

Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: A multicentre retrospective cohort study

Hye Jung Park¹ · Jung-Won Park² · Min-Suk Yang³ · Mi-Yeong Kim⁴ · Sae-Hoon Kim⁵ · Gwang Cheon Jang⁶ · Young-Hee Nam⁷ · Gun-Woo Kim⁸ · Sujeong Kim⁹ · Hye-Kyung Park¹⁰ · Jae-Woo Jung¹¹ · Jong-Sook Park¹² · Hye-Ryun Kang¹³

Received: 29 July 2016 / Revised: 6 October 2016 / Accepted: 28 November 2016
© European Society of Radiology 2016

Abstract

Objectives To evaluate the outcomes of re-exposure to low-osmolar iodinated contrast medium (LOCM) in patients with a history of moderate-to-severe hypersensitivity reaction (HSR).

Methods We retrospectively evaluated a cohort comprising all subjects satisfying the following conditions at 11 centres: (1) experienced a moderate-to-severe HSR to LOCM by December 2014, and (2) underwent contrast-enhanced computed tomography after the initial HSR between January 2014 and December 2014.

Results A total of 150 patients with 328 instances of re-exposure were included; the recurrence rate of HSR was 19.5%. Patients with severe initial HSR exhibited a higher recurrence rate of severe HSR compared to patients with moderate initial HSR, despite more intensive premedication. In the multivariate analysis, the independent risk factors for recurrence of HSR were

diabetes, chronic urticaria, drug allergy other than to iodinated contrast media (ICM) and severe initial HSR. The risk of recurrent HSR was 67.1% lower in cases where the implicated ICM was changed to another one (odds ratio: 0.329; $P = 0.001$). However, steroid premedication did not show protective effects against recurrent HSR.

Conclusion In high-risk patients who have previously experienced a moderate-to-severe initial HSR to LOCM, we should consider changing the implicated ICM to reduce recurrence risk.

Key points

- In patients with moderate-to-severe HSR, steroid premedication only shows limited effectiveness.
- Changing the implicated ICM can reduce the recurrence of HSR to ICM.
- Diabetes, chronic urticaria and drug allergies increase the risk of ICM HSR.

✉ Hye-Ryun Kang
helenmed@snu.ac.kr

¹ Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

² Division of Allergy and Immunology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

³ Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea

⁴ Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

⁵ Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

⁶ Department of Pediatrics, National Health Insurance Service, Ilsan Hospital, Korea

⁷ Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea

⁸ Department of Internal Medicine, Kwangju Christian Hospital, Gwangju, Korea

⁹ Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea

¹⁰ Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

¹¹ Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

¹² Soonchunhyang University Bucheon Hospital, Bucheon 420-767, Korea

¹³ Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Keywords Contrast media · Drug hypersensitivity · Hypersensitivity, Immediate · Premedication · Secondary prevention

Abbreviations

ACR	American College of Radiology
CI	Confidence interval
CT	Computed tomography
ESUR	European Society of Urogenital Radiology
GEE	Generalized estimation equation
HSR	Hypersensitivity reaction
ICM	Iodinated contrast medium
LOCM	Low-osmolar iodinated contrast medium
OR	Odds ratio

Introduction

Imaging modalities using iodinated contrast medium (ICM) are essential in current medical practice. However, as the use of ICMs has increased, ICM has become a major cause of drug hypersensitivity reactions (HSRs) [1]. The introduction of low-osmolar contrast medium (LOCM) has led to a reduction in serious reactions such as anaphylaxis adverse reactions, as well as in less serious ones such as injection-site pain, nausea and vomiting [2, 3]. Accordingly, most institutes have replaced high-osmolar contrast media with LOCM. Nevertheless, although LOCMs are still widely used, HSRs and recurrence of HSRs on re-exposure still occur.

The European Society of Urogenital Radiology (ESUR) guidelines suggest changing the ICM or using premedication in cases at risk of HSR [4]. However, premedication cannot completely prevent all recurrences of HSR [5, 6], and the preventive effects of changing the ICM also remain controversial [7–9]. The recent guidelines from the American College of Radiology, the ACR Manual on Contrast Media version 10.2, state that a change from one LOCM to another seems to provide little or no benefit, although the use of a different contrast agent may sometimes be helpful [10]. Clinical studies have failed to demonstrate unequivocal results regarding the preventive effect of corticosteroid premedication on ICM hypersensitivity [10], and more evidence is needed in order to develop a standardized prevention strategy for moderate-to-severe reactions to LOCM.

While ICM-related HSRs are relatively common, occurring in 1–15% of cases [11–13], moderate-to-severe HSRs are conversely very rare (0.04–0.28%) [14], and most patients with a history of moderate-to-severe HSR are informed not to undergo additional contrast-enhanced imaging studies because of

the potential risk of severe recurrence. Thus, it is difficult to perform a study to evaluate the outcomes of subsequent exposures after prior moderate-to-severe HSRs to ICM.

The present retrospective multicentre cohort study aimed to evaluate the outcomes and risk factors of recurrence of HSR among patients who underwent subsequent contrast-enhanced computed tomography after a previous moderate-to-severe initial HSR to LOCM.

Materials and methods

Ethics

The institutional review boards of all participating institutes approved this study. Because of the retrospective nature of the study, the requirement to obtain informed consent was waived.

Subjects

The study subjects were recruited from 11 centres (Severance Hospital, Seoul National Hospital, SMG-SNU Boramae Medical Center, Busan Paik Hospital, Seoul National University Bundang Hospital, Ilsan Hospital, Dong-A University Hospital, Kyungpook National Hospital, Pusan University Hospital, Chung-Ang University Hospital, and Soonchunhyang University Bucheon Hospital). This study included all patients who had previously experienced a moderate or severe initial HSR to LOCM and in whom the subsequent exposure occurred between 1 January 2014 and 31 December 2014.

We retrospectively reviewed the electronic medical records of the involved patients. The patients' underlying diseases, including hypertension, diabetes, liver disease, renal disease, asthma, allergic rhinitis, chronic urticaria and drug allergies to drugs other than ICMs, were assessed.

Iodinated contrast media (ICMs) used in this study

The LOCMs used in this study included six nonionic monomers, namely iobitridol (Xenetics®300, Xenetics®350; Biomedical Inc., Irvine, CA, USA), iohexol (Bonorex®350; Dai Han Pharm.Co., Ltd Seoul, Korea; Iobrix®350; TAEJOON Pharm, Seoul, Korea; Omnihexol®350; Korea United Pharm Co., Seoul, Korea; Omnipaque®350, Winthrop, Princeton, NJ, USA), iomeprol (Iomeron®400; Bracco S.p.a., Milan, Italy), iopamidol (Iopamiro®300, Iopamiro®370; Bracco S.p.a.; Pamiray®250, Pamiray®300, Pamiray®370; Dongkook Pharm, Seoul, Korea; Scanlux®300; Sanochemia, Vienna, Austria), iopromide (Neovist®370; Daewoong, Seoul, Korea; Prosure®370; LG Life Science, Seoul, Korea; Ultravist®300, Ultravist®370;

Schering, Berlin, Germany) and ioversol (Iversense®240; TAEJOON Pharm, Seoul, Korea; Optiray®320; Mallinckrodt, St. Louis, MO, USA), with an osmolality from 500–850 mOsm/kg H₂O, and one nonionic dimer, iodixanol (Visipaque®320; Nycomed, Oslo, Norway), which was the only iso-osmolar contrast agent, with an osmolality of 290 mOsm/kg H₂O.

Premedication

We defined premedication as antihistamines or systemic steroids prescribed with the aim of preventing recurrence of HSR. The premedication regimens used at the time of re-exposure were determined according to the decision of the physicians in charge. Steroids and antihistamines were administered 0.5–1 hour before re-exposure to LOCM.

Clinical parameters

The HSR severity was classified as follows: mild (itching, urticaria, flushing, nausea, mild vomiting and/or chills, i.e. symptoms that are self-limiting, without evidence of progression), moderate (severe vomiting, systemic urticaria, mild bronchospasm, face and/or larynx angioedema, throat tightness, tachycardia, bradycardia, mild dyspnoea, hypoxia and/or temporary hypotension, i.e. symptoms that are more pronounced and commonly require medical management), and severe (shock, pulmonary oedema, prolonged hypoxia, cardiopulmonary arrest and/or convulsions, i.e. symptoms that are often life-threatening and can result in permanent morbidity or death if not managed appropriately) [10]. The causality of the relationship between the administered ICM and the HSR was assessed by two allergy specialists, using the World Health Organization-Uppsala Monitoring Centre causality assessment algorithm [15, 16].

Statistics

The chi-square test was used to assess the associations of premedication and changing the ICM with the recurrence of HSR. Comparisons of the recurrence rate for HSR according to the introduction of premedication and changing the implicated ICM to another ICM were also assessed using the chi-square or Fisher's exact test. We used generalized estimating equation (GEE) analysis to identify the significant independent risk factors for recurrence of HSR. Univariate analyses were used to evaluate all parameters, including sex, underlying disease, smoking history, drinking history, changing the ICM and premedication. Known risk factors and significant risk factors in the univariate analyses were assessed by multivariate analysis. All analyses were performed using SPSS

software (version 18.0; SPSS Inc., Chicago, IL, USA), and *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

We identified a total of 150 patients from the 11 included centres. Among the study subjects, the proportion of males was 49.3% and the mean age was 61.7 ± 11.5 years (Table 1). The most common underlying diseases were hypertension (36.7%) and diabetes mellitus (12.7%). Allergic diseases were relatively uncommon (2% asthma, 3.3% allergic rhinitis, 4.0% chronic urticaria, 3.3% food allergies and 4.7% non-ICM drug allergies). In terms of the severity of the initial HSR, 130 (86.7%) and 20 (13.3%) patients experienced moderate and severe reactions, respectively.

Table 1 Characteristics of the study subjects

Characteristics	N (%)
Sex	
Male	74 (49.3)
Female	76 (50.7)
Age, y (mean $\pm$ SD)	61.7 $\pm$ 11.5
Past history	
Hypertension	55 (36.7)
Diabetes mellitus	19 (12.7)
Liver disease	20 (13.3)
Renal disease	3 (2.0)
Allergic disease	
Asthma	3 (2.0)
Allergic rhinitis	5 (3.3)
Chronic urticaria	6 (4.0)
Food allergy	5 (3.3)
Drug allergy	7 (4.7)
Smoking history	
Never smoker	64 (42.7)
Ex-smoker	23 (15.3)
Current smoker	25 (16.7)
Unknown	38 (25.3)
Alcohol history	
Not current drinker	122 (81.3)
Current drinker	23 (15.3)
Unknown	5 (3.3)
Severity of initial HSR	
Moderate	130 (86.7)
Severe	20 (13.3)
Total	150 (100.0)

SD standard deviation, *HSR* hypersensitivity reaction

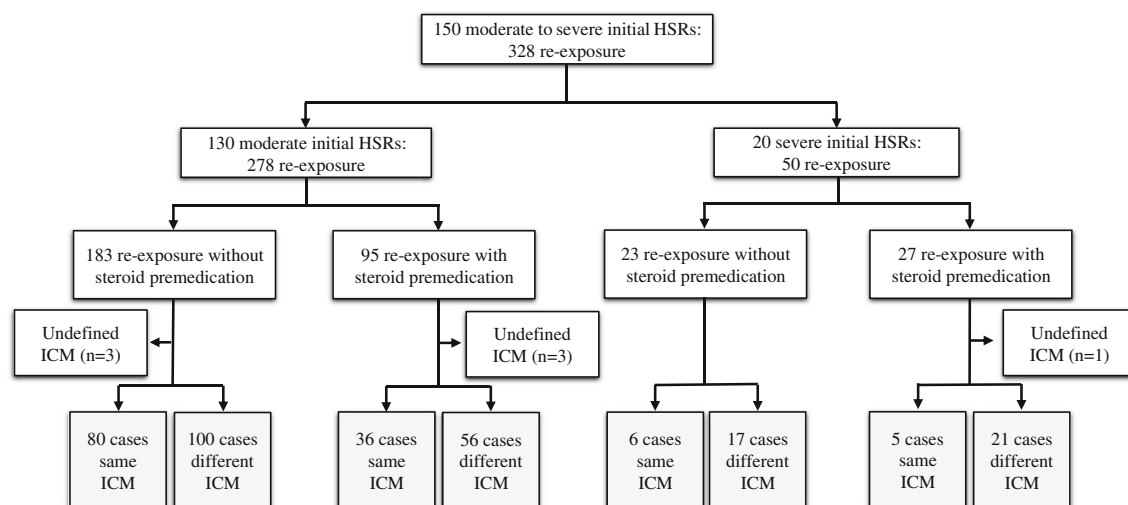


Fig. 1 Case distribution according to the severity of the initial hypersensitivity reaction (HSR), steroid premedication and iodinated contrast medium (ICM) change

Outcomes of re-exposure according to the severity of initial hypersensitivity reaction (HSR)

A total of 328 subsequent re-exposure events were identified during the study period, including 278 events following 130 moderate initial HSRs and 50 events following 20 severe initial HSRs (Fig. 1). The overall recurrence rate was 19.5%, and 75.0% of the recurring cases were moderate (Table 2). The overall recurrence rates were 18.7% and 24.0% in patients with moderate and severe initial HSRs, respectively. Compared to patients with a moderate initial HSR, patients with a severe initial HSR showed a significantly higher rate of recurrent severe HSR on re-exposure (0.4% vs. 10.0%; $P < 0.001$), in spite of more proactive preparation at the time of re-exposure. In fact, patients who had a severe initial HSR exhibited a

significantly higher changing rate of ICM compared to patients with a moderate first HSR (77.6% vs. 57.4%; $P = 0.008$) and were more likely to receive premedication including systemic steroids at the subsequent re-exposure (54.0% vs. 34.2%; $P = 0.008$) (Table 2).

Outcomes of re-exposure according to ICM changes and premedication use

Among a total of 328 cases of re-exposure, the ICM was changed in 59.1% and systemic steroids were administered as premedication in 37.2% of cases at the time of re-exposure (Table 2).

Changing the ICM was associated with a significantly lower recurrence rate of HSR compared to using the same ICM administered at the initial HSR (27.6% vs. 13.4%, $P = 0.002$)

Table 2 Change in ICM, premedication and recurrence rate of HSR on re-exposure according to the severity of the initial HSR

On re-exposure	Total (n = 328)	Severity of initial HSR		P-value
		Moderate (n = 278)	Severe (n = 50)	
Recurrent HSR	64 (19.5%)	52 (18.7%)	12 (24.0%)	0.384
Mild	10 (3.0%)	8 (2.9%)	2 (4.0%)	0.671
Moderate	48 (14.6%)	43 (15.5%)	5 (10.0%)	0.314
Severe	6 (1.8%)	1 (0.4%)	5 (10.0%)	<0.001
Change of ICM*	194 (59.1%)	156 (57.4%)	38 (77.6%)	0.008
Any premedication	240 (73.2%)	201 (72.3%)	39 (78.0%)	0.403
Premedication with antihistamine only	118 (36.0%)	106 (38.1%)	12 (24.0%)	0.050
Premedication including systemic steroid	122 (37.2%)	95 (34.2%)	27 (54.0%)	0.008

*Including seven missing values

HSR hypersensitivity reaction, ICM iodinated contrast media

(Fig. 2A). To evaluate the effect of changing the ICM according to the severity of the initial HSR and premedication use, we first classified the study subjects according to the severity of their initial HSR and subsequently sub-classified them based on the introduction of steroid premedication and changing the ICM (Fig. 1).

Among 180 re-exposures without steroid premedication following moderate initial HSR, changing the ICM significantly reduced the recurrence rate of HSR (22.5% vs. 11.0%; $P=0.037$). Among 92 re-exposures premedicated with systemic steroids following moderate initial HSR, the recurrence rate of HSR did not significantly differ (30.6% vs. 16.1% with the same vs. different ICM; $P=0.100$) (Fig. 2B). Among 23 re-exposures without steroid premedication following severe initial HSR, the recurrence rate was similar irrespective of whether the same ICM was used or not (33.3% vs. 23.5%; $P=0.632$). On the other hand, among 26 cases premedicated with systemic steroids

following a severe initial HSR, the recurrence rate was only 9.5% (2/21) when a different ICM was used, whereas four out of five cases (80.0%) using the same ICM experienced recurrence ($P=0.005$) (Fig. 2C).

Steroid premedication did not result in improvement of the overall outcomes at the subsequent re-exposure (16.5% vs. 23.0%, $P=0.250$) (Fig. 2A).

Outcomes of re-exposure according to steroid dose for premedication

Next, we divided the subjects premedicated with systemic steroids into two groups according to the dose of steroids. The recurrence rate of HSR was not statistically different between subjects premedicated with a steroid equivalent to <40 mg (19.7%; 13/66) or ≥ 40 mg of prednisolone (26.8%; 15/56) ($P=0.353$) (Table 3).

Fig. 2 Recurrence rates of hypersensitivity reactions (HSRs) according to iodinated contrast medium (ICM) changes and steroid premedication in the total patients (A), in patients with a moderate initial HSR (B) and in patients with a severe initial HSR (C)

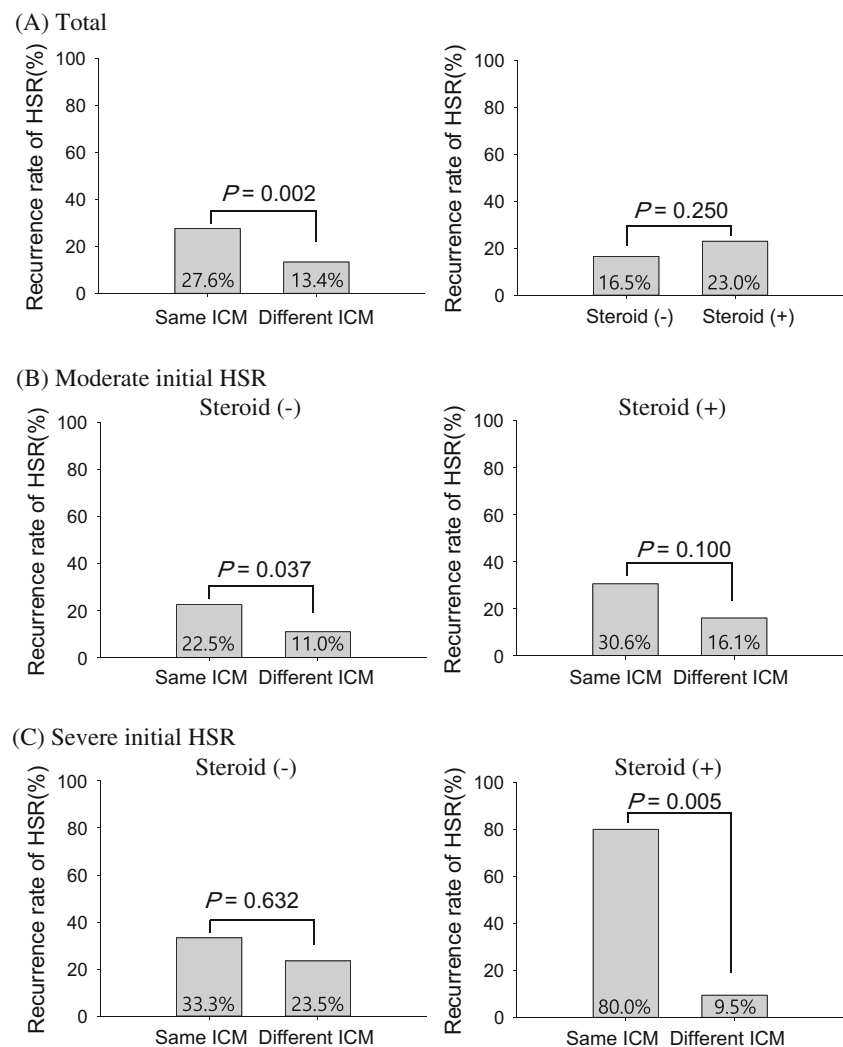


Table 3 Recurrence rate of HSR according to steroid dose for premedication

Steroid dose*	<40 mg (n = 66)	≥40 mg (n = 56)	P-value
Recurrence of HSR	13 (19.7%)	15 (26.8%)	0.353

*Equivalent dose to prednisolone

HSR hypersensitivity reaction

Univariate and multivariate generalised estimation equation (GEE) analyses for recurrence of HSR

In the univariate GEE analyses, the significant risk factors for recurrence of HSR were diabetes (odds ratio [OR]: 3.737, 95% confidence interval [CI]: 1.374–10.162; $P=0.010$), chronic urticaria (OR: 5.933, 95% CI: 1.409–24.985; $P=0.015$), and a non-ICM drug allergy (OR: 4.207, 95% CI: 1.372–12.902; $P=0.012$). A change in the ICM was significantly associated with a lower risk for recurrence of HSR (OR: 0.431, 95% CI: 0.236–0.786; $P=0.006$). However, steroid premedication was not associated with a significant reduction of recurrent HSR (OR: 1.115, 95% CI: 0.551–2.257; $P=0.762$). The severity of the initial HSR was not associated with the overall recurrence of HSR (OR: 1.673, 95% CI: 0.657–4.257; $P=0.280$). Among the total 150 patients, three patients had asthma and all of these patients experienced

recurrence of HSR. However, asthma could not be included as a covariate in the GEE analyses in this study, owing to the extremely high recurrence rate of HSR (100%) and small sample size.

In the multivariate GEE analyses, the significant risk factors for recurrence of HSR were diabetes (OR: 6.485, 95% CI: 2.375–17.706; $P<0.001$), chronic urticaria (OR: 7.614, 95% CI: 1.629–35.587; $P=0.010$), allergy to drugs other than ICMs (OR: 3.690, 95% CI: 1.178–11.558; $P=0.025$) and severity of the initial HSR (OR: 2.665, 95% CI: 1.046–6.793; $P=0.040$). A significantly lower risk for recurrence of HSR was associated with age (OR: 0.968, 95% CI: 0.939–0.997; $P=0.030$) and changing the ICM (OR: 0.329, 95% CI: 0.168–0.644; $P=0.001$). However, steroid premedication did not significantly affect the risk of recurrent HSR (OR: 0.907, 95% CI: 0.429–1.918; $P=0.799$) (Table 4).

Discussion

The present study provides data regarding the safety of re-exposure to ICM among patients who have experienced a moderate-to-severe HSR to ICM. We found that changing the ICM to another type of LOCM was associated with an approximately 67.1% lower risk for recurrence of HSR (OR:

Table 4 Univariate and multivariate generalized estimation equation analysis for recurrence of HSR

	Univariate effect estimate		Multivariate effect estimate	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Gender				
Female	Reference			
Male	0.868 (0.440–1.716)	0.685	0.781 (0.358–1.702)	0.534
Age	0.982 (0.956–1.010)	0.203	0.968 (0.939–0.997)	0.030
Underlying disease				
Diabetes mellitus	Reference		Reference	
	3.737 (1.374–10.162)	0.010	6.485 (2.375–17.706)	<0.001
Chronic urticaria	Reference		Reference	
	5.933 (1.409–24.985)	0.015	7.614 (1.629–35.587)	0.010
Drug allergy	Reference		Reference	
	4.207 (1.372–12.902)	0.012	3.690 (1.178–11.558)	0.025
Changing the ICM				
No	Reference			
Yes	0.431 (0.236–0.786)	0.006	0.329 (0.168–0.644)	0.001
Premedication				
No	Reference			
Yes	1.115 (0.551–2.257)	0.762	0.907 (0.429–1.918)	0.799
Severity of initial HSR				
Moderate	Reference		Reference	
Severe	1.673 (0.657–4.257)	0.280	2.665 (1.046–6.793)	0.040

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

0.329; $P = 0.001$). Although some guidelines suggest changing the ICM to prevent recurrence of HSR in high-risk patients [4], the scientific evidence is currently insufficient. Some studies have shown protective effects of changing the ICM [17, 18], whereas others have reported little or no benefit [7–9]. Moreover, to date, no confirmative study results are available in patients with a history of moderate-to-severe HSR, owing to the rarity of this condition. Therefore, our multicentre retrospective cohort study provides objective evidence supporting the notion that changing the ICM is useful for lowering the recurrence of HSR, especially in patients who have experienced moderate-to-severe HSR.

The present study also showed that premedication alone was not effective to prevent recurrence in patients with a history of moderate-to-severe HSR to ICM. The ESUR and ACR 2016 guidelines suggest that premedication may be helpful in high-risk patients to prevent HSR [4, 10]. However, the effectiveness of premedication is also controversial. Some studies have shown significant protective effects of premedication [17, 18], whereas others have presented contradictory results [5, 6]. The evidence supporting the protective role of premedication is relatively weak compared to that advocating the role of changing the ICM. Concordantly, Abe et al. reported that changing the ICM is more protective than premedication in high-risk patients [9]. As the subjects usually receive premedication in addition and simultaneously to changing the ICM, the exact effects of premedication are difficult to determine. In the present study, although we could not prove the significant protective role of steroid premedication, it seems to be partly due to unequal distribution of the severity of the initial HSR, because patients who had experienced a more severe reaction tended to have more intensive premedication. In fact, among cases premedicated with steroids, the proportion of patients with a severe initial HSR was twice as high compared with those without steroid premedication (22.1% vs. 11.2%, $P = 0.008$).

The significant risk factors for recurrence of HSR in this study were age, diabetes, chronic urticaria and allergy to drugs other than ICMs. It may also be relevant to consider asthma as a risk factor based on the results of previous studies [12, 19], although we could not analyse this factor because of the limited sample size in the present study. The results regarding chronic urticaria and drug allergies are in agreement with the findings of previous studies [5]. Moreover, this study reports, for the first time, a relationship between diabetes and recurrence of HSR. Considering that type 1 diabetes mellitus is a T-cell-mediated autoimmune disease associated with defective regulatory T-cells, it is probably linked with the risk of allergic disease and hypersensitivity [20]. In addition, type II diabetes is also closely associated with obesity, which is well known to be related to the risks of allergic disease and hypersensitivity [21, 22]. However, further studies are needed to confirm whether diabetes is a real risk factor for the recurrence of HSR to ICM.

The severity, signs and symptoms of the recurrent reaction are usually similar to those of the index reaction. In this study, the recurrence of severe HSR was more frequent among patients with a severe prior reaction than in patients with a moderate prior reaction (adjusted OR, 2.7).

On the other hand, a history of smoking or drinking was not significantly associated with the risk for recurrence of HSR in the present study (data not shown). Furthermore, the premedication protocol (i.e. steroid dose, histamine dose, premedication frequency and interval, and administrative route) was not significantly associated with the risk for recurrence of HSR (data not shown).

This study has some limitations. First, the retrospective design limits our data regarding the patients' underlying disease(s). Therefore, the prevalence of underlying diseases might be underestimated. For example, only 3.3% of the patients in the present study had allergic rhinitis, which is in stark contrast to the 30–40% prevalence of allergic rhinitis reported elsewhere. The other inherent limitation is the heterogeneity of premedication and ICM changing due to the absence of standardized protocols intra- and inter-institutes. Due to the limited sample sizes of patients receiving the different types and brands of ICM, we were unable to evaluate the differences among the different media in the present study. In order to reach a clear conclusion, a large-scale prospective cohort study with a common protocol is needed in the future.

In conclusion, the findings of the present study suggest that changing the ICM is useful for reducing the overall recurrence rate of HSR among patients who have previously experienced a moderate-to-severe HSR to ICM. Furthermore, re-exposure should be carefully considered for patients with diabetes, chronic urticaria, allergy to drugs other than ICM, asthma and/or severe initial HSR, as these factors were found to be closely associated with an increased risk for recurrence of HSR.

Acknowledgements The scientific guarantor of this publication is Hye-Ryun Kang. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. No complex statistical methods were necessary for this paper. Institutional Review Board approval was obtained. Written informed consent was waived by the Institutional Review Board. This was a retrospective observational multicentre study.

References

1. Yang MS, Lee SH, Kim TW, Kwon JW, Lee SM, Kim SH et al (2008) Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol* 100:31–36
2. Barrett BJ, Parfrey PS, McDonald JR, Hefferton DM, Reddy ER, McManamon PJ (1992) Nonionic low-osmolality versus ionic high-osmolality contrast material for intravenous use in

- patients perceived to be at high risk: randomized trial. *Radiology* 183:105–110
3. Steinberg EP, Moore RD, Powe NR, Gopalan R, Davidoff AJ, Litt M et al (1992) Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. *N Engl J Med* 326:425–430
 4. European Society of Urogenital Radiology. ESUR Contrast Media Guidelines version 8.1 <http://www.esur.org/guidelines/> Accessed June.3, 2016
 5. Davenport MS, Cohan RH, Caoili EM, Ellis JH (2009) Repeat contrast medium reactions in premedicated patients: frequency and severity. *Radiology* 253:372–379
 6. Freed KS, Leder RA, Alexander C, DeLong DM, Kliewer MA (2001) Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *AJR Am J Roentgenol* 176:1389–1392
 7. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K (1990) Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 175:621–628
 8. Schopp JG, Iyer RS, Wang CL, Petscavage JM, Paladin AM, Bush WH et al (2013) Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. *Emerg Radiol* 20:299–306
 9. Abe S, Fukuda H, Tobe K, Ibukuro K (2015) Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. *Eur Radiol*. doi:10.1007/s00330-015-4028-1
 10. Radiology ACo ACR Mannual on Contrast Media Version 10.2 2016. Accessed June. 3, 2016
 11. Jingu A, Fukuda J, Taketomi-Takahashi A, Tsushima Y (2014) Breakthrough reactions of iodinated and gadolinium contrast media after oral steroid premedication protocol. *BMC Med Imaging* 14:34
 12. Pradubongsa P, Dhana N, Jongjarearnprasert K, Janpanich S, Thongngarm T (2013) Adverse reactions to iodinated contrast media: prevalence, risk factors and outcome-the results of a 3-year period. *Asian Pac J Allergy Immunol* 31:299–306
 13. Bae YJ, Hwang YW, Yoon SY, Kim S, Lee T, Lee YS et al (2013) The effectiveness of automatic recommending system for premedication in reducing recurrent radiocontrast media hypersensitivity reactions. *PLoS One* 8, e66014
 14. Masch WR, Wang CL, Davenport MS (2016) Severe allergic-like contrast reactions: epidemiology and appropriate treatment. *Abdom Radiol (NY)* 41:1632–1639
 15. Edwards IR, Biriell C (1994) Harmonisation in pharmacovigilance. *Drug Saf* 10:93–102
 16. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR (1997) Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf* 17:374–389
 17. Mervak BM, Davenport MS, Ellis JH, Cohan RH (2015) Rates of breakthrough reactions in inpatients at high risk receiving premedication before contrast-enhanced CT. *AJR Am J Roentgenol* 205:77–84
 18. Abe S, Fukuda H, Tobe K, Ibukuro K (2016) Protective effect against repeat adverse reactions to iodinated contrast medium: Premedication vs. changing the contrast medium. *Eur Radiol* 26: 2148–2154
 19. Bumbacea RS, Petrutescu B, Bumbacea D, Strambu I (2013) Immediate and delayed hypersensitivity reactions to intravascular iodine based radiocontrast media – an update. *Pneumologia* 62:47–51
 20. Tan T, Xiang Y, Chang C, Zhou Z (2014) Alteration of regulatory T cells in type 1 diabetes mellitus: a comprehensive review. *Clin Rev Allergy Immunol* 47:234–243
 21. Hersoug LG, Linneberg A (2007) The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 62:1205–1213
 22. Park HJ, Lee JH, Park YH, Han H, Sim DW, Park KH et al (2016) Roflumilast ameliorates airway hyper-responsiveness caused by diet-induced obesity in a murine model. *Am J Respir Cell Mol Biol*. doi:10.1165/rcmb.2015-0345OC