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ORIGINAL RESEARCH • CONTRAST MEDIA

Allergic-like Hypersensitivity Reactions to Gadolinium-based Contrast Agents: An 8-year Cohort Study of 154 539 Patients

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Conflicts of interest are listed at the end of this article.

See also the editorial by Kallmes and McDonald in this issue.

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Background: With the widespread use of gadolinium-based contrast agents (GBCAs), the incidence of allergic-like hypersensitivity reactions (HSRs) to GBCAs is increasing. Research on the incidence and risk factors for HSRs to GBCAs is needed for their safe use.

Purpose: To determine the incidence of acute and delayed reactions to GBCAs and to discuss the risk factors and strategies for the prevention of HSRs to GBCAs.

Materials and Methods: All cases of HSRs to contrast media that occurred at the Seoul National University Hospital from July 1, 2012, to June 30, 2020, were assessed. Information including age, sex, GBCA type, onset, and severity of HSRs was retrospectively analyzed.

Results: Among the 331 070 cases of GBCA exposure in 154 539 patients, 1304 cases of HSRs (0.4%) were reported. Acute HSRs accounted for 1178 cases (0.4%), while 126 cases (0.04%) were delayed HSRs. While both premedication (odds ratio [OR] = 0.7, $P = .041$) and changing the type of GBCA (OR = 0.2, $P < .001$) showed preventative effects in patients with a history of acute HSRs, only premedication (OR = 0.2, $P = .016$) significantly reduced the incidence of HSRs in patients with a history of delayed reactions. The risk of an HSR to GBCA was higher in those with a history of an HSR to iodinated contrast media (OR = 4.6, $P < .001$).

Conclusion: The rate of hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) was 0.4%. The absence of premedication, repeated exposures to the culprit GBCA, and a history of HSRs to iodinated contrast media and GBCAs were risk factors for HSRs to GBCAs.

Online supplemental material is available for this article.

Gadolinium-based contrast agents (GBCAs) are chelates of gadolinium, a metal with paramagnetic properties capable of inducing a magnetic field to increase the signal during MRI (1). GBCAs have been used for MRI since the 1980s to improve diagnostic yield and to provide a more accurate depiction of disease (2). Although GBCAs are relatively safe, recent studies have reported several adverse reactions related to their use, including nephrogenic systemic fibrosis and allergic-like hypersensitivity reactions (HSRs) (3). In a study investigating the frequency of acute HSRs to intravenously administered GBCA, 48 reactions occurred in a total of 65 009 cases, yielding a reaction rate of 0.07% (3). Another study conducted by Behzadi et al (4) described an overall rate of allergic-like adverse reactions of 9.2 per 10 000 reactions, 6% (37 of 662) of which were severe cases. As the use of GBCAs continues to increase in the clinical setting, it is important to be aware of the adverse reactions associated with their use and to be able to identify potential risk factors for such reactions.

Adverse reactions to contrast media (CM) can be categorized as acute or delayed depending on the timing of the reaction: Acute reactions are defined as those that occur within 1 hour, and delayed reactions are those that occur beyond the 1st hour and mostly within 1 week after CM exposure (5). While acute reactions are either allergic-like HSRs or chemotoxic responses, delayed reactions are thought to be T cell mediated, although the exact pathophysiology remains obscure (6). Becasue of the rarity of delayed HSRs to GBCAs, current literature mostly focuses on acute HSRs to GBCAs, and studies on delayed HSRs are scarce (1,3,7). A comprehensive analysis of the incidence and risk factors of delayed HSRs is needed to better understand the mechanism behind delayed HSRs to GBCAs.

With the growing incidence of HSRs to GBCAs, identifying possible risk factors and high-risk populations for HSRs is necessary to ensure safer GBCA use. In general, multiple exposures to the same CM in patients with a

Abbreviations

CM = contrast media, CoSM²oS = Contrast Safety Monitoring and Management System, GBCA = gadolinium-based contrast agent, HSR = hypersensitivity reaction, ICM = iodinated contrast media, OR = odds ratio

Summary

In addition to the absence of premedication and repeated use of the culprit gadolinium-based contrast agents (GBCAs), a history of hypersensitivity reactions to iodinated contrast media and GBCAs may increase the risk of hypersensitivity reactions to GBCAs.

Key Results

- The recurrence rate for hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) was highest (31% [37 of 118]) in patients who neither received premedication nor switched to a different GBCA .
- Patients who received premedication and switched to a different GBCA showed the lowest rate of recurrence at 5% (21 of 441); in the remainder of the patients who either received premedication or switched to a different GBCA, recurrence rates were 19% (149 of 786) and 6% (six of 100), respectively.
- The risk of HSRs to GBCAs was higher in those with a history of HSRs to iodinated contrast media (odds ratio = 4.6, $P < .001$).

history of HSRs increases the likelihood of a recurrent reaction (8). Nelson et al reported that the rate of adverse reactions to GBCAs was 1.5 and 1.9 times higher in patients with a positive history of asthma and allergy, respectively (9). This study also reported that patients with a history of hypersensitivity to iodinated contrast media (ICM) were at higher risk of developing hypersensitivity to gadopentetate dimeglumine. The rate of HSRs to GBCAs may also depend on the type of GBCA used; a meta-analysis conducted by Behzadi et al including 716918 GBCA administrations showed a higher rate of reactions associated with ionic or cyclic GBCAs (4).

Despite being aware that patients with a history of allergy are at risk for developing adverse reactions to GBCAs, no standardized practices for the prevention of HSRs to GBCA exist. A previous study of 185 patients with mild HSRs to GBCAs reported that substituting the culprit CM for another lowered the recurrence rate of HSRs from 25.8% to 6.9% on repeated exposure (10). In the same study, however, the use of single-dose intravenous methylprednisolone premedication demonstrated no significant prophylactic effect on recurrence. As such, identifying effective ways to prevent GBCA HSRs is a topic that warrants further investigation. This 8-year retrospective study was designed to determine the incidence of acute and delayed HSRs to GBCAs, identify risk factors, and analyze the effectiveness of different strategies for the prevention of GBCA-related HSRs.

Materials and Methods

Study Design, Setting, and Participants

The study was approved by the institutional review board of the Seoul National University Hospital (approval no. 1911–080–1078). All cases that used GBCAs for MRI and ICM for CT scans at Seoul National University Hospital between July 1, 2012, and June 30, 2020, were reviewed using the electronic medical record–based Contrast Safety Monitoring and Management (CoSM²oS) database.

The reaction type was classified as an acute HSR if it occurred within 1 hour after CM administration and as a delayed HSR if the reaction occurred beyond 1 hour (11). All patients were kept under nurse surveillance for HSRs for 1 hour following CM injection. Symptoms and signs indicating an acute HSR to CM were monitored and recorded in the CoSM²oS database. To determine the incidence rate for delayed HSRs, we educated patients on the symptoms and signs associated with delayed HSRs and instructed them to contact the hospital via telephone if they experienced such symptoms upon discharge. Information about the reaction, including symptom onset and severity, was collected and recorded (12). Data including age, sex, past medical history, history of previous exposures to CM, history of HSRs to CM, types of CM used, premedication, onset and severity of reactions, and treatment of HSRs were collected retrospectively from the CosM²oS database.

Symptoms and Severity of HSRs

We classified HSRs based on the guidelines outlined in the American College of Radiology Manual on Contrast Media (Table E1 [online]). The manifestations of allergic-like HSRs to GBCAs are similar to those of allergic-like HSRs to ICM, and these reactions are further categorized according to severity as mild, moderate, and severe (8). Mild allergic-like HSRs to GBCAs were defined as limited urticaria or pruritus, cutaneous edema, throat discomfort, nasal congestion, sneezing, and rhinorrhea. Moderate reactions included diffuse urticaria or pruritus, diffuse erythema, facial edema without dyspnea, hoarseness without dyspnea, mild wheezing, and bronchospasms with mild or no hypoxia. Severe reactions were life-threatening symptoms, and these included diffuse edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor or hypoxia, wheezing or bronchospasms with hypoxia, symptomatic arrhythmias, and anaphylactic shock (Table E2 [online]) (8). Patients who experienced physiologic reactions including nausea, flushing, headache, and vasovagal reactions were excluded from the study.

Premedication Regimens

When an examination using CM is ordered for a patient with a history of HSRs to CM, CoSM²oS automatically recommends a premedication regimen in accordance with the severity of the previous reaction. The recommended premedication regimens were 4 mg of intravenous chlorpheniramine 30 minutes before CM administration for mild reactions and 40 mg of intravenous methylprednisolone with 4 mg of intravenous chlorpheniramine 1 hour before CM administration for moderate reactions. Patients with a history of severe reactions received a 40-mg dose of intravenous methylprednisolone 4 hours before CM administration and received an additional 40-mg dose of intravenous methylprednisolone with 4 mg of intravenous chlorpheniramine 1 hour before CM administration. The same premedication regimen was used for both GBCAs and ICM (13,14).

Types of GBCA Used

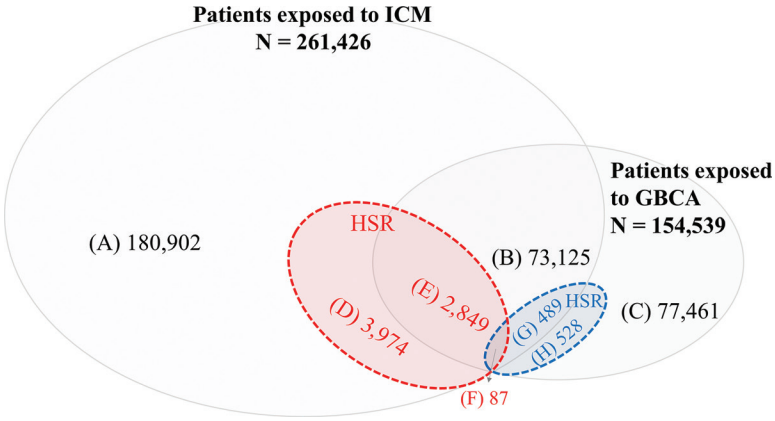
Seven different types of GBCA were used, including gadobutrol (Gadovist, Bayer Schering), gadoterate meglumine (Dotarem, Guerbet), gadoxetate disodium (Primovist, Bayer Schering), gadoteridol (Prohance, Bracco Imaging), gadopentetate dimeglumine (Magnevist, Bayer Schering), gadobenate dimeglumine (Multihance, Bracco Imaging), and gadodiamide (Omniscan, GE Healthcare). The GBCAs were administered intravenously at the standard recommended dosage. No patient received additional doses beyond the recommended dosage. As there are not set protocols that define when a certain type of GBCA should be used, GBCA selection was left to the discretion of the department of radiology.

Retrospective Assessment of Recurrent Reactions

Patients with repeated exposure to GBCAs or ICM were assessed for HSRs each time, and each event was counted as one case. Information regarding the use of premedication and whether certain GBCAs were switched on subsequent exposure was gathered. In addition, the incidence rate of ICM HSRs was obtained by reviewing the data from the CoSM²oS database. Retrospective analyses were performed to compare the incidence of HSRs to GBCA in patients with a history of HSRs to ICM to those without such history.

Statistical Analyses

The incidence of HSRs to CM during the study period was calculated by dividing the number of HSR cases by the total number of cases that received either GBCA or ICM. The prevalence was calculated by dividing the number of patients who experienced HSRs to CM by the total number of patients who underwent contrast-enhanced imaging tests during the study period. The χ^2 test was used to compare the incidence rates between groups. Multivariate logistic regression analyses were performed for re-exposure cases where HSR recurrence was set as the dependent variable and the following were included as covariates: age, sex, previous exposure to GBCAs, and previous history of HSRs to GBCAs. The odds ratios (ORs) for re-exposure cases were obtained through adjusted logistic regression analyses. Generalized estimating equations were used to adjust for clustered cases of



Venn diagram shows hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) and iodinated contrast media (ICM). **(A)** Number of patients exposed to ICM without HSRs. **(B)** Number of patients exposed to both ICM and GBCA without HSRs. **(C)** Number of patients exposed to GBCA without HSRs. **(D)** Number of patients exposed not to GBCA but to ICM with HSRs. **(E)** Number of patients exposed to both ICM and GBCA with HSRs to ICM only. **(F)** Number of patients exposed to both ICM and GBCA with HSRs to both ICM and GBCA. **(G)** Number of patients exposed to both ICM and GBCA with HSRs to GBCA only. **(H)** Number of patients exposed not to ICM but to GBCA with HSRs.

Table 1: Incidence of Hypersensitivity Reactions to Gadolinium-based Contrast Agents

	Overall		Male Patients		Female Patients	
Characteristic	GBCA Use	HSR	GBCA Use	HSR	GBCA Use	HSR
No. of cases	331 070	1 304 (0.4)	153 841	472 (0.3)	177 229	832 (0.5)
Age						
Mean (y)*	54 ± 21	51 ± 16	55 ± 22	52 ± 19	54 ± 19	50 ± 15
Median (y)†	59 (43–70)	54 (41–63)	61 (41–72)	57 (40–66)	58 (44–67)	52 (41–61)
<10 years	10 779	16 (0.2)	5930	6 (0.1)	4849	10 (0.2)
10–19 years	20 518	46 (0.2)	11 083	26 (0.2)	9335	20 (0.2)
20–29 years	19 749	90 (0.5)	10 632	37 (0.4)	9017	53 (0.6)
30–39 years	21 228	149 (0.7)	8836	47 (0.5)	12 292	102 (0.8)
40–49 years	36 956	245 (0.7)	13 065	60 (0.5)	23 771	185 (0.8)
50–59 years	59 993	322 (0.5)	21 775	97 (0.5)	37 914	225 (0.6)
60–69 years	78 654	305 (0.4)	36 601	123 (0.3)	41 753	182 (0.4)
70–79 years	58 192	107 (0.2)	31 375	61 (0.2)	26 607	46 (0.2)
80–89 years	22 921	23 (0.1)	12 819	14 (0.1)	10 002	9 (0.09)
⩾90 years	2080	1 (0.05)	1105	1 (0.09)	975	0 (0.00)

Note.—Unless otherwise indicated, data in parentheses are percentages. GBCA = gadolinium-based contrast agent, HSR = hypersensitivity reaction.

* Data are mean ± standard deviation.

† Data are the median, and data in parentheses are the interquartile range.

multiple re-exposures in one patient. $P < .05$ indicated a significant difference for all tests. All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

Results

Baseline Characteristics

Among the 331 070 MRI examinations with GBCAs performed in 154 539 patients during the study period, 1304 HSRs (0.4%) were reported in 1104 patients (0.7%) (Figure). During the same study period, a total of 1 202 207 CT scans using ICM were performed in 261 426 patients, and 7541 of ICM-related HSRs (0.6%) were reported in 6910 patients (3%). The incidence of HSRs to GBCAs was lower than that to ICM (OR = 0.6; 95% CI: 0.6, 0.7; $P < .001$).

The median age of patients with HSRs to GBCAs was 54 years (interquartile range, 41–63 years). The incidence of HSRs was higher in female patients at 0.5% compared with male patients at 0.3% (OR = 1.5; 95% CI: 1.4, 1.7; $P < .001$). In general, the incidence of HSRs to GBCAs was higher in patients aged 30–39 years and was relatively lower in patients younger than 29 years and those older than 70 years (Table 1).

Acute HSRs to GBCA

Acute HSRs accounted for 1178 cases among the total of 331 070 MRI examinations with GBCAs performed during the study period, yielding an incidence rate of 0.4%. Similar to the overall results, the incidence of acute HSRs was slightly higher in female patients at 0.4% (742 of 177 229) than in male patients at 0.3% (436 of 153 841) (OR = 1.5; 95% CI: 1.3, 1.7; $P < .001$). Acute HSRs to GBCA were classified according to symptom severity: 92% (1080 of 1178) were mild, 7% (86 of 1178) were moderate, and 1% (12 of 1178) were severe reactions (Table 2). A total of 2154 symptoms were reported among the 1178 acute HSRs. Itching and limited urticaria were the most frequently reported symptoms at 72% (847 of 1178) and 72% (843 of 1178), respectively. (Table E3 [online]). Severe reactions included 12 cases of anaphylaxis, with an incidence rate of 0.004% (12 of 331 070).

Delayed HSRs to GBCA

Delayed HSRs accounted for 126 cases among the total of 331 070 MRI examinations performed during the study period, yielding an incidence rate of 0.04% (Table 2). Female patients had higher odds of developing delayed HSRs compared to male patients at 0.05% (90 of 177 229) and 0.02% (36 of 155 841), respectively, and these odds were more pronounced in comparison with acute HSRs (OR = 2; 95% CI: 1.5, 3.2; $P < .001$). Delayed HSRs were classified according to symptom severity: 75% (95 of 126) were mild and 25% (31 of 126) were moderate reactions. A total of 217 symptoms were reported, and the most frequently observed symptoms were itching at 69% (87 of 126), limited urticaria at 49% (62 of 126), and skin rash at 24% (30 of 126) (Table E3 [online]).

Incidence of HSRs among Different Types of GBCA

The incidence rate of acute HSRs was compared among the different types of

Table 2: Characteristics of Hypersensitivity Reactions by Onset Type

Characteristic	Total HSRs	Acute HSRs	Delayed HSRs
Total cases (n = 331 070)	1304 (0.4)	1178 (0.4)	126 (0.04)
Male sex (n = 153 841)	472 (0.3)	436 (0.3)	36 (0.02)
Female sex (n = 177 229)	832 (0.5)	742 (0.4)	90 (0.05)
Age			
Mean (y)*	51 ± 16	51 ± 16	49 ± 20
Median (y)†	54 (41–63)	54 (41–62)	53 (39–64)
Severity			
Mild	1175 (0.4)	1080 (0.3)	95 (0.03)
Moderate	117 (0.04)	86 (0.03)	31 (0.01)
Severe	12 (0.004)	12 (0.004)	0 (0.0)

Note.—Unless otherwise indicated, data are number of cases or patients, and data in parentheses are percentages. HSR = hypersensitivity reaction.

* Data are mean ± standard deviation.

† Data are the median, and data in parentheses are the interquartile range.

Table 3: Incidence of Hypersensitivity Reactions for Each Gadolinium-based Contrast Agent

Contrast Agent	Total No. of Cases	No. of HSR Cases	No. of Mild HSR Cases	No. of Moderate HSR Cases	No. of Severe HSR Cases	No. of Acute HSR Cases	No. of Delayed HSR Cases
Gadobutrol	156 657	614 (0.4)	551 (0.4)	55 (0.04)	8 (0.01)	563 (0.4)	51 (0.03)
Gadoterate meglumine	117 006	374 (0.3)	338 (0.3)	36 (0.03)	0 (0.0)	316 (0.3)	58 (0.05)
Gadoxetate disodium	33 918	162 (0.5)	146 (0.4)	15 (0.04)	1 (0.003)	154 (0.5)	8 (0.02)
Gadoteridol	19 862	151 (0.8)	138 (0.7)	10 (0.05)	3 (0.02)	143 (0.7)	8 (0.04)
Gadobenate dimeglumine	3435	1 (0.03)	1 (0.03)	0 (0.0)	0 (0.0)	1 (0.03)	0 (0.0)
Gadopentetate dimeglumine	192	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.52)
Total	331 070	1304 (0.4)	1175 (0.4)	117 (0.04)	12 (0.004)	1178 (0.4)	126 (0.04)

Note.—Data in parentheses are percentages. HSR = hypersensitivity reaction.

GBCA (Table 3). Of the six types of GBCA, gadobutrol and gadoterate meglumine were the most frequently used types at 83% (273 663 of 331 070). With the exception of gadopentetate dimeglumine and gadobenate dimeglumine used in fewer than 10 000 cases, the HSR incidence was highest for gadoteridol at 0.8% (151 of 19 862). The GBCAs associated with anaphylaxis were gadoteridol at 0.02% (three of 19 862), gadobutrol at 0.01% (eight of 156 657), and gadoxetate disodium at 0.003% (one of 33 918); the incidence of GBCA-induced anaphylaxis did not show a significant difference among these types of GBCA (P = .16). Gadoterate meglumine accounted for the largest proportion of delayed HSRs at 16% (58 of 374), and no significant differences between delayed HSRs according to the different types of GBCA were observed.

Recurrence Rate: The Effects of Changing GBCA and Using Premedication

The total number of GBCA re-exposure cases was 1445 in 487 patients with a history of HSRs to GBCAs, and the average recurrence rate of HSRs was 15% (213 of 1445). Among the patients with a history of acute HSRs to GBCAs, 16% (206 of 1269) experienced recurrent HSRs, while only 8% (17 of 205) of patients with a history of delayed HSRs experienced recurrent reactions on subsequent exposure. The risk of recurrence was significantly higher in patients with a history of acute HSRs (OR = 2.0; 95% CI: 1.3, 3.6; P = .003).

Both the use of premedication and switching to a different GBCA were effective in preventing HSR recurrence. While the recurrence rate of HSRs was 20% (43 of 218) without premedication, this incidence was reduced to 14% (170 of 1227) with premedication (OR = 0.7; 95% CI: 0.5, 0.95; P = .02 by univariate analysis). Similarly, the recurrence rate of HSRs was significantly lower in patients who switched to a different type of GBCA on subsequent exposure. While HSRs were reported in 21% (186 of 904) of patients when the same GBCA was used, this incidence was reduced to 5% (27 of 541) when the culprit GBCA was changed to a different agent (OR = 0.2; 95% CI: 0.1, 0.3; $P < .001$ by univariate analysis).

We further divided the patient group into four different categories: patients who neither changed the GBCA nor received premedication, patients who used the same GBCA with premedication, patients who switched to a different GBCA without premedication, and patients who switched to a different GBCA with premedication to analyze the individual and combined effects of the two interventions. While the recurrence rate was highest at 31% (37 of 118) in patients who received neither intervention, patients who both switched to a different GBCA and received premedication showed the lowest rate of recurrence at 5% (21 of 441). In the remainder of the patients who either received premedication or switched to a different GBCA, the recurrence rates were 19% (149 of 786) and 6% (six of 100), respectively (Table 4).

Multivariate logistic regression analyses were performed to identify which measures were effective in the prevention of recurrent HSRs to GBCAs. The use of either premedication or changing the GBCA reduced the recurrence rate. Subgroup analyses according to the type of the initial HSR (ie, acute vs delayed) demonstrated that while both premedication (OR = 0.7; 95% CI: 0.3, 0.98; P = .04) and changing the GBCA (OR = 0.2; 95% CI: 0.1, 0.4; $P < .001$) had preventative

Table 4: Recurrence of Hypersensitivity Reactions by Prevention Method and Previous Onset Type

Recurrence and Effect of Intervention	Total Re-exposure	Re-exposure after Acute HSR	Re-exposure after Delayed HSR
Recurrence rate	213 of 1445 (15)	206 of 1269 (16)	17 of 205 (8)
Not premedicated	43 of 218 (20)	40 of 195 (21)	8 of 31 (26)
Premedicated	170 of 1227 (14)	166 of 1074 (16)	9 of 174 (5)
GBCA unchanged	186 of 904 (21)	181 of 770 (24)	15 of 162 (9)
GBCA changed	27 of 541 (5)	25 of 499 (5)	2 of 43 (5)
Not premedicated, GBCA unchanged	37 of 118 (31)	35 of 108 (32)	7 of 18 (39)
Premedicated, GBCA unchanged	149 of 786 (19)	146 of 662 (22)	8 of 144 (6)
Not premedicated, GBCA changed	6 of 100 (6)	5 of 87 (6)	1 of 13 (8)
Premedicated, GBCA changed	21 of 441 (5)	20 of 412 (5)	1 of 30 (3)
Effect of intervention*			
Premedication†	0.6 (0.4, 0.9) [.023]	0.7 (0.3, 0.98) [.041]	0.2 (0.04, 0.6) [.016]
GBCA change‡	0.3 (0.2, 0.5) [<.001]	0.2 (0.1, 0.4) [<.001]	0.4 (0.07, 1.8) [.103]
Premedication and GBCA change§	0.1 (0.06, 0.2) [< .001]	0.1 (0.06, 0.2) [<.001]	0.05 (0.01, 0.5) [.010]

Note.—Unless otherwise indicated, data are numbers of cases, and data in parentheses are percentages. A total of 29 cases have both acute and delayed hypersensitivity reaction (HSR) history. GBCA = gadolinium-based contrast agent.

* Multiple logistic regression analysis performed to adjust for age, sex, and severity of previous HSRs, and the generalized estimating equation was used to adjust for clustered cases of multiple re-exposures in one patient. Data are odds ratios, data in parentheses are 95% confidence intervals, and data in brackets are P values.

† Cases with premedication versus cases without premedication.

‡ GBCA changed cases versus GBCA unchanged cases.

§ Cases with premedication and change in GBCA versus cases without premedication and unchanged GBCA.

Table 5: Prevalence of HSR to ICM and GBCA according to a History of HSRs to One or the Other

Comparison	Population	HSR (%)	Odds Ratio	*P* Value
HSR to GBCA	1104 of 154 539	0.7	0.3 (0.25, 0.28)	<.001*
HSR to GBCA in ICM users	576 of 76 550	0.8	0.2 (0.17, 0.2)	<.001†
Without HSR to ICM	489 of 73 614	0.7	1	...
With HSR to ICM	87 of 2936	3	4.6 (3.6, 5.8)	<.001
HSR to ICM	6910 of 261 426	3	3.8 (3.5, 4.0)	<.001‡
HSR to ICM in GBCA users	2936 of 76 550	4	5.3 (4.8, 5.8)	<.001§
Without HSR to GBCA	2849 of 75 974	4	1	...
With HSR to GBCA	87 of 576	15	4.6 (3.6, 5.8)	<.001

Note.—Data in parentheses are 95% confidence intervals. Odds ratio was obtained with the χ^2 test. GBCA = gadolinium-based contrast agent, HSR = hypersensitivity reaction, ICM = iodinated contrast media.

* Compared with the risk of HSR to ICM.

† Compared with the risk of HSR to ICM in GBCA users.

‡ Compared with the risk of HSR to GBCA.

§ Compared with the risk of HSR to GBCA in ICM users.

effects in patients with a history of acute HSRs, only premedication reduced the incidence of HSRs in patients with a history of delayed reactions (OR = 0.2; 95% CI: 0.04, 0.6; $P = .01$) (Table 4).

GBCA HSRs in Patients with a History of ICM Hypersensitivity

The prevalence of HSRs to GBCAs was significantly higher in patients with a history of ICM hypersensitivity at 3% (87 of 2936) compared with patients without such history at 0.7% (489 of 73 614). Similarly, the prevalence of HSRs to ICM in patients with a history of GBCA hypersensitivity was higher at 15% (87 of 576) compared with patients without such history at 4% (2849 of 75 974). These results show that a history of hypersensitivity to either GBCA or ICM increases the risk of developing HSRs to the other (OR = 4.6, 95% CI: 3.6, 5.8; $P < .001$) (Table 5).

Discussion

Compared with iodinated contrast media, gadolinium-based contrast agents (GBCAs) are considered to be relatively safe considering the rarity of adverse reactions associated with their use (4). However, with the widespread application of GBCAs in the clinical setting, reports of allergic-like hypersensitivity reactions (HSRs) to GBCAs are on the rise. Allergic-like HSRs can be classified according to onset time (acute or delayed) and severity (mild, moderate, or severe), as stated in the American College of Radiology Manual on Contrast Media (8). Through an 8-year retrospective analysis of 154 539 patients and 331 070 cases of MRI examinations in a single tertiary medical center, we determined the incidence of both acute and delayed HSRs to GBCAs and identified possible risk factors and preventative measures for their safe use.

Findings from previous studies indicate that the overall adverse reaction rate to GBCAs ranges from 0.07% to 2% (8) (Table 6) (1–4,15,16). Compared with the incidence rate of 0.6% for HSRs to ICM, the overall incidence rate of HSRs to GBCAs observed in our study was significantly lower, at 0.4%, and these findings are in agreement with the results of past studies (8). Despite the differences in chemical structure and composition of the two CM, a previous study conducted by Nelson et al (9) showed that patients with a history of ICM hypersensitivity had a higher risk of developing HSRs to GBCAs. In accordance with the existing literature, our results also demonstrated that a history of hypersensitivity to either GBCAs or ICM increases the risk of developing HSRs to the other. Although the exact pathophysiology behind this phenomenon is unknown, Lee et al suggested that a genetic predisposition to developing Th2 reactions may increase the risk of HSRs to a different type of CM in patients with a history of HSRs to CM (12). Our findings suggest that ICM should be used carefully in patients with a history of HSRs to GBCA, and vice versa.

HSRs to GBCAs can be classified according to symptom severity as mild, moderate, or severe reactions. Most reactions are mild and physiologic, and severe life-threatening reactions are rare (8). The results of our study also showed that most HSRs to GBCAs were mild, as severe HSRs accounted for only 0.8% of all cases. These results were also in agreement with the findings of a meta-analysis of nine studies on acute HSRs caused by GBCAs, where 81% of the cases were classified as mild, 13% as moderate, and 6% as severe (3). A different study investigating the incidence of HSRs to GBCAs also found that 78.7% were mild cases, while severe cases accounted for only 4.3% (17). The incidence rate of anaphylactic reactions was 0.004%, and this rate is similar to that found in previous studies (18). These findings show that although extremely uncommon, severe reactions including anaphylaxis to GBCA do occur, and we must be prepared to adequately manage these events (15,19).

Compared with acute HSRs, delayed HSRs to GBCA are relatively rare occurrences, and the existing literature regarding delayed HSRs is scarce. One of the strengths of this study is that patients with delayed HSRs were included in the analyses. Most delayed HSRs manifested as cutaneous reactions, and no severe reactions were reported among the 331 070 cases. These findings were similar to the results of a previous study where delayed HSRs to gadobutrol most commonly presented as mild symptoms, such as urticaria (20). The clinical similarities shared between delayed reactions to ICM and GBCAs suggest the possibility that a common underlying mechanism exists (21): Just as perivascular CD4+ and CD8+ T cell infiltrations are observed in delayed HSRs to ICM, delayed HSRs to GBCAs are also considered to be T cell–mediated reactions (6).

We investigated re-exposure rates and recurrent reactions over a relatively long study period of 8 years. A total of 213 cases of HSRs to GBCAs occurred among the 1445 cases of re-exposure,

Table 6: Comparison of Hypersensitivity Reactions according to Severity and Symptoms

Study	No. of Cases	Types of GBCA	Reaction Rate (%)*	Frequently Observed Symptoms by Severity
Granata et al (1)	10 608	Gadobenate dimeglumine, gadobutrol, gadopentate dimeglumine, gadoterate meglumine, gadoxetic acid disodium	Overall: 0.3 (32/10 608) Mild: 75 (24/32) Moderate: 12.5 (4/32) Severe: 12.5 (4/32)	Mild: skin rash, urticaria Moderate: bronchospasm, mild laryngeal edema, symptomatic tachycardia Severe: respiratory distress, progressive angioedema, arrhythmia
Li et al (2)	9528	Gadodiamide, gadopentate dimeglumine, gadodterate meglumine	Overall: 0.48 (45/9528) Mild: 96 (43/45) Moderate: 0.01 (1/45) Severe: 0.01 (1/45)	Mild: nausea and/or vomiting, rash, urticaria Moderate: dyspnea, bronchospasm Severe: anaphylactic shock
Dillman et al (3)	78 353	Gadobenate dimeglumine, gadodiamide, gadopentetate dimeglumine	Overall: 0.07 (54/78353) Mild: 74 (40/54) Moderate: 19 (10/54) Severe: 7 (4/54)	Mild: urticaria, itchy throat, rash, mild dyspnea, nasal congestion, mild periorbital and/or facial edema Moderate: dyspnea, facial angioedema, bronchospasm, bronchospasm, hypotension Severe: respiratory distress, hypoxia, laryngeal edema
Behzadi et al (4)	716 978	Gadobenate, gadobutrol, gadodilamide, gadofosveset, gadopentate dimeglumine, gadoterate gadoteridol, gadoxetate	Overall: 0.14 (662/715 978) Mild: 81 (539/662) Moderate: 13 (86/662) Severe: 6 (37/662)	Mild: urticaria, pruritus, cutaneous edema, itchy throat, nasal congestion, sneezing, conjunctivitis, rhinorrhea Moderate: diffuse urticaria, erythema, facial edema, hoarseness, wheezing Severe: hypotension, laryngeal edema with hypoxia, bronchospasm, anaphylactic shock
Jung et al (15)	141 623	Gadobenate, gadobutrol, gadodilamide, gadopentate dimeglumine, gadoterate, gadoxetate	Overall: 0.079 (112/141 623) Mild: 83 (93/112) Moderate: 7.1 (8/112) Severe: 9.8 (11/112)	Mild: urticaria, skin rash, coughing, facial and/or orbital edema Moderate: bronchospasm, laryngeal edema, generalized erythema Severe: severe laryngeal edema, hypotension, arrhythmia, cardiopulmonary arrest
Sodagari et al (16)	147 624	Gadobenate dimeglumine, gadobutrol, gadofosveset trisodium, gadopentate dimeglumine, gadoxetate disodium	Overall: 0.17 (254/147 624) Mild: 91.7 (233/254) Moderate: 7.8 (20/254) Severe: 0.4 (1/254)	Mild: skin rash, urticaria, coughing, facial edema Moderate: bronchospasm, laryngeal edema, generalized erythema Severe: severe laryngeal edema, convulsions, hypotension, arrhythmia, cardiopulmonary arrest

Note.—GBCA = gadolinium-based contrast agent.

* Data in parentheses were used to calculate rates

yielding an average recurrence rate of 15%; this number is lower than that reported in previous studies. In a study that retrospectively analyzed the acute HSRs caused by GBCAs in 84 367 patients, the recurrence rate was reported to be as high as 30% (eight of 27) (15). In another study investigating the preventative effect of changing GBCAs in 185 patients with a history of acute HSRs to GBCAs, the recurrence rate was 19.6% (78 of 397) (10). Perhaps the longer follow-up period and larger number of re-exposure cases may explain the relatively lower recurrence rate observed in our study.

The frequency of adverse reactions to GBCAs has been reported to be eight times higher in patients with a history of GBCA hypersensitivity (8). Although results of a study conducted by Ryoo et al indicate that changing the CM to one of a different molecular structure class may reduce the chance of HSR recurrence (10), no official recommendations can be made, as there are no published large-scale randomized clinical trials to confirm the effectiveness of this approach. To identify which interventions were efficacious in reducing the likelihood of repeat reactions, we investigated both the individual and the

combined effects of premedication and switching to a different type of GBCA. While the recurrence rate was highest at 31% (37 of 118) in patients who received neither intervention, patients who had premedication and switched to a different type of GBCA showed the lowest rate of recurrence at 5% (21 of 441). In patients with a history of acute HSRs, both interventions were effective; however, in patients whose initial reaction was a delayed HSR, only premedication was effective in preventing repeat reactions. These findings suggest that acute and delayed HSRs have different underlying mechanisms: The process of antigen recognition is different for immunoglobulin E–mediated reactions and T cell receptor–mediated responses (22). Further studies are needed to elucidate these processes.

This study had several limitations. First, certain results of our study conflict with results from multi-institutional samples and meta-analyses. For example, our study shows a lower rate of HSRs to gadobenate compared with gadoteridol, which conflicts with results from a previous meta-analysis conducted by Behzadi et al (4). This may be due to smaller agent-specific sample sizes compared with past analyses. A multicenter study with a larger sample size involving a spectrum of GBCAs is needed to validate the findings of our study. Second, the incidence of delayed HSRs is likely to have been underestimated, as these events were recorded on a self-reporting basis. Third, as our study included only a limited number of cases with delayed HSRs to GBCAs, we were unable to identify an effective preventive strategy for delayed reactions to GBCAs.

In conclusion, acute and delayed hypersensitivity reactions (HSRs) were observed in 0.4% and 0.04% of patients exposed to gadolinium-based contrast agents (GBCAs), respectively. In all patients undergoing MRI with GBCA exposure, a detailed history of previous HSRs should be conducted, and when necessary, appropriate prevention measures such as using premedication and switching to a different type of GBCA should be implemented.

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