occurred 10 h after the first reaction. No deaths were reported. What makes the present study different from the other previous studies is that the effect of dose on biphasic reaction development time was evaluated in patients who received different doses of methylprednisolone. Furthermore, CSs were not administered to all patients who developed biphasic reactions and development times of biphasic reaction and drug dose provided to patients were not specified in other studies, further differentiating our study from the others. When biphasic reaction development times were evaluated in the present study, it was found that the earliest development time was 125 min and the latest development time was 2270 min. The patient who developed biphasic reaction first was in the low-dose group, whereas the patient who developed biphasic reaction last was in the high-dose group. Biphasic reaction development times were not significantly different between the low-dose [335 (IQR, 212–950) min] and high-dose [520 (IQR, 265–1150) min] groups (p = 0.24). We found that 46 (56.1%) of the reactions occurred during the follow-up in the ED and did not result in reported deaths. In the present study, skin findings were detected in 76.8% (63) patients who developed biphasic reactions. When the symptoms and findings that occurred during biphasic reaction were compared, no significant difference was noted between the groups (p > 0.05). Methylprednisolone was administered to all the patients in the ED. When patient symptoms at second admission to ED due to the biphasic reaction were compared, no statistically significant difference was noted in patient symptoms with respect to the dose administered (p > 0.05).

The side effects of CSs are more common in patients who take these drugs at high doses or for longer periods of time. High-dose CS administration (>5–20 mg/m2/day prednisolone) can cause serious side effects such as sudden death, cardiac rhythm disturbances, and

gastrointestinal bleeding (28). In the present study, high-dose methylprednisolone treatment did not affect biphasic reaction development time. Considering the side-effect profiles of corticosteroids, our study is important in avoiding unnecessary overdose therapy. Although observational studies have shown that patients with severe reactions are more likely to be administered CSs, there is no definitive evidence that the early administration of CSs prevents the progression of symptoms (29). There are also studies showing that CSs shorten the length of hospital stay while treating anaphylaxis (30). However, there is no evidence that CSs reduce the number of visits to EDs due to anaphylaxis (31). In the present study, the mean follow-up time of patients in the ED was 420 (IQR, 389−499) min. Although patients who were given high doses of methylprednisolone were followed-up in the ED for a longer period of time, there was no statistically significant difference between the groups (low-dose: 386 ± 35, high-dose: 492 ± 45 min, p > 0.05). We found that high-dose methylprednisolone administration did not reduce the length of hospital stay. These results are important in terms of shortening the length of hospital stay and enabling long-term medical costs to be reduced.

LIMITATIONS

There are certain limitations of the study. Firstly, the efficacy of CSs in preventing biphasic reactions cannot be evaluated based on our data because only patients who were administered methylprednisolone together with epinephrine were included in the study. Secondly, this study was conducted retrospectively in a single healthcare center.

CONCLUSION

Different doses are specified in different sources and the administered drug dose varies according to the experience and inclination of emergency physicians due to the lack of standards. The present study showed that the administration of two different doses of methylprednisolone has no effect on biphasic reaction development time.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee approval was obtained for this study (approval number: 2019/12-21).

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