



Case Report

Case report: management of differential diagnosis and treatment of severe anaphylaxis in the setting of spinal anesthesia☆



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Abstract The purpose of this case report is to educate fellow anesthesiologists of a complicated differential diagnosis for sudden cardiovascular collapse after spinal anesthesia. We report a case where anaphylaxis occurred while under spinal anesthesia and resulted in difficult resuscitation.

A 58-year-old woman undergoing bilateral knee replacements under spinal anesthesia experienced sudden seizure and cardiovascular collapse from acute anaphylactic shock while administering a cephalosporin. Local anesthetic toxicity, high spinal, and anaphylaxis were considered due to overlapping of symptoms. Successful resuscitation required prolonged advanced cardiac life support with substantially larger doses of epinephrine.

Anaphylactic shock under spinal anesthesia is an acute and life-threatening complication, worsened by the spinal-induced sympathectomy, and aggressive resuscitation is warranted. Despite the presence of overlapping symptoms of differential diagnoses, rapid identification of the cause of cardiovascular collapse is crucial given that resuscitation treatment modalities may conflict. Timing of antibiotic administration should be adjusted for spinal anesthesia cases to allow time to detect possible anaphylaxis.

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1. Introduction

Cardiac arrest has been reported after spinal anesthesia, usually as severe bradycardia progressing to asystole, from

2.73 to 6.4 arrests per 10,000 spinal anesthetics with a survival rate from 20% to 77% [1]. Several different mechanisms may contribute to arrest after spinal anesthesia, and cardiovascular collapse can occur in the absence of bradycardia or asystole. One study covering a 20-year study period at the Mayo Clinic demonstrated that 19% of the 26 patients who experienced a cardiac arrest during neuraxial anesthesia experienced ventricular fibrillation and 23% demonstrated ventricular tachycardia as the initial presenting symptom [2]. We report a case of a nonbradycardic pulseless arrest after an acute anaphylactic reaction induced by a cephalosporin administered within minutes after placement of spinal anesthetic. Successful

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resuscitation and treatment of anaphylaxis become difficult to manage with a significant sympathectomy due to a working spinal anesthetic. In addition, diagnosis can be challenging due to the overlapping temporal presentation of symptoms. The differential diagnoses include local anesthetic toxicity, high spinal, and anaphylaxis. We report successful diagnosis and resuscitation of anaphylactic shock faced with an initial presentation of tinnitus, seizure, and acute cardiovascular collapse refractory to conventional resuscitation measures.

2. Case

A 58-year-old woman, who consented to the reporting of this case, presented to the surgical suite for bilateral simultaneous knee arthroplasties done under spinal anesthesia. The patient's medical history was significant for osteoarthritis, hypertension, controlled hypothyroidism, controlled hyperlipidemia, and a clipping of an unruptured left posterior communicating artery aneurysm in 2002. The patient's medications included lisinopril, metoprolol, synthroid, and simvastatin, but as instructed, only the metoprolol and synthroid were taken the morning of surgery. The patient stated that she had allergies to latex and tetracycline, producing only minor local skin irritation and mild rash, and had never demonstrated an immediate hypersensitivity reaction to these agents or any other triggers. It did not qualify as a grade I reaction according to the 2011 updated Guidelines for Clinical Practice in Reducing the Risk of Anaphylaxis During Anesthesia, and therefore, no further investigation, such as skin prick tests, intradermal tests, or provocation tests, were warranted [3]. The patient denied any history of seizures or asthma. Given the patient's stated allergy to latex, care was taken to draw medications after first removing the rubber tops from the medication vials. No latex items were present in the operating room (OR).

Preoperative tests, including complete blood count, basic metabolic profile, and electrocardiogram were unremarkable. Airway and physical examinations were unremarkable. The patient was administered midazolam 2 mg via a peripheral intravenous (IV) site and brought into the OR. Standard American Society of Anesthesiologists monitors were placed, and oxygen was delivered via facemask at 4 L/min. She was then seated in the upright position on the operating table, and the patient's back was prepped and draped in a sterile fashion. Her anatomical landmarks were easily palpable. After anesthetizing the skin with 2% lidocaine, an introducer was inserted at the L3-L4 space followed by a 25 g Whitacre spinal needle. After positive return of clear nonblood tinged cerebral spinal fluid, a single shot 2-mL (15 mg) bolus of 0.75% hyperbaric bupivacaine and 25 µg of fentanyl were administered. The spinal needle was immediately removed, and the patient was placed supine.

After approximately 10 minutes, a T4 anesthetic level was achieved, and cefazolin was administered slowly via her IV. A test dose of 2 mL (20% of the total 2 g dose) of a 0.2 mg/mL concentration of cefazolin (0.4 mg) was administered, and the patient

began to have an immediate reaction upon entry of the drug in the bloodstream. She reported anxiety, tinnitus, dizziness, and nausea. Within seconds, she became unresponsive, seized, and blood pressure was undetectable with no palpable pulse. There was no bradycardia observed as the heart rate remained in the mid 60s. A code blue was called and full advanced cardiac life support (ACLS) protocol was initiated. The airway was immediately secured, and the patient was placed on mechanical ventilation. Because of the initial presentation of tinnitus and seizure, Intralipid was started immediately, whereas local anesthetic toxicity (LAST) was ruled out. ACLS protocol was then followed despite literature pointing toward using much smaller doses of epinephrine (<1 µg/kg) for resuscitation in LAST cases [2]. During the code, the patient required multiple boluses of epinephrine totaling 2 mg. Although the heart rate responded (130s-140s), blood pressure only marginally improved. In addition, amiodarone 300 mg and vasopressin 40 U were administered. The patient had return of spontaneous circulation 19 minutes after the initiation of ACLS with a measured blood pressure of 103/70. Severe hypotension persisted despite Trendelenburg positioning, aggressive fluid administration, diphenhydramine 50 mg, hydrocortisone 100 mg, famotidine 20 mg, and additional doses of epinephrine totaling 7 mg. The patient's SpO₂ had been 100% until the cardiac arrest occurred. With the cardiovascular collapse, the SpO₂ did not register as there was no pulse and ranged between 41% and 91% intermittently with cardiopulmonary resuscitation (CPR). The SpO₂ returned to 100% with the return of spontaneous circulation. Diffuse wheezing was appreciated on auscultation of the lungs during the code, and albuterol was administered via the endotracheal tube. An arterial blood gas (ABG) was performed 25 minutes into the code with the following results: pH 7.14, PCO₂ 42.1, PO₂ 321 (100% fraction of inspired oxygen), base excess (BE) -15, HCO₃ 14.3, and SaO₂ 100%. A severe metabolic acidosis was present with appropriate ventilation and diminished but reasonable oxygenation.

A transesophageal echocardiography (TEE) was performed to evaluate the heart for signs of ventricular dysfunction or presence of thromboemboli. There was no direct visualization of thromboemboli in the ventricles or visible pulmonary arteries and no evidence of right ventricular dysfunction, tricuspid regurgitation, and bowing of the interatrial septum. Both ventricles appeared to be contracting and functioning normally with a markedly empty left ventricle. Global contraction appeared normal. As the patient's condition was not improving despite ACLS and aggressive therapies, a cardiothoracic surgeon was called to the OR suite to cannulate for extracorporeal membrane oxygenation (ECMO). The discussion included heart/lung support for either extreme systemic vasodilation from a severe acute anaphylactic reaction or, considering local anesthetic toxicity, to allow sufficient dissociation of bupivacaine until heart function could return. Fifty-three minutes after the code was initiated, the patient's heart rate and blood pressure stabilized, and she did not require ECMO or any additional pressors. The patient was then transferred from the OR to the intensive care unit for further monitoring and stabilization. A serum tryptase level

was measured at 53 ng/mL (reference range, 2-10 ng/mL) upon arrival to the intensive care unit, 2 hours after the initial insult. Cardiac profile returned within normal limits. The patient remained in the hospital for 7 days and was discharged home without any sequelae.

3. Discussion

Spinal anesthesia is generally safe, and the incidence of cardiac arrest under a spinal is lower than with general anesthesia [2,4]. Before cardiovascular collapse, the most common initial signs include bradycardia and hypotension. These 2 signs are due to the sympathetic blockade from spinal anesthesia, which can be multiple dermatome levels higher than the sensory blockade. The loss of sympathetic tone results in peripheral vasodilation, resulting in decreased blood return to the heart. This decrease in preload may result in bradycardia through the Bezold-Jarisch reflex. In addition, inhibition of cardioaccelerator fibers (T1-T4) can result in severe bradycardia. All these factors combined can result in severe hypotension and asystole. Cardiac arrest during spinal anesthesia can potentially be staved off if signs are treated aggressively and early. If severe bradycardia and hypotension arise, IV atropine has been shown to be effective preventing or decreasing the severity of cardiac arrest [5]. In addition, treatment with vasopressors, such as ephedrine and epinephrine, that increase cardiac contractility and rate are useful in this setting. IV fluid boluses to increase preload and vascular tone are also prudent. If cardiac arrest occurs, CPR and ACLS should be initiated, although successful return of spontaneous circulation may not be achieved, as profound vasodilation is likely present. Our patient experienced an acute cardiovascular collapse in the absence of bradycardia.

A “high spinal” would also be unlikely given the relatively low dose of bupivacaine, as high spinals have generally been reported with larger epidural doses that were inadvertently injected intrathecally. In addition, the absence of bradycardia differentiates hypotension brought on by anaphylaxis vs high intrathecal anesthesia. In the setting of a high spinal, bradycardia is generally observed, as explained previously, whereas tachycardia is generally present in the setting of anaphylaxis [6]. In addition, bronchospasm can occur in the setting of anaphylaxis which would not be seen with a high spinal [6]. Our patient exhibited signs of diffuse rhonchi upon auscultation of the lungs during the event. Although not present in our case, flushing, urticaria, angioedema, and rash may or may not appear. If anaphylaxis is severe enough, cardiac collapse may be the inaugural or sole event [7]. In our case, the patient presented with extreme hypotension and normal heart rate that progressed to tachycardia (heart rate >130 beats per minute) and cardiovascular collapse, which is more consistent with anaphylactic shock.

LAST was a serious consideration due to the initial presentation of the patient’s symptoms, which included anxiety, tinnitus, grand mal seizure, and cardiovascular collapse. Although there was no evidence of intravascular injection

(clear cerebral spinal fluid return) and 15 mg of bupivacaine would not typically be a sufficient dose to elicit LAST and cardiovascular collapse, a 1.5 mg/kg bolus of IV Intralipid was quickly administered upon rapid risk-benefit assessment. It should be noted that the recommended Food and Drug Administration maximum dose of bupivacaine is 2 mg/kg up to a 175 mg dose, which is much less than the mean seizure dosage of bupivacaine in rhesus monkeys (4.4 mg/kg) and the LD50 in mice (6-8 mg/kg) [8].

Pulmonary embolism was also suspect given the acute nature of the cardiovascular collapse. Jugular venous distention was not apparent, and the findings of the ABG analysis were not exclusive. TEE evidence as described above is limited for direct visualization of thromboemboli, but evidence of right ventricular dysfunction such as dilation, hypokinesis, or regional wall motion abnormalities would be present in 96% of examinations with leftward interatrial septal bowing in 98% of examinations [9]. None of these signs were evident in our TEE examination, and the patient had no prior history of embolic disease or deep venous thrombosis. In addition, there was no manipulation of the legs by the surgeons before the acute cardiovascular collapse occurred.

Anaphylaxis during all types of anesthesia is estimated to occur between 1 in 3500 and 1 in 20,000 cases with a mortality rate from 3% to 9% [6]. Neuromuscular blocking drugs, more commonly implicated with allergic reactions, were not administered during this case, but antibiotics have been identified as another significant cause of anaphylaxis in the perioperative setting. One study that reviewed 4773 cases identified 717 cases of anaphylaxis and found that antibiotics were the most identifiable cause surpassing neuromuscular blocking drugs at 59% vs 23%, respectively [10]. The number of reactions due to penicillins and cephalosporins has increased rapidly in the last decade, and cefazolin has been implicated in an incidence of anaphylaxis up to 0.1%, which is a hundred times greater than that of penicillins [11]. We even considered a reaction to possible additives such as preservatives or stabilizing agents, but the cefazolin 1 g per vial for injection had a latex-free stopper and is sterile, nonpyrogenic, and preservative free.

There are reports of severe anaphylaxis, refractory to treatment and resuscitation efforts, necessitating the use of ECMO to sustain life [12]. Anaphylaxis with concurrent spinal anesthesia compounds the problem of peripheral vasodilation which could make CPR extremely difficult, if not impossible. An animal study reported that successful resuscitation during spinal anesthesia may require epinephrine doses of up to 0.1 mg/kg [13]. Based on that data, a theoretical dose as high as 7.4 mg of epinephrine would have been necessary to maintain a coronary perfusion pressure gradient of 15 to 20 mm Hg. Our patient received a total of 2.7 mg of epinephrine and may have benefitted from larger doses and an additional epinephrine drip. Guidelines for reducing the risk of anaphylaxis during anesthesia include an algorithm for the immediate treatment (Table 1) [3]. The attenuated response to vasopressors indicated higher doses of epinephrine and/or the addition of other agents such as noradrenaline (starting at

0.1 µg/kg per minute). In addition, glucagon (1-2 mg IV every 5 minutes) has been suggested as a treatment in patients with a refractory response [3]. Vasopressin (40 U administered in this case), causing a mild to moderate vasoconstriction from its action on the V1 and V2 receptors in vascular endothelium, has increasingly been used to treat hypotension associated with shock and has showed some promise in reversing mediator-induced vasodilatory shock in patients with anaphylaxis [14]. During our case, we considered the institution of ECMO as it has demonstrated value in managing severe anaphylaxis in patients who are unresponsive to general resuscitation [12]. Fortunately, this step was not necessary in our patient as the anaphylaxis broke after 53 minutes.

Besides the clinical signs and our working diagnosis of anaphylaxis, we strived for a confirmatory diagnosis through laboratory testing. A plasma histamine level may have been helpful with the diagnosis, but the elimination half-life is as short as 15 to 20 minutes [3]. Despite being present up to 2 hours in severe cases, the sample presented to the laboratory had unfortunately arrived hemolyzed and was unable to be tested. Other tests such as urinary leukotrienes and serum IgE assay have limited if any benefit in diagnosis [3].

Tryptase is a mast cell tetrameric neutral serine protease that is released in serum by mast cell degranulation during systemic anaphylaxis. Our patient demonstrated a definite increase in the concentration of serum tryptase at 53 µg/L where values greater than 25 µg/L are highly suggestive of an IgE-mediated mechanism [3]. A serum tryptase level is

therefore a very sensitive and specific marker for mastocytosis and mast cell degranulation as a cause of anaphylaxis [6]. A rise in total tryptase can be seen in plasma as soon as 15 minutes after onset of symptoms, with sampling recommended 60 to 120 minutes after the onset of anaphylaxis, but can remain positive for more than 6 hours in severe cases [3]. The levels decline via first-order kinetics with a half-life of 2 hours [7]. The fact that the serum tryptase levels remained more than twice the reference range in our patient, a full 2 hours after the initial insult, acute anaphylactic shock is highly suspect for causing the cardiovascular collapse in our patient. Given the temporal nature and exposure to only 4 drugs (midazolam, bupivacaine, fentanyl, and cefazolin), we believe that the antibiotic was the most likely culprit. Skin prick or intradermal testing would have aided in confirmation but must be done by an experienced allergist. We did counsel the patient of probable acute anaphylactic shock due to the cephalosporin and strongly urged pursuing proper allergy testing after discharge from the hospital, but the patient was unfortunately noncompliant.

Although it is a rare phenomenon, anaphylaxis under spinal anesthesia resulting in cardiac arrest has been reported in the literature for a variety of reasons [15,16]. This case report demonstrates that anaphylactic shock, particularly under spinal anesthesia, is an acute and life-threatening complication with a challenging differential due to the simultaneous nature of symptom presentation. Sudden cardiovascular collapse may be the only presenting symptom of severe anaphylaxis, and other signs such as bronchospasm or rash/urticaria may or may not occur. Resuscitation during anaphylactic shock may require more aggressive treatments including alternative vasopressors and even ECMO. Rapid diagnosis, treatment, and aggressive management of shock are the keys to a successful patient outcome.

Since this case, we have changed the timing of our antibiotic administration. In cases with a spinal anesthetic, the antibiotic is best given after monitors are placed but before the spinal anesthetic to allow time to detect possible anaphylaxis, thereby avoiding the deleterious hemodynamic combination of anaphylaxis and spinal anesthesia as described in this case report. We believe this practice to be important to note as many anesthesiologists are incorporating more spinal anesthetics into enhanced recovery after surgery protocols for total joint replacement surgeries.

Table 1 Treatment of immediate hypersensitivity reactions with emphasis on anaphylactic shock occurring during anesthesia: cardiac arrest [12]

- Initiate CPR and immediately call for help
- Secure airway and through tracheal intubation and control ventilation
- Administer 1-mg bolus of adrenaline every 1-2 min
- Place patient in Trendelenburg position
- Replenish vascular space by rapid infusion of isotonic crystalloid solutions up to 30 mL/kg and then replace with colloids
- For patients with sympathectomy or on beta blockers, adrenaline dose must be increased without delay. If unresponsive, consider glucagon (1-2 mg IV every 5 min), noradrenaline (0.1 µg/kg/min) or vasopressin (40 U).
- Treat bronchospasm with inhaled β agonist or intravenous adrenaline infusion
- Corticosteroids may attenuate late manifestations of shock: inject 200 mg of hydrocortisone hemisuccinate IV every 6 h
- Because of labile blood pressures, intensive monitoring should be maintained for at least 24 h
- Send labs such as serum tryptase and serum histamine within 2 h to aid in diagnosis. If anaphylaxis was due to a neuromuscular blocking agent, perform specific antitubercular test or P-aminophenylphosphoryl-coline radioimmunoassay

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