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Clinical value of radiocontrast media skin tests as a prescreening and diagnostic tool in hypersensitivity reactions

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ABSTRACT

Background: Some radiocontrast media (RCM) hypersensitivity reactions may have underlying IgE- or T-cell-mediated mechanisms. RCM skin testing may be useful for predicting future reactions.

Objective: To investigate the clinical value of RCM skin testing before computed tomography and after RCM hypersensitivity reactions.

Methods: Patients who underwent RCM skin testing were a prospective sample of convenience at a single medical center and were tested just before their pending nonionic RCM-enhanced computed tomogram. In addition, skin test data of patients who were referred to the allergy clinic because of their previous RCM hypersensitivity reactions were reviewed retrospectively.

Results: A total of 1048 patients enrolled in the study prospectively. Of these, 672 (64.1%) had never been exposed to RCM. Of the 376 previously exposed to RCM, 61 (16.2%) had a history of at least one mild RCM-associated reaction, 56 (91.8%) had immediate reactions, and 5 had no-immediate reactions. There was only 1 positive immediate hypersensitivity RCM skin test result (0.09%). There were 51 mild immediate reactions (4.9%), 1 moderate immediate reaction (0.09%), 8 mild nonimmediate reactions (0.76%), and 1 moderate nonimmediate reaction (0.09%). There was only 1 positive delayed hypersensitivity skin test result (0.09%), retrospectively determined, in 1 (11.1%) of the nonimmediate RCM-associated reactions. Sensitivity of RCM skin testing was significantly higher with severe immediate reactions (57.1%) than mild reactions (12.9%) and moderate reactions (25.0%) in the retrospective review of diagnostic skin test data ($P = .03$).

Conclusion: RCM skin testing for screening is of no clinical utility in predicting hypersensitivity reactions. RCM skin testing may have modest utility in retrospectively evaluating severe adverse reactions.

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Introduction

Radiocontrast media (RCM) diagnostic agents are used in more than 75 million radiographic procedures annually. Hypersensitivity reactions to RCM are one of the most common causes of drug adverse reactions and anaphylaxis in current clinical practice.^{1,2} RCM are triiodinated benzene derivatives, and the frequency of

hypersensitivity reactions differs among RCM types.^{3,4} Mild and severe immediate adverse reactions to ionic RCM occurred in 3.8% to 12.7% and 0.1% to 0.4% of procedures, respectively, whereas those to nonionic RCM occurred in only 0.7% to 3.1% and 0.02% to 0.04% of procedures, respectively.^{3,5} Thus, nonionic monomers and dimers are commonly used at present.³

Immediate-type hypersensitivity reactions to RCM have generally been considered to be caused by a nonimmunologic mechanism.^{6,7} Direct secretory effects on mast cells or basophils related to local changes in osmolarity and ion concentration, activation of the complement system, and activation of bradykinin-induced contact systems have been proposed as the pathophysiologic mechanism of the immediate reaction.^{3,8} Indirect evidence that patients react on the first exposure and that the reaction does not always recur support the non-IgE-mediated

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mechanism of RCM hypersensitivity.⁶ However, because the RCMs used have changed from ionic and high osmolar to nonionic and low/iso-osmolar, the proposed mechanism of RCM hypersensitivity has also been changing. Increasing evidence suggests that the mechanism of immediate hypersensitivity to RCM could be IgE mediated and that of the nonimmediate reaction is T-cell mediated.^{3,9–12} Recent data from the European Network of Drug Allergy multicentre study demonstrated that 50% of immediate and 47% of nonimmediate reactors were positive on skin tests.⁹ This study suggested that a substantial proportion of RCM hypersensitivity reactions was caused by immunologic mechanisms and that skin tests could be useful for the diagnosis of RCM allergy and selection of safe RCM.⁹ Several studies have reported the positivity rates or clinical usefulness of postevent diagnostic skin tests in patients who have previously experienced RCM adverse reactions.^{13,14} However, studies of the clinical value of skin tests using RCM as a prescreening tool before computed tomography (CT) are rare. In the current study, we aimed to investigate the clinical value of RCM skin testing as a prescreening tool before CT and RCM skin testing as a diagnostic tool after RCM hypersensitivity reactions.

Methods

Participants

We prospectively enrolled patients who were to undergo CT using RCM at Seoul National University Bundang Hospital from July to November 2010. Patients were asked about their history of RCM exposure, previous RCM-induced adverse reactions, history of other allergic disease, comorbidities, and current medication history. Patients who did not consent to the study or who had been administered premedications, such as steroids, antihistamines, or other medications that may have affected the skin test results, were excluded from the study. All participants provided written informed consent, and the study protocol was approved by the institutional review board of Seoul National University Bundang Hospital.

Skin Test and Study Protocol

Intradermal test with the RCM that was to be used in the pending nonionic RCM-enhanced CT was performed just before the CT examinations. The nonionic RCM used in our contrast CT scans were iopromide, iomeprol, iothexol, and iodixanol. Intradermal tests were conducted on the volar surface of the forearm with a negative control, saline. A 1:10 solution of RCM (0.03–0.05 mL), which has been accepted as a nonirritating concentration, was gently injected into the skin to produce a small superficial bleb of 2 to 4 mm.³ Skin test positivity was determined when the diameter of the wheal increased by at least 3 mm, and surrounding erythema was observed after 15 to 20 minutes. To detect delayed reactions of skin tests, patients were informed to contact the investigator if any skin change, such as erythema or induration, developed at their skin test site after they returned home.

If a patient had a negative response to skin tests, CT was performed as scheduled. If a patient had a positive response to skin tests, CT was postponed, and we conducted skin tests using other RCM on the patient to evaluate the cross-reactivity and identify RCM that produced negative skin test results. RCM that generated negative reactions were then used in the CT.

To evaluate whether the skin test response was converted to positive in patients who were initially skin test negative but had immediate hypersensitivity reactions after CT, we performed follow-up skin tests. Follow-up skin tests were performed with 3 nonionic monomers (iopromide, iomeprol, and iothexol) only when the patient agreed to revisit and receive the skin test again.

Assessment of Adverse Reactions After RCM Exposure

Hypersensitivity reactions were classified as immediate (those that occurred within 1 hour after RCM administration) and non-immediate (those that occurred 1 hour to 7 days after RCM administration).⁸ The Ring and Messmer system¹⁵ was used to classify the severity of immediate-type reactions: grade I, cutaneous and/or mucocutaneous symptoms (pruritus, skin eruption, urticaria, and angioedema); grade II, mild systemic reactions, including skin manifestations (not obligatory), abdominal symptoms (nausea, cramping), respiratory symptoms (rhinorrhea, hoarseness, dyspnea), cardiovascular symptoms (tachycardia); grade III, life-threatening systemic reactions, including shock; and grade IV, cardiac and/or respiratory arrest.

For evaluation of nonimmediate adverse reactions, patients were informed to contact the study coordinator if any type of skin eruption developed after they returned home. In addition, the absence of nonimmediate adverse reactions was rechecked by telephone 1 week after the study. Nonimmediate reactions were classified as mild, moderate, or severe as suggested previously⁹: mild, no treatment was required; moderate, the patient responded readily to an appropriate treatment and no hospitalization was needed; and severe, the reaction required treatment in hospital, was life-threatening, or resulted in death.

Retrospective Review of Results of Post-Adverse Reaction Diagnostic Skin Tests

We performed skin tests in patients who were referred to our allergy clinic for management of RCM hypersensitivity reactions to evaluate the culprit drug and cross-reactivity with other RCMs from January 2010 to June 2012. We additionally reviewed the RCM skin test data retrospectively to evaluate the sensitivity of post-adverse reaction diagnostic skin tests and to compare with the results of prescreening skin tests. Skin tests with each of 4 RCMs (iopromide, iomeprol, iothexol, and iodixanol) were performed, as mentioned previously.

Statistical Analysis

The Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables were used to compare the clinical characteristics and results of post-adverse reaction diagnostic skin tests according to the severity of the hypersensitivity reaction. Statistical analyses were performed using SPSS statistical software, version 18.0 (SPSS Inc, Chicago, Illinois); $P < .05$ was deemed to indicate statistical significance.

Results

Baseline Characteristics of Study Participants

A total of 1,048 patients were enrolled. Their mean (SD) age was 55.1 (14.5) years; 501 (47.8%) were male. Of these, 672 (64.1%) had never been exposed to RCM. Of the 376 previously exposed to RCM, 61 (16.2%) had a history of at least 1 mild RCM-associated reaction: 56 (91.8%) immediate and 5 (8.2%) nonimmediate reactions. Ninety-one (8.7%) had a history of other allergic diseases, such as asthma, allergic rhinitis, food allergy, or atopic dermatitis. Twenty patients (1.9%) had comorbidities of renal disease and 38 (3.6%) of cardiovascular disease (Table 1).

Outcomes of Patients With Negative Prescreening Skin Test Results

Among the 1,046 patients who had negative responses on skin tests, 52 (5.0%) showed immediate-type adverse reactions after CT using RCM. However, most reactions were mild and cutaneous, such as pruritus, urticaria, and mild angioedema. Only 1 patient (0.1%) had a grade II moderate immediate reaction accompanied by

Table 1
Baseline characteristics of the study participants

Characteristic	Finding ^a
Age, y	55.1 (14.5)
Male sex	501 (47.8)
Previous exposure to RCM	376 (35.9)
No. of exposures to RCM	0.8 (1.3)
Previous history of RCM-related hypersensitivity reaction	61 (5.8)
No. of immediate/nonimmediate reactions	56/5 (5.3/0.5)
Exposure to the culprit RCM of their prior reaction (yes/no/unknown)	38/3/20 (3.6/0.3/1.9)
Comorbidity	
Other allergic disease	91 (8.7)
Cardiovascular disease	38 (3.6)
Renal disease	20 (1.9)
Concomitant medication	
β -Blocker	7 (0.7)
ACE inhibitor	1 (0.1)
Contrast media used in the CT scan	
Iopromide	721 (68.8)
Iomeprol	323 (30.8)
Iohexol	3 (0.3)
Iodixanol	1 (0.1)

Abbreviations: ACE, angiotensin-converting enzyme; CT, computed tomography; RCM, radiocontrast media.

^aData are presented as number (percentage of the entire participant population) or mean (SD).

breathing difficulty and mild laryngeal edema, which were relieved with an antihistamine. Eight patients (0.8%) reported that they had non-immediate-type cutaneous reactions more than 1 hour after RCM exposure. All these nonimmediate reactions were mild and did not require special treatment (Figure 1).

Negative Predictive Value of Skin Tests

The negative predictive value of the prescreening skin test for immediate hypersensitivity reactions before RCM administration was 95.0%. The negative predictive value of the skin test for immediate hypersensitivity reactions in patients with a history of RCM hypersensitivity reactions was 80.3% ($n = 49/61$) and that in patients without a history was 95.9% ($n = 945/985$). The negative predictive value of the skin test for immediate hypersensitivity reactions in patients with prior RCM exposure was 93.3% ($n = 350/375$) and that in patients without prior exposure was 96.0% ($n = 644/671$). Of the patients who had immediate hypersensitivity reactions to RCM, none showed a positive response to prescreening skin tests for the culprit RCM before CT.

Outcomes of Patients With Positive Prescreening Skin Test

Two patients had a positive response to prescreening skin tests before RCM use. One, a 16-year-old girl who had a positive skin test response to iopromide (3-mm wheal size increase and surrounding flare), was subjected to additional skin tests using other RCMs. She had a negative response to iomeprol, iohexol, and iodixanol skin tests and received contrast CT with iomeprol. She completed the CT examination with no adverse reactions.

The other patient, a 44-year-old woman, reported 6-mm erythematous induration at the intradermal skin test site 12 hours after injection. Because this positive skin test reaction was detected after completion of CT, the culprit RCM (iopromide) could not be changed. She also had generalized maculopapular-form eruptions 24 hours after CT and was treated with a topical steroid and short-term oral steroid (Fig 1).

Skin Test Follow-up

We were able to follow up skin tests in 16 patients with negative prescreening skin test results but immediate ($n = 14$) or non-immediate ($n = 2$) hypersensitivity reactions after CT. The interval to follow-up skin tests varied according to the patients: 5 to 46 days after initial skin test and CT. We tried to perform the follow-up skin test 1 to 3 months after initial test. However, the patients' revisit dates were different, and we could not perform the skin tests at a proper time in all the patients, although skin test result could be false negative if the test was performed too soon (within 2–4 weeks) after the reaction.¹⁶

Most of the patients, with a single exception, also had a negative response to follow-up skin tests using 3 nonionic monomers. One, a 64-year-old woman who had experienced generalized urticaria and pruritus after abdominal CT in our study, had a positive conversion at a follow-up skin test result to iopromide, the culprit RCM, which had been negative at the initial prescreening skin test. She was taking oral hypoglycemic agents, a calcium channel blocker, and an angiotensin receptor antagonist for the underlying diabetes and hypertension and had received surgery and chemotherapy for treatment of sigmoid colon cancer. She had undergone contrast CT for regular cancer recurrence checkups without adverse reactions before enrollment in our study. This immediate hypersensitivity reaction was the first adverse event related to RCM exposure that she had experienced. After the first adverse event, the skin test response to the culprit drug was converted to positive (4-mm wheal size increase and surrounding erythema).

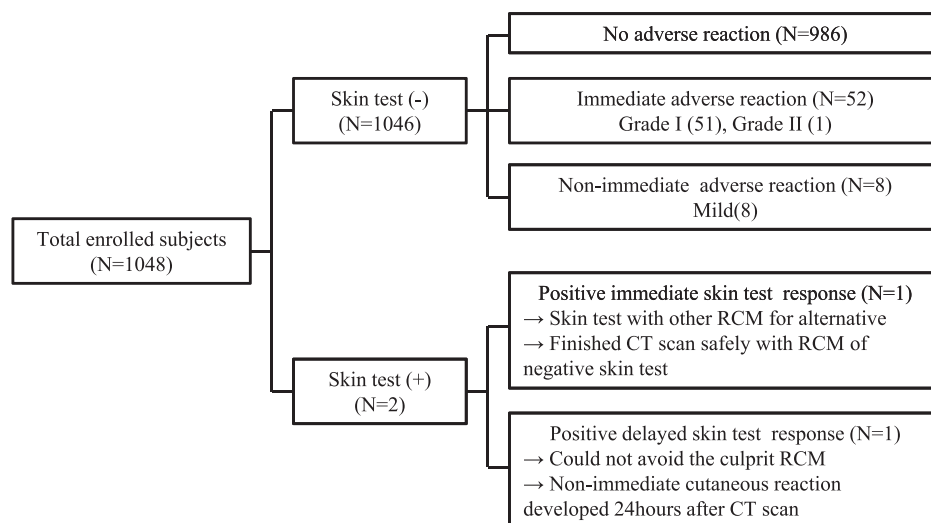


Figure 1. Outcomes of radiocontrast media prescreening skin tests before enhanced computed tomography.

Table 2Results of Post-adverse reaction skin tests according to the severity in patients with a history of RCM hypersensitivity reactions^a

Variable	Grade I (n = 31)	Grade II (n = 8)	Grade III (n = 7)	Total (N = 46)	P value ^b
Age, y	50.2 (12.4)	49.1 (12.3)	57.2 (12.0)	51.1 (12.3)	.46
Male sex ^c	13 (41.9)	4 (50.0)	2 (28.6)	19 (43.3)	.74
Culprit RCM (iopromide/iomeprol/iohexol/iodixanol)	16/11/3/1	4/2/1/1	5/2/0/0	25/15/4/2	.83
Presence of previous exposure to RCM before adverse event ^d	20/31 (64.5)	5/7 (71.4)	3/7 (42.9)	28/45 (62.2)	.64
Interval to skin test, d	204.8 (346.7)	226.5 (351.2)	668.8 (1,428.8)	276.4 (609.9)	.10
Positivity of prick test ^e	0/17 (0)	0/8 (0)	1/7 (14.3)	1/32 (3.1)	.23
Positivity of intradermal test results ^e	4/31 (12.9)	2/8 (25.0)	4/7 (57.1)	10/46 (21.7)	.03
Cross-reactivity to other RCM ^f	2/4 (50.0)	0/2 (0)	2/4 (50.0)	4/10 (40.0)	.54

Abbreviation: RCM, radiocontrast media.

^aData are presented as number (percentage) or mean (SD).^bStatistical analyses were performed using the Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables to compare the clinical characteristics and diagnostic skin test results among the 3 groups (grades I, II, and III).^cPercentage indicates the proportion of males in each group.^dPercentage indicates the proportion of patients with previous exposure to RCM before the adverse event. The data of 1 patient in the grade II group were not available.^ePercentage indicates the positive rate of skin test results. Fourteen patients in the grade I group underwent only an intradermal test.^fPercentage indicates the proportion of cross-reactivity to other RCM in the patients who had positive skin test responses to the culprit RCM.

Unfortunately, after the study period, when she received additional contrast CT 6 months later with the same RCM, iopromide, with premedication of antihistamine, life-threatening severe anaphylaxis accompanied by generalized urticaria, angioedema, respiratory difficulty, and cardiac arrest occurred during CT. She survived after 6 days of intensive care unit admission.

Diagnostic Value of Skin Tests According to Previous RCM Hypersensitivity Reaction Severity

Data from 32 patients who were referred to the allergy clinic because of immediate-type RCM hypersensitivity reactions and underwent skin tests for RCM between January 2010 and June 2012 were retrospectively reviewed. We analyzed their diagnostic skin test results combined with the follow-up skin test data of the prospective study (Table 2). The overall positive rate of skin test results (sensitivity) to the culprit RCM was 21.7% (n = 10/46). The sensitivity of skin tests for each severity group significantly increased with the severity of the previous immediate hypersensitivity reaction as follows: 12.9% (n = 4/31) in grade I, 25.0% (n = 2/8) in grade II, and 57.1% (n = 4/7) in grade III (P = .03). Four patients had cross-reactivity with other RCMs (cross-reaction rate, 40%). Two patients had a negative response to culprit RCM but a positive response to other RCMs, although the clinical significance of this was uncertain (data not shown).

Discussion

We initially designed a prospective study to evaluate the negative predictive value of prescreening RCM skin tests before contrast-enhanced CT. The positivity rate of RCM skin tests performed immediately before CT was low. Only 2 of 1,048 study participants had positive skin test results (1 immediate response and 1 delayed response). All 67 previous reactors who reported that they had experienced RCM-related adverse reactions also had a negative response to skin tests, although all of their previous reactions were mild. Moreover, the overall negative predictive value of the skin test (95.0%) was lower than expected. Of the 1,046 patients with a negative skin test result, 52 experienced immediate-type hypersensitivity reactions after CT. Given the historical incidence of immediate hypersensitivity reaction to nonionic RCM, prescreening skin tests were unlikely to assist prediction of the incidence of overall immediate hypersensitivity reactions. However, most of these were mild, cutaneous reactions, such as pruritus, limited urticaria, and cutaneous angioedema. Only 1 moderate-to-severe (grade $\geq$ II) adverse event occurred in a patient with a negative prescreening skin test result. No precise estimation of the negative predictive value for moderate-to-severe

hypersensitivity reactions is available because of the limited study population, but it may be very high.

The low prescreening skin test positivity rate and low incidence of severe systemic hypersensitivity reactions may be due to the high exclusion rate of patients with a history of moderate-to-severe RCM adverse reactions in our study. Most of these high-risk patients had already received pharmacologic premedication, such as antihistamines and systemic steroids, or refused to be included in the study. Thus, we could not evaluate the negative predictive value of prescreening tests for moderate-to-severe immediate hypersensitivity reactions adequately. However, the results of those with an increased skin test positivity rate according to the severity of hypersensitivity reactions in the retrospective review and the patient who had skin test conversion to positive after the first mild immediate hypersensitivity reaction with subsequent severe life-threatening anaphylaxis suggest that prescreening skin tests for RCM may have clinical usefulness in prediction of severe rather than mild immediate hypersensitivity reactions.

Several groups have reported skin test positivity in RCM-induced immediate hypersensitivity reactions; the results differed among investigators.^{9,13,14} One study of patients referred to the allergy department for RCM hypersensitivity during a 6-year period reported positive RCM skin test results in 9 of 23 patients with immediate hypersensitivity (31.2%). There was no significant difference in positivity rates according to reaction severity grade.¹⁴ In the recent European multicenter study by Brockow et al.,⁹ positive skin test results were identified in 32 of 122 patients with immediate reactions (26%; 95% confidence interval, 18%–34%). Skin test positivity according to severity was not evaluated in that study, but extensive cross-reactivity testing with 8 or more RCM was conducted in 11 patients, 5 (45.5%) of whom tested positive for at least 2 RCMs.⁹ Dewachter et al.¹³ reported a skin test positivity rate of 73.1% (19 of 26 patients) with immediate reactions. RCM skin test positivity increased with reaction severity: 56% in grade I reactions, 70% in grade II reactions, and 100% in grade III and IV reactions. Skin cross-reactivity to 1 or 2 RCMs other than the culprit was identified in 31.6% of patients.¹³

Our review of post-adverse reaction diagnostic skin test data revealed a lower positivity rate than found in previous studies. However, the positivity rate was similar to that of a large-scale European multicenter study, and the cross-reaction rate was similar to those reported previously. Conversely, our findings indicate a higher skin test positivity rate in severe immediate hypersensitivity, which is consistent with the report by Dewachter et al.¹³ On the basis of our data, skin tests seem to be more useful for diagnosis and prediction of severe immediate hypersensitivity. In patients with mild immediate hypersensitivity, prescreening skin

tests revealed no clinical value for prediction of mild immediate hypersensitivity reactions. In addition, only a small proportion of patients had a positive response in post-adverse reaction diagnostic skin tests for mild immediate reactions. The clinical usefulness of skin tests for diagnosis of mild cutaneous reactions appears to be lower than for diagnosis of severe reactions with systemic symptoms.

However, positive skin test results should not be ignored even in patients with a history of mild immediate hypersensitivity. Although we did not examine the specificity or positive predictive value of skin tests, a high specificity of RCM skin tests was demonstrated in a previous European multicenter study.⁹ In our study, 2 patients with a positive skin test result (one with a delayed skin test response and another with a positive immediate response at follow-up skin testing) experienced RCM-induced hypersensitivity reactions when rechallenged with the culprit RCM without adjustment. Moreover, a recent study revealed that none of the negative skin test patients who had experienced prior RCM-hypersensitivity reactions had a severe reaction during challenge with RCM.¹⁷ In that study, 2 patients with positive skin test results who were reexposed to RCM to which they exhibited a negative response had no additional adverse reactions, similar to our findings.¹⁷ Given its low positivity rate in the general population and in patients with mild-type immediate hypersensitivity, screening all patients with RCM skin tests before CT could be inefficient and time-consuming. However, a positive skin test result may indicate the underlying immunologic mechanisms of hypersensitivity reactions and has a potential risk of severe, life-threatening events on subsequent reexposure to the RCM. RCM skin tests may assist prediction of severe immediate hypersensitivity reactions and can help to avoid life-threatening events in the RCM-hypersensitivity high-risk population if an alternative, skin test negative RCM is used.^{9,17} We think it would be appropriate to perform a skin test at least in the patients with a previous history of moderate to severe RCM hypersensitivity reaction. If the skin test result is positive, selection of RCM with negative skin test response for the alternative would be better than the simple pharmacologic prevention for the patients. The timing of the skin test would be better to perform several days before CT rather than immediately before CT because the skin response may be delayed in those who show delayed hypersensitivity reactions. Further larger-scale prospective studies and cost-benefit analyses are warranted to verify the clinical value of prescreening skin tests to predict severe immediate hypersensitivity reactions.

The relatively high rate of reactions with nonionic RCM in this study could be caused by a high detection rate of mild reactions. We performed the study in a prospective manner and caught all the mild reactions, which could be missed in a retrospective manner.

Our study has several limitations. First, we were unable to evaluate the clinical value of prescreening tests sufficiently because of the small study population. Most patients had either no or mild previous reactions. No patients with moderate-to-severe previous reactions were enrolled, which may have affected the skin test positivity rates or outcomes of prescreening procedures. We tried to overcome this limitation by using additional retrospectively reviewed skin test data from those who were referred to our clinic due to RCM hypersensitivity reactions. However, many RCM-induced hypersensitivity reactions occur during the first exposure, regardless of skin test results^{6,9}; thus, our data may have clinical value despite the limitations of the study. Second, follow-up

skin tests could be performed in only a small proportion of patients who had RCM hypersensitivity reactions. Third, patients with mild immediate reactions comprised a relatively large proportion of the population in the retrospective analysis of diagnostic skin test results, which may have influenced the overall sensitivity of diagnostic skin tests in patients with previous immediate reactions.

Nevertheless, this study is, to our knowledge, the first to evaluate the value of prescreening skin tests for nonionic RCM and provides important findings concerning the clinical usefulness of skin tests for diagnosis of nonionic RCM hypersensitivity reactions. RCM skin testing is of no clinical utility in predicting future acute or delayed-onset reactions in individuals with no previous exposure to RCM, previous exposure without RCM-associated reaction, or history of mild RCM-associated reactions. RCM skin testing may have modest clinical value in the retrospective evaluation of severe immediate hypersensitivity reactions. RCM skin testing is even less useful in evaluating mild or moderate reactions. Further large-scaled, multicenter, prospective studies are needed for the confirmation of these results.

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The English in this document has been checked by at least 2 professional editors, both native speakers of English. For a certificate, please see: <http://www.textcheck.com/certificate/UrdbFo>.

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