

Hypersensitivity Reactions to Iodinated Contrast Media: A Multicenter Study of 196 081 Patients

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Background: Multicenter studies may be required for establishing guidelines for safe usage of iodinated contrast media (ICM).

Purpose: To identify the prevalence, patterns, risk factors, and preventive measures for ICM-related hypersensitivity reactions (HSRs).

Materials and Methods: Between March 2017 and October 2017, a total of 196 081 patients who underwent ICM administration were enrolled from seven participating institutions. The occurrence of HSRs and baseline patient information were recorded. χ^2 and Student *t* test were performed, and logistic regression analyses were used to identify risk factors that predict occurrence and recurrence of HSR.

Results: Among 196 081 patients (mean age $\pm$ standard deviation, 59.1 years $\pm$ 16.0; 105 014 men and 91 067 women) who underwent ICM administration, the overall prevalence of HSRs was 0.73% (1433 of 196 081), and severe reactions occurred in 0.01% (17 of 196 081). Conditional logistic regression for patients with HSR (*n* = 1433) and a control group (1:1 matched group for age, sex, ICM product, and institution) demonstrated that a patient's previous individual history of an ICM-related HSR (adjusted odds ratio [OR], 198.8; *P* < .001), hyperthyroidism (adjusted OR, 3.6; *P* = .04), drug allergy (adjusted OR, 3.5; *P* < .001), and other allergic diseases (adjusted OR, 6.8; *P* < .001) and a family history of ICM-related HSRs (adjusted OR, 14.0; *P* = .01) were predictors of HSR occurrence. Logistic regression analysis showed that use of premedication with antihistamine (OR, 0.5; *P* = .01) and change in the generic profile of ICM (OR, 0.5; *P* < .001) were preventive against recurrent HSR.

Conclusion: Family history as well as previous individual history of hypersensitivity reactions (HSRs) to iodinated contrast media (ICM) were risk factors for HSR occurrence, suggesting a potential genetic predisposition. A change in the culprit ICM and premedication with antihistamine are useful for reducing the recurrence of HSRs.

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Approximately 75 million CT scans are conducted each year in the United States, and half of them include the use of iodinated contrast media (ICM) (1,2). In Korea, it is estimated that more than 4 million CT scans involving ICM usage are performed each year (3).

As the use of ICM is rapidly growing, so is the occurrence of ICM-related hypersensitivity reactions (HSRs) (4,5). Most symptoms are known to be mild; however, ICM-related HSRs can still be life-threatening in rare instances (6,7). It has been reported that deaths due to anaphylaxis may occur in one to three individuals per 100 000–1 000 000 ICM administrations (8). Considering the large number of contrast agent-enhanced CT scans that are performed, examination of ICM safety profiles is essential for the prevention and optimal management of ICM-related HSRs. Moreover, it is important to identify

patients at high risk of HSR, because premedication (medication given in preparation for ICM administration to lower the rate of ICM-related HSRs) with corticosteroids and/or antihistamines and a change in the generic profile of ICM are known to prevent recurrent HSR (9–12). However, a systematic registry for ICM-related HSRs is currently lacking in Korea. Detailed investigation of the prevalence of HSRs and its patterns and risk factors are of interest, because there are only a few studies that have addressed these issues (13,14).

We hypothesized that a multicenter registry of patients who underwent ICM administration could be helpful to establish guidelines for safe usage of ICM and develop preventive measures to avoid recurrent HSRs. The aim of this study was twofold. First, we aimed to identify the patterns and prevalence of HSRs according to the ICM products

Abbreviations

CI = confidence interval, HSR = hypersensitivity reaction, ICM = iodinated contrast media, OR = odds ratio

Summary

Family history and previous individual history of hypersensitivity reaction to iodinated contrast media were risk factors for new hypersensitivity occurrence. Premedication and change of iodinated contrast media type were useful measures to prevent recurrent hypersensitivity reaction.

Key Results

- The overall prevalence of hypersensitivity reactions (HSRs) to iodinated contrast media (ICM) was 0.73% (1433 of 196 081), and severe reactions occurred in 0.01% (17 of 196 081) of patients.
- A patient's previous individual history of an ICM-related HSR (adjusted odds ratio [OR], 1.99; $P < .001$), hyperthyroidism (adjusted OR, 3.6; $P = .04$), drug allergy (adjusted OR, 3.5; $P < .001$), and other allergic diseases (adjusted OR, 6.8; $P < .001$) and a family history of ICM-related HSRs (adjusted OR, 1.4; $P = .01$) were predictors of hypersensitivity reactions.
- Premedication with antihistamine (OR, 0.53; $P = .01$) and a change in the ICM (OR, 0.51; $P < .001$) showed preventive effects against recurrent HSRs.

used, their generic profiles, and iodine concentrations. Second, we tried to identify risk factors for the occurrence of HSRs and preventive measures for breakthrough reactions.

Materials and Methods

The institutional review boards of the seven participating institutions approved this study. The requirements for written informed consent were waived because this study is a minimal-risk research study, which will not affect the rights of the participants, and all personal data were removed and coded as arbitrary numbers.

Patients

We recruited patients from seven tertiary referral hospitals in Korea (Seoul National University Hospital, Kyungpook National University Hospital, Chungbuk National University Hospital, Pusan National University Yangsan Hospital, Chonnam National University Hospital, Gyeongsang National University Hospital, and Chung-Ang University Hospital). This study included all patients who underwent contrast-enhanced CT examinations between March 2017 and October 2017. In total, 196 081 patients who underwent ICM administration were enrolled through the web-based registry system of the Korea National Institutes of Health (Clinical Research and Trial Management System [iCReaT], Cheongju, Korea). Data were collected on a weekly basis, and internal inspection was performed by a board-certified physician in preventive medicine (D.Y.K., with 10 years of experience) to minimize heterogeneity among institutions. He sent regular emails with quality assurance checklists to ensure that data were collected according to the criteria issued by the American College of Radiology, and reviewed the collected data every month to prevent missing values.

For each patient who underwent ICM administration, a case report form was submitted that included the following

information: (a) baseline characteristics of the patients, including age, sex, and underlying disease such as diabetes mellitus, heart failure, and hyperthyroidism; (b) previous individual history of ICM usage and ICM-related HSRs; (c) previous individual history of drug allergy, asthma, and other allergic diseases; (d) family history of ICM-related HSRs and allergic diseases, including asthma; (e) name of the administered ICM product; (f) regimen of premedication, if administered; and (g) in instances of HSR occurrence, the symptoms, severity (mild, moderate, and severe), and duration of the HSR, along with details on its management.

Prior to the patient enrollment, all participating institutions agreed to report and manage HSR according to the criteria issued by the American College of Radiology (15). In addition, they agreed to use premedication and/or change the culprit ICM to another contrast agent in patients who reported having a previous history of an HSR to ICM. Regimens for premedication were as follows: for patients who reported a mild index reaction, 4 mg of intravenous chlorpheniramine (Peniramin; Yuhan, Seoul, Korea) 30 minutes before ICM administration; for patients who reported a moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; and for patients who reported a severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before ICM administration and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration via the intravenous cannula inserted for ICM injection (16). However, physicians were allowed to modify the premedication regimen at their own discretion. The selection of an alternative contrast agent was left to the discretion and preference of each hospital.

To assess the risk factors for ICM-related HSRs, a control group was selected among patients without HSRs, after 1:1 matching for age, sex, ICM product used, and the institution. When the occurrence of HSR was reported, control group was selected on a case-by-case basis from the patients of the same age, sex, and institution with the same ICM product administered within 1-week interval from the HSR occurrence. Comparisons between patients with HSR occurrence during the study period and a control group without HSRs were performed. In addition, patients who experienced recurrent HSRs were compared with those who had previously experienced an HSR but had not shown recurrence, to identify the risk factors for its recurrence (Fig 1).

ICM Used

The ICM used in the study included 22 brands of contrast media from 11 companies: Bonorex 350 (Central Medical Service, Seoul, Korea); Iobrix 240, Iobrix 350, Iversense 240, Iversense 320, and Iversense 350 (Taejoon Pharmaceutical, Seoul, Korea); Iomeron 350 and Iomeron 400 (Bracco, Milan, Italy); Iopamigita 370 (Agfa Healthcare, Berlin, Germany); Omnihexol 350 (Korea United Pharmaceutical, Seoul, Korea); Omnipaque 300, Omnipaque 350, Visipaque 270, and Visipaque 320 (GE Healthcare, Milwaukee, Wis); Optiray 320 and Optiray 350 (Mallinck-

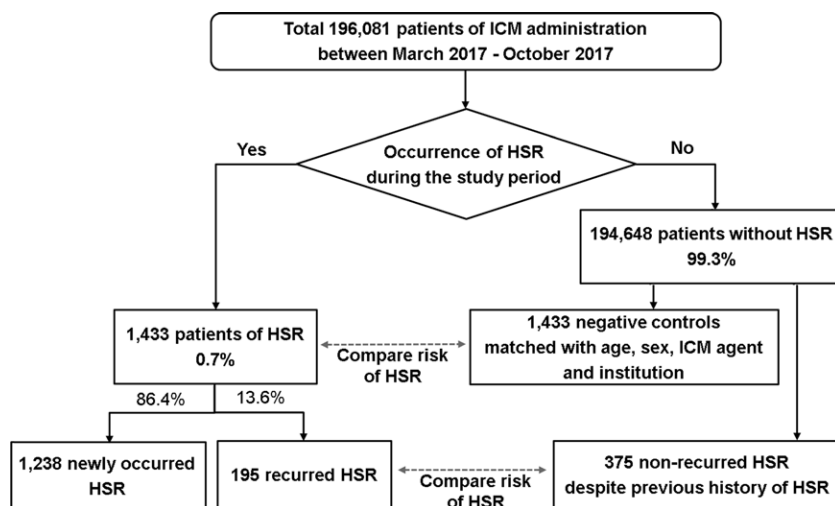


Figure 1: Flowchart shows study performance. HSR = hypersensitivity reaction, ICM = iodinated contrast media.

rodt Medical, St Louis, Mo); Pamiray 300 and Pamiray 370 (Dongkook Pharmaceutical, Seoul, Korea); Scanlux 370 (Tecmed Pharmaceutical, Midrand, South Africa); Ultravist 370 (Bayer Healthcare, Berlin, Germany); and Xenetix 300 and Xenetix 350 (Guerbet, Aulnay, France). Regarding generic profiles, six nonionic low-osmolar monomers were present, namely, iobitridol (14.1%), iohexol (26.3%), iomeprol (14.9%), iopamidol (27%), iopromide (3.7%), and ioversol (12.4%). There was one nonionic iso-osmolar dimer, iodixanol (1.6%).

ICM-related HSRs

HSRs were defined and classified according to the criteria issued by the American College of Radiology as follows: (a) mild (self-limited signs and symptoms without evidence of progression): limited urticarial and pruritis, limited cutaneous edema, itching or scratchy throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea; (b) moderate (more pronounced signs and symptoms that commonly require medical management): diffuse urticarial and pruritis, diffuse erythema with stable vital signs facial edema without dyspnea, throat tightness or hoarseness without dyspnea, and wheezing or bronchospasm with mild or no hypoxia; and (c) severe (life-threatening symptoms that can result in permanent morbidity or death if not managed appropriately): diffuse edema or facial edema with dyspnea, diffuse erythema with hypotension, anaphylactic shock with hypotension and tachycardia, and wheezing or bronchospasm with marked hypoxia (15). In addition to allergic-like reactions, gastrointestinal reactions such as nausea and/or vomiting and flushing, warmth, and/or chills were also closely monitored because there can be considerable overlap between hypersensitivity and physiologic reactions in clinical practice, making it hard to distinguish these reactions.

Statistical Analysis

SPSS (version 22.0; SPSS, Chicago, Ill), a commercially available software, was used for statistical analysis. Data

were expressed as mean and standard deviation for continuous variables, and number and percentage for categorical variables. χ^2 analyses were performed to compare the prevalence of HSRs according to the ICM product used, their generic profile, and iodine concentration. Poisson regression analysis was performed to identify positive or negative correlation between iodine concentration and the prevalence of HSRs. The Student t test for continuous variables and the χ^2 test for categorical variables were used to compare groups with and without HSRs. Conditional logistic regression analyses were performed to assess risk factors for HSR occurrence in patient-control matched data. Logistic regression analyses with a conditional-backward method were also

performed to identify risk factors that predict recurrent HSR. For all statistical tests, $P < .05$ was considered to indicate statistical significance, except for the application of Bonferroni correction on analysis of iodine concentration and HSR prevalence.

Results

Baseline Information and Overall Prevalence and Severity of HSRs

A total of 196 081 patients (mean age $\pm$ standard deviation, 59.1 years $\pm$ 16.0; 105 014 men and 91 067 women) who underwent ICM administration were enrolled (Fig E1 [online]). Table 1 includes a list of ICM used during the study period and the occurrence of HSRs according to the ICM constituents and product. Among the 196 081 patients, 1 433 reported experiencing an HSR, with an overall prevalence of 0.73% (1 433 of 196 081). Among them, for 0.63% (1 238 of 196 081), this was the first occurrence of an HSR. In terms of severity, 83.2% of the events were classified as mild HSRs, with an overall prevalence of 0.61% (1 192 of 196 081); 15.6% as moderate HSRs (0.11%; 224 of 196 081); and 1.2% as severe HSRs (0.01%; 17 of 196 081). The prevalence and severity of HSR differed according to the ICM products used (all $P < .001$).

HSR Occurrence according to ICM Generics and Iodine Concentration

Figure 2 demonstrates the prevalence and severity of HSRs according to ICM generics. When we analyzed the prevalence of HSRs according to the generic profiles by comparing the prevalence of HSRs for each with the combined prevalence of HSRs for the others, iobitridol (0.89%; 247 of 27 613) and iomeprol (0.95%; 278 of 29 247) were found to be associated with higher rates of HSR ($P = .001$ and $P < .001$, respectively), whereas iopromide (0.37%; 27 of 7 335) and iohexol (0.62%; 321 of 51 586) were associated with lower rates of HSRs ($P < .001$ and $P = .001$, respectively). There was no difference in the occurrence of HSRs for iodixanol (0.99%;

Table 1: Prevalence and Severity of HSRs to ICM according to the Product and Generic Profile

Generic and Product*	ICM Usage	HSR (%)	Mild (%)	Moderate (%)	Severe (%)
Iobitridol					
Iobitridol 300 (ICM 1)	852	0 (0)	0 (0)	0 (0)	0 (0)
Iobitridol 350 (ICM 2)	26 761	247 (0.92)	203 (0.76)	42 (0.16)	2 (0.01)
Iodixanol					
Iodixanol 270 (ICM 3)	752	5 (0.66)	2 (0.27)	3 (0.40)	0 (0)
Iodixanol 320 (ICM 4)	2291	25 (1.09)	15 (0.66)	8 (0.35)	2 (0.09)
Iohexol					
Iohexol 350A (ICM 5)	8553	30 (0.35)	27 (0.32)	3 (0.04)	0 (0)
Iohexol 240 (ICM 6)	1124	18 (1.6)	17 (1.51)	1 (0.09)	0 (0)
Iohexol 350B (ICM 7)	11 782	99 (0.87)	88 (0.75)	9 (0.08)	2 (0.014)
Iohexol 350C (ICM 8)	13 118	126 (0.88)	105 (0.80)	20 (0.15)	1 (0.01)
Iohexol 300 (ICM 9)	4327	18 (0.41)	13 (0.30)	4 (0.09)	1 (0.02)
Iohexol 350D (ICM 10)	12 682	30 (0.24)	20 (0.16)	9 (0.07)	1 (0.01)
Iomeprol					
Iomeprol 350 (ICM 11)	19 235	114 (0.58)	104 (0.54)	10 (0.05)	0 (0)
Iomeprol 400 (ICM 12)	10 012	164 (1.63)	134 (1.34)	26 (0.26)	4 (0.044)
Iopamidol					
Iopamidol 370A (ICM 13)	4167	94 (2.3)	87 (2.09)	6 (0.14)	1 (0.024)
Iopamidol 300 (ICM 14)	5365	70 (1.29)	64 (1.19)	6 (0.11)	0 (0)
Iopamidol 370B (ICM 15)	39 120	171 (0.43)	137 (0.35)	31 (0.08)	3 (0.01)
Iopamidol 370C (ICM 16)	4385	36 (0.84)	32 (0.73)	4 (0.09)	0 (0)
Iopromide					
Iopromide 370 (ICM 17)	7335	27 (0.37)	20 (0.27)	7 (0.10)	0 (0)
Ioversol					
Ioversol 240 (ICM 18)	621	5 (0.81)	5 (0.81)	0 (0)	0 (0)
Ioversol 320A (ICM 19)	2290	4 (0.17)	0 (0)	4 (0.18)	0 (0)
Ioversol 350A (ICM 20)	7757	61 (0.79)	45 (0.58)	16 (0.21)	0 (0)
Ioversol 320B (ICM 21)	7581	78 (1.03)	65 (0.86)	13 (0.17)	0 (0)
Ioversol 350B (ICM 22)	5971	11 (0.18)	9 (0.15)	2 (0.03)	0 (0)
Total	196 081	1433 (0.73)	1192 (0.61)	224 (0.11)	17 (0.01)

Note.—Data are the number of patients, with percentages in parentheses. HSR = hypersensitivity reaction, ICM = iodinated contrast media.

* Specific product names are anonymized.

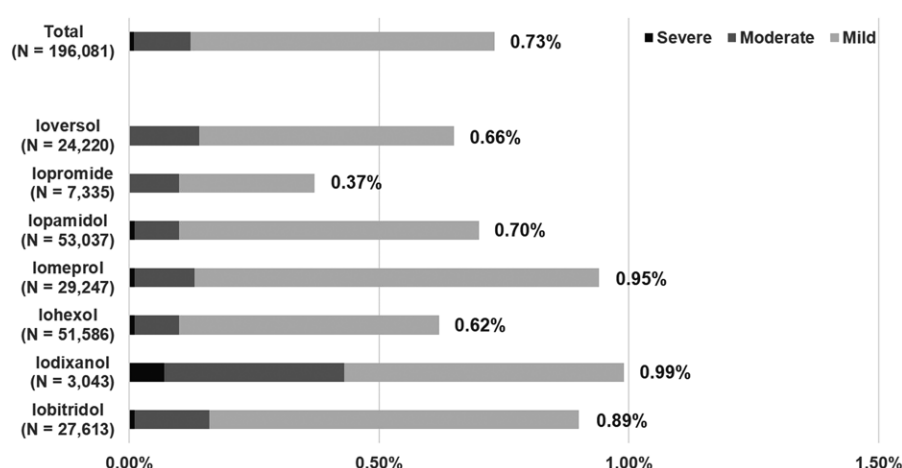


Figure 2: Image shows prevalence and severity of hypersensitivity reaction according to the generic profile of iodinated contrast media.

30 of 3043), iopamidol (0.70%; 371 of 53 037), and ioversol (0.66%; 159 of 24 220) ($P = .096$, $P = .32$, and $P = .15$, respectively).

analyses demonstrated no positive or negative linear association between the prevalence of HSR and the iodine concentration in ICM ($P = .32$).

Regarding iodine concentration, the frequency of HSRs differed according to iodine concentration for every ICM generic ($P \leq .014$), except for iodixanol ($P = .397$) (Fig 3). When we compared the occurrence of HSRs according to the iodine concentration overall, regardless of the product used and the generic profile, the prevalence differed (240 mg/mL, 1.32% [23 of 1745]; 270 mg/mL, 0.66% [five of 752]; 300 mg/mL, 0.83% [88 of 10 544]; 320 mg/mL, 0.88% [107 of 12 162]; 350 mg/mL, 0.68% (718 of 105 859); 370 mg/mL, 0.60% (328 of 55 007); and 400 mg/mL, 1.64% (164 of 10 012)] ($P < .001$). However, Poisson regression

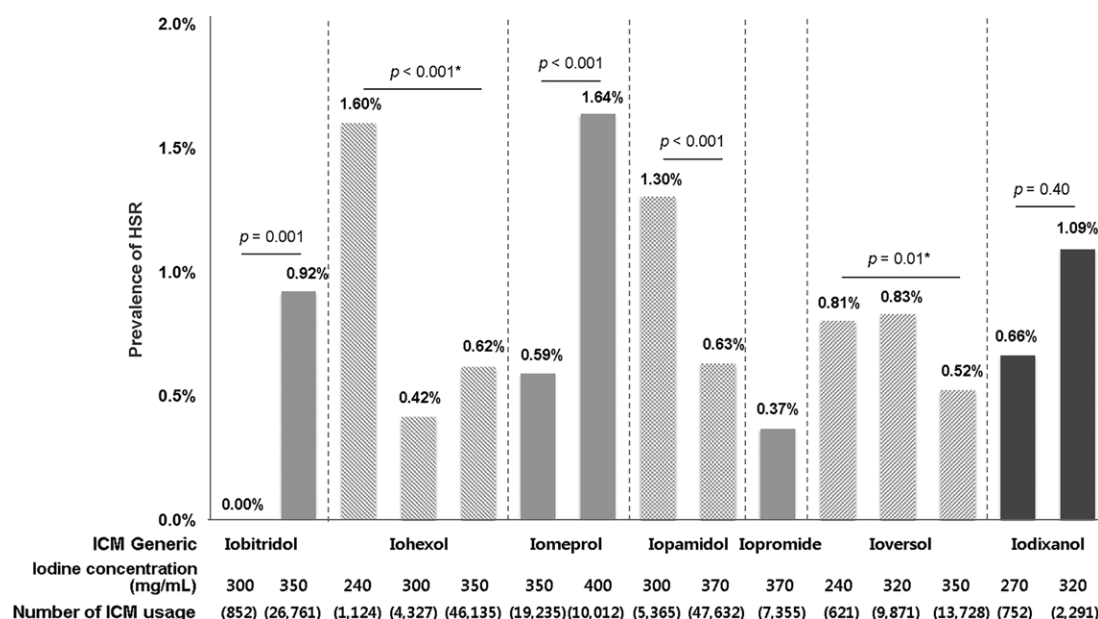


Figure 3: Graph shows comparison of prevalence of hypersensitivity reactions (HSRs) according to iodine concentration and generic profile of iodinated contrast media (ICM). * = Bonferroni correction was applied.

Management of ICM-related HSRs

Among the 1433 patients who experienced HSRs, 986 (68.8%, 986 of 1433) recovered without treatment. For the 447 patients who did not recover spontaneously, intensive bedside monitoring and management was performed. Antihistamines were administered to 274 patients (19.1%, 274 of 1433) and both antihistamines and systemic steroids were administered to 87 (6.1%, 87 of 1433). For seven patients (0.5%, seven of 1433), epinephrine was injected followed by intravenous steroid injection. Other drugs such as analgesics and antiemetics were used for nine patients (0.6%, nine of 1433). Seventy patients (4.9%, 70 of 1433) were transferred to the emergency department or hospitalized, and their symptoms were managed in the wards by allergy specialists.

Risk Factors for the Occurrence and Recurrence of ICM-related HSRs

In the comparison between patients with HSRs ($n = 1433$) and those without HSRs ($n = 1433$), a previous individual history of ICM-related HSRs (195 vs four; $P < .001$); patients' previous individual history of hyperthyroidism (16 vs four; $P = .01$), drug allergy (55 vs 12; $P < .001$), asthma (23 vs 10; $P = .03$), and other allergic diseases (55 vs six; $P < .001$), and a family history of ICM-related HSR (11 vs one; $P = .01$) were found to be risk factors for HSRs. A previous use of ICM without an HSR within the past decade was associated with a lower risk of HSR occurrence (935 vs 1041; $P < .001$) (Table 2). Conditional logistic regression demonstrated that a patient's previous individual history of an ICM-related HSR (adjusted odds ratio [OR], 198.8; 95% confidence interval [CI]: 49.2, 802.5; $P < .001$), hyperthyroidism (adjusted OR, 3.6; 95% CI: 1.1, 11.8; $P = .04$), drug allergy (adjusted OR, 3.5; 95% CI: 1.9, 6.5; $P < .001$), and other allergic diseases (adjusted OR, 6.8; 95% CI: 3.2, 14.8; $P < .001$) and a family history of ICM-related HSRs (adjusted OR, 14.0; 95% CI: 1.8, 112.1; $P = .01$) were predictors of HSR occurrence (Table 3).

Among the 196081 patients, 570 patients reported experiencing an HSR to ICM in the past, and 94.9% (541 of 570) patients underwent preventive measures before ICM administration. Premedication only was conducted in 213 patients (37.4%, 213 of 570); 187 patients received antihistamine only and 26 patients received antihistamine with corticosteroids) and change of ICM only was performed in 52 patients (9.1%, 52 of 570). In 276 patients (48.4%, 276 of 570), both premedication and change of ICM were performed (203 received antihistamine with change of ICM and 73 received antihistamine and corticosteroids with change of ICM). Among 570 patients who had experienced an HSR to ICM in the past, 195 patients experienced recurrent HSR, whereas 375 patients did not show any symptoms of recurrence. A total of 176 of 541 patients (32.5%) experienced recurrent HSR despite premedication and/or change of ICM, and 158 patients experienced breakthrough reactions (131 patients received antihistamine and 27 patients received antihistamine with corticosteroids) (Table 4). In addition, recurrent events occurred in 92 of 328 (28.1%) patients for whom culprit agents were changed. Logistic regression analysis demonstrated that premedication with antihistamine (OR, 0.53; 95% CI: 0.33, 0.86; $P = .01$) and a change of ICM (OR, 0.51; 95% CI: 0.36, 0.73; $P < .001$) were associated with a lower risk of HSR recurrence (Table 5).

Discussion

A total of 196081 patients who underwent intravenous injections of iodinated contrast media (ICM) in 2017 were included in this nationwide Korean registry. The overall prevalence of hypersensitivity reactions (HSRs) was 0.73%, and 0.63% of the population experienced the first HSR event of their lifetime. Because the introduction of nonionic low-osmolality ICM contributed to a reduction of overall prevalence and severity of ICM-related HSRs, most of the events were mild. However, 16.8% (241 of 1433) of the events were classified as moderate to severe HSRs, with an overall prevalence of 0.12% in our study.

Table 2: Comparison of Characteristics between Patients Who Experienced HSRs and Healthy Control Group

Characteristic	Patients with HSR (n = 1433)	Healthy Control Group (n = 1433)	Odds Ratio	95% Confidence Interval	P Value
Age (y)*	55.2 ± 14.8	55.2 ± 14.8	...	...	...
Sex					
Male	630	630	...	...	...
Female	803	803	...	...	...
Underlying disease					
Diabetes mellitus	163 (11)	155 (10.82)	1.1	0.8, 1.3	.68
Heart failure	10 (0.70)	3 (0.21)	3.4	0.9, 12.2	.09
Hyperthyroidism†	16 (1.1)	4 (0.28)	4.0	1.4, 12.1	.01
Drug allergy†	55 (3.8)	12 (0.84)	5.2	2.8, 9.7	<.001
Asthma†	23 (2.6)	10 (0.70)	2.3	1.1, 4.9	.03
Other allergic disease†	55 (3.8)	6 (0.42)	9.5	4.1, 22.1	<.001
Past history of ICM exposure†					
No HSR to ICM usage	935 (65)	1041 (71)	0.7	0.6, 0.8	<.001
HSR to ICM	195 (13)	4 (0.28)	56.3	20, 151	<.001
Family history					
HSR to ICM†	11 (0.77)	1 (0.07)	11.1	1.4, 85.9	.01
Allergic disease, including asthma	19 (1.33)	11 (0.77)	1.7	0.8, 3.7	.20

Note.—Unless otherwise specified, data are numbers, with percentages in parentheses. A healthy control group was randomly selected from patients without hypersensitivity reaction (HSR) after 1:1 matching for age, sex, iodinated contrast media (ICM) product, and institution with those patients who experienced HSR.

* Data are means ± standard deviation.

† Indicates $P < .05$.

Table 3: Conditional Logistic Regression Analysis for 1:1 Matched Patients Who Experienced HSRs and Healthy Control Group

Characteristic	Adjusted Odds Ratio	95% Confidence Interval	P Value*
Underlying disease			
Hyperthyroidism	3.6	1.1, 12	.04
Drug allergy	3.5	1.9, 6.6	<.001
Asthma	1.9	0.9, 4.0	.09
Other allergic disease	6.8	3.2, 14.8	<.001
Past history of ICM exposure			
No HSR to ICM usage	0.5	0.4, 0.6	<.001
HSR to ICM	199	49, 802	<.001
Family history			
HSR to ICM	14	2, 112	.01

Note.—Multiple regression analysis was performed with variables for which a statistically significant correlation was found in the univariable analysis. HSR = hypersensitivity reaction, ICM = iodinated contrast media.

* Indicates $P < .05$.

population. History of ICM-related HSR, presence of allergic diseases, hyperthyroidism, and a family history of ICM-related HSR were risk factors for HSR. In terms of preventive measures, premedication with antihistamine and change of ICM to another contrast agent reduced the risk of recurrent HSR.

Although all participating institutions agreed to conduct premedication or change of ICM in patients with high risk, we found that 29 of 570 patients (5.1%) with prior HSRs underwent ICM administration without any precaution. Moreover, breakthrough reactions occurred in 158 of 489 patients (32.3%) despite adequate premedication; recurrent

events occurred in 92 of 328 patients (28.1%) for whom culprit agents were changed. The relatively high rate of breakthrough reactions we found despite premedication and changes in ICM emphasizes the importance of a registry for supervision of high-risk groups (17,18).

The prevalence of HSR observed in our study was similar to or lower than those noted in previous large studies, such as Wang et al (6) and Motosugi et al (19). Also consistent with prior studies, our study showed individual history of ICM-related HSR and presence of allergic diseases, such as drug allergies, were risk factors for HSR (10,20). Allergic diseases have been reported to

Table 4: Comparison of Characteristics between Patients Who Experienced Recurrent HSR and Those Who Had Previously Experienced HSR Without Any Recurrent Events

Characteristic	Patients with Recurrent HSR (n = 195)	Patients without Recurrent HSR (n = 375)	Odds Ratio	95% Confidence Interval	P Value
Age (y)*	56.3 ± 13.0	58.6 ± 13.0	...	...	.05
Sex					.66
Men	81 (42)	164 (43.7)	...	...	...
Women	114 (58.5)	211 (56.3)	...	...	...
Underlying disease					
Diabetes mellitus	29 (15)	53 (14.1%)	1.1	0.7, 1.7	.81
Heart failure	2 (1.03)	1 (0.27)	3.9	0.4, 43.0	.27
Hyperthyroidism	3 (1.5)	1 (0.27)	5.9	0.6, 56.7	.12
Drug allergy	8 (4.1)	7 (1.9)	2.3	0.8, 6.3	.17
Asthma	2 (1.03)	11 (2.9)	0.3	0.1, 1.6	.24
Other allergic disease	10 (5.1)	16 (4.27)	1.2	0.5, 2.7	.67
Family history					
HSR to ICM	1 (0.51)	1 (0.27)	1.9	0.1, 31.0	> .99
Allergic disease, including asthma	2 (1.03)	2 (0.53)	1.9	0.8, 13.8	.61
Preventive measure					
None†	19 (9.7)	10 (2.7)	3.9	1.8, 8.7	<.001
Premedication only†	84 (43)	129 (34)	1.4	1.0, 2.1	.04
Antihistamine	73 (37)	114 (30.4)	1.4	1.0, 2.0	.09
Antihistamine and corticosteroids	11 (5.6)	15 (4.0)	1.4	0.9, 1.9	.37
Change of ICM only	18 (9.2)	34 (9.1)	1.0	0.6, 1.9	.95
Premedication and change of ICM†	74 (37.9)	202 (54)	0.5	0.4, 0.8	.001
Antihistamine and change of ICM	58 (29.7)	145 (38.7)	0.7	0.5, 1.0	.03
Antihistamine and corticosteroid and change of ICM	16 (8.2)	57 (15.2)	0.5	0.3, 0.9	.02

Note.—Unless otherwise specified, data are numbers, with percentages in parentheses. HSR = hypersensitivity reaction, ICM = iodinated contrast media.

* Data are means ± standard deviation.

† Indicates $P < .05$.

Table 5: Effect of Preventive Measures to Reduce Hypersensitivity Reaction Recurrence

Measure	Odds Ratio	95% Confidence Interval	P Value
Premedication with antihistamine	0.53	0.33, 0.86	.010
Change of iodinated contrast media	0.51	0.36, 0.73	< .001

Note.—Multiple regression analysis was performed for preventive measures with the conditional-backward methods.

be strongly associated with high prevalence rates of autoimmune thyroid diseases, including Graves disease and Hashimoto thyroiditis (21,22). In our study, it was found that a family history of HSR to ICM is a risk factor for HSR. Of note, HSR is affected by both environmental and genetic factors (23). As susceptibility genes for asthma, allergic rhinitis, and atopic dermatitis have been identified (24), we suggest a potential genetic predisposition for HSRs to ICM. Further investigations on HSR-related genetic profiles may provide more insight into this issue.

Premedication with antihistamine and change from culprit ICM to another contrast agent were associated with a low risk of HSR recurrence, confirming previous reports (7,10–12,16,25). European Society of Urogenital Radiology guidelines suggest that changing the ICM or using premedication reduces recurrent events in patients with risk of HSR (26). Version 10.3 of the American

College of Radiology Manual on Contrast Media (15) also indicated that substituting the culprit ICM with a low-osmolar agent of the same class may reduce the likelihood of a subsequent HSR.

One major limitation of our study was that types, prevalence, and indications of ICM used in each institution varied, making it difficult to generalize our results. We acknowledge a number of patient characteristics, details of the various protocols, and local specific customs in the various hospitals that were not controlled for in this large registry. There was also variability in the use of premedication, reporting, severity grading, and management of patients with HSRs according to physicians and institutions, which was difficult to control. Furthermore, the period of patient enrollment of our study was 8 months, which is relatively short. Last, our study lacked detailed scan information, such as scanned area, contrast agent injection rate, and volume and

temperature of injected ICM, which may have affected the occurrence of HSRs (27).

In conclusion, we investigated the safety profile of hypersensitivity reaction (HSR) to iodinated contrast media (ICM) by building a nationwide database in Korea. Our study emphasizes the necessity for standardized reporting protocols and of the establishment of a nationwide integrated registry for ICM-related HSRs as the basis for establishing a strategy to prevent recurrent HSR. Future large-scale and long-term registries involving continuous data collection with standardized protocols may still be required to unravel all aspects of contributions to HSRs.

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