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Protective Effect of Oral Steroid Premedication: Adverse Reactions to Nonionic Iodine Contrast Media for Computed Tomography

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Abstract

This study aimed to investigate the protective effect of oral steroid premedication in terms of adverse reactions to non-ionic contrast media. We investigated the incidence of adverse reactions among patients who underwent contrast-enhanced computed tomography. Patients in the premedication group took 30 mg of prednisolone orally the night before and on the morning of the scheduled computed tomography. Sixty-five patients received the same contrast media. Among them, 56 took prednisolone orally prior to the procedure (premedication without change of contrast media group) and nine without premedication (no premedication and no change of contrast media group). In total, 379 patients received different contrast media. Among them, 340 took prednisolone orally (premedication with change of contrast media group), while 39 did not take the premedication (no premedication with change of contrast media group). The adverse reaction rates in the premedication with change of contrast media and no premedication with change of contrast media groups were 1.8% (6/340 cases) and 2.6% (1/39 cases) (P = 0.54), respectively. The incidence of adverse reaction after the administration of non-ionic iodinated contrast media did not differ significantly based on whether an oral steroid was administered prior to compute tomography. Our evaluation is limited due to the small sample size of the contrast media-changed group. However, even if premedication with steroids is effective, it may only result in an adverse reaction reduction rate of ≤3%.

Keywords

Iodine Contrast Media, Oral Steroid Premedication, Breakthrough Reaction,

Prednisolone, Adverse Reactions

1. Introduction

Contrast media used for computed tomography (CT) imaging usually contain iodine that efficiently absorbs x-rays. They have high clinical utility in the assessment of anatomical structures. Iodine contrast media can be classified as ionic or nonionic. Their use may be associated with side effects, especially in patients allergic to them. The incidences of side effects are reportedly 4.17% - 12.66% and 0.69% - 3.13% for ionic [1] [2] and nonionic contrast media [1] [2] [3], respectively. Serious adverse reactions requiring immediate treatment reportedly occur in 0.22% and 0.004% - 0.04% of patients due to ionic and nonionic contrast media, respectively.

Although the American College of Radiology guidelines have proposed oral steroid premedication protocols to prevent adverse reactions [4], some patients may still experience reactions to contrast media despite premedication (breakthrough reaction) [5]. Steroid premedication can reduce the rate of adverse reactions to ionic contrast media [6]. Patients who have experienced adverse reactions to contrast media had a higher incidence of adverse reactions than those who have not [1]. In contrast, another study reported no significant difference in the incidence of adverse effects due to nonionic contrast media after steroid administration [7]. However, the problem with this study is that the results were tabulated by including cases in which antihistamines were used in combination with steroid premedication and intravenous administration. Previous studies have reported that the incidence of side effects differs depending on the type of contrast media used [8]. Therefore, this study aimed to investigate the effects of oral steroids taken before the procedure in preventing adverse reactions to nonionic contrast media. In addition, we also examined whether the incidence of side effects differed depending on the contrast media to which the patient had previously experienced adverse reactions.

2. Methods

This study was approved by the Institutional Review Board of our institution. The need for informed consent was waived due to the retrospective nature of the study.

2.1. Selection of Contrast Media

We used four different types of iodinated contrast media, including Iopamidol (Iopamiron; Bayer Co. Ltd., Osaka, Japan), Iohexol (Omnipaque; GE Healthcare Pharma Co. Ltd., Tokyo, Japan), Iomeprol (Iomeron; Bracco-Eisai Co. Ltd., Tokyo, Japan), and Ioversol (Optiray; Gerbe Japan Co. Ltd., Tokyo, Japan) according to the body weight of the patient. The contrast media were warmed to

36.5˚C before intravenous administration.

2.2. Administration of Oral Steroids as Premedication

The decision to administer oral steroids as premedication was made by the clinician according to individual case conditions and the patient's preferences. This was a non-interventional study on the effect of oral steroid premedication in preventing adverse events after the administration of contrast media. The patients were verbally informed about the physician's decision to administer oral steroids and were premedicated with an oral steroid if they had a history of allergic reactions to iodine-based contrast media. At our institution, medication administration before the use of contrast media was in accordance with the recommendations of the American College of Radiology [4]. Patients in the premedication group were administered 30 mg of prednisolone orally the night before and the morning when the CT was performed. Intravenous injection of steroids or antihistamines was used in cases of emergency CT scans; however, these cases were excluded from this study.

Patients who were premedicated with oral prednisolone took it at least 3 h before undergoing contrast-enhanced CT. This timing was based on the findings of a previous study where the incidence of adverse reactions was not reduced if the patient was premedicated with steroids < 3 h before contrast-enhanced CT [9].

2.3. Study Population

This cross-sectional study investigated the incidence of adverse reactions in patients who underwent contrast-enhanced CT at our hospital between July 2017 and March 2022. Patients who experienced side effects owing to the administration of contrast media included those who underwent contrast-enhanced CT before July 2017. These comprised patients who experienced adverse events after contrast media administration at other hospitals and underwent examinations at our hospital. Patients with a history of asthma, food allergies, and cardiac disease were excluded. The patients enrolled in the study were selected using the continuous sampling method.

Sixty-five study participants received the same contrast media. Among them, 56 patients took 30 mg of prednisolone orally before the procedure (Premedication and without change of contrast media group), while nine took no premedication (No premedication and without change of contrast media group). In total, 379 patients received different contrast media. Among them, 340 patients took 30 mg of prednisolone orally (Premedication and with change of contrast media group), while 39 did not take premedication (No premedication and with change of contrast media group). A total of 64,673 patients had no history of adverse reactions to contrast media; these patients were exposed to contrast media for the first time or subsequently (non-history of adverse reaction group). The demographic data and characteristics of the patients included in the study and the

type of contrast medium associated with previous adverse reactions are shown in Table 1.

2.4. Statistical Analysis

Fisher's exact test was used to assess the differences between the groups. A *P*-value of < 0.05 was considered statistically significant [10]. Residual analysis was performed if a significant difference was found in the statistical analysis of multiple groups. The significance level of the calculated adjusted residual absolute value was 1.96. To determine a relationship, residual analysis was performed on the data for each type of contrast media that had led to a previous adverse reaction in the premedication and change in contrast media group.

Statistical analysis was performed using the R software (version 3.4.1, R Foundation, Vienna, Austria) and SPSS (ver. 23.0 for Windows; IBM Corp., Armonk, NY, USA).

The sample size was calculated using *G Power* 3.1 software, which gave a statistical power of 0.95 [11].

2.5. Rate of Adverse Reactions

The severity of the adverse reaction was graded based on the American College of Radiology guidelines [4], and the rate of adverse reactions was calculated for each group. The grading systems of adverse reactions were as follows:

Table 1. Demographics and characteristics of the patients and the type of contrast medium associated with previous adverse reactions.

	Number of cases	Premedication without change of contrast media group	Premedication with change of contrast media group	No premedication and no change of contrast media group	No premedication with change of contrast media group
		39	340	56	9
Age	Mean (years)	67.5	67.1	61.3	64.6
Sex	Male	31	178	39	5
	Female	8	162	17	4
Severity of previous adverse reactions	Grade 1	39	337	56	9
	Grade 2	0	3	0	0
	Grade 3	0	0	0	0
Type of contrast media that led to previous adverse reactions	Iopamidol	22	196	3	5
	Iomeprol	5	38	0	0
	Iohexol	12	101	41	3
	Iopamidol/Iomeprol	0	0	0	0
	Iopamidol/Iohexol	0	5	10	1
	Iohexol/Iomeprol	0	0	1	0
	Iopamidol/Iohexol/Ioversol	0	0	1	0

Grade 1: nausea, mild vomiting, urticarial rash, itching, and mild laryngeal discomfort; Grade 2: severe vomiting, severe urticarial rash, bronchospasm, facial and/or laryngeal edema, and vasovagal reaction; Grade 3: hypotensive shock, respiratory arrest, cardiac arrest, and convulsions.

The incidence of breakthrough reactions was determined, and the type and severity of the breakthrough reactions were compared with those of the index reactions.

In previous reports on the determination of sample size, the adverse reaction rate with the use of a nonionic contrast media was 0.7% [4], whereas it was 5.2% in the group that changed the contrast media [7]. Therefore, since oral steroid premedication may reduce the incidence of adverse drug reactions by approximately 3.0%, the sample size was determined by estimating the incidence of adverse drug reactions after oral steroid premedication as 2.0%. The required sample size was calculated to be 378 by setting β as 0.2 to ensure that sufficient power $(1 - \beta)$ to determine the sample size was 0.8 [12] [13].

3. Results

The incidence and grade of adverse reactions are shown in **Figure 1** and **Table 2**. The incidence of adverse reactions in the Premedication and with change of contrast media group (Premedication and with change of contrast media group) was 1.8% (6/340 cases), while that in the change in contrast media-alone group

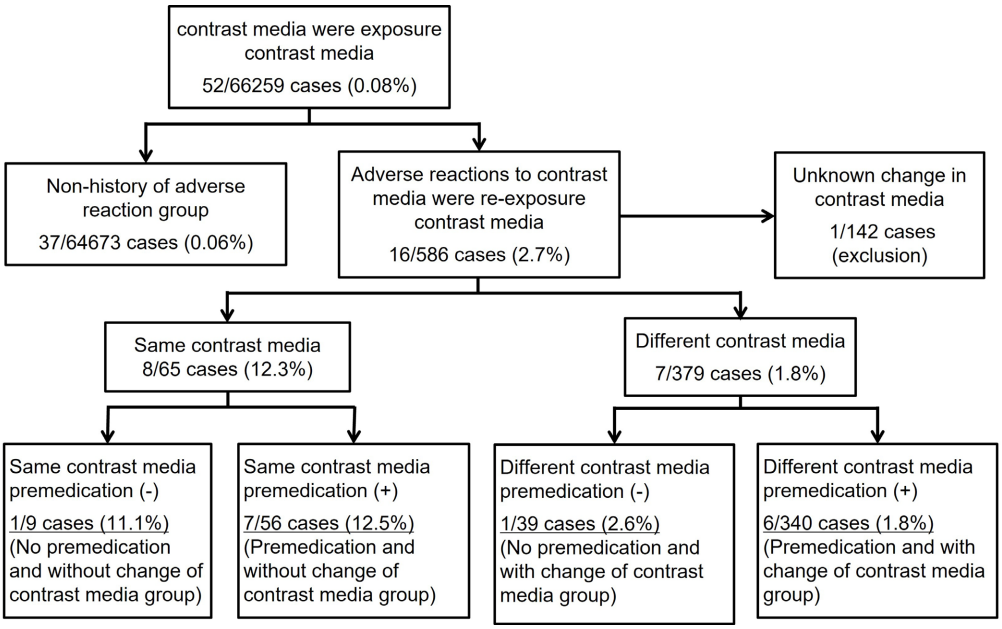

Figure 1. Flowchart of the patient population and adverse reaction rate. The incidence of adverse reactions in the premedication and changing contrast media group was 1.8% (6/340 cases), while that in the change in contrast media-alone group was 2.6% (1/39 cases) ($P = 0.49$). The rate of adverse reactions in the no-premedication and no-change in contrast media group was 11.1% (1/9 cases), while that in the premedication-alone group was 12.5% (7/56 cases) ($P = 1.00$). The rate of adverse reactions in the non-risk group (no history of adverse reactions to contrast media) was 0.06% (37/64,673 cases).

Table 2. Severity of previous adverse reactions to iodinated contrast media. Differences in the grade of adverse reactions to previous contrast media administration is compared with that of present contrast administration. Only one patient in the premedication alone group had a higher grade of adverse reaction in the current study than that in the previous study. The other groups either had no adverse reactions or had the same adverse reaction grade as that of the previous study.

	Reaction rates	Non-history of adverse reaction group		Premedication without change of contrast media group		Premedication with change of contrast media group		No premedication and no change of contrast media group		No premedication with change of contrast media group	
		37/64,673	0.06%	1/39	2.6%	6/340	1.8%	7/56	12.5%	1/9	11.1%
Total reactions grade	Grade 1	35		1		6		6		1	
	Grade 2	1		0		0		1		0	
	Grade 3	1		0		0		0		0	

(No premedication and with change of contrast media group) was 2.6% (1/39 cases) (P = 0.49). The rate of adverse reactions in the no-premedication and no-change in contrast media group (No premedication and without change of contrast media group) was 11.1% (1/9 cases), while that in the premedication-alone group (No premedication and without change of contrast media group) was 12.5% (7/56 cases) (P = 1.00). The rate of adverse reactions in patients with no history of adverse reactions was 0.06% (37/64,673 cases).

Only one patient in the premedication alone group had a higher grade of adverse reaction in this study than that in the previous CT scan. The remaining groups had no adverse reactions or the same adverse reaction grades as in the previous CT scan (Table 2).

In the premedication and change in the contrast media group, the adverse reaction rates for the different contrast media were 0.5% (1/196 cases), 5.0% (5/101 cases), 0.0% (0/38 cases), and 0.0% (0/5 cases) for Iopamidol, Iohexol, Iomeprol, and other contrast media group (Iopamidol and Iohexol) ($P < 0.05$), respectively. The results of the residual analysis are shown in Figure 2 and Table 3. The number of adverse events that occurred in this study was compared with the number of adverse events that occurred after a previous administration of different types of contrast agents. Significant differences were found when Fisher's exact probability test was performed among Iopamidol, Iohexol, and Iomeprol for the type of adverse reactions that had occurred previously. In addition, the residual analysis showed that the number of patients who experienced adverse reactions due to contrast media was significantly higher among those who experienced adverse reactions to Iohexol and significantly lower among those who experienced adverse reactions to Iopamidol.

4. Discussion

The ACR guidelines have not established the efficacy of steroid premedication in reducing the side effects. However, premedication may be effective in reducing the occurrence of side effects; therefore, premedication may be considered. Approximately 20% of imaging facilities administer steroids intravenously before

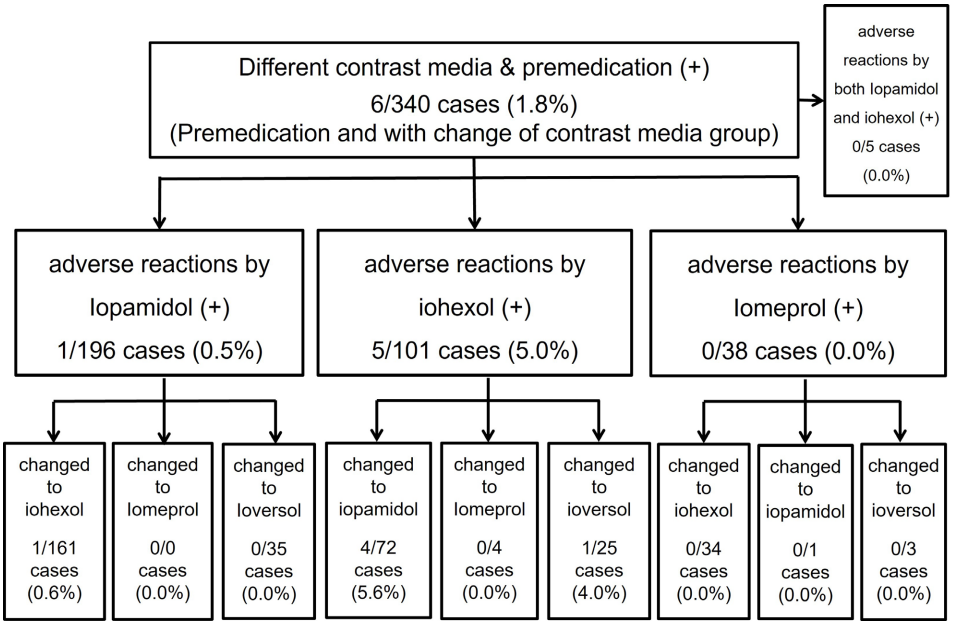

Figure 2. The number of adverse reactions to contrast media with previous adverse reactions. In the premedication with change in contrast media group, the adverse reaction rates for the different contrast media were 0.5% (1/196 cases), 5.0% (5/101 cases), 0.0% (0/38 cases), and 0.0% (0/5 cases) for Iopamidol, Iohexol, Iomeprol, and other contrast media (Iopamidol and Iohexol), respectively.

Table 3. Number of adverse reactions to previously administered contrast media. The number of adverse reactions that occurred in this study was compared with the number of adverse reactions occurring after previous administration of different types of contrast media. When Fisher's exact probability test was performed among Iopamidol, Iohexol, and Iomeprol for the type of adverse reactions that had occurred previously, significant differences were found. In addition, the residual analysis showed that the number of patients who experienced side effects due to contrast media was significantly higher among those who experienced side effects with Iohexol and significantly lower among those who experienced side effects with Iopamidol.

			Type of contrast media that led to previous adverse reactions		
			Iopamidol	Iohexol	Iomeprol
Adverse reactions that occurred in this study	+	n	1	5	0
		adjusted residual	−2.1*	2.9*	−0.9
	−	n	195	96	38
		adjusted residual	2.1*	−2.9*	0.9

* = $P < 0.05$.

acquiring CT images with iodine-based contrast media [14]. A previous study [7] reported that the incidence of adverse drug reactions after the contrast media was changed and steroid premedication was administered was 2.7%, whereas the incidence of adverse drug reactions when steroid premedication was not administered was 5.2%. According to the present study, steroid premedication is

more effective in reducing adverse effects, possibly due to the influence of the concomitant use of antihistamines and intravenous steroid premedication.

Unlike previous studies [7], this study investigated whether oral steroids, without concomitant antihistamines or intravenous steroids, could reduce the incidence of contrast-induced adverse effects. However, the results did not suggest that oral steroids could reduce the incidence of adverse reactions. The power and significance of the results vary depending on the sample size. However, in the case of the 379 samples collected in this study, even if oral steroids were effective in reducing the side effects of contrast media, they could only reduce side effects by 3.0% or less. However, premedication with intravenous steroids is reportedly effective in patients who previously experienced adverse reactions to nonionic contrast media [15]. These results suggest that intravenous steroids may be more useful than oral steroids in reducing adverse reactions to nonionic contrast media. However, as the effectiveness of steroids was too low to determine the efficacy, the risk of premedication with steroids should also be considered.

Moreover, oral premedication in high-risk inpatients is associated with an increased length of hospital stay, increased time to CT, increased risk of hospital-acquired infections, and increased costs compared with non-premedicated controls [16]. Therefore, caution must be exercised when administering steroids prophylactically. Changing the contrast media and administering antihistamines may also reduce the rate of adverse reactions to contrast media [7] [17]. Therefore, patients at high risk of developing adverse reactions to contrast media should consider changing the contrast media and administering antihistamines.

There was a significant difference in the incidence of adverse reactions in this study, which was lower in the group with a history of adverse reactions to Iopamidol and higher in the group with a history of adverse reactions to Iohexol. It has been reported that the incidence of adverse reactions decreases in patients in the order of those receiving Iomeprol, Iopamidol, and Iohexol [8]. Therefore, even if a contrast media that previously caused an adverse reaction is replaced with another contrast media during the subsequent scan, the recurrence rate of adverse reactions may vary depending on which contrast media previously caused the adverse reactions. Therefore, it may be necessary to classify the types of contrast media that have previously caused adverse reactions and consider the risks.

It has been reported that non-contrast studies can also cause symptoms similar to those of contrast-induced side effects [18]. In this study, whether an adverse reaction was caused by contrast media was determined based on the patient's complaints and the physician's examination to confirm that it was caused by the contrast media. The results have been tabulated. Therefore, we believe that only contrast-induced side effects were included in the data. Our study had some limitations. The sample size was small, and the statistical power calculated after the result was as low as 0.26 with *G power*. However, we postulate that the statistical power was low because the adverse reactions reduction effect of stero-

ids was almost non-existent. Furthermore, our results did not support the efficacy of steroids, but further increases in sample size may support the efficacy.

Moreover, we did not consider the differences in the rate of adverse reactions to the different types of contrast media administered. In the future, it is necessary to analyze this aspect further.

Furthermore, patients with high severity of previous adverse reactions (≥Grade 2) have been reported to have an increased risk of adverse reactions to contrast media [19]; however, in this study, most patients had mild (Grade 1) previous adverse reactions to contrast media, and this may have affected the results.

5. Conclusions

Premedication with oral steroids may not have significantly affected the incidence of adverse reactions after nonionic iodinated contrast media administration in CT. However, our evaluation is limited due to the small sample size of the contrast media-changed group, and even if premedication with steroids is effective, it may only result in an adverse reaction reduction rate of ≤3%.

Adverse reaction rates vary depending on the type of contrast media to which the previous adverse reaction occurred. Therefore, it may be necessary to classify the types of contrast media that have previously caused adverse reactions and consider the risks.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

CT: Computed Tomography