*Kim et al. World Allergy Organization Journal* (2021) 14:100561
http://doi.org/10.1016/j.waojou.2021.100561

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

# Pharmacological prevention of delayed hypersensitivity reactions caused by iodinated contrast media

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## ABSTRACT

**Background:** Delayed hypersensitivity reactions (DHRs) to radiocontrast media (RCM) occur in approximately 0.5–23.0% of patients and are thought to be caused by T cell-mediated mechanisms. However, an optimal pharmacological preventive strategy is not yet established in patients with histories of delayed reactions to RCM.

**Objective:** We aimed to evaluate the efficacy of pharmacological prevention in patients with histories of delayed reactions to non-ionic low-osmolar RCM when re-exposed to RCM.

**Methods:** A retrospective review of electronic medical records of 117 patients with previous histories of DHRs to RCM who visited an allergy clinic for the prevention of reactions after the re-exposure to RCM was conducted. The effects of pharmacological prevention were compared according to the symptom scores of previous reactions based on their intensities and durations with electronic medical records (EMRs).

**Results:** Of the 117 patients who experienced DHRs after RCM injection, we confirmed the outcomes of RCM re-exposure in 101 patients. For pharmacological prevention, 92 patients (91.1%) received steroids before RCM injection and among them, 50 patients (49.5%) received additional steroids after RCM injection. With this pharmacological prevention, patients of symptoms improved or no recurrence, recurrence of similar previous symptoms, and recurrence of worse symptoms were 98 (97.0%), 2 (2.0%), and 1 (1.0%), respectively. The proportions of no recurrence after pharmacological prevention were lower in patients with severe reactions and higher symptom scores.

**Conclusion:** Pharmacological prevention showed a beneficial effect in most patients with delayed hypersensitivity to RCM. Further investigations are needed to establish an effective protocol for the prevention of delayed reactions to RCM.

**Keywords:** Delayed hypersensitivity, Radiocontrast

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Full list of author information is available at the end of the article https://doi.org/10.1016/j.waojou.2021.100561

http://doi.org/10.1016/j.waojou.2021.100561
Received 1 March 2021; Received in revised from 27 May 2021; Accepted 1 June 2021
Online publication date 1 July 2021

## INTRODUCTION

Radiocontrast media (RCM) are used more than 75 million times per year for enhancing radiographic images, and frequent adverse reactions after RCM administration are well known.[1,2] Hypersensitivity reactions due to RCM are classified as 1) immediate reactions, which occur within 1 h after RCM administration, and 2) delayed reactions, which occur after more than 1 h of RCM exposure.[3,4] Although the frequency of immediate adverse reactions to RCM was 3.8–12.7% in patients receiving high-osmolar ionic RCM and 0.7–3.1% in patients receiving low-osmolar non-ionic RCM, delayed adverse reactions occurred in approximately 0.5–23.0% of patients with a large variation because it is not clear whether the occurrence of apparent symptoms is due to RCM.[4–6] Moreover, it is assumed that delayed reactions are probably as common or more common than immediate adverse reactions.[7]

Delayed hypersensitivity reactions (DHRs) most frequently clinically manifest as mild maculopapular exanthema. Drug-related eosinophilia and systemic symptoms, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) may also be rarely present.[8–10] In a previous study, approximately 19% of DHRs presented as urticaria, but the mechanism remains unclear.[11] Most of these reactions are thought to be due to T cell-mediated mechanisms, and positive skin patch tests and lymphocyte transformation tests support this pathogenesis.[2,10,12–14]

Currently, although the incidence of DHRs to RCM is growing as much as that of immediate reactions,[15–18] a large proportion of delayed-type reactions comprise mild reactions in which symptoms are seen only in the skin, and they are generally self-limited or easily controlled with medication.[5,19,20] Our allergy clinic frequently encountered clinical situations requiring preventive management in patients who had experienced DHRs to RCM and needed radiological tests or procedures using RCM. Although the standard prophylactic protocol has not yet been validated, we had administered pharmacological preventive management in these patients.

In non-immediate reactions, the likelihood of recurrence during re-exposure is high due to frequent cross-reactivity of RCM, and changing to an alternative RCM by skin test result is now recommended for patients who had experienced DHR to RCM.[2,12,21,22] A pharmacological prevention regimen is not usually recommended in non-severe reaction, and data to support the efficacy of premedication in patients with delayed reactions to RCM are lacking.[4,21] Although administration of corticosteroid is considered in patients who have experienced previously severe DHR with positive skin test result, the optimal pretreatment regimen with proven efficacy is not yet established.[21,23] To evaluate the efficacy of pharmacological prevention in patients with previous delayed reactions to non-ionic low osmolar RCM when they were re-exposed to RCM, we retrospectively analyzed the outcomes of pharmacological preventions and the clinical factors related to failure of the pharmacological prevention.

## METHODS

### Study design and participants

A retrospective review of electronic medical records was conducted in 117 patients with a history of DHRs to iodinated RCM who visited the allergy clinic for the prevention of reaction after the re-exposure to non-ionic, low-osmolar RCMs at referral hospital from January 1, 2015, to December 31, 2018. Patients were aged $\geq$18, and those who had previously experienced severe adverse reactions such as SJS or TEN were excluded from the rechallenge. After re-exposure to RCM, the patient visited an allergy clinic or the clinic that had prescribed the imaging test. The outcomes of pharmacological prevention after re-exposure to RCM were evaluated by a clinician to determine whether the delayed reaction had recurred and to assess the severity of symptoms if they recurred. The protocol was approved by the institutional review board of Seoul National University Bundang Hospital (IRB no. B-1804-465-105) with waiver of informed consent.

### Pharmacological prevention

Pharmacological prevention options were determined by an allergist prior to the next RCM

administration for the patients, depending on the previous extent and duration of the adverse reactions to RCM. Systemic corticosteroids and antihistamines were used for the prevention before and/or after RCM exposure without changing the previously administered RCM. After the pharmacological prevention, the patient was referred to the allergy clinic to check whether the prevention was effective.

### Symptom severity score for prior delayed-type reaction

We scored the symptom severity of prior reactions according to the duration of the symptom and the extent of the involvement and classified the severity into 3 grades (mild, moderate, and severe) according to the scores. According to symptom duration, the scores were defined as follows: 1) symptoms that disappear within 24 h without treatment, 2) symptoms that persist for 24–72 h or require medication to improve them, and 3) any symptoms that last for >72 h. According to involvement, the symptom scores were defined as follows: 1) skin reaction in one part of the body (each body part was divided into head and neck, upper extremities, lower extremities, and trunk) or nausea only; 2) skin reactions in 2 or more parts or angioedema only; and 3) whole body skin lesion or any skin lesion with angioedema or any other systemic reaction. By multiplying the score of symptom duration with that of involvement, the final values ranging from 1 to 9 were divided into 3 groups, and the symptom severity was classified into mild, moderate, and severe grades.

### Outcome assessment

The primary objective of this study was to determine whether patients had recurrent symptoms during re-exposure to contrast media after pharmacological prevention. For the outcome assessment, the patients were classified into responders and non-responders according to the degree of recurrence after pharmacological prevention. Depending on the symptoms following pharmacological prevention, and compared to the previous reaction to contrast media, the patients were classified into: 1) a recurrence of worse symptoms group with an increased range or a longer duration of symptoms, 2) a recurrence of similar previous symptoms group with a similar range or duration of symptoms, 3) a partial-improvement group with a reduced range or a shorter duration of symptoms, and 4) a no recurrence group without any symptoms. Of these, the no recurrence and partial-improvement groups were regarded as responders whereas the other groups were considered as non-responders. As a secondary objective, the clinical factors affecting the outcomes of pharmacological prevention were also evaluated. The clinical characteristics of the patient groups who had recurrent hypersensitivity reactions despite pharmacological prevention were compared with those of the no recurrence group.

### Statistical analyses

Comparisons of continuous variables between groups were performed using Student's *t*-test. The categorical variables were analyzed using Fisher's exact test and the chi-square test. P values $< 0.05$ were considered statistically significant. All the analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). To analyze the odds ratio of clinical variables for complete remission, a binary logistic regression test adjusted for age, sex, and severity grade of the previous reaction was performed.

## RESULTS

### Clinical characteristics of study participants and previous reactions

Among the 117 patients who had experienced previous DHRs after RCM injection and were planned to be re-exposed to RCM, the outcomes of RCM rechallenge could be confirmed in 101 patients. The mean age of the study population was 56.5 ± 12.5 years of which 68.4% (n = 80) were women. The time of onset of reactions was between 1 and 12 h after exposure in 41% of the patients, and there were 6 patients whose symptoms occurred more than 3 days after exposure to RCM. Hypersensitivity reactions occurred during the first RCM administration in 34 patients (29.1%). Skin manifestations were present in most patients (96.6%, n = 113), and urticaria (41.6%) and

| Variables | |
|---|---|
| **Age (mean ± SD, years)** | 56.5 ± 12.5 (n = 117) |
| **Sex (female %, n)** | 68.4 (n = 80) |
| **Onset of previous symptoms after contrast exposure (hours)** | |
| 1–12 | 41.0 (n = 48) |
| 12–24 | 31.6 (n = 37) |
| 24–48 | 11.1 (n = 13) |
| 48–72 | 11.1 (n = 13) |
| 72~ | 5.1 (n = 6) |
| **Occurred when RCM was administered for the first time (yes, %)** | **29.2 (n = 28)** |
| **Number of RCM administration before hypersensitivity occurred (mean ± SD)** | 3.9 ± 3.2 (n = 63) |
| **Types of previous delayed reactions to RCM** | |
| **Cutaneous system** | **96.6 (n = 113)** |
| Urticaria only | 36.3 (n = 41) |
| Urticaria with angioedema | 5.3 (n = 6) |
| Angioedema only | 8.8 (n = 10) |
| Maculopapular exanthema | 38.9 (n = 44) |
| Itching only | 10.6 (n = 12) |
| **Gastrointestinal** | **4.3 (n = 5)** |
| **Cardiovascular** | **0.9 (n = 1)** |
| **Respiratory** | **6.8 (n = 8)** |
| **Nervous system** | **1.8 (n = 2)** |
| **Others** | **3.5 (n = 4)** |
| **Underlying disease (%)** | |
| Neoplasm (solid malignancy) | 59.0 (n = 69) |
| Diabetes mellitus | 9.4 (n = 11) |
| Hypertension | 14.5 (n = 17) |
| Thyroid disease | 6.8 (n = 8) |
| Kidney disease | 1.7 (n = 2) |
| Cardiovascular disease | 18.8 (n = 22) |
| **Past history of allergic disease** | **26.5 (n = 31)** |
| Asthma | 16.1 (n = 5) |
| Allergic rhinitis | 29.0 (n = 9) |
| Atopic dermatitis | 3.2 (n = 1) |
| Chronic urticaria | 29.0 (n = 9) |
| Food hypersensitivity | 12.9 (n = 4) |
| Drug hypersensitivity[a] | 16.1 (n = 5) |

**Table 1.** Demographic and clinical characteristics of the study subjects *Abbreviations: RCM: radiocontrast media. [a]Histories of hypersensitivities to radiocontrast media were excluded*

maculopapular exanthema (38.9%) were the most common (Table 1).

## The outcomes of pharmacological prevention

Of the 101 patients in whom the results of pharmacological prevention were confirmed, through chart review, 98 (97.0%) were categorized as responders, ie, symptoms improved in these patients, whereas similar symptoms occurred in 2 patients, and symptoms worsened in 1 patient after RCM re-exposure with pharmacological prevention (Fig. 1 (A), Supplemental Table 1). All the 3 non-responders were administered systemic corticosteroids before RCM administration, and 2 patients were administered systemic steroid after RCM administration; however, the symptoms were not mitigated after RCM exposure (Supplemental Table 2). These non-responders repeatedly performed the tests using iodine contrast media 1–3 times afterwards, but non-immediate reaction recurred continuously. Eventually, 1 patient no longer used iodine contrast and replaced the examination method to MRI (Magnetic Resonance Imaging). The number of non-responders was too small to evaluate the statistical difference in clinical factors determining the response of pharmacological prevention. A total of 89 patients (90.8%) were administered systemic steroids before RCM exposure (methylprednisolone 40 mg intravenous (IV) or methylprednisolone 20 mg IV 1 h before RCM exposure), and 48 patients (49.0%) were administered systemic steroids after RCM exposure in responders (Supplemental Table 1).

When the patients were divided into mild, moderate, and severe groups according to the symptom score system, significant differences in outcomes were observed among the 3 groups. The proportion of complete remission was significantly smaller in the severe groups than in the other groups (Fig. 1 (B)). There were no significant differences in the clinical outcomes according to the administration of systemic steroids before or after RCM exposure. This seems to be related to more frequent premedication with steroids in severe cases (Fig. 1(C)).

## Clinical factors affecting outcomes

On comparing the patients with symptom recurrence with those with no recurrence, the mean age was greater and the female sex was prevalent in patients with symptom recurrence despite pharmacological prevention. The patients with recurrence had previous RCM reactions of more severe symptoms with longer durations and wider involvements of the body (Table 2). Next, we performed a logistic regression analysis with age,

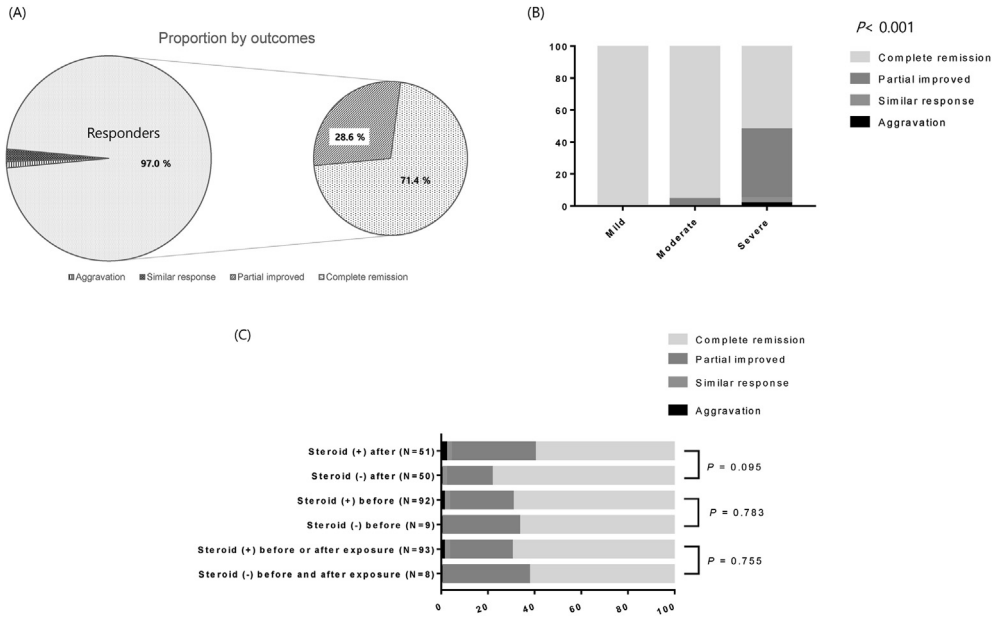


**Fig. 1** Outcomes of pharmacological prevention for delayed radiocontrast media hypersensitivity. (A) Proportions by outcomes in the total number of patients. (B) Outcomes by symptom severity. (C) Outcomes of radiocontrast media re-exposure by systemic steroid administration. - Data were analyzed by Fisher's exact test.

| | Symptom recurrence (n = 31) | No recurrence (n = 70) | *P*-value |
|---|---|---|---|
| **Age (mean ± SD, years)** | 61.0 ± 11.0 | 54.5 ± 12.4 | **0.011** |
| **Sex (female %, n)** | 51.6 (n = 16) | 72.9 (n = 51) | **0.037** |
| **Onset of previous symptoms after contrast exposure (hours)** | | | |
| 1–12 | 45.2 (n = 14) | 42.9 (n = 30) | 0.282 |
| 12–24 | 29.0 (n = 9) | 27.1 (n = 19) | |
| 24–48 | 3.2 (n = 1) | 15.7 (n = 11) | |
| 48–72 | 12.9 (n = 4) | 11.4 (n = 8) | |
| 72~ | 9.7 (n = 3) | 2.9 (n = 2) | |
| **Occurred when RCM was administered the first time (yes, %)** | 41.9 (n = 13) | 23.1 (n = 15) | 0.057 |
| **Number of RCM administration before hypersensitivity occurred (mean ± SD)** | 5.3 ± 4.0 (n = 16) | 3.7 ± 3.0 (n = 39) | 0.110 |
| **Underlying disease (%)** | | | |
| Neoplasm (solid malignancy) | 64.5 (n = 20) | 62.9 (n = 44) | 0.873 |
| Diabetes mellitus | 6.5 (n = 2) | 12.9 (n = 9) | 0.496 |
| Hypertension | 16.1 (n = 5) | 14.3 (n = 10) | 0.771 |
| Thyroid disease | 9.7 (n = 3) | 5.7 (n = 4) | 0.673 |
| Kidney disease | 6.5 (n = 2) | - | 0.092 |
| Cardiovascular disease | 22,6 (n = 7) | 15.7 (n = 11) | 0.406 |
| Allergy history[a] | 32.3 (n = 10) | 24.3 (n = 17) | 0.404 |
| **Steroid prescription before RCM administration** | 90.3 (n = 28) | 91.4 (n = 64) | 1.000 |
| **Steroid administration after RCM administration** | 64.5 (n = 20) | 42.9 (n = 30) | 0.054 |
| **Symptom duration** | | | |
| Gr 1) <24 h | - | 17.1 (n = 12) | < **0.001** |
| Gr 2) 24–72 h, needed administration of medication | 22.6 (n = 7) | 55.7 (n = 39) | |
| Gr 3) >72 h or needed hospital admission | 77.4 (n = 24) | 27.1 (n = 19) | |
| **Symptom involvement** | | | |
| Gr 1) Skin reaction in 1 part[a] or nausea only | - | 22.9 (n = 16) | < **0.001** |
| Gr 3) skin reactions in two or more parts or angioedema only | 12.9 (n = 4) | 31.4 (n = 22) | |
| Gr 3) whole body skin lesion or any skin lesion with angioedema or any systemic reaction | 87.1 (n = 27) | 45.7 (n = 32) | |
| **Severity** | | | |
| Mild (1,2) | - | 20.0 (n = 14) | < **0.001** |
| Moderate (3,4) | 3.2 (n = 1) | 32.9 (n = 23) | |
| Severe (6,9) | 96.8 (n = 30) | 47.1 (n = 33) | |

**Table 2.** Clinical features of patients with symptom recurrence and complete remission after pharmacological prevention *Abbreviations: RCM: radiocontrast media.* [a]*P values were calculated using Student's t-test for continuous variables and the chi-square test for categorical variables. P values < 0.05 are in bold*

sex, and symptom score by multiplying symptom duration with symptom involvement. The severity of previous reactions was a significant clinical risk factor for determining the failure of pharmacological prevention in DHRs to RCM (Table 3).

## DISCUSSION

In this study, we confirmed that even in DHRs to RCM, the recurrence of the reaction can be inhibited or the severity of the symptoms could be mitigated by pharmacological intervention before or after RCM injection without changing the contrast media. The group with persistent symptoms despite pharmacological prevention showed male dominance and a higher mean age. In addition, it was found that if the previous reactions were more severe and had long durations and a wider involvement, the symptoms could persist despite pharmacological prevention. To the best of our knowledge, this is the first report to evaluate the outcome of pharmacological prevention of DHRs to RCM.

As the use of radiological tests and interventions has increased in healthcare and clinical practice, the use of contrast media has increased enormously and has become inevitable in many clinical situations, for example, in diagnostic and therapeutic radiological interventions for vascular diseases and for the evaluation of malignancy. Hypersensitivity to RCM is the most important clinical condition in which the use of RCM is avoided, if possible. However, if the degree of hypersensitivity is mild or tolerable with preventive management and symptomatic treatment and the use of RCM is required for more precise diagnostic evaluation and more effective treatment, the risks and benefits of RCM use should be considered.

The use of systemic steroids was based on previous case reports of preventive management or on proposed mechanisms of delayed hypersensitivity reactions.[7,24–27] Immediate hypersensitivity reactions to RCM are known to be mediated by IgE-mediated reactions as well as non-immunologic reactions associated with histamine release from basophils or mast cells.[2] Unlike immunological reactions, the mechanism of delayed, non-immediate type of reactions is attributed to a T cell-mediated hypersensitivity reaction. Conceptually, systemic steroids are expected to suppress T cell activation and inflammation induced by cell-mediated hypersensitivity.[20,28–30] Antihistamines were administered with steroids in the majority of patients to prevent and relieve cutaneous manifestations such as pruritus.[7,31,32] Our study revealed that pharmacological prevention using steroids and/or antihistamines was effective in most patients, except in a few with severe previous reactions. The severity of the prior reaction was the most critical factor in determining the outcome of preventive measures, although the majority of patients with severe previous reactions showed favorable responses to the prevention. Our study suggests that pharmacological prevention may be applied to delayed hypersensitivity reactions to RCM with special caution for patients with severe prior reactions.

In our study, we evaluated the outcomes of pharmacological prevention in patients who were re-exposed to the RCM without opting for an alternative. Recent studies of hypersensitivity

| Variable | Category | Odds ratio | 95% CI | | *P* value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| **Age** | Years | 0.962 | 0.922 | 1.004 | 0.077 |
| **Severity** | When symptom duration score and involvement scores were multiplied;<br>Mild to moderate; score 1–4<br>Severe: score 6–9 | 0.029 | 0.004 | 0.227 | 0.001 |
| **Sex** | Female to male | 2.685 | 0.059 | 0.965 | 7.469 |

**Table 3.** Factors affecting outcomes of pharmacological prevention in delayed hypersensitivity to radiocontrast media *Binary logistic regression adjusted for age, sex, and severity by multiplied symptom score.Abbreviations: CI: confidence interval.*

reaction to RCM demonstrated that changing RCM is helpful in reducing the recurrence of reactions on re-exposure.[33,34] The cross-reactivity between RCM is frequent as reported about 67% in both immediate and delayed hypersensitivity to RCM.[22] The cross reaction in non-immediate reaction could be related to the chemical structures and a group of RCM with carbamoyl side chain showed high cross-reactivity.[22,32,35,36] Changing to RCM in other groups of chemical structures or RCM showing negative skin test could be an option to prevent non-immediate hypersensitivity reaction to RCM.[21,22,36] However, in order to evaluate the effect of pharmacological prevention, the patients who underwent the test or procedure with RCMs different than the previous one were excluded from our study.

Our study has several limitations. First, since the unified intervention protocol was not planned before the study and the analysis was performed through retrospective EMR review, there were differences in the cumulative total dose and timing of systemic steroids and antihistamine administrations. Larger amounts of steroids were administered to patients with more severe prior reactions according to the judgment of the clinician. To overcome this limitation, we adjusted the severity of the prior reaction in the analysis of risk factors for unfavorable outcomes of prevention. In delayed RCM hypersensitivity, systemic steroids are administered at least 24 h prior to RCM exposure and for several days after exposure if the clinician determines that steroid administration is helpful[2,7,25] However, to date, there is no standardized premedication regimen for DHR with proven efficacy and evidence for a premedication.[36] Second, there was no separate control group with re-exposure to RCM without any pharmacological intervention. In practice, it is difficult to re-administer RCM without any preventive measures in patients who had previously experienced hypersensitivity to RCM. A prospective study with control group will be needed to clarify the effectiveness of pharmacological prevention in the future. Third, delayed hypersensitivity to RCM was diagnosed by the assessment of clinical history without other diagnostic tests such as patch tests, *in vitro* tests, or intravenous provocation. Therefore, the effectivity of pharmacologic intervention could be overestimated in our study, related to the fact that some patients were not hypersensitive to RCM, thus they would have tolerated RCM even without premedication. A recent guideline recommended to perform skin prick test or intradermal test with delayed reading followed by patch test with RCM before additional exposure to RCM.[21,35] Skin testing for RCM is also performed to provide guidance on tolerability of alternatives in patients with a history of RCM-induced immediate reaction and DHR,[18,21,35] and there have been several reports supporting the need for skin test in delayed RCM hypersensitivity[5,32,37,38] However, it takes at least 48–72 h to perform the skin test for DHR, which could be applied according to each medical situation in real clinical practice. The drug provocation test might be a confirmatory test and could be necessary to identify a safe alternative RCM, but it is also hardly performed for the diagnosis of delayed hypersensitivity to RCM in clinical practice.[8,18,19] Lastly, there may be concerns about adverse effects induced by systemic steroid use. However, the total amount of steroids prescribed to patients was similar to the amount generally recommended for premedication for immediate RCM hypersensitivity reactions.[20,39] In line with the opinions of expert groups, we support that the benefits of pharmacological prevention could outweigh the potential harm.[40]

Despite these limitations, our study provides novel information regarding delayed hypersensitivity to RCM that pharmacological prevention using steroids and/or antihistamines may be helpful for inhibiting or mitigating the recurrence of reactions when patients are re-exposed to RCM. Furthermore, the severity of the previous reaction was revealed to be an important risk factor for unfavorable responses to pharmacological prevention. A prospective study to validate the efficacy of pharmacological prevention is warranted for better management of delayed hypersensitivity to RCM in the future.

## Abbreviations

RCM, radiocontrast media; DHR, delayed hypersensitivity reaction.

### Funding source
There is no funding source.

### Submission declaration
This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal.

### Author contributions
Study design: JH Kim, SH Kim, YS Chang; data collection: JH Kim, SH Kim, SI Choi, YJ Lee, BK Kim, YS Chang; data analysis: JH Kim, SH Kim, YS Chang, HW Park, SH Cho; data interpretation: all authors; writing of the manuscript: JH Kim and SH Kim; reviewing of the manuscript: all authors; final approval of the manuscript: all authors.

### Consent for publication
We hereby declare that we all participated in the study and in the development of the manuscript titled "Pharmacological prevention of delayed hypersensitivity reactions caused by iodinated contrast media". We have read the final version and give our consent for the article to be published in the *World Allergy Organization Journal*.

### Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

### Ethics approval
The protocol of this study was reviewed and approved by the institutional review board from Seoul National University Bundang Hospital. (IRB approval number: B-1804-465-105).

### Declaration of competing interest
The authors declare that there are no conflicts of interest.

### Acknowledgement
None.

### Appendix A Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100561.

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