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컴퓨터 단층촬영을 위한 요오드화 조영제 사용으로 인한 부작용 발생의 위험인자 연구

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Risk Factors for Adverse Reactions to Iodinated Contrast Media in Computed Tomography

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ABSTRACT

Objective: The increasing use of imaging examinations such as computed tomography (CT) results in increased contrast media use, which increases contrast media–induced adverse reactions (AR). This study investigated the risk factors of ARs to nonionic iodinated contrast media. **Methods:** This study evaluated patients who were administered iodinated contrast media during CT scanning in Yeouido St. Mary's Hospital in Seoul, Korea in 2012. Among the subjects, those with contrast media–induced ARs were classified as the AR group. The control group included individuals without ARs who were selected through simple random sampling. The effects of sex, age, contrast media type and dose, CT region, previous contrast media administration, allergy history, and comorbidity were analyzed in the AR and control groups. **Results:** Multivariate logistic regression analyses were performed to evaluate the identified AR risk factors in 103 subjects in the AR group and 412 subjects in the control group. The results confirmed that the risk of developing ARs was significantly higher in females [odds ratio (OR): 2.206; 95% confidence interval (CI): 1.353–3.598], in individuals administered lohexol (OR: 9.981; 95% CI: 2.361–42.193), in individuals with an allergy history (OR: 3.982; 95% CI: 1.742–9.101), and in individuals with comorbid asthma (OR: 6.619; 95% CI: 1.377–31.826). Most of the ARs were mild and immediate. **Conclusion:** In patients who were administered contrast media during CT scans, female gender, lohexol use, allergy history, and asthma were risk factors for ARs. Therefore, special care is required for patients with such risk factors to prevent ARs.

KEY WORDS: Iodinated contrast media, adverse reactions, risk factor, computed tomography

Computed tomography (CT) scans are being used increasingly often to diagnose disease. The use of iodinated contrast media, which influence radiation penetration in organs and lesions when used in association with CT, is therefore also increasing.[1,2] Iodinated contrast media induce changes in radiation penetration or radiation absorption to accurately locate organs and lesions in the human body and are mainly used in CT scans.[3]

Among the types of iodinated contrast media that are used in CT scans, low osmolar nonionic contrast media, which are currently widely used, show markedly reduced adverse reactions compared to hyperosmolar ionic contrast media, which were mainly used in the past. However, a broad spectrum of adverse reactions, from mild adverse reactions to severe complications, still occur following the use of low osmolar nonionic contrast media.[4]

Contrast media-induced adverse reactions occur in approximately 12-13% of patients who are administered ionic iodinated contrast media and in approximately 2-3% of patients who receive nonionic iodinated contrast media. Severe acute hypersensitivity develops in 0.1-0.4% of patients who receive ionic

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iodinated contrast media and in 0.02-0.04% of patients who receive nonionic iodinated contrast media.[5-7] Hypersensitivity reactions are the most common adverse reactions to contrast media, with a high incidence of mild acute dermatologic hypersensitivity such as urticaria and pruritus.[8,9]

Based on time of onset, adverse reactions are classified as either immediate adverse reactions that occur within 1 hour of contrast media administration or delayed adverse reactions that occur over 1 hour after administration; 70% of adverse reactions occur within 5 minutes of contrast media administration.[5,10]

Previous studies have found that the risk factors for adverse reactions to iodinated contrast media include adverse reaction history after contrast media administration, allergic history to drugs other than contrast media, urticaria, hypertension, diabetes, contrast media concentration > 70%, contrast media dose > 65 g, and age < 50 years.[11-14]

As discussed in the previous studies noted above, the general risk factors that lead to the occurrence of adverse reactions to iodinated contrast media have been partially identified, but limited studies have been performed on the risk factors for the occurrence of adverse reactions to iodinated contrast media in Koreans or on the frequency of adverse reaction occurrences.

Therefore, the objectives of this study were to identify the risk factors for adverse reactions in Korean patients who were administered iodinated contrast media during CT scans through a retrospective prescription analysis and electronic medical record investigation and to analyze the frequency of adverse reaction occurrences.

Methods

Study subjects

This study evaluated patients who were administered iodinated contrast media during CT scans at Yeoeuido St. Mary's Hospital, a tertiary teaching hospital in Seoul, Korea, from January to December 2012.

Data collection and methods

This study was approved by the St. Mary's Hospital IRB Committee. Adult patients aged 18 years or older who were administered iodinated contrast media during CT scans between January 1 and December 31, 2012, were included. Patients were excluded if they had no follow-up or lacked electronic medical records. Data on each subject's age, sex, CT region, and dose and type of contrast media used were collected. The subjects who experienced contrast media-induced adverse reactions were classified into the adverse reaction (AR) group. The control group was populated by selecting 4 times as many subjects as the number of patients in the AR group out of a group of patients without adverse reactions using simple random sampling. The electronic medical records of the patients of the AR and control groups were examined to investigate previous contrast media administration, allergy history, comorbidity, and contrast media-induced adverse reactions, which ultimately enabled the identification of risk factors for contrast media-induced adverse reactions and the analysis of the frequency of adverse reaction occurrences.

Definitions of adverse reactions

Adverse reactions that developed within 1 hour of the administration of contrast media were defined as immediate adverse reactions. Adverse reaction severity was classified as mild, moderate, or severe based on the guidelines in the ACR Manual on Contrast Media, version 9.[15]

Statistical analysis

Frequency analyses and basic statistical analyses were performed to analyze the general characteristics of the subjects. For both the AR group and the control group, continuous variables, including age and dose, were presented as the mean and standard deviation (SD), and t-tests were performed. The other categorical variables were subjected to cross tabulation analyses with Chi-square tests and Fisher's exact tests. Moreover, univariate logistic regression analyses were conducted on all variables recorded for the AR and control groups, and multivariate logistic regression analyses were additionally performed. Frequency analyses were used to assess the frequency of contrast media-induced adverse reaction occurrences. Statistical analyses were performed with SAS version 9.2, and p values of less than 0.05 were considered statistically significant.

Results

General characteristics of study subjects

During the study period, the total number of subjects who were administered iodinated contrast media while undergoing CT scans was 17,408. The AR group, which included individuals who experienced contrast media-induced adverse reactions, included 103 subjects, and the control group, which was designed to have 4 times as many subjects as the AR group,

included 412 subjects.

Outpatient-based examinations were performed on 11,449 subjects (65.8%), and inpatient-based examinations were performed on 5,959 subjects (34.2%). There were slightly more males than females, with 8,951 male subjects (51.4%). The mean subject age was 55.6 ± 16.9 years (mean ± SD). With regard to the types of contrast media used, iopromide was used in 12,437 subjects (71.4%), and it was therefore the most commonly used contrast medium. The mean dose of contrast media was 67.9 ± 12.0 g (mean ± SD). Regarding CT region, in cases where the same patient underwent CT scans of different regions, each region was calculated separately, and the results showed that the abdomen (pelvis) was the most commonly scanned region with 3,856 subjects (22.2%), followed by the chest with 3,416 subjects (19.6%), and the liver/spleen/pancreas with 3,199 subjects (18.4%) (Table 1).

Table 1. General characteristics of the included patients.

Characteristics		Overall (N = 17,408)
		N (%)
Patient status	Inpatient	5,959 (34.2)
	Outpatient	11,449 (65.8)
Sex	Male	8,951 (51.4)
	Female	8,457 (48.6)
Age (mean ± SD[a], y)	55.6 ± 16.9	
Age (y)	0~19	459 (2.7)
	20~29	1,015 (5.8)
	30~39	1,722 (9.9)
	40~49	2,494 (14.3)
	50~59	3,876 (22.3)
	60~69	3,853 (22.1)
	70~79	3,114 (17.9)
	≥ 80	875 (5.0)
CM[b]	Iohexol	709 (4.1)
	Iomeprol	2,311 (13.3)
	Ioversol	1,301 (7.5)
	Iopromide	12,437 (71.4)
	Iodixanol	650 (3.7)
Dose (mean ± SD[a],g)	67.9 ± 12.0	
CT[c] region	Abdomen (Pelvis)	3,856 (22.2)
	Chest	3,416 (19.6)
	Liver/spleen/pancreas	3,199 (18.4)
	Brain	2,743 (15.8)
	Neck	2,646 (15.2)
	Stomach	831 (4.8)
	Kidney	709 (4.1)
	Thyroid	423 (2.4)
	Others	1,354 (7.8)

[a]SD: Standard deviation
[b]CM: Contrast Media
[c]CT: Computed Tomography

The percentage of females was significantly higher in the AR group than in the control group, and the mean age was significantly higher in the control group than in the AR group. The percentage of subjects with allergy histories and asthma as comorbidity was statistically significantly higher in the AR group than in the control group (Table 2).

There was a statistically significant difference in the types of contrast media used between the AR group and the control

Table 2. Statistical analysis of the characteristics and medical histories of subjects with and without adverse reactions to contrast media.

Variables	AR[a] Group N = 103	Control group N = 412	p-value
	N (%)	N (%)	
Sex			0.0009[b]
Male	40 (38.8)	235 (57.0)	
Female	63 (61.2)	177 (43.0)	
Age (mean ± SD[c], y)	51.3 ± 14.5	55.0 ± 17.3	0.0270[d]
Age (y)			0.0103[e]
0~19	2 (1.9)	12 (2.9)	
20~59	72 (69.9)	220 (53.4)	
≥ 60	29 (28.2)	180 (43.7)	
Allergy history			0.0106[e]
Yes	12 (11.7)	20 (4.9)	
CM[f]	7 (6.8)	6 (1.5)	
Antibiotics	2 (1.9)	4 (1.0)	
Any drugs	3 (2.9)	4 (1.0)	
Others	0 (0)	6 (1.5)	
No	91 (88.3)	392 (95.1)	
Comorbidity			
Asthma			0.0071[e]
Yes	5 (4.9)	4 (1.0)	
No	98 (95.1)	408 (99.0)	
Hypertension			0.4963[b]
Yes	27 (26.2)	122 (29.6)	
No	76 (73.8)	290 (70.4)	
Diabetes			0.4756[b]
Yes	13 (12.6)	42 (10.2)	
No	90 (87.4)	370 (89.8)	
Dyslipidemia			0.0872[b]
Yes	7 (6.8)	13 (3.2)	
No	96 (93.2)	399 (96.8)	
Cancer			0.4996[b]
Yes	44 (42.7)	161 (39.1)	
No	59 (57.3)	251 (60.9)	
Previous CM[f]			0.0857[b]
Yes	59 (57.3)	197 (47.8)	
No	44 (42.7)	215 (52.2)	

[a]AR: Adverse Reaction
[b]Chi-square test
[c]SD: Standard deviation
[d]T-test
[e]Fisher's exact test
[f]CM: Contrast Media

Table 3. Statistical analysis of contrast media administration details in subjects with and without adverse reactions to contrast media.

Variables	AR[a] Group N = 103	Control group N = 412	p-value
	N (%)	N (%)	
CM[b]			< 0.0001[c]
Iohexol	16(15.5)	12(2.9)	
Iomeprol	7(6.8)	63(15.3)	
Ioversol	10(9.7)	10(10.0)	
Iopromide	65(63.1)	281(68.2)	
Iodixanol	5(4.9)	15(3.6)	
Dose (mean ± SD[d], g)	69.8 ± 15.9	66.9 ± 12.0	0.0845[e]
CT[f] region			
Abdomen (Pelvis)			0.0158[c]
Yes	11(10.7)	87(21.1)	
No	92(89.3)	325(78.9)	
Liver/spleen/ pancreas			0.2899[c]
Yes	21(20.4)	66(16.0)	
No	82(79.6)	346(84.0)	
Chest			0.4565[c]
Yes	16(15.5)	77(18.7)	
No	87(84.5)	335(81.3)	
Brain			0.3446[c]
Yes	14(13.6)	72(17.5)	
No	89(86.4)	340(82.5)	
Neck			0.2251[c]
Yes	14(13.6)	77(18.7)	
No	89(86.4)	335(81.3)	
Kidney			0.0075[c]
Yes	9(8.7)	12(2.9)	
No	94(91.3)	400(97.1)	
Thyroid			0.1500[c]
Yes	6(5.8)	12(2.9)	
No	97(94.2)	400(97.1)	
Others			0.1553[c]
Yes	20(19.4)	57(13.8)	
No	83(80.6)	355(86.2)	

[a] AR: Adverse Reaction
[b] CM: Contrast Media
[c] Chi-square test
[d] SD: Standard deviation
[e] T-test
[f] CT: Computed Tomography

group. The percentage of CT scans of the kidney was significantly higher in the AR group than in the control group, whereas the percentage of scans of the abdomen (pelvis) was significantly lower (Table 3).

Univariate logistic regression analysis

Among the included patient factors, females [odds ratio (OR): 2.091; 95% confidence interval (CI): 1.345-3.252], allergy history (OR: 2.707; 95% CI: 1.274-5.752), and comorbid asthma (OR: 5.203; 95% CI: 1.372-19.735) were confirmed as significant variables that increase the risk of contrast media-induced adverse reactions.

Regarding contrast media factors, using Iohexol as a contrast medium (OR: 11.995; 95% CI: 4.067-35.379) and scanning the kidney during CT (OR: 3.191; 95% CI: 1.307-7.795) were confirmed to be significant variables that increased the risk of adverse reactions, whereas scanning the abdomen (pelvis) during CT (OR: 0.447; 95% CI: 0.229-0.872) was confirmed as a significant variable that decreased the risk of adverse reactions.

Table 4. Multivariate logistic regression analysis determining the effects of different factors on adverse reactions to contrast media.

Risk factors	Odds Ratio (95% CI)	p-value
Sex (female)	2.206(1.353-3.598)	0.0015
Age (years)	0.987(0.973-1.002)	0.0813
Dose (g)	1.001(0.998-1.003)	0.6472
CM[a]		
Iohexol vs. Iomeprol	9.981(2.361-42.193)	0.0023
Ioversol vs. Iomeprol	1.659(0.498-5.520)	0.2280
Iopromide vs. Iomeprol	2.308(0.893-6.342)	0.7321
Iodixanol vs. Iomeprol	2.858(0.688-11.876)	0.8302
Allergy history (yes)	3.982(1.742-9.101)	0.0011
Comorbidity (Asthma, yes)	6.619(1.377-31.826)	0.0183

[a] CM: Contrast Media

Multivariate logistic regression analysis

The characteristics of the subjects who underwent kidney CT scans were exactly the same as those who were administered the contrast medium Iohexol and they were therefore excluded from multivariate logistic regression analysis.

The results of the multivariate logistic regression analysis showed that the risk of contrast media-induced adverse reactions was 2.206-fold higher in females than in males (OR: 2.206; 95% CI: 1.353-3.598). The use of Iohexol resulted in a 9.981-fold higher risk of adverse reactions compared to the use of Iomeprol, which had the lowest frequency of adverse reactions (OR: 9.981; 95% CI: 2.361-42.193). The presence of an allergy history was associated with a 3.982-fold higher risk of adverse reactions compared to the absence of one (OR: 3.982; 95% CI: 1.742-9.101), and the presence of asthma as comorbidity led to a 6.619-fold higher AR risk (OR: 6.619; 95% CI: 1.377-31.826) (Table 4).

Table 5. Distribution of adverse reactions to contrast media by patient status, manifestations of adverse reactions, and total number of adverse reactions.

AR[a] group	Overall (N = 103)
	N (%)
Patient status	
Inpatient	16 (15.5)
Outpatient	87 (84.5)
Manifestations of AR[a]	
Moderate	
Dyspnea	3 (2.9)
Mild	
Hives	89 (86.4)
Itching	85 (82.5)
Flushing	14 (13.6)
Rash	3 (2.9)
Edema	10 (9.7)
N/V[b]	4 (3.9)
Cough	4 (3.9)
Nasal discharge	2 (1.9)
Chills	1 (1.0)
Dizziness	2 (1.9)
Total number of AR[a]	
1 type	11 (10.7)
2 types	75 (72.8)
More than 3 types	17 (16.5)

[a]AR: Adverse Reaction (If more than 2 types of AR occurred in the same patient, each AR was considered as one manifestation)
[b]N/V: Nausea/Vomiting

Frequency of contrast media-induced adverse reaction occurrence

Within our study group, no severe adverse reactions were reported. For moderate adverse reactions, dyspnea was found in 3 subjects (2.9%). For mild adverse reactions, hives were the most common, occurring in 89 subjects (86.4%), followed by itching in 85 subjects (82.5%) and flushing in 14 subjects (13.6%). Two types of adverse reactions simultaneously occurring were reported in 75 subjects (72.8%), and three types were reported in 17 subjects (16.5%) (Table 5).

Among patients with adverse reactions, outpatient-based examinations were conducted on 87 subjects (84.5%), accounting for the majority. Regarding the time of adverse reaction onset, 96 subjects (93.2%) had immediate adverse reactions, whereas 7 subjects (6.8%) had late adverse reactions.

Discussion

Low osmolar nonionic contrast media are commonly used during CT scans and produce notably fewer adverse reactions compared to hyperosmolar ionic contrast media, which were more commonly used in the past. However, various adverse reactions and deaths have still been reported.[4] This study investigated the risk factors for adverse reactions and analyzed the frequency of adverse reaction occurrences in patients who were administered iodinated contrast media during CT scans at Yeoeuido St. Mary's Hospital, a tertiary teaching hospital in Seoul, Korea.

In this study, patients were administered various types of iodinated contrast media, including iohexol, iomeprol, ioversol, iopromide, and iodixanol. Iohexol, iomeprol, ioversol, and iopromide are nonionic, monomeric, low osmolar contrast media, while iodixanol is a nonionic, dimeric, iso-osmolar contrast medium.[12,16]

Of the 17,408 subjects who underwent CT scans with iodinated contrast media during the study period, adverse reactions were reported in 103 subjects (0.6%).

The results of multivariate logistic regression analysis showed that the risk of contrast media-induced adverse reactions was 2.206-fold higher in females, which was consistent with the results from a study by Wendt-Nordahl *et al*.[17] In that study, age did not affect the risk of contrast media-induced adverse reactions. However, a study by Kobayashi *et al*. found that the risk of contrast media-induced adverse reactions was 1.8-fold higher in subjects younger than 50 years old.[11]

These results showed that subjects who have an allergy history and/or asthma exhibited 3.982- and 6.619-fold higher risks of incurring contrast media-induced adverse reactions, respectively, which is similar to the study results of Wendt-Nordahl *et al.*[17] In a study by Kobayashi *et al*., the risk of contrast media-induced adverse reactions increased by 1.9-fold in the presence of an allergy history, while the presence of asthma did not affect contrast media-induced adverse reactions.[11]

Katayama *et al*. indicated that the risk of adverse reactions was high in patients with a history of contrast media administration,[5] but the present study showed no association between previous contrast media administration and the risk of contrast media-induced adverse reactions. When analyzing the results with respect to the types of contrast media used, the use of Iohexol was associated with a 9.981-fold higher risk of adverse reactions based on logistic regression analysis using Iomeprol as a reference.

Most of the contrast media-induced adverse reactions that were considered in this study were adverse skin reactions, which occurred in 98 subjects (95.1%). This was similar to the

results of a study by Mortele *et al*., which showed adverse skin reactions in 98.7% of patients who had contrast media-induced adverse reactions.[8)]

Of the patients with adverse reactions, outpatient-based examinations were performed on 87 subjects (84.5%), and inpatient-based examinations (including in emergency rooms) were performed on 16 subjects (15.5%). For inpatients, their histories could be sufficiently verified, and further examinations could be conducted after proper premedication when necessary. Conversely, for outpatients, consent for examination was supplied during examinations that had occurred several months prior, and the occurrence of previous adverse reactions during the use of contrast media, allergy history, and major comorbidity were confirmed by the patients in the examination room on the day of the examination. Because this case relied only on patients' memories, it has limitations regarding the sufficient collection of data on factors that increase the risk of adverse reactions.

In the results, immediate adverse reactions that occurred within 1 hour of contrast media administration were identified in 96 subjects (93.2%), which accounts for the majority of the adverse reactions. Such results showing that most contrast media-induced adverse reactions are immediate adverse reactions are in agreement with previous studies.[5,18)]

This study had the following limitations: 1) It was a retrospective study using electronic medical records and therefore the included data may be incomplete; 2) It was performed in a single medical center on a relatively small number of patients.

Conclusion

This study found that female sex, the use of Iohexol as a contrast medium, an allergy history, and comorbid asthma were risk factors for contrast media-induced adverse reactions. For safe contrast media utilization, evaluations of whether an individual patient possesses risk factors for contrast media-induced adverse reactions should be performed prior to contrast media administration. Furthermore, health care professionals are required to prevent adverse reactions in at-risk patients by methods such as proper premedication administration.

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