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A Retrospective Study to Compare the Effects of Methylprednisolone and Dexamethasone in 35 Patients with Anaphylactic Shock Due to Iodinated Contrast Media During Cardiac Catheterization

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Background: This retrospective study aimed to compare the effects of methylprednisolone and dexamethasone in 35 patients with anaphylactic shock due to iodinated contrast media (ICM) during cardiac catheterization.


Material/Methods: Thirty-five patients diagnosed with ICM-related anaphylactic shock were enrolled. Nineteen patients received methylprednisolone, while 16 patients received dexamethasone.

Results: The mean age of patients was 59.8 years in the methylprednisolone group and 57.2 years in the dexamethasone group ($P=0.502$). Most patients were male (82.9% [26/35]). The groups were matched for cardiac function, kidney function, comorbidities, prior contrast, previous radiocontrast media reactions, and allergic tendencies (all $P>0.05$). The severity of coronary artery disease, assessed using the SYNTAX II score, was similar between groups ($P=0.620$). Six patients died from ICM-induced anaphylactic shock. There was no significant difference in mortality between the 2 groups ($P=1.000$).

Conclusions: There was no significant difference in patient mortality from anaphylactic shock associated with ICM during cardiac catheterization between the methylprednisolone and dexamethasone groups.


Keywords: 21-((aminopropyl)thio)dexamethasone • Corticosteroid Methanetriol Mixture • Iodine Compounds

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Background

Adverse reactions to iodine contrast media (ICM) are classified as either acute or delayed reactions. Acute adverse drug reactions are defined as those occurring within 1 h after injection of ICM, compared with delayed reactions, which occur within 1 to 7 h [1]. Anaphylactic shock caused by ICM is the most serious manifestation of ICM allergy, which is a rapid-onset reaction. If left untreated, it can lead to catastrophic consequences. Although anaphylactic shock induced by ICM is uncommon, with an incidence of 0.001 to 0.003% [2,3], once it occurs, it can have catastrophic results, and prompt recognition and immediate treatment are essential. Studies have shown that these adverse drug reactions are mainly related to the activation of complement and fibrinolytic systems as well as to the release of histamine, prostaglandins, leukotrienes, and bradykinins [1,4]. The production of prostaglandins and leukotrienes is dependent on the mobilization of arachidonic acid from cell membranes [5]. Steroids have long been known to reduce inflammation and suppress immune reactions. From this perspective, corticosteroids are likely to be useful for the treatment of adverse reactions. According to the European Society of Urogenital Radiology (ESUR), intravenous (i.v.) injection of high-dose corticosteroids can have an immediate stabilizing effect on the cell membrane and could be used as a second-line treatment [6]. However, there is currently no consensus on how to use corticosteroids in ICM-induced anaphylactic shock [7-9]. Many questions remain, including which corticosteroid to use, at what dose and for how long. Therefore, this retrospective study aimed to compare the effects of methylprednisolone and dexamethasone in 35 patients with anaphylactic shock due to ICM during cardiac catheterization.

Material and Methods

Design and Setting

This study protocol was approved by the local Institutional Review Board (no. 2015641). Written informed consent was obtained from patients or guardians. We used a retrospective study design to assess the effectiveness of methylprednisolone and dexamethasone in ICM-related anaphylactic shock.

Selection of Patients

We used the electronic medical database in our hospital to search for patients with ICM-induced anaphylactic shock, based on the ATC code of causative agents, from January 2009 to December 2020. All patients who underwent cardiac catheterization for the evaluation of coronary artery lesions with ICM-induced anaphylactic shock were eligible according to the inclusion criteria. The exclusion criteria were as follows: (1) patients on corticosteroid

therapy for any reason, (2) pregnant and lactating women, and (3) intraoperative echocardiography showing medium- or large-sized pericardial effusion. ICM-induced anaphylactic shock was defined as a systolic blood pressure lower than 90 mmHg accompanied by decreased peripheral tissue perfusion, which occurred within 1 h after injection of ICM. If the patient was diagnosed with ICM-related anaphylactic shock, they received a bolus of 500 to 1000 mg of methylprednisolone, or 10 mg of i.v. dexamethasone. The patients with anaphylactic shock were divided into methylprednisolone and dexamethasone groups.

Data Collection

The patients' baseline information was extracted from the electronic medical record.

General information, including age, sex, chronic disorder, smoking, food and drug history of allergy, current medicine, laboratory test results, number of contrast exposures, and underlying diseases based on ICD-10, were collected. Lifestyle habits, height (cm), and weight (kg) were recorded, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The severity of coronary arterial disease assessment was calculated by the SYNTAX II score [10]. The SYNTAX II score was measured by an intervention cardiologist that was blind to the grouping of patients. If patients had a history of allergy with some drugs and/or food or with allergic asthma, these patients were considered to have allergic tendency.

Skin Tests

Skin tests with ICM were done with undiluted and 1:10 diluted solutions [11]. The results were interpreted 15 min after the prick or intradermal injection. The interpretation of the skin prick test was with the method reported by Caimmi et al [12].

Statistical Analysis

Based on the normality of variables, continuous variables are presented as means with standard deviations or as medians (interquartile range). Group differences were compared with the independent *t* test or Mann-Whitney U test. Categorical variables are expressed as absolute numbers and percentages. Differences between groups were analyzed with the chi-squared or Fisher's exact test. Statistical analyses were performed with SPSS for Windows (version 21, IBM Corp, Armonk, NY, USA). A *P* value <0.05 was considered statistically significant.

Results

All the patients used the non-ionic contrast medium during the procedure. Thirty-five patients diagnosed with ICM-induced

Table 1. Basic characteristics of the study patients with anaphylactic shock.

Variables	Dexamethasone (n=16)	Methylprednisolone (n=19)	P
Clinical characteristics			
Age, years	57.2±10.9	59.8±11.6	0.502
Male, n (%)	13 (81.3%)	16 (84.2%)	1.000
BMI (kg/m ²)	25.2±2.7	26.0±2.7	0.412
NYHA FC I-II	15 (93.8%)	18 (94.7%)	1.000
NYHA FC III-IV	1 (6.2%)	1 (5.3%)	1.000
Comorbidities, n (%)			
Hypertension	11 (68.8%)	15 (78.9%)	0.700
Dyslipidemia	11 (68.8%)	16 (84.2%)	0.424
Diabetes mellitus	6 (37.5%)	7 (36.8%)	1.000
Old myocardial infarction	7 (43.8%)	7 (36.8%)	0.739
Old cerebral infarction	1 (6.2%)	2 (10.5%)	0.077
Blood test			
NT-proBNP, pg/mL	485.0 (147.6, 1079.9)	190.0 (121.0, 449.0)	0.621
eGFR(ml/min/1.73 m ²)	84.3±26.3	79.6±25.1	0.594
Prior contrast	10 (62.5%)	15 (78.9%)	0.454
Previous RCM reactions	1 (6.3%)	0 (0.0%)	0.457
Allergic tendencies	5 (31.3%)	5 (26.3%)	1.000

Data are presented as means±SD, median, or as numbers and percentages. BMI – body mass index; NYHA – New York Heart Function; NT-proBNP – N-terminal pro-brain natriuretic peptide; eGFR – estimated glomerular filtration rate; RCM – radiocontrast media.

anaphylactic shock who met the inclusion criteria were enrolled. A total of 19 patients received methylprednisolone, and 16 received dexamethasone. Baseline characteristics are summarized in **Table 1**. The mean age of patients was 59.8±11.6 and 57.2±10.9 years in the methylprednisolone and dexamethasone groups, respectively ($P=0.502$). The youngest patient was 33 years old and the oldest was 81 years old. The distribution of age in the groups is depicted in **Figure 1**. Most patients were men (82.9% [26/35]). The 2 groups were matched for cardiac function, kidney function, comorbidities, prior contrast, previous radiocontrast media reactions, and allergic tendencies (all $P>0.05$).

Table 2 shows a comparison of the procedural characteristics, allergic manifestations, usage of medication, and mortality between the methylprednisolone and dexamethasone groups, respectively. Anaphylactic shock occurred most often 5 to 25 min after the injection of ICM. The main symptoms were hypotension, skin rash, dyspnea, and abnormal consciousness. The most common symptom was hypotension. The condition of 9 patients did not improve after treatment with medications; therefore, they received intra-aortic balloon pumping. Three patients underwent tracheal intubation because oxygen saturation could not be maintained; 1 patient was in the dexamethasone group, and 2 were in the methylprednisolone

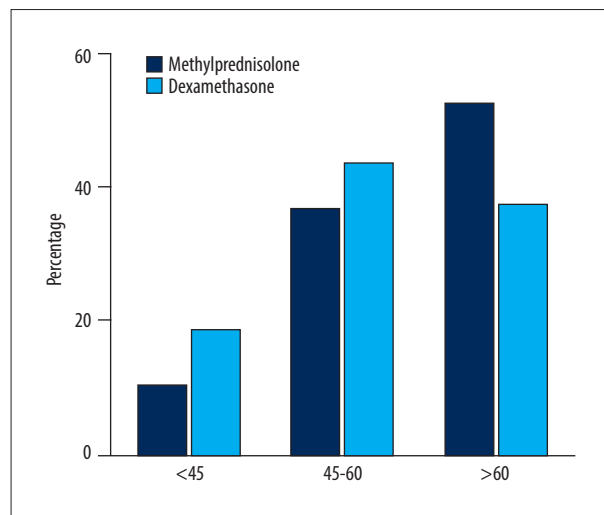


Figure 1. The age distribution with iodine contrast media-related anaphylactic shock between methylprednisolone group and dexamethasone group.

group. Six patients died from ICM-induced anaphylactic shock. There was no significant difference in mortality between the 2 groups ($P=1.000$).

Table 2. The characteristics, allergic manifestations and management during operation.

Variables	Dexamethasone (n=16)	Methylprednisolone (n=19)	P
Contrast dose, mL	13.1±4.3	15.8±13.6	0.447
Symptoms			
Hypotension	16 (100.0%)	19 (100%)	1.000
Urticaria	4 (25.0%)	3 (15.8%)	0.677
Dyspnea	3 (18.8%)	5 (26.3%)	0.700
Abnormal consciousness	2 (12.5%)	3 (15.8%)	1.000
Medication			
Epinephrine	16 (100%)	19 (100.0%)	1.000
H1-receptor blocker	3 (18.8%)	5 (26.3%)	0.700
Norepinephrine	3 (18.8%)	6 (31.6%)	0.460
Dopamine	15 (93.8%)	17 (89.5%)	1.000
SYNTAX II score	24.6±11.8	26.5±11.1	0.620
IABP	4 (25.0%)	5 (26.3%)	1.000
Mechanical ventilation	1 (6.2%)	2 (10.5%)	1.000
Mortality rate	3 (18.8%)	3 (15.8%)	1.000

Data are presented as means±SD or as numbers and percentages. IABP – intra-aortic balloon pump.

Discussion

In the present study, we compared 2 corticosteroids for the treatment of ICM-induced anaphylactic shock. Our results indicated that there was no significant difference in mortality between the methylprednisolone and dexamethasone groups. To the best of our knowledge, there are no data comparing corticosteroids in patients with ICM-related anaphylactic shock.

Ionic high-osmolar radioactive contrast media (RCM) agents are ionic salts that dissociate into cations and anions in solution, while non-ionic low-osmolar RCM agents do not dissociate into separate particles [13]. Adverse reactions related to contrast agents have significantly decreased with the widespread use of non-ionic hypotonic contrast agents. Wang et al reported that allergic-type reactions occurred in 545 (0.6%) patients injected with non-ionic ICM [14]. However, there has been no obvious reduction in severe allergic reactions, and the incidence of mortality resulting from ICM-related anaphylactic shock is similar for ionic and non-ionic contrast media [14-16]. To date, there is no reliable approach that can accurately predict which patients will experience anaphylactic shock after contrast agent injection. However, some studies have found that this is associated with age. Wysowski et al reported that death caused by ICM is more common in the elderly and women [2]. Additionally, Huang et al and Kim et al found that older age, previous multiple exposures to RCM, and iopromide use were related to anaphylactic shock [3,17]. In the study of Kim et al, the mean age of patients with anaphylactic shock

was 57.4±13.2, which was very similar to that in our study. Interestingly, we found that prior multiple exposures to ICM and iopromide use increased the risk of anaphylactic shock. In the present study, 18 (51.4%) patients used iopromide during coronary angiography, and 25 (71.4%) patients had at least 1 prior exposure to contrast agents (data not shown). In other words, although patients had been exposed to ICM without an allergic reaction in the past, that does not guarantee the next exposure to ICM will also be safe. On the contrary, a patient can be more prone to severe allergic reactions. One point that needs to be clarified is that the causal relationship between anaphylactic shock and the type of contrast agent used remains unclear. The number of administrations of other ICMs in the present study was too small to obtain a statistically significant difference. Hence, we cannot conclude that iopromide was more likely to lead to anaphylactic shock than any other ICM; however, iopromide was linked to more severe adverse reaction in patients with anaphylactic shock.

Very little is known about the pathophysiological mechanisms underlying allergic reactions to contrast agents. The mechanism of anaphylactic shock caused by contrast agents is complicated. Mita et al reported that contrast agent-induced adverse reactions can be mediated by immunoglobulin E (IgE) [18]. Another group of investigators also found that histamine release and mast cell triggering are related to severe reactions resulting from iodinated contrast agents, suggesting that an IgE-related mechanism may be associated with severe ICM-induced reactions [19]. However, some studies suggested that

a non-IgE-mediated mechanism is considered to be the cause of fatal reactions to ICM. ICM-induced anaphylaxis is mediated by mast cells. The main etiology of severe allergic reactions is the ionic nature of the compound and the tonicity of the solution [20,21]. Other potential mechanisms include complement activation, release of a variety of cytokines, and the production of bradykinin [22,23]. Corticosteroids are used to treat a variety of inflammation-related diseases, including thyroiditis, autoimmune diseases, and septic shock [24-26]. Adrenaline is the first-line treatment for ICM-related anaphylactic shock. According to the ESUR, i.v. injection of high-dose corticosteroids can have an immediate stabilizing effect on the cell membrane and could be used as second-line treatment [6]. However, there are no data on the use of corticosteroids during the rescue of ICM-induced anaphylactic shock. In the present study, we compared the efficacy of methylprednisolone and dexamethasone in cardiac catheterization with ICM-related anaphylactic shock. Our results suggest that there is no significant difference in mortality between the methylprednisolone and dexamethasone groups. Given that dexamethasone is more easily available and cheap, it is feasible to make dexamethasone as a second-line treatment in patients with ICM-related anaphylactic shock. Interestingly, a recent study showed that dexamethasone and methylprednisolone are both equally effective in treating moderate to severe COVID-19 [27].

Prevention is the best treatment for ICM-associated adverse reactions. Premedication with corticosteroids prior to contrast administration was most effective at reducing the occurrence of mild or moderate reactions. It is worth noting that although steroids can be used prophylactically, there is no guarantee that ICM-induced anaphylactic shock will not occur [28]. Of note,

even if the preoperative skin testing of iodine solution is negative, the patient can still experience anaphylactic shock. As seen in the present study, a patient with a positive iodine test was switched to another ICM and had a negative skin allergy test, but still suffered from ICM-induced anaphylactic shock during the operation.

This study has several limitations. First, it was a retrospective study from a single center. Second, the sample size was relatively small. However, it is difficult to enroll a large number of patients with ICM-induced anaphylactic shock due to the very low incidence rate. Third, no serum sample collection was performed during the operation, and we failed to analyze the mechanisms related to ICM-induced anaphylactic shock.

Conclusions

There was no significant difference in patient mortality from anaphylactic shock associated with ICM during cardiac catheterization between the methylprednisolone and dexamethasone groups.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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