Case Report

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Sudden cardiovascular collapse caused by severe anaphylaxis after cisatracurium use
-a case report-

Syn-Hae Yoon, Ji-Yeon Bang, Hyungseok Seo, and Jun-Gol Song

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Kounis syndrome is an acute coronary syndrome concurrently occurs with allergic or hypersensitivity reactions. In patient with this syndrome, inflammatory mediators released due to an allergic reaction implicate to induce coronary artery spasm and atheromatous plaque rupture. We describe a patient with coronary artery disease who developed acute perioperative myocardial infarction leading to cardiac arrest after the anaphylactic reaction to cisatracurium, which led to a suspicion of Kounis syndrome. Anesthesiologists should be aware that anaphylaxis or allergic reactions can progress to acute coronary syndrome, thereby significantly change the course of the disease. (Korean J Anesthesiol 2014; 67: 412-415)

Key Words: Anaphylaxis, Cisatracurium, Kounis syndrome, Myocardial infarction.

Anaphylaxis is of great concern due to its potential of life-threatening nature. During anaphylaxis or allergic reactions, various inflammatory mediators are released that could progress to acute coronary syndromes. This is termed as "allergic myocardial infarction (MI)," or Kounis syndrome [1]. Although it is not frequently well known and most of the information comes from case reports, coronary artery involvement after allergic reactions are being increasingly reported [1,2]. Various drugs, animals and insect bites associated with allergic reaction have been reported to develop Kounis syndrome [1]. We report a case of acute perioperative MI concurrently occurred with anaphylaxis after cisatracurium administration during general anesthesia.

Case Report

A 66-year-old man a past smoker with a medical history of acute myocardial infarction on the inferior wall due to coronary artery spasm 8 years ago (weight, 67.2 kg; height, 163.5 cm; American Society of Anesthesiologists physical status classification II) was scheduled to undergo laparoscopy-assisted distal gastrectomy with gastroduodenostomy. His functional capacity was higher than 4 metabolic equivalents and he had no previous experience of general anesthesia. Preoperative evaluation showed a normal electrocardiogram (ECG) and no specific lung lesion was found by chest radiography. There was no abnormal

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Corresponding author: Hyungseok Seo, M.D., Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea. Tel: 82-2-3010-3868, Fax: 82-2-470-1363, E-mail: seohyungseok@gmail.com

finding in a pulmonary function test or in conventional laboratory exams. Preoperative thallium single photon emission computerized tomography (SPECT) detected a perfusion defect on the inferior wall, and transthoracic echocardiography (TTE) showed a moderate degree of akinesia on the inferior wall. Both of these findings in thallium SPECT and TTE were detected for 8 years after the previous attack with no development of new ischemic lesions.

When the patient arrived in the operation room, his blood pressure (BP; systolic/diastolic), heart rate, and peripheral oxygen saturation (SpO_2) were 166/94 mmHg, 76 beats/min, and 99% respectively. Preoxygenation with 80% oxygen was performed followed by intravenous administration of midazolam 2 mg and lidocaine 20 mg. Induction was started with a target controlled infusion (TCI; Asan Pump, version 2.0, BionetCo., Seoul, Korea) of propofol and remifentanil at 2 μg/ml and 3 ng/ml, respectively. Cisatracurium (12 mg) was administered and mask-valve ventilation was started after the patient lost his spontaneous breathing. During mask ventilation, a depression in ST segment of more than 3 mm was detected in ECG, and difficulty in manual ventilation was noted. Propofol and remifentanil infusion were immediately stopped, and the patient was promptly intubated followed by ventilation with 100% oxygen. A few minutes later, SpO_2 rapidly decreased and his BP, initially 128/78 mmHg, dropped to 64/42 mmHg. Although vasoactive drugs including phenylephrine and epinephrine were administered, the BP continued to decrease to an undetectable level by a noninvasive BP cuff. Direct arterial pressure was monitored, and a central venous catheter was inserted to maintain fluid therapy and continuous drug administration. The patient quickly developed ventricular fibrillation and we thus initiated a sequential algorithm of cardiopulmonary cerebral resuscitation (CPCR). Immediate defibrillation (200J) followed by manual chest compression was performed with repeated intravenous administration of atropine (0.5 mg) and epinephrine (1 mg). A portable transesophageal echocardiography (TEE) was obtained 20 minutes after CPCR was initiated, which showed global hypokinesia in the myocardial wall with akinesia in the inferior wall. However, the patient had not return of spontaneous circulation for 40 minutes, and the patient showed repeated ventricular fibrillation refractory to defibrillation. An emergent consultation of cardiac surgeons was requested to apply veno-arterial type extracorporeal membrane oxygenation (ECMO) to substitute cardiac function. The patient was transferred to the intensive care unit (ICU) and remained intubated during the application of ECMO. In the ICU, sequential laboratory tests including cardiac enzymes were performed. Upon arrival in the ICU, the patient's serum troponin-I and creatine kinase-MB (CK-MB) levels were 6.292 ng/ml and 34.6 ng/ml respectively, and within 5 hours they were increased to 44.099 ng/ml and 107.3 ng/ml. After 8 hours of ICU admission, 12-lead ECG showed normal sinus rhythm with right bundle branch block. On the same day, the patient had return of drowsy consciousness level from comatose state. After showing improvement on serial ECG and the hemodynamic status of the patient, the ECMO circuit was successfully weaned on the following day. He was remain intubated and sedated for three more days to continue conventional therapies for recovery and discharged to the general ward on the day of extubation. Cardiac enzymes levels were normalized (troponin-I, 1.5 ng/ml;CK-MB, 3.7 ng/ml) 5 days after the incidence had occurred.

On suspicion of anaphylactic reaction as a cause of perioperative MI, serum tryptase level was measured and an intradermal skin test was performed to all anesthetic drugs that had been used during the induction period. The level of serum tryptase was detected on the day of the incidence occurred. Serum tryptase level was 28.6 μg/L, which was higher than normal value (13.5 μg/L). Three days after the incidence, an intradermal skin test was performed and a positive reaction was only seen in cisatracurium at a 1 : 100 dilution. All other drugs rendered negative results.

Discussion

We presented a case of life-threatening anaphylactic reaction to cisatracurium, which concurrently developed with MI. The patient developed ventricular arrhythmia followed by cardiac arrest very rapidly, but no classical features of anaphylaxis or hypersensitivity reactions were detected. However, we had previously experienced several cases of sudden cardiovascular collapse and respiratory failure caused by anaphylaxis due to cisatracurium, thereby prompt management targeting anaphylaxis along with sequential resuscitation process was possible [3].

Perioperative acute coronary syndrome is difficult to be detected during general anesthesia. Instead of classical physical symptoms such as chest pain and dyspnea, ST segment changes on ECG and an elevation in serum cardiac enzymes levels such as troponin-I are considered to be useful measures [4,5]. In the present case, ST depression on ECG and marked elevation of serum troponin-I and CK-MB levels were detected, suggesting acute coronary syndrome. However, perioperative TEE could not find any new lesion that could cause sudden acute coronary involvement, suggesting that such an acute coronary syndrome must have been triggered from an another event. Anaphylaxis was suspected to be a possible reason for the sudden cardiovascular collapse.

Neuromuscular blocking agents (NMBA) account for the most causative agents for anaphylaxis during anesthesia [6]. Cisatracurium is known to have low potency of activating nonspecific mast cell and basophil that are responsible for hypersensitivity reaction compared with other NMBAs such as ro-

curonium or succinylcholine [7]. However, serial case reports of anaphylactic reaction to cisatracurium with a variety of severe clinical manifestations have been reported [3,8]. The diagnosis of anaphylaxis is routinely made by estimating the serum tryptase level and by an intradermal skin test [6]. In the present case, we investigated the serum tryptase level and performed a skin test for all of the drugs used in general anesthesia. Although epinephrine is known to cause Kounis syndrome and is involved in various allergic responses [9], we did not include it in allergic testing since it was used only after hemodynamic instability had occurred. We found that the serum tryptase level was elevated and the skin test showed a positive result for cisatracurium, while all other drugs rendered negative results.

During hypersensitivity reactions, inflammatory mediators including histamine and tryptase are released into the circulation [10]. Once released, tryptase can activate metalloproteinases, leading to plaque disruption or rupture [11]. Histamine is able to implicate platelet activation, thickening of intima, coronary vasoconstriction, platelet activation and tissue factor expression [12]. In fact, tissue factors activated by histamine are frequently elevated in patients with unstable angina [13]. Tryptase has also been proposed for its therapeutic efficacy as a biomarker of coronary artery disease in asymptomatic patients, since its levels were significantly elevated in non-allergic patients with severe coronary artery disease [14]. The recruitment of these inflammatory mediators is now widely accepted as a cause of acute coronary syndromes [10].

Various coronary syndromes, including Kounis syndrome, have been described during anaphylaxis. Kounis syndrome describes one of the mechanisms that could possibly take place under circumstances where there are concurrent occurrence of acute coronary syndrome and allergic reaction, resulting in a sudden cardiovascular collapse [1]. There are two variants of this syndrome. Type I variant includes subjects with normal coronary arteries without cardiac morbidities, while type II variant includes subjects with previous coronary artery disease in whom acute allergic events manifest into plaque rupture leading to acute coronary artery spasm or acute MI [1]. The syndrome suggests that coronary artery spasm or atheromatous plaque rupture is related to the release of allergic mediators [1]. Not only anesthetic drugs, but also epinephrine may be an important causative agent for Kounis syndrome. In addition, various drugs, animals, and insect bites have been reported to develop Kounis syndrome [9].

In our present case, the patient likely suffered from the type II variant of Kounis syndrome due to his preexisting coronary disease. Although newly formed wall motion abnormality was not observed, myocardial ischemia or coronary artery spasm were suspected from ST segment changes on ECG, global hypokinesia in TEE, and elevated cardiac enzymes levels. It is also possible that sudden cardiovascular collapse may not have been associated with newly developed MI, but with allergic mediators from anaphylaxis, resulting in an acute coronary syndrome suggesting Kounis syndrome or hypotension due to anaphylactic shock that further decompensated blood flow to coronary arteries affected by previous coronary disease.

Hypersensitivity reactions can progress to acute coronary involvement and sudden cardiovascular collapse [1]. Cases of anaphylactic or allergic reactions associated with coronary events are frequently encountered in clinical practice. It is therefore crucial to suspect the possibility of individual hypersensitivity reactions especially in patients who develop coronary events [15]. Lack of understanding and awareness of the association between allergic reactions and acute coronary syndrome could lead to inappropriate management and under-reporting. In addition to immediate and appropriate clinical management of hemodynamic instability, acute coronary syndrome with allergic symptoms should raise suspicion for the possibility of Kounis syndrome.

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