



Stratified premedication strategy for the prevention of contrast media hypersensitivity in high-risk patients

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ABSTRACT

Background: Although the severity of hypersensitivity reactions to iodinated contrast media varies, it is well correlated with the severity of recurrent reactions; however, prophylaxis protocols are not severity-stratified. **Objective:** To assess the outcomes of tailored prophylaxis according to the severity of hypersensitivity reactions to iodinated contrast media.

Methods: Our premedication protocols were stratified based on the severity of previous reactions: (1) 4 mg of chlorpheniramine for mild reactions, (2) adding 40 mg of methylprednisolone for moderate reactions, and (3) adding multiple doses of 40 mg of methylprednisolone for severe index reactions. Cases of reexposure in patients with a history of hypersensitivity reactions were routinely monitored and mandatorily recorded.

Results: Among a total of 850 patients who underwent enhanced computed tomography after severity-tailored prophylaxis, breakthrough reactions occurred in 17.1%, but most breakthrough reactions (89.0%) were mild and did not require medical treatment. Additional corticosteroid use did not reduce the breakthrough reaction rate in cases with a mild index reaction (16.8% vs 17.2%, $P = .70$). However, under-premedication with a single dose of corticosteroid revealed significantly higher rates of breakthrough reaction than did double doses of corticosteroid in cases with a severe index reaction (55.6% vs 17.4%, $P = .02$). Changing the iodinated contrast media resulted in an additional reduction of the breakthrough reaction rate overall (14.9% vs 32.1%, $P = .001$).

Conclusion: In a total severity-based stratified prophylaxis regimens and changing iodinated contrast media can be considered in patients with a history of previous hypersensitivity reaction to iodinated contrast media to reduce the risk of breakthrough reactions.

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Introduction

Patients with a previous history of hypersensitivity reaction to iodinated contrast media (ICM) are at significantly increased risk for recurrent hypersensitivity reaction upon subsequent exposure to ICM. However, symptoms and severity of repeat hypersensitivity reactions are largely predictable because they are usually similar to those of the index reaction, and the risk of developing a severe breakthrough reaction (BTR) is very low in patients with a mild index reaction.^{1,2}

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Although it is still a precautionary principle to avoid causative agents once drug hypersensitivity occurs, enhanced computed tomography (CT) has become an essential part of modern medicine and is sometimes irreplaceable with other imaging modalities. To address this issue, diverse strategies have been considered, including premedicating patients,^{3–6} changing the ICM,^{7,8} and performing skin tests to determine ICM cross-reactive to the causative agent.⁸

However, owing to the paucity of large-scale studies to prove the efficacy of these strategies, global guidelines to prevent hypersensitivity to ICM have not been standardized. Several premedication regimens have revealed efficacy in preventing recurrent hypersensitivity reactions in observational studies^{3,9–11}; nevertheless, an optimal premedication approach has not been

determined because severe reactors were not included in most studies, and there was no distinct strategy for mild reactors, which comprised most cases. Therefore, we aimed to evaluate the potential benefit of severity-tailored prophylaxis in patients at risk of recurrent hypersensitivity reactions to ICM.

Methods

Study Participants and Injected Contrast Media

This study included all patients with a history of immediate ICM hypersensitivity who underwent enhanced CT between July 2012 and June 2014. Symptoms suggestive of ICM hypersensitivity were monitored and mandatorily recorded by trained nurses in real-time in the electronic medical record-based Contrast Safety Monitoring and Management System (CoSM²oS) at Seoul National University Hospital. Data such as age, sex, injected ICM agent, and previous history of exposure and hypersensitivity reactions to ICM were also collected from the same system. Throughout the entire study period, 5 kinds of low-osmolar nonionic ICM (LOCM) were used for CT: iobitridol, iohexol, iomeprol, iopamidol, and iopromide.

Severity of Immediate Hypersensitivity Reactions

Immediate hypersensitivity reaction was defined as a reaction that occurred within 1 hour of ICM administration. Patients' symptoms and signs were classified into 3 categories based on the American College of Radiology manual on contrast media: mild, moderate, or severe reactions.² Mild reactions included limited urticaria, pruritus, cutaneous edema, nasal congestion, rhinorrhea, and conjunctivitis. Moderate reactions included diffuse urticaria, erythema, facial edema without dyspnea, laryngeal edema, and mild wheezing without hypoxia. Severe reactions included signs and symptoms that are often life-threatening, such as diffuse erythema and edema with dyspnea, hypotension (defined as systolic blood pressure <90 mm Hg), laryngeal edema with hypoxia, wheezing with hypoxia, unresponsiveness, cardiopulmonary arrest, and clinically manifested arrhythmias.

Prophylaxis Strategy for High-Risk Cases on Reexposure to ICM

In CoSM²oS, a premedication regimen determined by the severity of the index hypersensitivity reaction was recommended via an order communication system when physicians reordered enhanced CT for those who previously experienced a hypersensitivity reaction to ICM; regimens were as follows: (1) for patients with a mild index reaction, 4 mg of intravenous chlorpheniramine 30 minutes before ICM administration; (2) for patients with a moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; and (3) for patients with a severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration via the intravenous catheter inserted for ICM injection. For antihistamine premedication, 4 mg of intravenous chlorpheniramine was used instead of 50 mg of diphenhydramine because of the latter's unavailability in Korea.

For patients with near-fatal anaphylactic shock, life-threatening reactions, including hypotension that requires epinephrine injection in the previous exposure, a skin test to rule out potentially provoking ICM, and hospital admission for close monitoring were also recommended. Alternative ICM were determined if the agent was not related to previous hypersensitivity events and had a negative result on the skin test.

Physicians were allowed to modify a premedication regimen recommended by CoSM²oS. Patients were identified as underpremedicated if a lower dose or fewer kinds of premedication drugs were administered and were identified as overpremedicated if a

higher dose or more kinds of premedication were administered compared with the CoSM²oS recommendation.

Monitoring Strategy on Reexposure

After ICM reexposure, participants were monitored for an hour to determine the occurrence of immediate hypersensitivity reaction. BTR was defined as a repeat contrast reaction that occurred despite premedication. CT was considered successfully performed when patients had no symptoms or only mild reactions not requiring medical treatment.

Statistical Analysis

The incidence rate was calculated by dividing the number of cases of ICM hypersensitivity reactions by the number of cases undergoing contrast-enhanced CT during the study period. The differences between the groups with and without hypersensitivity reactions were assessed using the χ^2 test for categorical variables and the *t* test for continuous variables. The results after reexposure were analyzed as a whole and according to the severity of previous index reactions. Risk factors for BTR were determined by multiple logistic regression models. Analyses were adjusted for age, sex, previous ICM exposure history, and history of previous ICM hypersensitivity. A backward stepwise model was used, with the likelihood ratio criterion of a *P* < .05 to retain a variable; analyses were performed using the SPSS software package, version 22.0 (SPSS Inc, Chicago, Illinois).

Ethics Statement

This retrospective cohort study was conducted according to the ethical guidelines for epidemiologic research designed by the Korean Ministry of Health and Welfare and was approved by the institutional review board of Seoul National University Hospital. The need for informed consent was waived. The anonymous identifiers were obtained, and the participants' privacy was protected in a secure manner.

Results

During the study period, a total of 850 index cases with a history of prior immediate hypersensitivity reaction (762 mild, 65 moderate, and 23 severe cases) were premedicated at the time of reexposure to ICM in accordance with the CoSM²oS recommendations. Their clinical characteristics are summarized in Table 1. Separately from these cases following the recommendations, there were 273 underpremedicated cases and 95 overpremedicated cases for which the severity-tailored prophylaxis recommendations were not applied.

Table 1

Clinical Characteristics of the 850 Patients With Previous Hypersensitivity Reactions^a

Characteristic	Finding
Age, mean (SD), y	57.4 (0.3)
Female	459 (54.0)
Type of contrast media	
Iobitridol	251 (29.5)
Iohexol	255 (30.0)
Iomeprol	30 (3.5)
Iopamidol	73 (8.6)
Iopromide	241 (28.4)
Previous LOCM exposure	448 (52.7)
Total previous exposure time to contrast media, mean (SD)	4.9 (0.2)

Abbreviation: LOCM, low osmolar contrast media.

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

Outcomes of Severity-Tailored Prophylaxis on Reexposure to ICM

Among a total of 850 patients who received severity-tailored prophylaxis, 705 (82.9%) had no hypersensitivity reaction at all. Varying severity levels of BTRs were observed in 145 patients (17.1%), but most cases (129 [89.0%] of 145) were mild. Consequently, only 16 patients (1.9%) experienced a recurrence of moderate to severe hypersensitivity reaction, and 834 (98.1%) of 850 patients successfully underwent enhanced CT without any clinically significant symptomatic hypersensitivity reaction requiring medical treatment.

The overall rate of hypersensitivity reactions diminished owing to appropriate premedication, and BTR rates were not different according to the severity of the index hypersensitivity reaction (17.2% in mild, 15.4% in moderate, and 17.4% in severe index reactions, $P = .65$). However, the severity of BTR still reflected the severity of the index hypersensitivity reaction. Most of BTR cases (93.1%) were mild on reexposure in the mild index reaction group. However, 30% of BTR cases occurred in the moderate index reaction group were moderate in severity. In the severe index reaction group, the proportion of severe reaction increased up to 50% of BTR cases (Fig 1).

Compared with severity-tailored prophylaxis, overpremedication with systemic corticosteroids in addition to antihistamines did not produce significant beneficial outcomes compared with antihistamines only in reducing the BTR rate (16.8% vs 17.2%, $P = .70$) among patients with a history of mild index reaction. In patients with a history of moderate or severe index reaction, overpremedicated cases were not available.

When patients were underpremedicated, the BTR rates were slightly higher but did not reach statistical significance in general or among patients with a history of moderate hypersensitivity reaction (20.1% vs 17.1%, $P = .33$, and 18.3% vs 15.4%, $P = .69$, respectively). However, the BTR rate in patients with a severe prior reaction revealed a drastic increase of BTR rate up to 55.6% when underpremedicated compared with 17.4% in patients who had been properly premedicated with chlorpheniramine and double doses of systemic steroids based on the CoSM²oS recommendation ($P = .02$) (Fig 2).

Outcomes According to Changes in Contrast Media

Among 850 patients administered severity-tailored prophylaxis, the outcomes of ICM alteration were assessed. Changing the ICM agent to be injected conferred protection for BTR overall (14.9% vs 32.1%, $P = .001$). This tendency of protective effect was found in all

severity groups but statistical significance was proven only in patients with a history of mild hypersensitivity reactions (15.6% vs 32.5%, $P = .002$). Patients with a moderate index reaction (6.9% vs 50.0%, $P = .06$) and severe index reaction (7.7% vs 33.3%, $P = .22$) also had fewer BTRs in the ICM-changed group compared with the ICM-unchanged group, but this difference was not statistically significant (Fig 3).

Especially among 10 patients with a near-fatal severe index reaction who avoided culprit contrast media and had proper premedication, only 1 had BTR (10%). On the contrary, 3 of 10 patients with nonfatal severe index reactions had BTR (30%) when alternative contrast media were not changed or unable to change because of lack of information. The detailed information of skin tests and the outcome of reexposure in patients with severe index reaction, including near-fatal reactions, were given in eTable 1.

Risk Factors and Characteristics of BTRs

Among 850 patients premedicated based on the severity of previous index reactions, we compared the characteristics of 145 patients with BTRs with those of 705 patients without any BTR. Patients in the BTR group were younger (mean [SD] age, 54.9 [1.0] vs 58.4 [0.4], $P = .001$) and had a higher proportion of severe index reactions (mean [SD], 6.2% [2.7%], $P = .02$) compared with the tolerant group. The proportion of patients who received a different ICM instead of the culprit ICM was higher in the group who did not experience any BTR than in the BTR group (81.5% vs 59.7%, $P = .001$; Table 2).

When analyzing together the outcomes of 850 patients who received severity-tailored prophylaxis and 368 patients who did not follow the severity-based recommendations, multivariate logistic regression identified exposure to ICM more than 4 times (hazard ratio [HR], 1.834; 95% confidence interval [CI], 1.204–2.792; $P = .02$), age younger than 50 years (HR, 1.662; 95% CI, 1.183–2.335; $P = .003$), severe index reaction (HR, 1.509; 95% CI, 1.384–4.921; $P = .002$), and injection of the same ICM agent that caused the prior reaction (HR, 1.405; 95% CI, 1.258–1.637; $P < .001$) as significant risk factors for the development of BTR.

Discussion

To evaluate the outcomes of severity-tailored prophylaxis, we monitored a large retrospective cohort of 850 patients with a history of previous hypersensitivity reaction to ICM based on the real-time monitoring of immediate hypersensitivity reactions and found that prevention strategies could be differentiated according to the severity of index reactions. Recently, the use of ICM has been rapidly increasing worldwide.^{12,13} In addition, there has been an increase in the number of people exposed to ICM and the frequency of exposure to ICM per person. During the study period, the overall incidence of immediate hypersensitivity reaction to ICM was 0.97% and the incidence of severe reaction was 0.02% (S.-Y.L. and H.-R.K., unpublished data, 2016). To use ICM agents safely, appropriate prevention strategies should be applied for high-risk patients who have experienced previous ICM hypersensitivity because they are highly susceptible to recurrence.^{2,14,15} As a part of protective strategies against ICM hypersensitivity, conventional premedication protocols with corticosteroids and antihistamines are widely used before ICM is administered in patients with risk factors^{3–5} as follows: 50 mg of prednisolone at 13, 7, and 1 hour before or 32 mg of methylprednisolone at 12 and 2 hours before exposure in conjunction with antihistamine 1 hour before contrast reexposure.² This premedication regimen is used for cases of ICM hypersensitivity reactions of any severity. Therefore, it is still questionable whether these premedication protocols are requisite in cases with mild index reactions and are safe enough for severe reactors. Especially for patients with a history of severe reactions to ICM, the

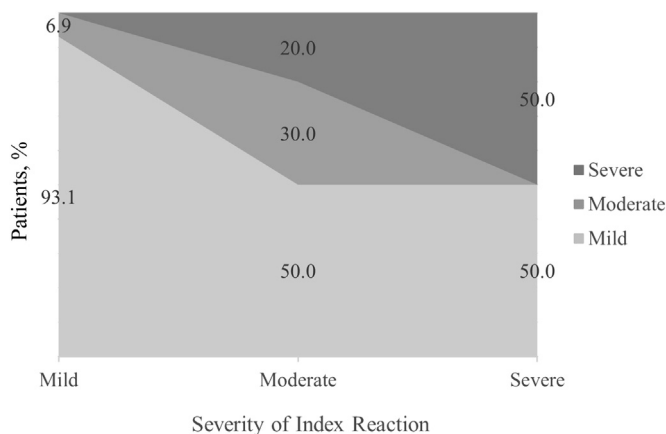


Figure 1. The severity of index reaction among patients who had severe breakthrough reactions (BTRs) on reexposure to iodinated contrast media. The severity of the BTRs was correlated with that of the index reaction.

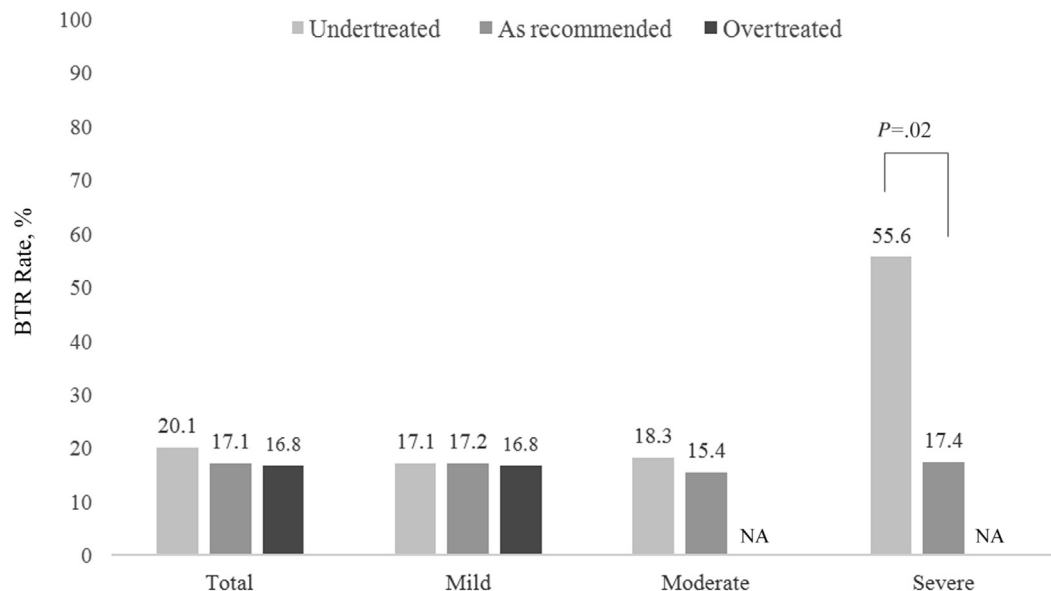


Figure 2. Patients with a severe index reaction had a significant decrease in the breakthrough reaction (BTR) rate when they were appropriately treated as per the recommendation compared with undertreated patients. There were no overpremedicated cases among patients with moderate and severe index reactions. NA, not applicable.

optimal approach has not yet been established because of infrequency and the potential risk of severe recurrence. In this study, we evaluated outcomes of reexposure to ICM in 23 patients with severe index reaction and compared them with outcomes of other severity groups. The outcomes of patients with severe index reactions were comparable to those of patients with mild and moderate index reactions if premedicated using our severity-tailored prophylaxis regimens.

This severity-tailored premedication strategy obtained overall good results. In the present study, 98.1% of high-risk patients successfully completed enhanced CT scans without any serious

hypersensitivity, and only 1.9% experienced significant hypersensitivity reactions requiring medical treatment.

Although the introduction of LOCM has reduced the prevalence of adverse reactions to ICM, 0.7% to 3.1% of patients exposed to LOCM still experience hypersensitivity reactions, including rare but life-threatening events^{8,16,17}; the BTR rate has still been reported to range from 4.5% to 46% despite premedication.^{4,6,18} The effect of premedication using corticosteroids has been established with high-osmolar ICM (HOCM),^{19,20} but premedication is not fully validated with LOCM.^{3,21,22} Generally, a short course of steroid use usually causes no adverse reactions. However, it should be

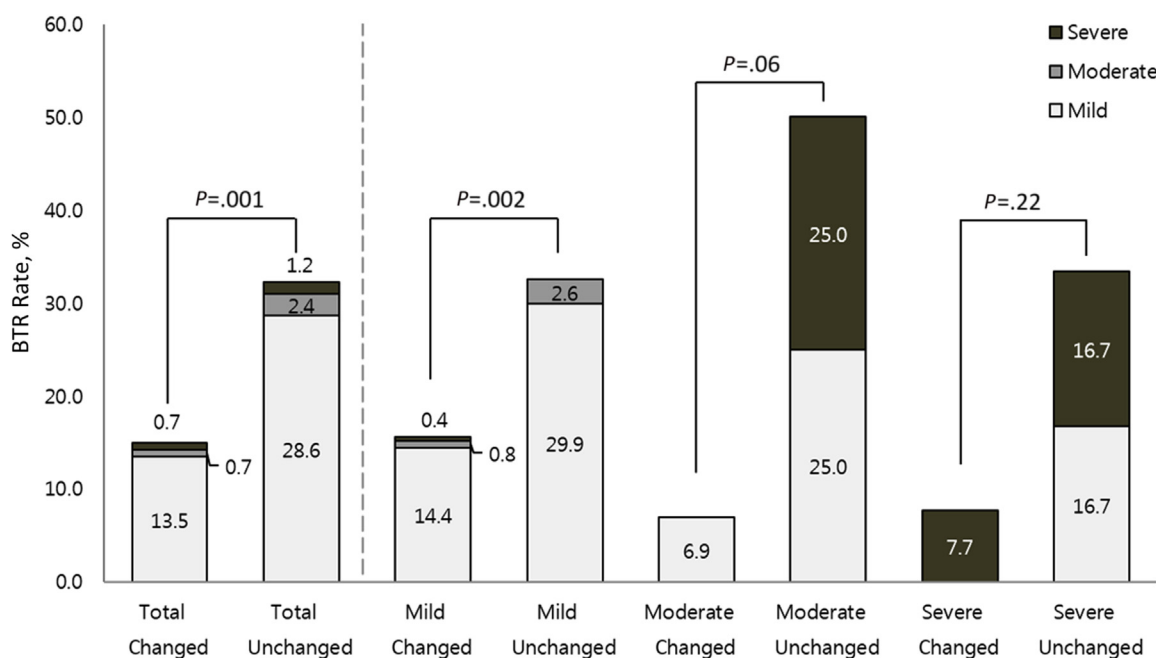


Figure 3. Breakthrough reaction (BTR) rates according to the use of the causative contrast agents: changing the iodinated contrast media agent decreased the overall BTR (14.9% vs 32.1%, $P = .001$) and the BTR rate in those with a mild (15.6% vs 32.5%, $P = .002$) index reaction.

Table 2

Characteristics of the Patients With or Without a Breakthrough Reaction on Reexposure^a

Characteristic	No breakthrough reaction (n = 705)	Breakthrough reaction (n = 145)	P value
Age, mean (SD), y	58.4 (0.4)	54.9 (1.0)	.001
Female	370 (52.5)	74 (51.0)	.78
Previous severe reaction	19 (2.7)	19 (6.2)	.02
Changing culprit ICM agents	256/314 (81.5)	43/72 (59.7)	.001
History of allergic disease	52 (7.4)	10 (6.9)	.88

Abbreviation: ICM, iodinated contrast media.

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

administered when it provides a proven medical benefit because its use can be harmful in some critically ill patients. By using differentiated protocols based on the severity of index reactions, we could reduce the total dose of systemic corticosteroids compared with conventional premedication methods.

Recurrent reactions on reexposure are usually mild in most patients with mild index hypersensitivity reactions.¹ In this study, steroid premedication did not reveal an additional protective effect compared with antihistamine premedication in patients with mild index reactions. Therefore, for those with mild index reactions, premedication with only antihistamines can be an optimized safe alternative option on reexposure, and steroid premedication can be exempted. This study also identified that most moderate ICM hypersensitivity cases are preventable through a premedication regimen with a single dose of systemic steroids. However, a single dose of systemic steroids resulted in a huge increase of BTR rate in cases with severe index reactions. Therefore, doses of corticosteroids should be stratified based on the severity of previous hypersensitivity reactions. By combining all these findings observed in each severity group, it is conceivable that the severity of the index reaction is exceedingly important in risk stratification for BTR, and a differentiated approach should be used for the prevention of recurrence.

Previous studies have reported the effect of avoiding the causative agent and changing the ICM to be injected,^{7,8} and HOCM is associated with a much higher rate of adverse events, and low cross-reactivity is associated with LOCM. The fact that patients with hypersensitivity to HOCM did not have BTRs when they received LOCM⁷ is a testimony of the greater safety of LOCM and low cross-reactivity between the 2 ICM classes. In another study, an alternative agent was successfully selected in accordance with the result of the ICM skin tests and the chemical property of the culprit ICM (monomeric or dimeric); none of the 36 patients presented with an immediate hypersensitivity reaction.⁸ Among patients who received LOCM, approximately one-third of patients with immediate ICM hypersensitivity had a cross-reactivity.²³ Compared with previous studies, the composition of patients in this study was homogenous within the subgroups with regard to regimen and severity of hypersensitivity reaction to ICM. Therefore, the effects of changing the ICM could be evaluated more properly. Changing the ICM decreased the overall BTR rate and the BTR rate in patients with a moderate index reaction but not in those with mild and severe index reactions. If an alternative ICM were selected with the help of an ICM skin test, changing the ICM may contribute more to reduction of the BTR rate.

Risk factors for BTRs include a history of long-term steroid use, severe allergies, and allergy to multiple allergens.^{1,6,24,25} In the present study, age younger than 50 years, multiple previous exposures to ICM, previous severe reaction, and repeated exposure to the culprit ICM were identified as risk factors for the recurrence of ICM hypersensitivity, but not a single factor could determine the prediction or prevention of BTRs.

Our study has some limitations and raises unanswered questions. First, the exact efficacy of the premedication regimen used in this study could not be clearly evaluated because the exact recurrence rate without premedication is not known. However, a randomized controlled study with a placebo premedication to overcome this limitation is unethical because previous a hypersensitivity reaction itself is a very strong risk factor and is highly likely to recur without any premedication. Second, the selection of alternative ICM was not based on skin test results because the evidence supporting the clinical role of skin test in patients with ICM hypersensitivity was not strong enough during the study period. Therefore, potential cross-reactivity between LOCMs was not ruled out. Third, a strategy on changing contrast media was not established in this study. The recent guidelines from the American College of Radiology state that a different contrast agent may sometimes be helpful, but a change in LOCM appears to provide little or no benefit. In addition, alternative contrast media cannot be chosen because the information of culprit contrast media was not available in patients who experienced ICM hypersensitivity in other hospitals.

Despite these limitations, we believe that the reported results provide new clinical implications to complement current unstratified fixed premedication regimens with a severity-tailored prophylaxis strategy.

In conclusion, this is the first large retrospective cohort study that evaluated severity-tailored prophylaxis in patients with a history of immediate ICM hypersensitivity for the prevention of recurrence of ICM hypersensitivity; moreover, preventive outcomes were satisfactory across all severity groups.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.11.027>.

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Supplementary Data

eTable 1

Outcome of Patients With Severe Index Reaction

Patient no.	Age, y	Sex	Changing agents	Culprit CM	CM on reexposure	Outcome after reexposure	Skin test result
1^a	72	Male	Changed	lobitridol	lohexol	No reaction	Negative
2^a	55	Female	Changed	lobitridol	lohexol	No reaction	ND
3^a	43	Male	Changed	lobitridol	lopromide	No reaction	lobitridol
4	55	Female	Changed	lobitridol	lohexol	No reaction	ND
5^a	74	Male	Changed	lomeprol	lohexol	No reaction	lomeprol
6	62	Male	Changed	lomeprol	lohexol	No reaction	ND
7^a	76	Female	Changed	lopamidol	lobitridol	No reaction	lopromide
8^a	40	Female	Changed	lohexol	lopamidol	Severe BTR	lohexol, iopromide
9^a	55	Female	Changed	lohexol	lopamidol	No reaction	lobitridol, iomeprol, iopromide
10^a	48	Female	Changed	lohexol	lopamidol	No reaction	Negative
11^a	47	Female	Changed	lohexol	lopromide	No reaction	Negative
12^a	68	Female	Changed	lohexol	lomeprol	No reaction	lobitridol, iopamidol, iopromide
13	57	Female	Changed	lohexol	lobitridol	No reaction	ND
14	7	Female	Not changed	lobitridol	lobitridol	No reaction	ND
15	27	Female	Not changed	lobitridol	lobitridol	Mild BTR	ND
16	76	Male	Not changed	lohexol	lohexol	Severe BTR	ND
17	68	Female	Not changed	lomeprol	lomeprol	No reaction	ND
18	63	Male	Not changed	lopromide	lopromide	No reaction	ND
19	68	Female	Not changed	lopromide	lopromide	No reaction	ND
20	60	Male	NA	lobitridol	lobitridol	No reaction	ND
21	81	Female	NA	lomeprol	lomeprol	No reaction	ND
22	63	Female	NA	lopamidol	lopamidol	Mild BTR	ND
23	56	Male	NA	lopromide	lopromide	No reaction	ND

Abbreviations: BTR, breakthrough reaction; CM, contrast media; NA, not available; ND, not done.

^aNear-fatal cases are in boldface type.