

Novel Strategy for the Prevention of Recurrent Hypersensitivity Reactions to Radiocontrast Media Based on Skin Testing



Oh Young Kwon, MD^{a,*}, Ji-Hyang Lee, MD^{a,*}, So-Young Park, MD, PhD^{a,b}, Bomi Seo, MD^a, Ha-Kyeong Won, MD^a, Yewon Kang, MD^a, Jin An, MD^a, Hyouk-Soo Kwon, MD, PhD^a, Woo-Jung Song, MD, PhD^a, You Sook Cho, MD, PhD^a, Hee-Bom Moon, MD, PhD^a, and Tae-Bum Kim, MD, PhD^a *Seoul, Korea*

What is already known about this topic? Hypersensitivity reaction to iodinated contrast media (ICM) is a persistent clinical issue with the increased use of computed tomography. In contrast to the traditional concept, growing evidence indicates an underlying allergic mechanism.

What does this article add to our knowledge? When the culprit ICM produced an intradermal skin test (IDT)-positive result, IDT-negative ICM could be used as a safer alternative. However, when the culprit ICM was IDT-negative, further skin tests were not helpful.

How does this study impact current management guidelines? When patients with a history of ICM hypersensitivity require further computed tomography scanning, we recommend physicians perform an IDT using the culprit ICM to guide the next step.

BACKGROUND: Hypersensitivity reactions to iodinated contrast media (ICM) is a persistent clinical issue with increased use of computed tomography. With the evidence indicating underlying allergic mechanisms, there have been studies regarding the skin tests using ICM.

OBJECTIVE: This study aimed to evaluate the intradermal skin test (IDT) as a tool for preventing recurrent hypersensitivity reactions to ICM in patients with prior reactions to a known culprit agent.

METHODS: Sixty-nine patients who had experienced immediate hypersensitivity reactions to ICM were included in the study. All patients underwent IDT with 7 different ICMs, including the causative ICM. We analyzed clinical data from 38 patients who were reexposed to ICMs, grouped by the IDT results to their original culprit ICM.

RESULTS: Thirty-eight patients showed positive IDT results to the culprit ICM (CULPRIT+), whereas 31 patients showed negative results (CULPRIT-). Sixteen patients from the CULPRIT+ group and 22 from the CULPRIT- group were subsequently exposed to an ICM. In the CULPRIT+ group, 4 of the 5 patients who were subsequently exposed to an IDT-positive ICM reexperienced hypersensitivity reactions. When patients were exposed to IDT-negative ICM as an alternative, hypersensitivity reactions were not observed. In the CULPRIT- group, IDT-positive ICMs did not provoke hypersensitivity reactions whereas 2 patients using IDT-negative ICMs experienced hypersensitivity reactions.

CONCLUSIONS: When the IDT results are positive for the culprit ICM, additional IDTs with other ICMs are needed to select a safe alternative. If the IDT results are negative against the culprit ICM, further IDTs might not play a role in selecting a safe alternative. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2707-13)

Key words: Hypersensitivity reaction; Intradermal skin test; Iodinated contrast media; Premedication; Skin tests

INTRODUCTION

An estimated 75 million computed tomography (CT) scans enhanced with iodinated contrast media (ICM) are performed annually worldwide.¹ Because CT scanning is fast, affordable, and accurate, it is preferred to other imaging modalities such as magnetic resonance imaging or ultrasonography. However, using ICM always presents the possibility of unexpected immediate hypersensitivity reactions (IHRs). Introduction of low-osmolar nonionic ICM in place of high-osmolar ionic agents has decreased estimations of the frequency of IHRs from 3.8%-

^aDepartment of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

^bDepartment of Internal Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Konkuk University Medical Center, Seoul, Korea

This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant nos. HI15C1074 and HI18C1392). Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication October 17, 2018; revised April 21, 2019; accepted for publication April 23, 2019.

Available online May 10, 2019.

Corresponding author: Tae-Bum Kim, MD, PhD, Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. E-mail: tbkim@amc.seoul.kr.

*These authors contributed equally to this work.
2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2019.04.036>

Abbreviations used*CT*-Computed tomography*ICM*-Iodinated contrast media*IDT*-Intradermal skin test*IHR*-Immediate hypersensitivity reaction

12.7% to 0.7%-3.1%.^{2,3} However, there still are fatal cases 1 in 100,000 to 1 in 1,000,000 people who were injected with ICM.⁴

IHRs to ICM have traditionally been classified as non-immunologic reactions.⁵ However, there is growing evidence supporting the presence of an underlying allergic mechanism in some reactions. Positive skin test results and basophil activation, as well as detection of specific IgE in patients with hypersensitivity reactions to ICM, indicate that some cases of ICM hypersensitivity could be explained by IgE-associated immunologic mechanisms.^{6,7} Accordingly, there have been trials to evaluate the clinical value of skin testing using ICM.^{6,8-10}

Overall, the skin tests can be used for 2 distinct purposes. First, to predict hypersensitivity reaction before undergoing a CT scan. Second, to diagnose hypersensitivity to ICM and use the result to identify safer substitutes.

The intradermal skin test (IDT) has failed to show its clinical usefulness as a prescreening tool predicting hypersensitivity reactions when performed before a CT scan, irrespective of the patient's history of hypersensitivity reactions.¹¹ On the contrary, as a diagnostic tool, the European Network of Drug Allergy group multicenter study found out that 50% of patients with previous hypersensitivity reactions were positive on skin tests.¹² A recent meta-analysis by Yoon et al⁶ reported that pooled per-patient positive rates of skin test results were 16.8% in patients with IHRs, increasing to 52% when confined to severe IHRs. This suggests that the IDT can play an important role in postexposure evaluation of IHRs and can help determine the selection of safer alternatives.

When patients experience adverse reactions to ICM, they become more vulnerable to repeat adverse reactions.¹³ Abe et al¹⁴ observed that changing contrast media had a more protective effect against repeat adverse reactions compared with premedication with either antihistamines or systemic steroids. Concordantly, in a multicenter study reviewing the cases of reexposure to ICM in patients with a history of moderate-to-severe hypersensitivity reactions, changing the implicated ICM significantly reduced the recurrence rate of hypersensitivity reactions.¹⁵ Both studies indicate that changing the ICM is a more effective way of preventing the recurrence of hypersensitivity reactions compared with the premedication. However, no studies have yet investigated systematic approaches for trialing alternative contrast media.

This study aimed to evaluate the role of IDT in contributing to the selection of safe alternative contrast media for patients with a history of hypersensitivity to ICM.

METHODS

Subjects

We obtained the medical records of the patients who had experienced IHRs to ICM and were referred to the allergy clinic in Asan Medical Center from April 2015 to April 2018. The patients with

unknown culprit ICM were excluded. The study was approved by the Internal Review Board and Ethics Committee of Asan Medical Center (2015-0439).

Skin test

All patients underwent IDT with 7 different ICM. The agents used in the test were as follows: (1) iopromide (Ultravist; Bayer Healthcare, Brussels, Belgium), (2) iohexol (Omnipaque; GE Healthcare, Chicago, Ill), (3) iopamidol (Pamiray; Dongkook Pharm Co., Ltd, Korea), (4) ioversol (Optiray; Mallinckrodt PLC, St Louis, Mo), (5) iobitridol (Xenetics; Guerbet, Gorinchem, Netherlands), (6) iomeprol (Iomeron; Bracco, Milano, Italy), and (7) iodixanol (Visipaque; GE Healthcare). All solutions had a strength of 270 to 370 mg/mL (iopromide, 370 mg/mL; iohexol, 300 mg/mL; iopamidol, 300 mg/mL; ioversol, 320 mg/mL; iobitridol, 300 mg/mL; iomeprol, 300 mg/mL; iodixanol, 270 mg/mL). An IDT was performed with 1/10 diluted ICMs. It was the recommended concentration by the previous study considering as the maximal nonirritant concentration.¹⁶ Histamine and saline were used as positive control and negative control, respectively. The IDT was read after 15 minutes; the result was considered positive when the median diameter of the wheal increased by at least 3 mm compared with the initial bleb with surrounding erythema.¹² Because positive rate of skin prick test had been reported to be significantly lower than that of IDT, especially in IHRs, we only conducted IDT without preceding skin prick test, although this was not recommended.^{6,12,17}

Reexposure to ICM and evaluation

Because skin testing was done in the allergy clinic for diagnostic purposes originally, the results of the IDT were not checked by CT technicians when selecting the ICM in case of reexposure. However, the culprit radiocontrast media was avoided according to the preexisting guidelines in our institute. As a result, a contrast media that had not caused an adverse reaction was used for the CT examination, some of which were IDT-positive. Because all subjects were previous reactors, they were prescribed premedication, which is routinely recommended in our center, and informed of possibility of breakthrough reactions.¹⁸ The premedication regimen was based on the severity of the previous IHRs. For patients with a mild index reaction, only antihistamine (chlorpheniramine 4 mg) was administered intravenously an hour before the examination. For those who had experienced a moderate IHR, corticosteroid (methylprednisolone 40 mg) was given in addition to chlorpheniramine. For the patients with a history of severe IHRs, 50 mg of prednisolone was administered by mouth at 13 hours, 7 hours, and 1 hour before ICM injection, in addition to chlorpheniramine 1 hour before CT scanning. The dose or administration time of each medication may have varied slightly between physicians. In addition, emergency kits were ready to use in case of breakthrough reaction.

The severity of the reaction was classified on the basis of the American College of Radiology manual on contrast media.¹⁹ Mild reactions included limited urticaria/pruritis, limited cutaneous edema, limited "itchy"/"scratchy" throat, nasal congestion, and sneezing/conjunctivitis/rhinorrhea. Moderate reactions included diffuse urticaria/pruritis, diffuse erythema, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, and wheezing/bronchospasm with mild or no hypoxia. Finally, severe reactions included diffuse edema, or facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm, significant hypoxia, and

anaphylactic shock. The presence/absence of an IHR, and the associated symptoms, was reported on the electronic medical chart.

Medical records were retrospectively analyzed, and the data were compared according to the IDT results using the culprit ICM. We hypothesized that if the skin test result was positive, indicating the presence of an underlying IgE-mediated reaction, the result might provide a clue when selecting safer ICM. The negative result of the skin test means a non-IgE-mediated reaction, which might not be used as a clue.

Statistical analysis

Statistical analyses were performed using the SPSS 22 software package (SPSS, Chicago, Ill). The results are presented as mean $\pm$ SD for continuous variables and as raw numbers (%) for categorical variables. Differences between continuous variables were analyzed by the Student *t* test. The categorical variables were analyzed using Fisher exact test and the chi-square test, as appropriate. A *P* value of less than .05 was considered significant.

RESULTS

Skin tests

We found 73 patients with a history of IHR to ICM, who were referred to allergists for further evaluation from April 2015 to April 2018. Four patients were excluded because their culprit ICM could not be identified, and the remaining 69 patients were included in the study. All patients underwent IDT with a panel of 7 ICMs. Sixty (87%) patients tested positive against at least 1 ICM. On average, 3 ICMs were reported positive per patient.

The subjects were divided into 2 groups according to the IDT results using the culprit ICM (Figure 1). Thirty-eight (55%) patients showed a positive result in the skin test with the culprit ICM (CULPRIT+ group), and 31 (45%) showed a negative result in the skin test with the culprit ICM (CULPRIT– group). In the CULPRIT+ group, 16 patients were reexposed to contrast media following the IDT. In the CULPRIT– group, 22 patients underwent repeated CT scanning.

Baseline and clinical characteristics of patients who underwent IDT are summarized in Table I. When comparing the CULPRIT+ group and the CULPRIT– group, their mean age,

sex, body mass index, underlying allergic disease as well as smoking history showed no difference. Regarding comorbidities other than allergic disease, diabetes mellitus was more common in the CULPRIT– group while prevalence of malignancy and hypertension was not significantly different between the 2 groups. Severity of index event, exposure history to the ICM, and interval between the IHR and the IDT also showed no significant difference between the 2 groups. The number of positively skin tested ICMs was significantly higher in the CULPRIT+ group (Table I).

Results of IDTs and outcome of IHRs

Among the 38 patients in the CULPRIT+ group, only 16 (42%) underwent additional CT examination after the IDTs. Five of 16 patients were exposed to the ICM that showed a positive IDT result. In spite of the premedication before the CT examination, 4 (80%) of these patients experienced repeated IHRs. Meanwhile, the remaining 11 CULPRIT+ patients were exposed to ICMs that showed negative skin test results. None of them experienced adverse reactions related to ICM.

Among the CULPRIT– group, CT was performed again in 22 (71%) patients, 5 of whom used ICMs that had produced a positive IDT result. However, all 5 patients underwent the additional CT scanning without any adverse events. Meanwhile, the remaining 17 patients were exposed to IDT-negative ICMs. Two of them experienced IHRs while the others did not (Figure 1). The details of IDT results, rechallenged ICM, and severity of IHR are summarized in Tables II and III.

The severity of the hypersensitivity reactions of all patients is depicted in Figure 2. The inner colored circle reflects the severity of the initial IHR, whereas the outer colored circle reflects the severity of the subsequent IHR of the patients when exposed to the alternative ICM. In the CULPRIT+ group, 4 patients who used an IDT-positive ICM experienced an IHR again. The reaction severity did not appear to change even though the patients used different ICM, in addition to administration of premedication. However, when the patients in the CULPRIT+ group used an IDT-negative ICM, none of them experienced IHRs regardless of the severity of their previous

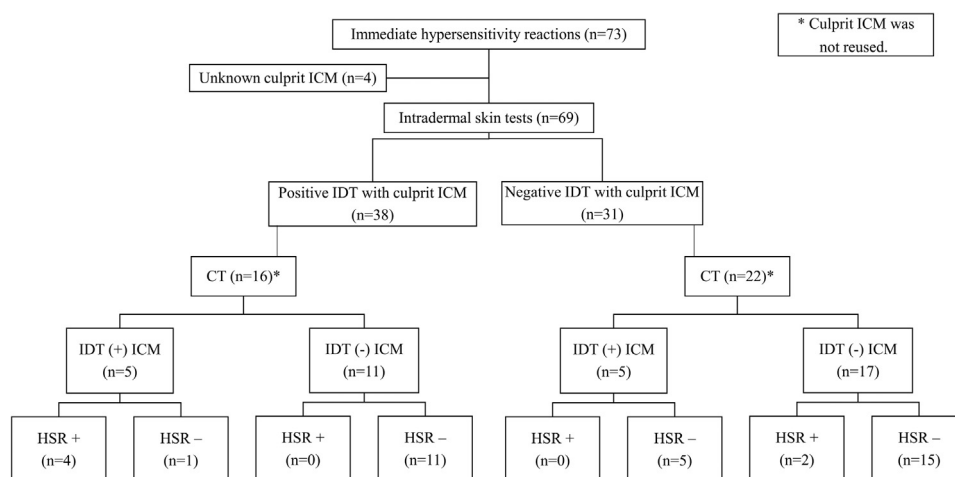


FIGURE 1. Intradermal skin testing and reexposure to ICM. The study flowchart. *HSR*, Hypersensitivity reaction; *ICM*, Iodinated contrast media; *IDT*, Intradermal skin test.

TABLE I. Patient characteristics according to the skin test results

Characteristic	CULPRIT+ (N = 38), n (%)	CULPRIT- (N = 31), n (%)	P value
Age (y)	58.8 ± 10.9	56.6 ± 14.0	0.46
Sex: female	24 (63.2)	16 (51.6)	0.33
Body mass index	24.2 ± 3.0	23.9 ± 2.78	0.70
Current smoker	4 (10.5)	6 (19.4)	1.00
Comorbidities			
Allergic disease	5 (13.2)	6 (19.4)	0.53
Malignancy	18 (47.4)	18 (58.1)	0.78
Diabetes mellitus	1 (2.6)	6 (19.4)	0.02
Hypertension	6 (15.8)	10 (32.3)	0.11
Severity of index event (severe/moderate/mild)	24/3/11 (63.2/7.9/28.9)	15/2/14 (48.4/6.5/45.2)	0.38
History of ICM exposure			0.80
Never exposed	6 (15.8)	6 (19.4)	0.70
No. of ICM exposures	11.1 ± 15.6	11.0 ± 13.5	0.97
Interval to IDT (>7 wk)	18 (47.4)	17 (64.5)	0.19
No. of skin test-positive ICMs	4.4 ± 1.4	1.1 ± 1.4	0.00

CULPRIT+ and CULPRIT-: patients with positive and negative IDT results, respectively, to the culprit ICM.

Data are presented as mean ± SE and n (%).

reaction. In the CULPRIT- group, 5 patients who had originally experienced severe and mild IHRs completed the CT scan safely when using the IDT-positive ICM. It was interesting to see that 2 of the 17 patients who were exposed to IDT-negative ICM experienced an IHR. One patient whose previous reaction was a severe anaphylaxis experienced localized urticaria in the subsequent CT scan. The other patient was subjected to 2 additional CT scans using 2 different ICMs, both of which had been IDT-negative. This patient experienced repeated anaphylaxis when using the first IDT-negative ICM (ioversol). However, when he used another IDT-negative ICM (iohexol) in the following CT scan, no adverse reaction occurred (Figure 2).

DISCUSSION

In our study, 69 patients with history of IHR to ICM were analyzed. Patients were divided into 2 groups according to the IDT results using the culprit contrast agent. Thirty-eight patients showed positive result to the causative ICM (CULPRIT+ group), whereas 31 showed negative result (CULPRIT- group).

Of the 38 CULPRIT+ patients in this study, 16 were reexposed to an ICM, and 5 of those were reexposed to an IDT-positive ICM. IHRs occurred in all except for 1 patient, and the severity of those reactions was equivalent to that of the initial IHR. Meanwhile, none of the 11 patients exposed to IDT-negative ICM experienced any adverse reactions related to

TABLE II. Reexposure to ICM in the CULPRIT+ group

Patient No.	Age (y)/sex	Panel of ICM used for skin test							Reexposure		
		Iopromide	Iohexol	Iopamidol	Ioversol	Iobitridol	Iomeprol	Iodixanol	ICM	IDT	Change in severity
1	70/F	+	—	—	—	—	+	—	Iohexol	—	3→0
2	38/F	—	—	—	+	+	—	—	Iomeprol	—	3→0
3	57/F	—	+	+	+	+	—	—	Iodixanol	—	1→0
4	66/F	—	—	+	—	+	—	—	Ioversol	—	3→0
5	35/F	+	+	+	—	+	—	+	Ioversol	—	3→0
6	66/M	—	+	+	+	—	+	+	Iobitridol	—	3→0
7	51/F	+	+	—	+	—	+	+	Iopamidol	—	3→0
8	47/M	+	—	—	+	+	+	+	Iopamidol	—	2→0
9	81/M	—	+	+	+	—	+	+	Iobitridol	—	1→0
10	40/F	+	+	+	—	—	—	+	Iobitridol	—	3→0
11	70/M	—	—	—	+	+	+	+	Iopamidol	—	3→0
12	67/M	+	+	+	+	+	—	+	Iohexol	+	1→0
13	59/F	+	—	+	+	—	—	—	Ioversol	+	2→2
14	57/M	+	+	+	+	—	+	—	Iopamidol	+	3→3
15	70/F	+	+	+	+	+	+	—	Iobitridol	+	1→1
16	29/F	+	+	+	+	+	+	—	Iohexol	+	1→1

F, Female; M, male.

Table II summarizes the results of skin test using a panel of ICMs and the results of reexposure.

*Culprit ICM.

TABLE III. Reexposure to ICM in the CULPRIT– group

Patient		Panel of ICM used for skin test							Reexposure		
No.	Age (y)/sex	Iopromide	Iohexol	Iopamidol	Ioversol	Iobitridol	Iomeprol	Iodixanol	ICM	IDT	Change in severity
17	75/F	–	–	–*	–	–	–	–	Iobitridol	–	1 → 0
18	49/M	–*	–	–	–	–	–	+	Iopamidol	–	3 → 0
19	65/F	–*	–	–*	–	–	–	–	Iohexol	–	1 → 0
20	37/M	+	–	–*	–	–	–	–	Iohexol	–	3 → 1
21	57/M	+	+	–	–	+	–	–*	Ioversol	–	3 → 0
22	64/F	–*	–	–	–	–	–	–	Iopamidol	–	3 → 0
23	63/M	–	–	+	–	–	–*	–	Iohexol	–	3 → 0
									Ioversol	–	3 → 3
24	64/M	+	–	–	–*	+	+	–	Iopamidol	–	3 → 0
25	34/F	+	–*	–	+	+	–	–	Iopamidol	–	2 → 0
26	78/M	+	–	–	–	–	–	–*	Ioversol	–	3 → 0
27	58/M	–	–	–	–*	–	–	–	Iobitridol	–	1 → 0
28	43/M	–	–	–	–	–	–*	–	Iohexol	–	1 → 0
29	67/M	–	–	–*	–	–	–	–	Iobitridol	–	1 → 0
30	34/F	+	+	–*	–	+	+	+	Ioversol	–	3 → 0
31	59/M	–	–	–*	–*	–	–	–	Iobitridol	–	1 → 0
32	65/M	–	–	–	–	–	–*	–	Iopamidol	–	1 → 0
33	62/F	–	–	–	–	–	–*	–	Iopamidol	–	1 → 0
34	46/M	+	+	–*	+	–*	–	–	Iopromide	+	1 → 0
35	60/F	+	+	–	–	+	–*	–	Iohexol	+	3 → 0
36	69/M	–	+	+	–	+	–	–*	Iohexol	+	3 → 0
37	73/F	–	+	–	–*	–	–	–	Iohexol	+	1 → 0
38	56/F	–*	+	–	–	–	+	–	Iohexol	+	3 → 0

F, Female; M, male.

Table III summarizes the results of skin test using a panel of ICMs and the results of reexposure.

*Culprit ICM.

contrast media. These results can be explained by the cross-reactivity of IgE antibodies with allergens in ICMs. Cross-reactivity was commonly observed between iodixanol, iohexol, ioversol, and iomeprol.²⁰ However, in our study, iopromide, iobitridol, and iopamidol also reported cross-reactivity. For the patients in the CULPRIT+ group, whose IgE-mediated IHR was confirmed by IDTs, cross-reactivity between contrast media should be considered.

Of 31 patients in the CULPRIT– group, 22 patients were reexposed to an ICM. All 5 patients who were exposed to IDT-positive ICM completed CT scanning without any adverse events. This could be explained by the false-positive results and the low positive predictive value of IDT especially in the patients whose previous hypersensitivity reaction might have been nonimmunologic. Two of the 17 patients who were exposed to an IDT-negative ICM experienced IHR. The results of the single patient who experienced IHR when exposed to one IDT-negative ICM, but not when exposed to another IDT-negative ICM, implies the possibility of involvement of both immunologic and nonimmunologic mechanisms in a person with different contrast media. When the culprit ICM showed a negative result in IDT, a skin test using the other contrast media did not have a role in predicting the adverse reaction in the subsequent exposure. In this group, changing the ICM regardless of the IDT results, accompanied by premedication, alleviated the IHR and indicated that a non-IgE-mediated mechanism might contribute to the reaction.

In 2013, Prieto-Garcia et al¹⁰ showed that the patients with a history of IHR to ICM with positive skin test results to the culprit ICM had tolerated subsequent exposure to an alternative skin test–negative ICM with no premedication. However, they used “controlled challenge testing” when using the alternative agent, which requires dose escalation every 30 minutes. Moreover, their sample size was smaller than that in the present study.¹⁰

In our study, the overall recurrence rate of IHR to skin test–negative ICM in patients with a history of IHRs to ICM was 7% (2 of 28), consistent with the meta-analysis conducted by Yoon et al⁶ in 2015. The study of Schrijvers et al⁸ included 172 patients with a history of IHR who were exposed to skin test–negative ICM. The recurrence rate of IHR to skin test–negative ICM in these patients was 6.2%, which was also similar to our results.⁸ However, in both studies, the initial culprit ICM was not identified in many patients. In addition, the present study uniquely included patients who were subsequently exposed to a skin test–positive ICM, and the analysis was based on the results of IDTs using the culprit ICM.

The final goal of this study was to generate an algorithm for minimizing future IHRs in patients with a history of IHRs. From analysis of 69 cases, we suggest an algorithm based on the IDT results from the causative ICM (Figure 3). When the culprit agent produces a positive IDT result, additional skin tests with other available agents should be carried out to identify safe substitutes. If all tested agents are IDT-positive, the physicians should consider changing the diagnostic or treatment modalities for which ICM is not required. If any IDT-negative agents are

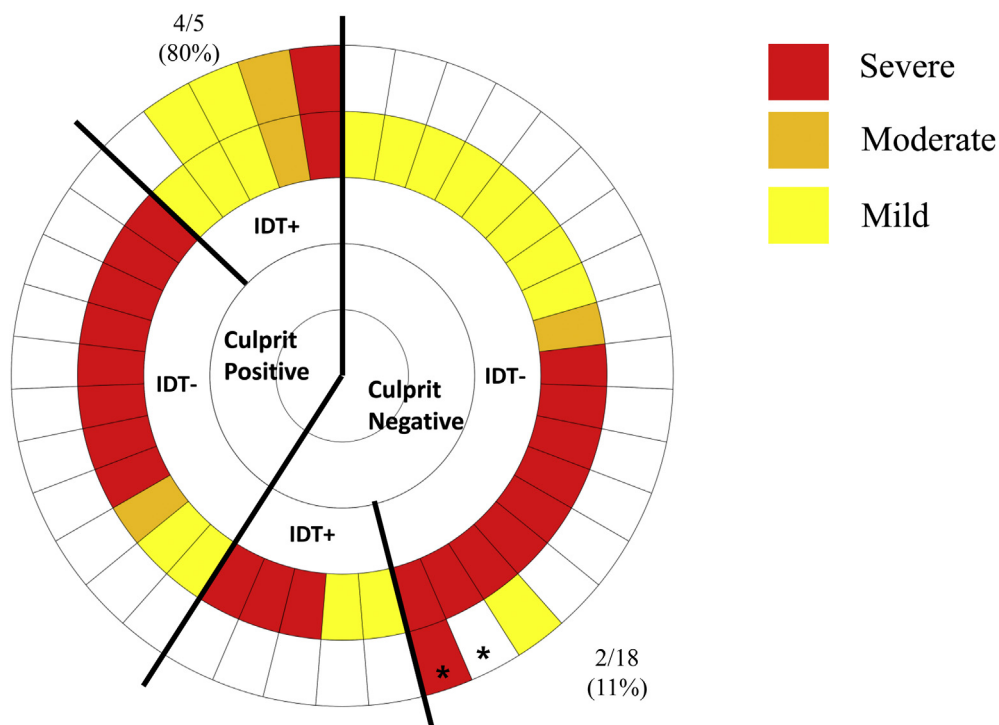


FIGURE 2. Hypersensitivity reactions to alternative ICM. The inner colored circle reflects the severity of the index event, while the outer colored circle shows the severity of the hypersensitivity reaction when using alternative ICMs. The circles are grouped by the IDT result of the culprit ICM ("Culprit positive/negative") and then by the IDT result of the alternative ICMs. *The patient with 2 different hypersensitivity reactions to subsequent exposures.

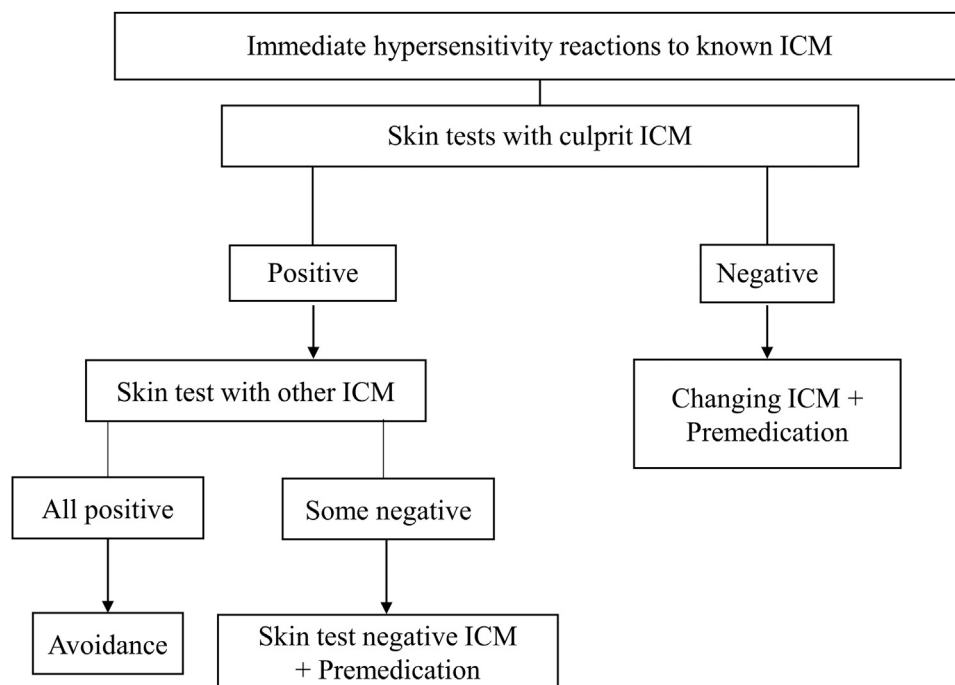


FIGURE 3. Skin test-based algorithm for selection of alternative ICM in patients with a history of hypersensitivity reactions to known ICM. The suggested algorithm is based on the results of IDTs to culprit contrast media.

available, they should be selected for the next exposure to ICM. For patients whose culprit ICM is IDT-negative, additional skin testing might not be helpful for selecting safe alternative (Figure 3).

Unfortunately, there are several limitations in this study. First, premedication was not consistent between subjects. Even though the premedication was mainly administered according to the American College of Radiology guidelines, the injection time and dosage of each drug were slightly different between the patients. Second, because culprit agents were not reused in all cases, the outcomes of rechallenge with IDT-negative culprit ICM were not evaluated in this study. Finally, the number of patients was low because it was a single-center study. Additional multicenter studies are required with a larger number of patients. To address this, we have built up a network composed of 13 referral hospitals, known as The Korean Network of Allergists & Radiologists for Research to Radio-contrast Media-associated Adverse Reactions (KOAR³A). Validating our algorithm is one of the projects that KOAR³A is planning under the sponsorship of the Korean government. Upon completion of this larger-scale study, the result could be adopted clinically and reflected in the international guidelines.

In conclusion, by using the IDT result with the culprit ICM, we could tell whether or not IHRs are IgE-mediated. When the culprit ICM was IDT-positive, an additional IDT with other ICMs was helpful to select an IDT-negative ICM for the following exposure. However, when the culprit ICM was IDT-negative, further IDTs did not play a role in predicting IHRs in this study. Although further validation is required, the results of the present study suggest a practical algorithm for preventing the recurrence of hypersensitivity reactions in patients with a history of reactions to a known culprit ICM.

REFERENCES

1. Kvedariene V, Martins P, Rouanet L, Demoly P. Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period. *Clin Exp Allergy* 2006;36:1072-7.
2. Katayama H. Adverse reactions to contrast media: what are the risk factors? *Invest Radiol* 1990;25:S16-7.
3. Thomsen HS, Bush WH Jr. Adverse effects of contrast media: incidence, prevention and management. *Drug Saf* 1998;19:313-24.
4. Cashman JD, McCredie J, Henry DA. Intravenous contrast media: use and associated mortality. *Med J Aust* 1991;155:618-23.
5. Brockow K, Ring J. Anaphylaxis to radiographic contrast media. *Curr Opin Allergy Clin Immunol* 2011;11:326-31.
6. Yoon SH, Lee SY, Kang HR, Kim JY, Hahn S, Park CM, et al. Skin tests in patients with hypersensitivity reaction to iodinated contrast media: a meta-analysis. *Allergy* 2015;70:625-37.
7. Laroche D, Namour F, Lefrancois C, Aimone-Gastin I, Romano A, Sainte-Laudy J, et al. Anaphylactoid and anaphylactic reactions to iodinated contrast material. *Allergy* 1999;54:13-6.
8. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin testing for suspected iodinated contrast media hypersensitivity. *J Allergy Clin Immunol Pract* 2018;6:1246-54.
9. Della-Torre E, Berti A, Yacoub MR, Guglielmi B, Tombetti E, Sabbadini MG, et al. Proposal of a skin tests based approach for the prevention of recurrent hypersensitivity reactions to iodinated contrast media. *Eur Ann Allergy Clin Immunol* 2015;47:77-85.
10. Prieto-Garcia A, Tomas M, Pineda R, Tornero P, Herrero T, Fuentes V, et al. Skin test-positive immediate hypersensitivity reaction to iodinated contrast media: the role of controlled challenge testing. *J Investig Allergol Clin Immunol* 2013;23:183-9.
11. Kim SH, Jo EJ, Kim MY, Lee SE, Kim MH, Yang MS, et al. Clinical value of radiocontrast media skin tests as a prescreening and diagnostic tool in hypersensitivity reactions. *Ann Allergy Asthma Immunol* 2013;110:258-62.
12. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media: a European multicenter study. *Allergy* 2009;64:234-41.
13. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;175:621-8.
14. Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: premedication vs. changing the contrast medium. *Eur Radiol* 2016;26:2148-54.
15. Park HJ, Park JW, Yang MS, Kim MY, Kim SH, Jang GC, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: a multicentre retrospective cohort study. *Eur Radiol* 2017;27:2886-93.
16. Brockow K. Immediate and delayed cutaneous reactions to radiocontrast media. *Chem Immunol Allergy* 2012;97:180-90.
17. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy* 2014;69:420-37.
18. Bae YJ, Hwang YW, Yoon SY, Kim S, Lee T, Lee YS, et al. The effectiveness of automatic recommending system for premedication in reducing recurrent radiocontrast media hypersensitivity reactions. *PLoS One* 2013;8:e66014.
19. American College of Radiology. ACR manual on contrast media: version 10. Reston, VA: American College of Radiology; 2015.
20. Rosado Ingelmo A, Dona Diaz I, Cabanas Moreno R, Moya Quesada MC, Garcia-Aviles C, Garcia Nunez I, et al. Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast media. *J Investig Allergol Clin Immunol* 2016;26:144-55.