



Outcomes of corticosteroid prophylaxis for hypersensitivity reactions to low osmolar contrast media in high-risk patients



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ABSTRACT

Background: Corticosteroid prophylaxis has been widely adopted for the prevention of acute allergic-like reactions to iodinated contrast media, but its use is still controversial because there is no strong evidence supporting its efficacy before administration of nonionic low osmolar contrast media (LOCM).

Objective: To assess the outcomes of premedication in patients with previous acute allergic-like reactions to LOCM in clinical practice.

Methods: A retrospective study was performed on 322 high-risk patients who were reexposed to LOCM after premedication composed of antihistamines and/or systemic corticosteroids because of a previous history of acute allergic-like reactions to LOCM.

Results: After premedication, 275 patients (85.4%) did not experience any reaction, but 47 patients (14.6%) still experienced a breakthrough reaction. The premedication rate and amount of corticosteroid administered were significantly higher in the nonrecurrence group than in the recurrence group ($P = .04$ and $P = .04$, respectively), and a linear trend was observed in the use of corticosteroid premedication and the efficacy of prevention (P for trend = .02). Multivariate binary logistic regression revealed that corticosteroid premedication was effective in preventing recurrence (odds ratio, 0.284; 95% confidence interval, 0.103–0.784). Nonetheless, despite corticosteroid premedication, 3.4% of high-risk patients still experienced moderate to severe reactions, and 14.3% of patients with a severe index reaction again had a severe reaction.

Conclusion: Premedication with corticosteroids seems to be helpful in reducing the overall rate of recurrence of acute allergic-like reactions to LOCM in high-risk patients, but patients with severe index reactions are still at risk of developing severe reactions despite corticosteroid premedication.

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Introduction

Acute allergic-like reactions to iodinated contrast media (ICM) vary from mild urticaria to fatal anaphylaxis. Since the advent of nonionic low osmolar contrast media (LOCM), the incidence of total acute allergic-like reactions and severe acute allergic-like reactions has decreased from 3.8% to 12.7% to 0.7 to 3.1% and from 0.1% to 0.4% to 0.02% to 0.04%, respectively.^{1–3} However, because of the rapid increase of contrast imaging studies,^{4,5} the risk of acute

allergic-like reactions is still a pressing issue in clinical practice despite the widespread use of LOCM.

A patient's history of acute allergic-like reactions to ICM appears to be an important risk factor for recurrence; a history of an allergic-like reaction increases the likelihood of recurrence by up to 4 to 6 times.^{6,7} Even though the general recommendation is to avoid reexposure to ICM and to use another imaging modality in patients with a history of acute allergic-like reactions to ICM, many high-risk patients still undergo enhanced computed tomography (CT) because the use of ICM is often regarded as essential for accurate diagnosis and evaluation.

Given these circumstances, premedication with systemic corticosteroids and histamine₁ (H₁)– and histamine₂ (H₂)–antihistamines is widely adopted to reduce recurrence of acute allergic-like reactions to ICM in high-risk patients.^{8–11} However, it is difficult for

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clinicians to determine whether LOCM can be safely administered after premedication because there is no consensus on the efficacy of premedication before reexposure to LOCM in high-risk patients.^{12,13} This situation motivated us to assess the outcomes of premedication and the potential risk factors for recurrence in patients with previous acute allergic-like reactions to LOCM in clinical practice.

Methods

Study Participants

This study was approved by the institutional review board of Seoul National University Hospital, and informed consent was waived. A total of 322 high-risk patients, defined as those who had a previous history of acute allergic-like reactions to LOCM, underwent CT enhanced with LOCM after premedication at Seoul National University Hospital between June 2010 and May 2012. Patient demographics, comorbid diseases, and prescription medications taken at the time the patients underwent CT were extracted from electronic medical records. A retrospective review of the following information was performed: nature and severity of previous reactions, recurrence of hypersensitivity after premedication, interval between ICM exposures, and the details of the premedication regimen.

Definition of Acute Allergic-like Reaction to ICM

In this study, acute allergic-like reaction was defined as any hypersensitivity that developed within 1 hour after administration of ICM. The severity of the hypersensitivity reaction was classified as mild when itching, urticaria, flushing, and/or nasal symptoms developed; moderate when bronchospasm, angioedema of the face, throat tightness, and/or hoarseness developed; and severe when arrhythmia, cardiopulmonary arrest, severe laryngeal edema, convulsions, and/or profound hypotension developed.¹⁴ Patients who experienced vomiting, sweating, warmth, or pain at the injection site without any of the aforementioned symptoms were excluded from the study.¹⁴ Hypersensitivity symptoms were assessed by 2 allergy specialists (J.-W.J and H.-R.K.) on the basis of the World Health Organization–Uppsala Monitoring Center causality assessment algorithm, and cases determined to be certain or probable were taken to indicate a causal relationship between the administered ICM and hypersensitivity reactions.^{15,16}

Premedication

During the study period, the institutional policy for premedication before reexposure to ICM did not follow the recommendation of the American College of Radiology; the premedication regimen was decided on an individual basis by clinicians. Forty milligrams of methylprednisolone was intravenously administered once or multiple times at least 1 hour before reexposure to LOCM and/or antihistamines (4 mg of chlorpheniramine and/or 20 mg of famotidine) were intravenously administered 0.5 to 1 hour before reexposure to LOCM.

Statistical Analysis

All statistical analyses were performed using SPSS statistical software, version 16.0 (SPSS Inc, Chicago, Illinois). Continuous variables are expressed as mean (SD). Fisher exact tests, χ^2 tests, Mann-Whitney tests, and analyses of variance were used to compare differences among groups. Risk factors for recurrence of acute allergic-like reactions to ICM were assessed using multivariate binary logistic regression and are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). $P < .05$ was considered statistically significant.

Results

Clinical Characteristics of Study Participants With Acute Allergic-like Reactions to LOCM

Among a total of 322 high-risk patients who underwent enhanced CT with premedication, 46.3% were males, and the mean age of all patients was 56.22 (12.47) years (eTable 1). On the basis of the severity of previous index reactions, 219 patients (68.0%) were classified into the mild reaction group, 82 patients (25.5%) into the moderate reaction group, and 21 patients (6.5%) into the severe reaction group. The mean age and serum creatinine level of the severe reaction group were significantly higher than those of the mild and moderate reaction groups (61.57 [14.61] years vs 55.85 [12.25] years, $P = .049$, and 1.81 [3.19] mg/dL vs 0.89 [0.88] mg/dL, $P = .03$, respectively).

Premedication and Clinical Outcomes of Reexposure to LOCM

Of the 322 patients included in this study, H₁-antihistamines were administered to 320 patients (99.4%) before reexposure to LOCM; 314 patients received 4 mg of intravenous chlorpheniramine maleate and 6 patients received oral H₁-antihistamines. Systemic corticosteroids (mean prednisolone equivalent dose of 59.61 [38.25] mg) and H₂-antihistamines (famotidine, 20 mg) were administered to 116 patients (36.0%) and 60 patients (18.6%), respectively.

Although H₁-antihistamines were used in nearly all patients across the 3 severity groups, corticosteroids and H₂-antihistamines were more frequently given to patients who had experienced more severe previous reactions (P for trend $< .001$) (Fig 1A). Corticosteroids were given to every patient in the severe reaction group.

After premedication, 275 patients (85.4%) did not experience any reaction to LOCM, whereas allergic-like reactions recurred in 47 patients (14.6%) (Fig 1B). Of the 47 patients who reexperienced allergic-like reactions, 36 (76.6%) experienced mild reactions not requiring additional treatment, 8 (17%) had moderate reactions, and 3 (6.4%) had severe reactions. In other words, 96.6% of patients were given ICM for CT without reexperiencing moderate to severe acute allergic-like reactions.

We investigated the allergic-like reactions in different organs and systems. The prevalence of skin symptoms significantly decreased after premedication ($P < .001$ for individual symptoms) (eFig 1), whereas the prevalence of gastrointestinal symptoms, such as nausea and vomiting, did not significantly decrease after premedication.

Factors Related to the Recurrence of Acute Allergic-like Reactions

Table 1 compares the clinical characteristics of patients who experienced recurrence and those who did not. Patients who experienced recurrent allergic-like reactions were younger by 4.9 years than those who did not (52.09 [13.30] vs 56.98 [12.20] years, $P = .01$).

Although the use of H₁- and H₂-antihistamines did not appear to be related to recurrence, the premedication use rate and administered dose of corticosteroids were significantly higher in the non-recurrence group than in the recurrence group (38.2% vs 23.4%, $P = .04$, and 22.73 [37.8] mg vs 11.6 [3.76] mg, $P = .04$) (Fig 2).

In terms of the frequency of corticosteroid premedication, corticosteroids were administered once in 81 patients (1 hour before the procedure; prednisolone, 45.08 [25.64] mg), twice in 5 patients (12 hours and 1 hour before the procedure; total amount of prednisolone, 75.25 [55.71] mg), and 3 times in 30 patients (13 hours, 7 hours, and 1 hour before the procedure; total amount of prednisolone, 95.25 [40.83] mg). Prevention of recurrence of allergic-like reactions increased with the total number of corticosteroid administrations (82.5% with no corticosteroids, 89.4% with

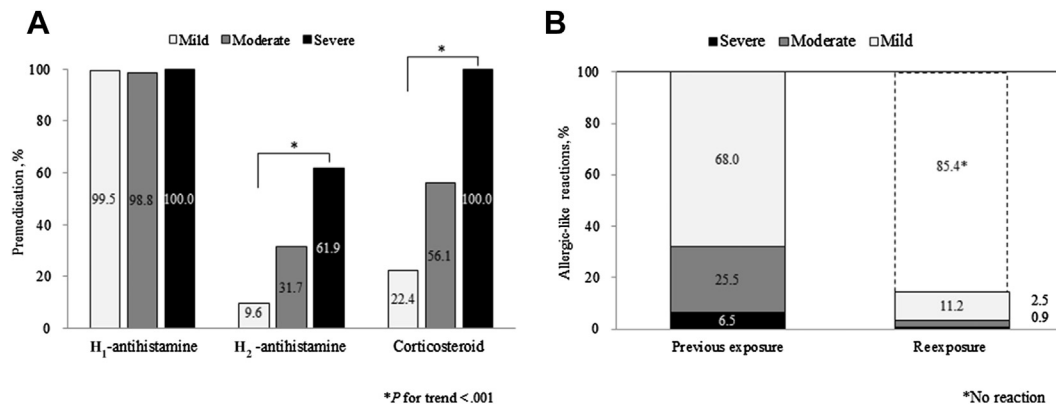


Figure 1. Premedication and acute allergic-like reactions at the time of previous nonpremedicated exposure and premedicated reexposure to iodinated contrast media. The premedication rate of each drug is ranked by the severity of the previous reaction (A) and the severity of the hypersensitivity reaction at the time of previous exposure and reexposure after premedication (B). H₁ indicates histamine₁; H₂, histamine₂.

corticosteroids given once or twice, and 96.8% with 3 corticosteroid administrations, P for trend = .02) (Fig 2C).

We performed multivariate binary logistic regression analysis using the following independent variables: age, sex, comorbid allergic diseases, previous severity, and premedication. Corticosteroid premedication was strongly associated with a significantly lower risk of recurrence (OR, 0.284; 95% CI, 0.103–0.784; P = .02) (Table 2).

Analysis of the results according to the severity of index reactions revealed a significant reduction in the recurrence rate after corticosteroid premedication in the mild reaction group (4.1% vs 17.7%, P = .01) but not in the moderate reaction group (8.7% vs 16.7%, P = .22) (Table 3). Older patients had a slightly lower risk of recurrence (OR, 0.968; 95% CI, 0.944–0.993; P = .01). Overall, a

history of previous severe reaction appeared to be the strongest risk factor for recurrence (OR, 8.884; 95% CI, 2.108–37.442; P = .003) (Table 2). The recurrence rate was 14.7% in the mild reaction group, 12.2% in the moderate group, and 23.8% in the severe group. Given that the use of corticosteroid premedication differed among the 3 reaction groups, the instance and severity of recurrence were reassessed based on whether a corticosteroid was used for premedication (Table 3). Given this criteria, the recurrence rate clearly increased in groups with more severe previous reactions (4.1% in the mild group, 8.7% in the moderate group, and 23.8% in the severe group, P for trend = .02) despite corticosteroid premedication.

The severity of the index reactions was also related with the severity of the recurrent reactions; 96.6% of allergic-like reactions experienced by those in the mild group were mild, 69.7% of reactions in the moderate were moderate, and 60.1% of the reactions cases in the severe group were severe. Although no patients in either the mild or moderate reaction groups experienced severe reactions, 14.3% of patients experienced severe reactions after reexposure in the severe reaction group (P < .001) (Fig 3).

Table 1
Characteristics of the Nonrecurrence and Recurrence Groups at the Time of Reexposure to Iodinated Contrast Media After Premedication^a

Characteristic	Nonrecurrence group (n = 275 [85.4%])	Recurrence group (n = 47 [14.6%])	P value
Male patients	124 (45.1)	25 (53.2)	.30
Age, mean (SD), y	56.98 (12.20)	52.09 (13.30)	.01
BMI, mean (SD)	24.07 (3.70)	24.50 (3.01)	.46
Interval of RCM reexposure, mean (SD), d	394.61 (609.43)	479.50 (555.74)	.15
White blood cell counts, mean (SD), /mm ³	5776.22 (2791.70)	6147.14 (2275.05)	.20
Eosinophil counts, mean (SD), /mm ³	149.38 (190.25)	146.71 (184.94)	.85
Creatinine, mean (SD), mg/dL	0.97 (1.26)	0.84 (0.17)	.61
Alanine aminotransferase, mean (SD), IU/L	33.29 (53.02)	27.61 (21.67)	.65
Allergic disease	34 (12.4)	7 (14.9)	.63
Bronchial asthma	3 (1.1)	2 (4.3)	.16
Allergic rhinitis	11 (4.0)	4 (8.5)	.16
Chronic urticaria	4 (1.5)	1 (2.1)	.55
Food allergy	8 (2.9)	2 (4.3)	.44
Other drug allergy	13 (4.7)	1 (2.1)	.37
Severity of previous reactions			.41
Mild	187 (68.0)	32 (68.1)	
Moderate	72 (26.2)	10 (21.3)	
Severe	16 (5.8)	5 (10.6)	
Premedication			
H ₁ -antihistamines	273 (99.3)	47 (100)	.73
H ₂ -antihistamines	53 (19.3)	7 (14.9)	.48
Systemic corticosteroid	105 (38.2)	11 (23.4)	.04

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared); H₁, histamine₁; H₂, histamine₂; RCM, radiocontrast media.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Discussion

As far as we know, this study is the largest retrospective cohort study performed to date that assesses the outcomes of premedication in high-risk patients with a previous history of acute allergic-like reactions to LOCM. In this study, after premedication for acute allergic-like reactions to LOCM, 96.6% of high-risk patients were given LOCM for CT without experiencing moderate to severe recurrence; moderate reactions occurred in 2.5% of cases, and severe reactions occurred in only 0.9% of the high-risk patients. These results suggest that most high-risk patients can tolerate LOCM after premedication, and corticosteroid prophylaxis appears to be helpful in preventing the recurrence of allergic-like reactions to LOCM. However, even after premedication with corticosteroids, the risk of severe recurrence still remains for patients who had previous severe reactions. Hence, close monitoring for severe hypersensitivity reactions should be mandatory for such patients.

Previous studies have proposed direct mast cell activation, complement activation, and bradykinin formation as non-immunologic mechanisms related to the development of acute allergic-like reactions to ICM.^{4,17} However, recent studies have demonstrated that acute allergic-like reactions to ICM may be associated with IgE-mediated immune system activation in some cases.^{18–25}

For the prevention of recurrence of acute allergic-like reactions, premedication was introduced for subjects who needed repeated contrast studies. In 1972, the effectiveness of intravenous

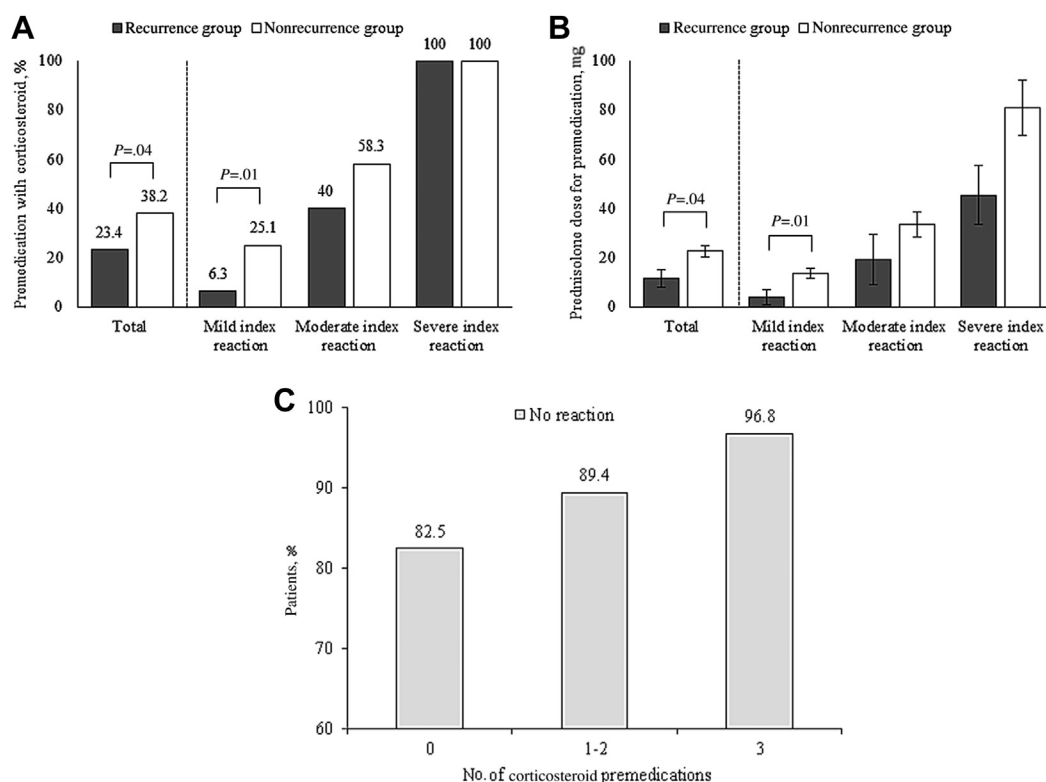


Figure 2. The effects of corticosteroid premedication on the recurrence of acute allergic-like reactions to iodinated contrast media. The rate of corticosteroid premedication sorted by the severity of previous reactions (A), the dose of prednisolone used for premedication sorted by the severity of previous reactions (B), and recurrent reactions according to the number of administrations of corticosteroid used for premedication (C).

diphenhydramine premedication (10 mg 1 minute prior to reuse of ionic contrast media) was reported based on the result of the study in 2,000 previous reactors.²⁶ The three milestones were set in 1975; first, diphenhydramine premedication protocol was changed as the current dosage of 50 mg either intravenously or orally.²⁷ Second, the first study result of high-dosage steroid premedication was published.²⁸ With 150 mg of oral prednisone or equivalent per day in divided dose, most subjects with a history of rash (34/37) or anaphylactoid reactions (8/9) to ionic contrast underwent contrast study without adverse reactions.²⁸ Third, based on these two studies, a prednisone-diphenhydramine combination regimen was suggested. Later, this combination protocol (prednisone 50 mg orally every 6 hours for 3 doses ending one hour prior to contrast exposure with intramuscular diphenhydramine 50 mg one hour prior to contrast exposure) was proved as an effective one for

prevention of recurrence,²⁹ and is currently recommended in guidelines.³⁰ However, these and following other studies mainly investigated the preventive effect of combination protocol for reactors to ionic contrast media.^{31–33} Therefore, the current study has distinguished itself in the way that it delineated the result of steroid premedication in reactors to LOCMs.

One of the following 2 regimens are often used as premedication to prevent acute allergic-like reactions to ICM: prednisolone, 50 mg at 13 hours, 7 hours, and 1 hour before contrast media injection,³⁴ or methylprednisolone, 32 mg at 12 and 2 hours before contrast media injection.³⁵ However, a gold standard for premedication has not yet been established,² and the general recommendation for patients with a previous history of severe acute allergic-like reactions to ICM is to undergo radiologic evaluations rather than contrast imaging studies to prevent the occurrence of rare but potentially catastrophic reactions. Given the potential risks, there is an ethical dilemma that essentially precludes researchers from conducting a randomized clinical study with a placebo to directly evaluate the effectiveness of premedication. Thus, the true

Table 2

Risk Factors for Recurrence of Acute Allergic-like Reactions at the Time of Reexposure to Iodinated Contrast Media After Premedication

Risk factor	OR (95% CI)	P value ^a
Male	0.753 (0.383–1.477)	.41
Age (years)	0.968 (0.944–0.993)	.01
Bronchial asthma	5.773 (0.763–11.554)	.09
Allergic rhinitis	2.727 (0.677–10.983)	.16
Chronic urticaria	0.955 (0.079–11.554)	.97
Food allergy	0.262 (0.027–2.521)	.25
Other drug allergy	0.936 (0.166–5.275)	.94
Previous severe reaction	8.884 (2.108–37.442)	.003
H ₂ -antihistamines premedication	0.748 (0.257–2.178)	.59
Corticosteroid premedication	0.284 (0.103–0.784)	.02

Abbreviations: CI, confidence interval; H₂, histamine₂; OR, odds ratio.

^aMultivariate binary logistic regression taking into account age, sex, comorbid allergic diseases, severity of previous immediate hypersensitivity reaction, and premedication.

Table 3

Recurrence Rate (Percentage) of Acute Allergic-like Reactions According to the Severity of the Index Reaction in the Presence or Absence of Corticosteroid Premedication

Corticosteroid premedication	Mild reactions ^a	Moderate reactions ^b	Severe reactions
Absent	17.7	16.7	NA
Present ^c	4.1	8.7	23.8

Abbreviation: NA, not applicable.

^aP = .01.

^bP = .22.

^cP for trend = .02.

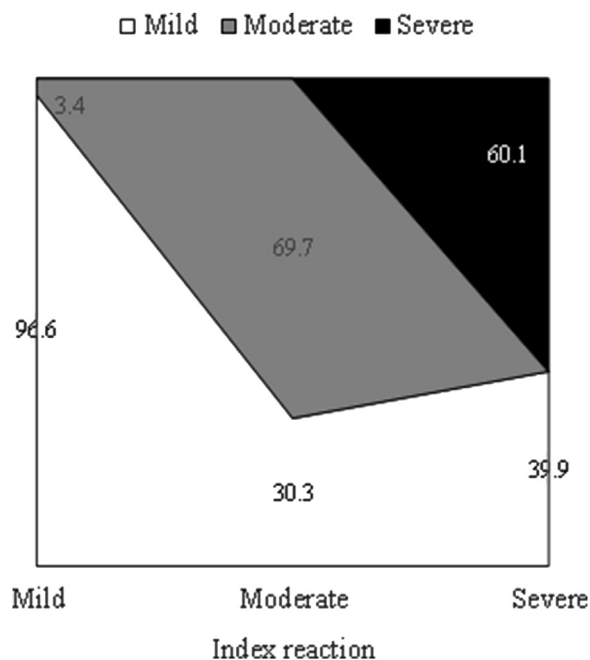


Figure 3. Severity of recurrent reactions according to the severity of index reactions.

recurrence rate of acute allergic-like reactions to ICM is difficult to determine, given the wide and varied use of premedication with antihistamines and/or corticosteroids.

Several small studies investigated the recurrence rate of acute allergic-like reactions after premedication. Kim et al⁸ found that of 30 patients with a previous history of acute allergic-like reactions to nonionic LOCM, 17% had recurrent reactions after premedication with H₁-antihistamines, H₂-antihistamines, and/or corticosteroids (3 doses of 50 mg of prednisolone or 40–50 mg of methylprednisolone). Freed et al¹¹ reported that only 10% of 52 patients with a previous history of acute allergic-like reactions to ICM developed acute allergic-like reactions after premedication with prednisolone (5 doses of 20 mg of prednisolone every 6 hours). In our study, 14.6% of 322 patients developed recurrent reactions after premedication; this finding is consistent with the results of previous studies. Given the relatively low dosages and rate of premedication with corticosteroids (11.6 [3.76] mg and 23.4%) in the recurrence group and the existence of a linear association between corticosteroid dose and prevention rate, further studies are needed to establish the optimal dose of corticosteroids for premedication to increase the prevention rate.

A previous report found that the rate of recurrence of acute allergic-like reactions to ICM significantly decreased in patients with a previous history of such reactions as the rate of premedication with corticosteroids increased.¹⁰ In the current study, the corticosteroid premedication rate was 1.6 times higher in the nonrecurrence group than in the recurrence group. Furthermore, the dose and the total number of administrations of corticosteroids were significantly higher in the nonrecurrence group. There was a 76.8% reduction in recurrence in patients with mild index reactions who were premedicated with corticosteroids, and this difference was statistically significant (17.7% vs 4.1%, $P = .01$). In patients with moderate index reactions, there was a 47.9% reduction after corticosteroid premedication, although this result was not statistically significant (16.7% vs 8.7%, $P = .22$). The difference could not be evaluated in patients with severe index reactions because none of them were reexposed to LOCM without being premedicated with corticosteroids. Taken together, these results suggest that

premedication with corticosteroids is effective in preventing recurrence of hypersensitivity reactions to LOCM.

Several other reports provide support for the association between the degree of severity of previous reactions and that of recurrent reactions.^{8,9,11,36} Davenport et al³⁶ recently reported that the severity of recurrent reactions in patients with mild index reactions was usually mild, and when the index reaction was severe, the breakthrough reaction was usually moderate or severe. These results imply that patients with a previous history of severe acute allergic-like reactions to ICM are at a greater risk of developing severe reactions on reexposure, and such patients should be administered ICM only after sufficient premedication under close monitoring. This study found that the more severe the previous index reactions were, the more likely reactions were to recur. Although the recurrent reactions after premedication in both the mild and moderate reaction groups were tolerable in severity, 60% of recurrent reactions that occurred in the severe reaction group were severe, even with the use of corticosteroid premedication.

The findings of this study provide useful clinical information; nevertheless, it has some limitations. First, there were the methodological limitations of the study: a retrospective design and the absence of an institutional standard premedication protocol. Therefore, the pretreatment protocols were heterogeneous and randomly selected by physicians. Although subjects with more intensive premedication had more severe index reactions, the absence of an objective indication for choosing different premedication protocols is a factor that may impede a straightforward conclusion in the role of steroid premedication. Second, because this study did not include information on the particular ICM that sparked the index reactions or any information on the ICM used for reexposure, the effect of changing the type of ICM after a recurrence could not be assessed.

In conclusion, the results of this study suggest that most patients with a previous history of mild to moderate acute allergic-like reactions may safely be given ICM if properly premedicated and that corticosteroid premedication seems to be effective in preventing the recurrence of allergic-like reactions to LOCM. However, special attention should be paid to those patients with a previous history of severe reactions because they may potentially develop severe reactions despite premedication with corticosteroids.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.07.010>.

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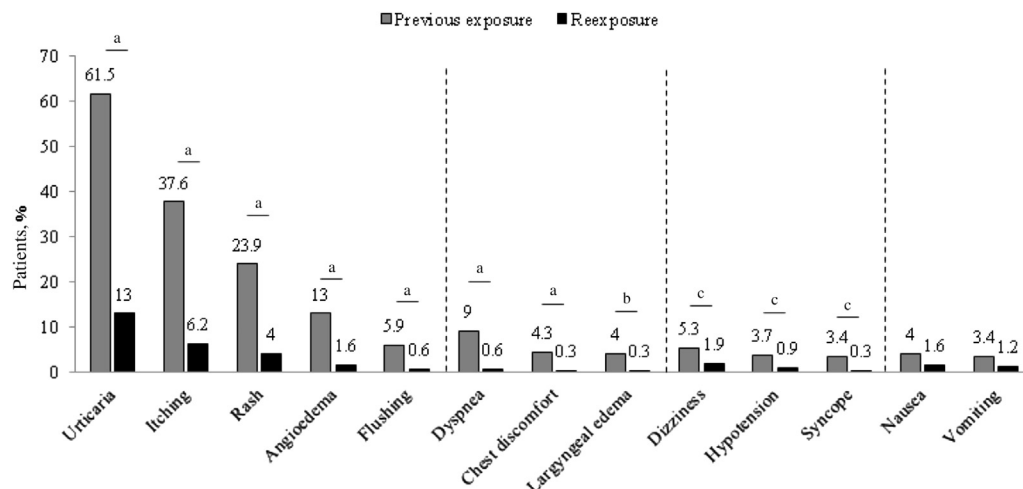


Figure 1. Acute allergic-like reactions at the time of previous nonpremedicated exposure and premedicated reexposure to iodinated contrast media.

^a $P < .001$.

^b $P < .01$.

^c $P < .05$.

Table 1

Baseline Characteristics of Patients Who Experienced Mild, Moderate, and Severe Acute Allergic-like Reactions to Previous Administration of Iodinated Contrast Media^a

Characteristic	Total patients (N = 322)	Mild reactions (n = 219 [68.0%])	Moderate reactions (n = 82 [25.5%])	Severe reactions (n = 21 [6.5%])	P value
Male patients	149 (46.3)	113 (51.6)	26 (31.7)	10 (47.8)	.009
Age, mean (SD), y	56.22 (12.47)	56.83 (12.01)	53.22 (12.55)	61.57 (14.61)	.01
BMI, mean (SD)	24.11 (3.64)	24.29 (3.23)	23.69 (4.88)	23.76 (2.63)	.64
White blood cell counts, mean (SD), /mm ³	5816.58 (2737.47)	5728.83 (2742.65)	6247.73 (2922.62)	5237.50 (1789.76)	.42
Eosinophil counts, mean (SD), mm ³	149.08 (189.18)	159.73 (201.71)	131.18 (166.70)	97.50 (98.47)	.43
Creatinine, mean (SD), mg/dL	0.96 (1.19)	0.92 (1.00)	0.80 (0.19)	1.81 (3.19)	.02
Alanine aminotransferase, mean (SD), IU/L	32.62 (50.33)	36.64 (58.70)	24.82 (18.45)	17.54 (8.07)	.21
Allergic diseases	41 (12.7)	21 (9.6)	16 (19.5)	4 (19.0)	.048
Bronchial asthma	5 (1.6)	3 (1.4)	2 (2.4)	0	.67
Allergic rhinitis	15 (4.7)	5 (2.3)	10 (12.2)	0	.001
Chronic urticaria	5 (1.6)	4 (1.8)	1 (1.2)	0	.78
Food allergy	10 (3.1)	5 (2.3)	4 (4.9)	1 (4.8)	.46
Other drug allergy	14 (4.3)	8 (3.7)	3 (3.7)	3 (14.3)	.07

Abbreviation: BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared).

^aData are presented as number (percentage) of patients unless otherwise indicated.