JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, May 2012, Vol. 57, No. 3
doi: 10.1111/j.1556-4029.2012.02062.x
Available online at: onlinelibrary.wiley.com

Commentary on: Dudley MH, Fleming SW, Garg U, Edwards JM. Fatality involving complications of bupivacaine toxicity and hypersensitivity reaction. J Forensic Sci 2011;56(5):1376–9.

Sir,

Patients subjecting to local or general anesthesia are under risk and influence of several factors that can induce allergic reactions affecting the heart, the lung, and other vital organs. Neuromuscular blocking drugs, antibiotics, latex exposure, contrast media, hypnotic agents, opioids, colloids, apronitin, protamine, chlorhexidine, dyes, and blood transfusion are some of the offenders during general anesthesia. Furthermore, passive transfer of peanut hypersensitivity by fresh frozen plasma has been described recently (1,2).

True allergic reactions to local anesthetics are rare and represent <1% of all adverse local anesthetic reactions (3–6). The main characteristics of the local anesthetic-induced allergic reactions according to French Pharmacovigilance database (7) include the following: cutaneous erythema, vesicular erythema, erythematous edema, urticaria, Quincke edema, anaphylactic shock, bronchospasm, and tachycardia. However, local anesthetics have been associated with acute coronary syndromes manifesting with symptoms resembling to those of Kounis syndrome (8–10).

In the very important paper published in this journal (11), the authors reported on a young male patient who died soon after injection of bupivacaine near the scalene nerve. The patient developed seizures, bradycardia, and cardiac arrest immediately after the injection. Propofol was also given to sedate the patient before surgery. One year previously, the patient had a similar local injection of bupivacaine but without any sequelae. Postmortem examination revealed hypertrophic cardiomyopathy, myocardial bridging, and lipomatous hypertrophy of the interatrial septum. However, tryptase levels were found raised in cardiac serum (45.1 ng/mL) and in suclavian serum (7.4 ng/mL). Therefore, the authors of this report correctly anticipated that the moderately elevated tryptase levels associated with the cardiovascular arrest and rapid onset of seizures after the bupivacaine injection support the possibility that the patient's death was because of a severe hypersensitivity reaction.

Kounis syndrome (12) has been described, 20 years ago, as the concurrence of acute coronary syndromes with conditions associated with mast cell activation involving other interrelated inflammatory cells. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet-activating factor, and a variety of cytokines and chemokines released during the activation process. It seems possible that the described patient suffered a type II variant of Kounis syndrome, which is seen in patients with abnormal coronary arteries with or without predisposing factors for coronary artery disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins, or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. The described patient was found, on autopsy, to have myocardial coronary bridging, and the authors correctly commented on this abnormality as a contributing factor in the development of myocardial infarction, angina, myocardial ischemia, cardiac arrhythmias, and sudden death (13–15). On the other hand, type I variant of Kounis syndrome includes patients with normal or nearly normal coronary arteries in whom the allergic insult can induce coronary artery spasm alone or progressing to acute myocardial infarction. A type III variant of Kounis syndrome has been described recently (16) in patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively.

In this report, clinical symptoms and signs of hypersensitivity reaction following the local anesthetic administration were not mentioned. Such symptoms and signs (17) are graded as Grade I involving cutaneous-mucus signs, Grade II involving mild cutaneous-mucus signs that may be combined with cardiorespiratory signs, Grade III involving cutaneous-mucus signs and/or bronchospasm with cardiovascular collapse, and Grade IV denoting cardiac arrest. The latter two grades correspond with the Kounis syndrome symptomatology. Furthermore, clinical, electrocardiographic, and laboratory findings including cardiac enzymes and troponins were not given. However, the following reasons support the notion that this patient had suffered a severe hypersensitivity coronary syndrome, namely Kounis syndrome, which has led, this patient, to death.

First, this particular patient had received two anesthetics bupivacaine and propofol and during the procedure might have come in contact with disinfectants and glove latex agents that are known to induce allergic reactions. The involvement of four agents during this procedure seems to have caused direct or IgE-mediated mast cell degranulation which was confirmed by the increase in tryptase. It is known that mast cell surface brings 500,000 to 1 million IgE molecules, and degranulation occurs when 2000 of these molecules, which is a critical number, make 1000 bridges by antigens. These bridges can be made by antigens of different specificities as it happens in patients during anesthesia (18). It looks likely that the more antigens an anesthetized patient is exposed to, the easier and quicker the degranulation occurs (19–22).

Second, this patient was found at autopsy to have a congenital abnormality affecting the coronary arteries known as myocardial bridging. Normally, the major coronary arteries are located in the sub-epicardial region and perfuse the myocardium during diastole. In myocardial bridging, segments of major coronary arteries are tunneled and travel intramurally through the myocardium beneath a muscle bridge. During cardiac systole, temporary systolic coronary arterial luminal narrowing takes place and the patient experiences typical or atypical chest pain related or unrelated to exercise. Although myocardial bridging usually has a benign prognosis, some cases are associated with myocardial ischemia, infarction, coronary spasm, arrhythmias, and sudden death. Such events, particular coronary spasm, might well have been induced by inflammatory mediators released during hypersensitivity reaction culminating in the type II variant of Kounis syndrome.

Although tryptase levels were measured in this patient, assessment for reactivity to skin disinfectants and latex seems not to have been carried out. All patient cases of perioperative cardiovascular arrest require additional workup to identify the offending agent and to avoid future reactions. This workup should include, apart from tryptase measurements, patch testing, skin prick, and intradermal skin testing to all drugs the patient has received or is going to receive.

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