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Changing Gadolinium-Based Contrast Agents to Prevent Recurrent Acute Adverse Drug Reactions: 6-Year Cohort Study Using Propensity Score Matching

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Objective: To determine the preventive effect of changing gadolinium-based contrast agents (GBCAs) to reduce the recurrence of GBCA-associated acute adverse drug reactions (ADRs).

Materials and Methods: This retrospective, observational, single-center study—conducted between January 2016 and December 2021—included 238743 consecutive GBCA-enhanced MRI examinations. We focused on a subgroup of patients who experienced acute GBCA-associated ADRs during any of these examinations and subsequently underwent follow-up GBCA-enhanced MRI examinations up until July 2023. The follow-up examinations involved either the same (non-change group) or different (change group) GBCAs compared to the ones that initially caused the acute ADR. Baseline participant characteristics, generic profile of the GBCAs, administration of premedication, history of prior ADR to iodinated contrast media, and symptoms of GBCA-associated acute ADRs were retrospectively analyzed. Multivariable logistic regression with generalized estimating equations and propensity score matching were used.

Results: A total of 1042 instances of acute ADRs (0.44%; 95% confidence interval [CI]: 0.41%–0.46%) were reported. Three-hundred and seventy-three patients underwent GBCA-enhanced MRI examinations after experiencing GBCA-associated acute ADRs within the study period; 31.9% (119/373) reexperienced acute ADRs at any of the follow-up examinations. The ADR recurrence was significantly lower in the GBCA change group than in the non-change group according to multivariable logistic regression (adjusted odds ratio [OR]: 0.35; 95% CI: 0.13–0.90; $P = 0.03$) and analysis with propensity score matching (14.3% [6/42] vs. 36.9% [31/84], respectively; OR: 0.32, 95% CI: 0.11–0.94; $P = 0.04$). A history of an ADR to iodinated contrast media (OR: 1.14, 95% CI: 0.68–1.90; $P = 0.62$) and premedication (adjusted OR: 2.09, 95% CI: 0.93–4.68; $P = 0.07$) were not significantly associated with GBCA-associated acute ADR recurrence. A separate analysis for recurrent allergic-like hypersensitivity reactions demonstrated similar results (adjusted OR: 0.20, 95% CI: 0.06–0.65; $P < 0.01$).

Conclusion: Changing GBCAs may reduce the risk of GBCA-associated acute ADR recurrence.

Keywords: Contrast media; Drug-related side effects and adverse reactions; Propensity score; Matched-pair analysis

INTRODUCTION

Despite the relative safety and wide application of gadolinium-based contrast agents (GBCAs) in magnetic resonance imaging (MRI) examinations for contrast-enhanced imaging, the GBCA adverse drug reaction (ADR)

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Korean Journal of Radiology
KJR

rate ranges from 0.015%–0.9%. The overall rate of patients with immediate allergic-like reactions was reported to be 0.92%, and life-threatening GBCA-associated ADRs—including anaphylaxis—may occur [1]. Therefore, GBCA-associated ADRs require careful monitoring and evaluation. ADRs to contrast media can be categorized in accordance with the time from injection to symptom onset. Acute ADRs occur within 1 hour and comprise either an allergic-like hypersensitivity reaction (HSR), or a physiologic reaction [2,3]. Manifestations of allergic-like HSRs and physiologic reactions frequently overlap and are not usually differentiated in clinical practice. Delayed ADRs occur after 1 hour, mostly within 1 week, and are considered T-cell-mediated reactions [4]. In the clinic, only acute ADRs are typically assessed because delayed ADRs are relatively rare and may prove difficult to evaluate.

Several recent studies indicate that changing the GBCA may reduce the risk of GBCA-associated ADR recurrence. Ryoo et al. [5] showed that changing the previous GBCA significantly reduced the ADR recurrence rate in consecutive MRI examinations in patients with a prior mild ADR from 25.8% (69/267) to 6.9% (9/130). A larger subsequent study conducted at the same institution showed that the ADR recurrence rate decreased from 20.6% (186/904) to 5.0% (27/541) when the previous GBCA was replaced by a different contrast agent [6]. However, additional evidence is required to confirm the preventive effect of changing the previous GBCA on GBCA-associated ADR recurrence. Furthermore, selection bias in previous studies with a retrospective design may have influenced the significance of the results [5,6]. To reduce selection bias, conducting a prospective study is advantageous; however, owing to the need for large cohorts in contrast agent ADR research, conducting a prospective study becomes challenging.

We aimed to determine the preventive effect of changing GBCAs for reducing the recurrence of GBCA-associated acute ADRs.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2021-1063), and the requirement for written informed consent was waived. This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [7].

The study population included patients who underwent contrast-enhanced MRI examinations using GBCAs at the outpatient department of Asan Medical Center between January 2016 and December 2021. Since January 2016, our institution has implemented an electronic medical records (EMRs) database system to track ADRs related to contrast agents. This system records the responsible agent, all associated symptoms, the severity of reactions, and whether premedication was administered. A subgroup of patients was identified based on the following additional eligibility criteria: having experienced GBCA-associated acute ADRs during any MRI examinations performed within the study period (January 2016 to December 2021); and having undergone any follow-up GBCA-enhanced MRI examinations up to July 2023, following their first GBCA-associated acute ADR event recorded during the 2016–2021 study period (referred to as the 'primary' MRI examination hereinafter).

Data Collection

We recorded the baseline characteristics of patients, including age, sex, history of prior ADR to iodinated contrast media (ICM), and the generic profile of the GBCA used in the primary MRI examination wherein GBCA-associated ADRs had occurred. For each participant, the records of the subsequent GBCA-enhanced MRI examination were analyzed. We retrospectively determined the generic profile of the GBCA used, administration of premedication, and symptoms, if any, of GBCA-associated acute ADRs from the EMRs. There were no incomplete or missing data.

Definition of GBCA-Associated Acute ADRs

The definition and severity classification criteria for GBCA-associated acute ADRs were based on the descriptions in the American College of Radiology (ACR) Manual on Contrast Media version 2023 [3]. GBCA-associated acute ADRs were classified as follows: 1) Mild: Self-limited, without evidence of progression, 2) Moderate: Pronounced and commonly requiring medical management, and 3) Severe: Often life-threatening and possibly resulting in permanent morbidity or death if not appropriately managed. Specific classifications of the severity for each sign and symptom are described in the ACR manual [3]. All manifested acute ADRs were categorized into allergic-like HSRs and physiologic reactions according to the ACR Manual on Contrast Media version 2023 [3].

Types of GBCAs Used

As our large, single institution performs >50000 GBCA-

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enhanced MRI examinations annually, four different types of GBCAs were used intravenously for MRI examinations in this study: gadobutrol (0.1 mmol/kg; Gadovist, Bayer Schering, Leverkusen, Germany), gadoterate meglumine (0.1 mmol/kg; Dotarem, Guerbet, Chicago, IL, USA; Uniray, Dongkook Pharmaceutical, Seoul, South Korea), gadoxetate disodium (0.025 mmol/kg; Primovist, Bayer Schering), and gadoteridol (0.1 mmol/kg; Prohance, Bracco Imaging, Milan, Italy). The GBCA change group was defined as patients who received a GBCA with a different generic name from the agent they had previously been administered; the GBCA non-change group was defined as patients who received a GBCA with the same generic name as before.

Premedication Regimens

The institutional EMR system automatically recommends the administration of premedication when an examination using GBCA is prescribed for patients with a history of moderate-to-severe GBCA-associated acute ADR; the recommended premedication regimens include: two doses of oral prednisolone (5 mg), 12 hours before and 1 hour before GBCA administration; and intravenous chlorpheniramine (4 mg) 30 minutes before GBCA administration. For examinations prescribed on the same day, intravenous methylprednisolone (40 mg) and intravenous chlorpheniramine (4 mg) were administrated 1 hour and 30 minutes before GBCA administration, respectively.

Variable Selection for Propensity Score Analyses

To adjust for intergroup differences and to compare outcomes between the groups, we retrospectively collected information from the EMRs on 16 baseline variables of the participants: age, sex, diabetes mellitus, cardiac disease, hyperthyroidism, renal insufficiency, a history of malignancy, anxiety, asthma, allergic rhinitis, chronic urticaria and atopy, food allergy, drug allergy, allergy to ICM, premedication, and severity of acute ADRs [2]. Cardiac disease was defined as any of the following: heart failure, arrhythmia, pulmonary hypertension, or severe aortic stenosis. Renal insufficiency was defined as an estimated glomerular filtration rate <45 ml/min/1.73 m^2 within 3 months from the date of the initial MRI scan.

Statistical Analysis

Acute ADR recurrence was defined as the occurrence of acute ADRs at any follow-up examinations using GBCA after the primary MRI (i.e., the first GBCA-associated acute ADR event recorded during the 2016–2021 study period). Each patient had varying primary MRI dates, different follow-up lengths, and varying numbers of follow-up examinations, with the latest follow-up available up to July 2023. The first event of ADR recurrence in each patient was selected for the analysis. The ADR recurrence rate within the follow-up period was calculated by dividing the number of patients who had acute ADR recurrence by the number of patients who had GBCA reexposure. The downgrade rate was calculated by dividing the number of downgraded patients by the number of reexposure patients, where a downgraded patient was defined by either no acute ADR recurrence, or a reduction in severity of the acute ADR [8].

Differences in baseline patient characteristics were compared with the Student's *t*-test and Chi-squared test or Fisher's exact test. Univariable and multivariable logistic regressions with the generalized estimating equation (GEE) were used to estimate the association strength between GBCA change and acute ADR recurrence as odds ratios (ORs) and their 95% confidence intervals (CIs). Multivariable analysis was adjusted for the variables with $P < 0.2$ in the univariable analysis, including age, sex, history of malignancy, allergic rhinitis, chronic urticaria and atopy, food allergy, premedication, severity of the acute ADRs on the primary examination, and the generic name of the GBCA used in the selected follow-up MRI examination.

The propensity score was estimated with the GBCA change as the dependent variable by multiple logistic regression analysis [9]. A full nonparsimonious model that included all the variables was developed. Model discrimination was assessed using C statistics, and model calibration was assessed using Hosmer–Lemeshow statistics. Propensity score matching was performed by Greedy matching at a 1:2 ratio using a caliper of 0.2 standard deviations of the logit of the propensity score. The absolute standardized difference was used to diagnose the balance after matching. Acute ADR recurrence was compared with the use of the GEE for matched data and total data. Inverse probability of treatment weighting was also performed.

The analyses were performed for all recurrent acute ADRs, and separately for recurrent allergic-like HSRs. Statistical analyses were conducted with SAS Analytics Software (SAS Institute; Cary, NC, USA). All tests were two-sided, with the significance level at 0.05.

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Korean Journal of Radiology
KJR

RESULTS

Overall Incidence of GBCA-Associated Acute ADRs

During the study period, a total of 238743 GBCA-enhanced MRI examinations were performed; 1042 instances of acute ADRs (0.44%; 95% CI: 0.41%–0.46%) were reported among 915 patients. The ADRs were mostly mild (928 instances, 89%), with few numbers of moderate (83 instances) and severe (31 instances) severities. Regarding contrast agents, the incidence was highest in examinations wherein gadoteridol was used (0.984% [12/1220] for total; 0.164% [2/1220] for moderate-to-severe ADRs), followed by gadoxetate disodium (0.643% [184/28620] for total; 0.056% [16/28620] for moderate-to-severe ADRs), gadobutrol (0.640% [86/13444] for total; 0.052% [7/13444] for moderate-to-severe ADRs), and gadoterate meglumine (0.389% [760/195459] for total; 0.046% [89/195459] for moderate-to-severe ADRs).

Baseline Characteristics

Among the 915 patients who experienced acute ADRs at the primary MRI examination, 542 patients did not undergo any further GBCA-enhanced MRI examinations. Consequently, a total of 373 patients who underwent 1412 follow-up GBCA-enhanced MRI examinations were included in the analyses, with a median of two follow-up GBCA-enhanced MRI examinations (interquartile range [IQR]: 1–5) (Fig. 1). The median time interval between the primary MRI examination and the selected follow-up examination was 343 (IQR: 107–573) days. There was no statistical difference in moderate or severe reactions between patients who underwent follow-up GBCA-enhanced MRI examinations (12.3%, 46/373) and patients who did not undergo any further GBCA-enhanced MRI examinations (12.5%, 68/542).

Of the 373 included patients, 42 patients were administered a different GBCA from the agent that they had previously received (GBCA change group), while the remaining 331 patients received the same GBCA as before (GBCA non-change group). No significant intergroup differences were observed for the proportions of any variable (Table 1).

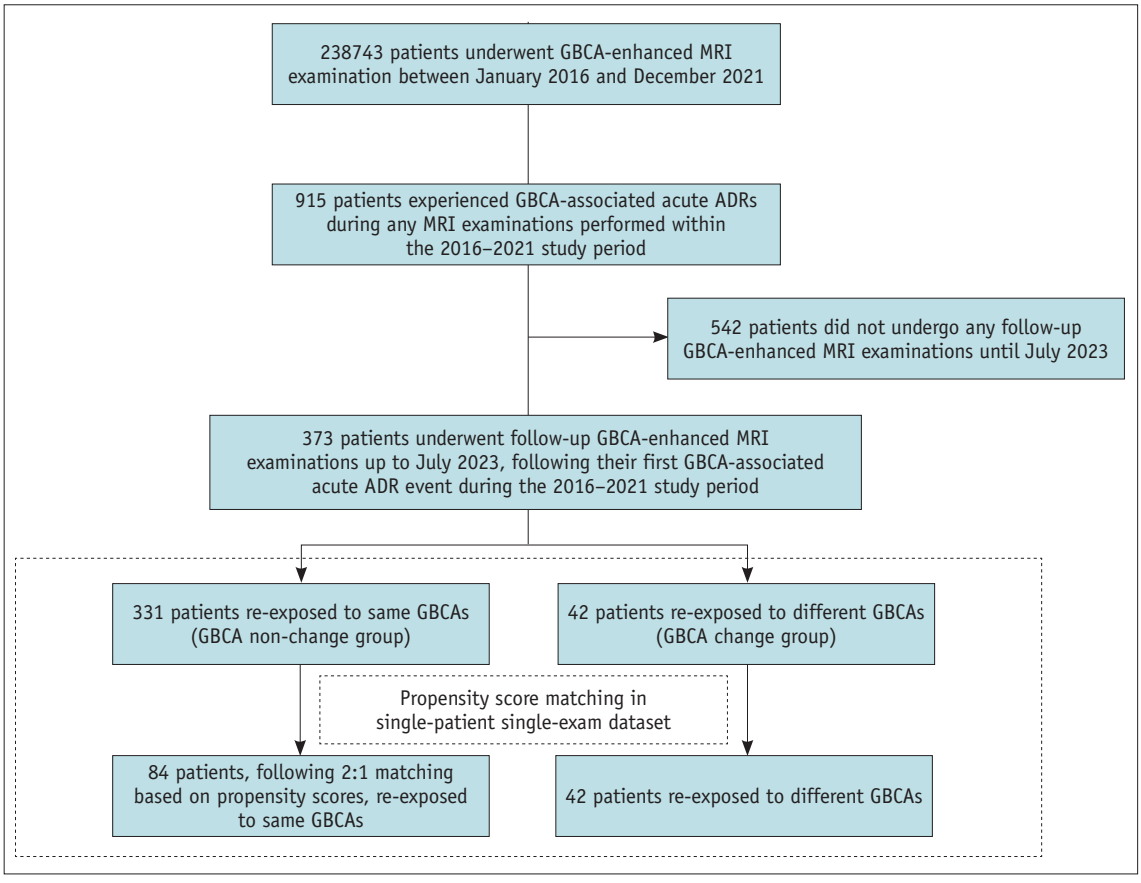

Fig. 1. Flow chart. GBCA = gadolinium-based contrast agent, ADR = adverse drug reaction

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Effects of GBCA Change on Acute ADR Recurrence

Among the 373 patients included, 119 (31.9%) experienced acute ADR recurrence during the follow-up period: 82 patients at the first follow-up; 21 at the second follow-up; and 16 at a later follow-up. Multivariable logistic regression analysis revealed that the acute ADR recurrence rate was significantly lower in the GBCA change group (adjusted OR: 0.35, 95% CI: 0.13–0.90; $P = 0.03$) (Table 2).

After propensity score matching, 84 and 42 patients were included in GBCA non-change and GBCA change groups, respectively. The C statistics of the propensity score model was 0.711, and the model was well-calibrated without rejection of the null hypothesis on Hosmer–Lemeshow analysis ($P = 0.42$). The absolute values of the standardized mean differences were all <0.1, excluding age and diabetes mellitus (Table 1). After adjustment with propensity score matching, the recurrence rate was significantly lower in the GBCA change group than GBCA non-change group (14.3% [6/42] vs. 36.9% [31/84], respectively; OR: 0.32, 95% CI: 0.11–0.94; $P = 0.04$).

Unadjusted univariable analysis revealed that a history of an ADR to ICM was not significantly associated with acute ADR recurrence (OR: 1.14, 95% CI: 0.68–1.90; $P = 0.62$) (Table 3). Multivariable logistic regression analysis demonstrated that the ADR recurrence rate was significantly lower in patients with a history of malignancy (adjusted OR: 0.52, 95% CI: 0.32–0.86; $P = 0.01$). Premedication administration was not significantly associated with acute ADR recurrence rate (adjusted OR: 2.09, 95% CI: 0.93–4.68; $P = 0.07$), and a history of chronic urticaria and atopy was not a significant risk factor for GBCA-associated acute ADR recurrence (adjusted OR: 2.54, 95% CI: 0.37–17.4; $P = 0.34$).

Effects of GBCA Change on Downgrade Rate

Among the 373 patients included, a total of 264 patients were considered downgraded patients (254 patients without ADR recurrence, and 10 patients with less severe ADR at recurrence, from moderate to mild in 8, and from severe to

Table 1. Baseline characteristics of the participants

Variable	All patients (n = 373)				Patients selected with propensity score matching (n = 126)		
	GBCA non-change (n = 331)	GBCA change (n = 42)	*P*	SMD	GBCA non-change (n = 84)	GBCA change (n = 42)	SMD
Age, yrs	52.5 ± 14.8	54.3 ± 14.6	0.45	0.13	52.3 ± 14.6	54.3 ± 14.6	0.13
Sex			0.20	0.21			0.02
Male	161 (48.6)	16 (38.1)			33 (39.3)	16 (38.1)	
Female	170 (51.4)	26 (61.9)			51 (60.7)	26 (61.9)	
Diabetes mellitus	46 (13.9)	6 (14.3)	0.95	0.01	9 (10.7)	6 (14.3)	0.11
Cardiac disease*	17 (5.1)	5 (11.9)	0.09	0.24	8 (9.5)	5 (11.9)	0.08
Hyperthyroidism	4 (1.2)	1 (2.4)	0.45	0.09	2 (2.4)	1 (2.4)	0
Renal insufficiency†	2 (0.6)	1 (2.4)	0.30	0.15	2 (2.4)	1 (2.4)	0
History of malignancy	181 (54.7)	16 (38.1)	0.04	0.34	29 (34.5)	16 (38.1)	0.07
Anxiety	6 (1.8)	2 (4.8)	0.22	0.17	4 (4.8)	2 (4.8)	0
Asthma	5 (1.5)	1 (2.4)	0.51	0.06	3 (3.6)	1 (2.4)	0.07
Allergic rhinitis	20 (6.0)	2 (4.8)	>0.99	0.06	4 (4.8)	2 (4.8)	0
Chronic urticaria/atopy	6 (1.8)	0 (0)	>0.99	0.19			
Food allergy	23 (6.9)	1 (2.4)	0.50	0.22	3 (3.6)	1 (2.4)	0.07
Drug allergy	126 (38.1)	17 (40.5)	0.76	0.05	36 (42.9)	17 (40.5)	0.05
Iodinated contrast media allergy	75 (22.7)	10 (23.8)	0.87	0.03	21 (25)	10 (23.8)	0.03
Premedication	291 (87.9)	38 (90.5)	0.80	0.08	74 (88.1)	38 (90.5)	0.08
Severity of initial ADR			0.75	0.12			0
Mild	306 (92.4)	40 (95.2)			80 (95.2)	40 (95.2)	
Moderate/severe	25 (7.6)	2 (4.8)			4 (4.8)	2 (4.8)	

Data are number of patients with percentage in parentheses, except for age which is presented as mean ± standard deviation.
*Cardiac disease includes any of the following: heart failure, arrhythmia, pulmonary hypertension, severe aortic stenosis, †Renal insufficiency means estimated glomerular filtration rate <45 ml/min/1.73 m^2 before or after 3 months from the date of initial CT scan.
GBCA = gadolinium-based contrast agent, SMD = standardized mean difference, ADR = adverse drug reaction

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Korean Journal of Radiology
KJR

Table 2. Summary of the outcomes between change and non-change of culprit GBCA in per-patient analysis

	GBCA change	GBCA non-change	OR (95% CI)	*P*
Acute ADR recurrence				
Univariable analysis	6/42 (14.3)	113/331 (34.1)	0.32 (0.13–0.79)	0.01
Multivariable analysis	6/42 (14.3)	113/331 (34.1)	0.35 (0.13–0.90)	0.03
Inverse probability of treatment weighting*	7/42 (16.3)	114/331 (34.4)	0.40 (0.15-1.06)	0.07
Propensity score matching	6/42 (14.3)	31/84 (36.9)	0.32 (0.11–0.94)	0.04
Downgrading				
Univariable analysis	36/42 (85.7)	228/331 (68.9)	2.71 (1.11–6.63)	0.03
Multivariable analysis	36/42 (85.7)	228/331 (68.9)	2.57 (1.00–6.60)	0.05
Inverse probability of treatment weighting*	35/42 (83.7)	227/331 (68.5)	2.15 (0.80–5.79)	0.13
Propensity score matching	36/42 (85.7)	55/84 (65.5)	2.83 (0.95–8.43)	0.06
Recurrent allergic-like hypersensitivity reaction				
Univariable analysis	4/32 (12.5)	87/208 (41.8)	0.20 (0.07–0.59)	<0.01
Multivariable analysis	4/32 (12.5)	87/208 (41.8)	0.20 (0.06–0.65)	<0.01
Inverse probability of treatment weighting*	6/32 (20.1)	87/208 (41.6)	0.35 (0.11–1.10)	0.07
Propensity score matching	4/32 (12.5)	27/61 (44.3)	0.23 (0.06–0.84)	0.03

Data are number of patients with percentage in parentheses.
*In inverse probability of treatment weighting, the numerator was rounded, and the percentage in parentheses was calculated using the raw data.
GBCA = gadolinium-based contrast agent, OR = odds ratio, CI = confidence interval, ADR = adverse drug reaction

Table 3. Univariable and multivariable analyses of the effect of GBCA change on acute ADR recurrence in per-patient analysis

Variable	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
GBCA change	0.32 (0.13–0.79)	0.01	0.35 (0.13–0.90)	0.03
Age, yrs	1.00 (0.99–1.02)	0.77	1.01 (0.99–1.02)	0.46
Sex				
Female	Reference category		Reference category	
Male	1.87 (1.20–2.90)	<0.01	1.74 (1.09–2.77)	0.02
Diabetes mellitus	1.27 (0.69–2.35)	0.44		
Cardiac disease*	0.61 (0.22–1.70)	0.35		
Hyperthyroidism	1.43 (0.24–8.68)	0.70		
Renal insufficiency†	1.07 (0.10–11.9)	0.96		
History of malignancy	0.61 (0.40–0.95)	0.03	0.52 (0.32–0.86)	0.01
Anxiety	0.71 (0.14–3.55)	0.67		
Asthma	2.16 (0.43–10.9)	0.35		
Allergic rhinitis	1.85 (0.78–4.41)	0.17	1.24 (0.48–3.23)	0.66
Chronic urticaria/atopy	4.38 (0.79–24.3)	0.09	2.54 (0.37–17.4)	0.34
Food allergy	2.26 (0.98–5.20)	0.06	1.74 (0.69–4.40)	0.25
Drug allergy	0.83 (0.53–1.30)	0.41		
Iodinated contrast media allergy	1.14 (0.68–1.90)	0.62		
Premedication	1.95 (0.91–4.21)	0.09	2.09 (0.93–4.68)	0.07
Repeat GBCA				
Gadobutrol	Reference category		Reference category	
Gadoterate meglumine	1.94 (0.71–5.32)	0.20	1.48 (0.50–4.41)	0.48
Gadoxetate disodium	2.50 (0.85–7.38)	0.10	2.12 (0.65–6.90)	0.21
Severity of initial ADR				
Mild	Reference category		Reference category	
Moderate/severe	1.79 (0.81–3.95)	0.15	1.51 (0.65–3.51)	0.34

*Cardiac disease includes any of the following: heart failure, arrhythmia, pulmonary hypertension, and severe aortic stenosis, †Renal insufficiency means estimated glomerular filtration rate <45 ml/min/1.73 m^2 before or after 3 months from the date of initial MRI scan.
GBCA = gadolinium-based contrast agent, ADR = adverse drug reaction, OR = odds ratio, CI = confidence interval

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mild in 2). Multivariable logistic regression analysis revealed that the downgrade rate was higher in the GBCA change group with borderline significance (adjusted OR: 2.57, 95% CI: 1.00–6.60; $P = 0.05$).

Effects of GBCA Change on Acute Recurrent Allergic-Like HSRs

Among the 119 patients who experienced acute ADR recurrence on follow-up MRI examinations, symptoms indicative of allergic-like HSR were observed in 91 patients (87 patients in the GBCA non-change group and 4 patients in the GBCA change group).

Multivariable logistic regression analysis revealed that the recurrent allergic-like HSR rate was significantly lower in the GBCA change group (adjusted OR: 0.20, 95% CI: 0.06–0.65; $P < 0.01$) (Table 2). After adjustment with propensity score matching, the recurrent allergic-like HSR rate was significantly lower in the GBCA change group than GBCA non-change group (12.5% [4/32] vs. 44.3% [27/61], respectively; OR: 0.23, 95% CI: 0.06–0.84; $P = 0.03$).

DISCUSSION

GBCAs have been increasingly used in clinical settings, and concern about the adverse events of GBCAs is increasing. This 6-year retrospective analysis performed at a single tertiary medical center revealed that the recurrence rates of GBCA-associated acute ADRs and allergic-like HSRs decreased when the previous GBCA was changed.

The prophylactic effect of changing the previous GBCA on reducing the recurrence of GBCA-associated acute ADRs has been previously reported [5,6]. Ryoo et al. [5] reported a decreased incidence of GBCA-associated HSR recurrence after changing the previous agent to one of a different molecular structure and ionicity, suggesting that the pathophysiology of GBCA-associated HSR is influenced by different GBCA types. Ahn et al. [6] reported a decreased incidence of GBCA-associated acute HSR recurrence after changing the previous GBCA, whereas the delayed HSR recurrence rate did not significantly decrease despite changing the previous agent. As in the previous studies, our study revealed a significantly lower recurrence rate of GBCA-associated acute ADRs and allergic-like HSRs in the GBCA change group. Additionally, we observed a significant decrease in the severity of acute ADRs in the GBCA change group.

In per-patient multivariable analysis, the acute ADR recurrence rate was significantly lower in patients with a history of malignancy. After propensity score matching, we adjusted the history of malignancy between two groups, demonstrating that the recurrence rate of GBCA-associated acute ADRs was significantly lower in the GBCA change group than GBCA non-change group (OR: 0.32, 95% CI: 0.11–0.94, $P = 0.04$). Currently, there are no guidelines that recommend changing the previous GBCA to reduce recurrent acute ADRs. Thus, further confirmative prospective study is needed [2,3,10].

There is a controversy regarding the use of premedication in the prophylaxis of GBCA-associated ADRs. Owing to the lack of sufficient evidence, the ACR and European Society of Urogenital Radiology no longer recommend the concomitant administration of systemic corticosteroids and antihistamines before the infusion of contrast media [3,10]. This controversy has continued in the patient population in South Korea [5,6]. Ryoo et al. [5] reported that premedication is ineffective as a prophylaxis of GBCA-associated HSRs, whereas Ahn et al. [6] suggested a preventive effect of premedication for lowering the recurrence of both acute and delayed GBCA-associated HSRs. The per-patient multivariable analysis of our study showed that a premedication regimen of a systemic corticosteroid plus antihistamine was ineffective for preventing GBCA-associated acute ADR recurrence. As corticosteroids and antihistamines only have effect on HSRs and not on physiologic reactions, our results may not directly support or deny the effectiveness of premedication in the prevention of GBCA-associated acute ADR recurrence. However, a debate exists regarding whether symptoms that are currently classified as physiological reactions—such as gastrointestinal symptoms, including nausea and vomiting—may occur as symptoms of HSRs induced by intestinal angioedema [11,12]. In one study, antihistamine premedication effectively decreased the recurrence rate of gastrointestinal symptoms [11,13]. Further investigation is needed to clarify the pathophysiology of each symptom of ADR and whether premedication can prevent the recurrence of such symptoms.

It is generally believed that there is no cross-reactivity between GBCA and ICM [14]. However, some studies have reported a higher prevalence of GBCA-associated HSRs in patients with a history of allergy to ICM [6,15]. Ahn et al. [6] revealed that the prevalence of HSRs of GBCAs was significantly higher in patients with a history of ICM hypersensitivity. In our risk-factor analysis using univariable logistic regression, a history of ICM allergy did not significantly contribute to the incidence of GBCA-associated

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Korean Journal of Radiology
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acute ADR recurrence. Interestingly, patients with a history of malignancy demonstrated a significantly lower incidence of GBCA-associated acute ADR recurrence. Further studies are needed to determine whether this phenomenon is clinically significant.

Cross-reactivity between GBCAs is not clearly identified to date. Kolenda et al. [16] reported that skin test-confirmed cross-sensitization was most frequent between gadoteric acid and gadobutrol. In our study, cross-reactivity between multiple GBCAs was reported in 12 patients (0.004%; 95% CI: 0.002%–0.008%), suggesting that cross-reactivity between GBCAs is a very rare phenomenon. Among them, 11 patients had acute ADRs to both gadobutrol and gadoterate meglumine, and the remaining case had acute ADRs to both gadoteridol and gadoterate meglumine.

Using allergy skin tests in patients with a history of GBCA-associated HSRs to select an alternate GBCA option that can reduce the risk of recurrent reactions is controversial. A meta-analysis by Walker et al. [17] revealed that the HSR rate after allergy skin testing did not significantly differ from the HSR rate when using same agent with premedication. These controversial results, along with the large number of patients that require GBCA-enhanced imaging, makes physicians reluctant to prescribe allergy skin tests before GBCA administration.

This study has several limitations, including those associated with the retrospective, single-center design. Further research through a randomized controlled trial with multicenter analysis could confirm the preventive effect conferred by changing the previous GBCA for lowering the GBCA-associated acute ADR recurrence rate. Second, the exclusion of 542 of the 915 patients (59.2%) from the study may represent a significant selection bias. However, there was no statistical difference in moderate or severe reactions between the 373 patients (12.3%, 46/373) who underwent follow-up GBCA-enhanced MRI examinations and patients who did not (12.5%, 68/542). Third, the types of GBCA were significantly different. While the numbers of examinations using gadoteridol or gadobutrol were relatively lower than examinations using gadoterate meglumine in our study, the actual numbers of examinations—1220 for gadoteridol and 13444 for gadobutrol—seemed substantial. Excluding these examinations may induce selection bias. Indeed, other large single-center retrospective studies involved relatively sparse use of GBCAs; for example, Ahn et al. [6] reported on 192 and 3435 examinations using gadopentetate dimeglumine and gadobenate dimeglumine, respectively, while McDonald et al. [18] included 8053 examinations using gadoterate meglumine. Furthermore, there were no significant differences in acute adverse events between our study and the literature (gadobutrol, 0.55% vs. 0.64%; gadoteridol, 0.67% vs. 0.98%) [3,19].

In conclusion, changing GBCAs may be effective for lowering the risk of recurrence of GBCA-associated acute ADRs.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Chong Hyun Suh, who holds respective positions on the Assistant to the Editor of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. The remaining author has declared no conflicts of interest.

Author Contributions

Conceptualization: Chong Hyun Suh, Choong Wook Lee. Data curation: Chong Hyun Suh, Kyung-Hyun Do. Formal analysis: Min Woo Han, Chong Hyun Suh, Pyeong Hwa Kim, Seonok Kim, Ah Young Jung. Funding acquisition: Chong Hyun Suh, Choong Wook Lee. Investigation: Min Woo Han, Chong Hyun Suh, Pyeong Hwa Kim, Seonok Kim, Jeong Hyun Lee. Methodology: Min Woo Han, Chong Hyun Suh, Pyeong Hwa Kim. Project administration: Chong Hyun Suh, Kyung-Hyun Do, Jeong Hyun Lee, Dong-Il Gwon, Choong Wook Lee. Resources: Chong Hyun Suh, Choong Wook Lee. Software: Chong Hyun Suh, Seonok Kim. Supervision: Dong-Il Gwon, Ah Young Jung, Choong Wook Lee. Validation: Min Woo Han, Chong Hyun Suh, Pyeong Hwa Kim, Seonok Kim, Dong-Il Gwon. Visualization: Min Woo Han, Chong Hyun Suh, Ah Young Kim, Kyung-Hyun Do, Jeong Hyun Lee, Ah Young Jung. Writing—original draft: Min Woo Han. Writing—review & editing: Chong Hyun Suh, Ah Young Kim, Kyung-Hyun Do, Jeong Hyun Lee, Dong-Il Gwon, Ah Young Jung, Choong Wook Lee.

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