PERI-ANESTHESIA ANAPHYLAXIS (PAA): WE STILL HAVE NOT STARTED POST-PAA TESTING FOR INCITING ANESTHESIA-RELATED ALLERGENS

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Anaphylaxis during anesthesia is uncommon. Diagnosis of peri-anesthesia anaphylaxis (PAA) requires anesthesia providers’ vigilance for prompt diagnosis and treatment. In this case report, we present a challenging case with suspected PAA including its perioperative management, intensive care unit (ICU) course, and post-discharge follow-up. A 44-year-old female (body mass index = 26) presented for elective abdominal panniculectomy. Post-intubation, severe bronchospasm occurred that was non-responsive to nebulized albuterol and intravenous epinephrine. Continuous infusion of epinephrine was initiated. After aborting surgical procedure, the patient was transferred to ICU on continuous intravenous infusion of epinephrine. Venous blood sampling showed elevated troponin level. Echocardiography revealed ejection fraction of 25% suspicious of Takotsubo cardiomyopathy (mid cavitary variant). Tracheal extubation was only possible after three days. Subsequently, patient was discharged home with a cardiology follow-up appointment and a referral to an allergy specialist. Unfortunately at our institution (an academic university hospital in United States) along with neighboring institutions in near-by areas, the only allergy skin tests available are for local anesthetics and antibiotics, while neuromuscular blocking agents (NMBAs) cannot be tested (the suspected anaphylactic agent in our case was presumably rocuronium). In summary, PAA requires and responds to emergent diagnosis and immediate treatment; however there is still a long way to go to ensure post-PAA testing for inciting anesthesia-related allergens.

Introduction

Anaphylaxis during anesthesia is uncommon with reported range of incidences from 1 in 6,000 anesthetics/procedures (Norwegian study) to 1 in 10,000 anesthetics/procedures (French study) and to 1 in 20,000 anesthetics/procedures (Australian study)1-4. Diagnosis of peri-anesthesia anaphylaxis (PAA) requires anesthesia providers’ vigilance for prompt diagnosis and treatment. In this case report, we present a challenging case with suspected PAA including its perioperative management, intensive care unit (ICU) course, and post-discharge follow-up.

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Case report

A 44-year-old female (body mass index = 26) presented for elective abdominal panniculectomy. Her past medical history was significant for gastro-esophageal reflux disease, penicillin allergy, laparoscopic banding for intentional weight loss, cigarette smoking and recreational alcohol use. Patient had history of phentermine use for weight loss which she had stopped a week earlier. She had been prescribed beta-blocker after her bariatric surgery for two weeks but she never followed up with her cardiologist. However she had very good exercise tolerance and could walk and run many miles. Additionally, patient had denied any psychosocial stressors. Pre-surgical evaluation revealed an asymptomatic non-distressed patient along with normal vital signs. Airway assessment was deemed easy with Mallampati score as grade II and intact dentition. Cardiovascular and respiratory examinations were within normal limits. Intra-operatively, standard monitors were applied. Anesthesia was induced with propofol, fentanyl and rocuronium after adequate pre-oxygenation. The airway was intubated with a 7.5 cuffed endotracheal tube under direct laryngoscopy with Cormack-Lehane grade I view. However, no breath sounds were detected on auscultation and no end tidal carbon dioxide was observed on the monitor. At this point, severe bronchospasm was diagnosed and immediate therapy was initiated with nebulized albuterol and intravenous epinephrine (50mcg one time dose). After one-minute, end tidal carbon dioxide became apparent along with peak airway pressures @ 48-50 cm of water. Oxygen saturation levels dropped to low 80s (82%-85%) that was accompanied with fall in systolic blood pressure into the range of 65-80mmHg. Examination of the patient revealed no skin rashes, and at this point a tentative diagnosis of anaphylaxis was made with treatment consisting of epinephrine as intermittent boluses of 50-100 mcg intravenously along with intravenous one time dose of hydrocortisone and diphenhydramine. Patient’s clinical status was not improving and continuous infusion of epinephrine was initiated along with arterial line and central venous line insertions. Arterial blood gas analysis revealed arterial hypoxemia, metabolic acidosis, and hypokalemia. Sodium bicarbonate and potassium chloride infusions were infused. An emergent bronchoscopy revealed normal tracheobronchial mucosa and small amount of clear secretions were suctioned out. Chest skiagram revealed bilateral lung field fluffy opacities and hence furosemide 20mg was given intravenously to counteract possible acute pulmonary congestion/edema. Due to patient’s critical condition, the surgical procedure was aborted after discussion with the surgeon. The patient was transferred to ICU on continuous intravenous infusion of epinephrine. On ICU arrival, respiratory therapists performed alveolar recruitment maneuvers repeatedly that improved patient’s oxygen saturation levels to the low 90s. Venous blood sampling showed elevated troponin level and white blood cell count whereas electrolytes panel and hemoglobin/hematocrit levels were normal. First lab sample for tryptase levels was sent within hours of suspected anaphylactic reaction; however there was a lab error and correct reactive tryptase levels could not be determined because a second sample was sent only after more than 24hrs of suspected anaphylactic reaction.

Due to elevated troponin levels, cardiology team initiated treatment for non-ST-elevation myocardial infarction. Echocardiography revealed an increase in left ventricular cavity size with normal left ventricular thickness, and there was a severely decreased left ventricular systolic function with ejection fraction of 25% suspicious of Takotsubo cardiomyopathy (mid cavity variant). Over the next 48-72 hrs, her poor cardiac function and limited/restricted cardio-pulmonary reserve secondary to pulmonary edema led to multiple failed weaning trials and potential airway edema led to failed cuff leak tests. Tracheal extubation was only possible after three days; however she was subsequently transferred to medical floor in stable condition soon after. Cardiac catheterization revealed global left ventricular function’s depression with ejection fraction 25 % but coronary arteries did not show any evidence of obstructive atherosclerosis/ arteriosclerosis. As clinically improved, patient was discharged home with a cardiology follow-up appointment and a referral to an allergy specialist. Unfortunately at our institution (an academic university hospital in United States) along with neighboring institutions in near-by areas, the only allergy skin tests available are for local anesthetics and antibiotics, while neuromuscular blocking agents (NMBAs) cannot be
tested (the suspected anaphylactic agent in our case was presumably rocuronium). Hereafter, patient was lost to follow-up and it could not be determined if her echocardiographic findings resolved that would have given affirmation that patient was suffering from Takotsubo (stress) cardiomyopathy secondary to acute stress of clinically suspected anaphylaxis although anaphylaxis was unconfirmed due to poorly timed tryptase levels that were drawn after 24hrs of event when post-anaphylaxis tryptase levels come down to normal baseline values unless patients are suffering from mastocytosis wherein even baseline tryptase levels are high. Additionally, as there was no pre-procedure echocardiogram available in our records for comparison with post-event echocardiogram so it could not be completely ruled out if she was just suffering from acute peri-operative worsening of chronically pre-existent non-ischemic cardiomyopathy.

Discussion

Allergic reactions include wide variety of symptoms from dermatological symptoms, airway reactivity events, hemodynamic compromise, deteriorating perfusion at tissue level, plethora of gastrointestinal symptomatolgy, to anaphylaxis-related fatality secondary to refractory cardiovascular collapse and cardiac arrest. Pathophysiology of anaphylaxis is mediated via IgE antibodies that develop due to patient’s prior exposure to an antigen (or a similar structure substance) and the second exposure to the antigenic substance triggers accentuated/accelerated mast cell degranulation and basophil breakdown leading to release of histamine, tryptase and chemotactic factors in massive amounts. Comparatively, anaphylactoid reactions do not need pre-sensitization/IgE antibodies but involve direct destabilization of mast cells and basophils by the inciting agents. Histamine can be measured in plasma within a few minutes of an anaphylactic reaction but has very short half life often precluding its appropriately timed laboratory evaluation in a highly dynamic emergent clinical management scenario of suspected anaphylaxis with potential of fatal/irreversible cardiorespiratory outcome wherein immediate management based on clinical suspicion overrides the laboratory confirmation of histamine levels. However, tryptase that is also released during anaphylaxis, has a half-life of 120 minutes which is much longer than histamine’s half-life allowing time for rapid response clinical team to timely send tryptase levels for confirmation of suspected anaphylaxis. Hence, it is recommended to sample within first 120 minutes of a suspected anaphylactic reaction. To obtain baseline levels of tryptase (so as to rule out abnormally high baseline values of tryptase in cases of pre-existent mastocytosis), another blood sample needs to be examined after at least 24 hours.

The suspected anaphylactic agent in our patient was rocuronuim, because allergic reactions secondary to propofol and fentanyl are somewhat less common. Different European studies have revealed that NMBAs are most likely to cause PAA with one French study reporting up to 58% of all PAA events being related to NMBAs as causative agent with at least 4% mortality after post-NMBA PAA events despite prompt management per another study. Rocuronium is the most common NMA that accounts for more than half of all post-NMBA PAA events; and cross reactivity between different NMBAs exists with cisatracurium having the lowest cross-reactivity in patients who had suffered post-rocuronium PAA events. A recent study from Mayo clinic, United States demonstrated antibiotics as the most common agent inciting severe PAA leading to abortions/cancellations of the surgical cases, myocardial ischemic events, and unplanned admissions to ICUs. Our patient had clinical manifestations that raised a high degree of clinical suspicion for the diagnosis of PAA; unfortunately tryptase levels were obtained more than 24hrs after resuscitation mitigating their value in the confirmation of our clinical diagnosis. Our patient was resuscitated successfully with fluids and continuous infusion of epinephrine that was weaned very slowly over the period of 48hrs. No other vasoactive agents were required. Although sugammadex (reversal antidote for rocuronium) is not available in the United States because it has not been approved by U.S. Food and Drug Administration (FDA), several case reports have observed an effective role of sugammadex in the management of refractory anaphylactic reactions after rocuronium, with complete resolution of anaphylactic symptoms within a few minutes.
During post-discharge outpatient follow-up, several tests can be utilized to confirm the diagnosis of anaphylaxis and delineate the plethora of agents inciting anaphylaxis/other allergies. These tests include skin prick test (SPT), intradermal test (IDT), and serum specific IgE antibodies. The anesthesiologist should be responsible for referring PAA patients for further investigations to allergy specialist. SPTs are highly sensitive for NMBAs and gelatins but have poor sensitivity for barbiturates, benzodiazepines, and opiates. IDTs are usually performed when SPTs are negative despite clinical suspicion for drug-related anaphylaxis being very high; however, the specificity of IDTs is still unknown. Skin testing is usually carried out 4–6 weeks after PAA event. Patients should be instructed to stop all antihistamines for five days prior to the scheduled skin testing17-18.

The processes to do when PAA is suspected is all well-known but we should also discuss what all it entails if as a healthcare institution, we are not able to do SPTs/IDTs for the patients after their PAA events. During peri-anesthesia period, the patients receive many medications almost simultaneously or in quick succession that makes it difficult to pinpoint which agent precipitated PAA. Now without outpatient SPTs/IDTs that could delineate the specific peri-anesthesia medications as the inciting agent for the PAA event, it becomes a dicey scenario for future anesthetic administrations because anesthesia practice is commonly based on limited plethora of medications and anesthetics as a whole class cannot be branded/avoided assuming “anesthesia” caused anaphylaxis. Therefore, it is general accepted that the drug responsible for PAA needs to be determined via investigation, collaborative outpatient clinics need to be established for efficient post-hoc investigations of PAA, with perioperative timely investigation of mast cell tryptase levels and appropriately timed outpatient SPTs/IDTs being the optimal methods for confirming clinical diagnosis of anaphylaxis18-19. In our case, we contacted our allergy and immunology department; however skin testing for anesthetic medications was not performed in our institution due to unavailability of tests with possible underlying reasons: (a) medically questionable non-definite sensitivity/specificity of SPTs/IDTs for anesthetic agents as anaphylactic agents limiting these post-PAA testing/investigations to only major tertiary healthcare institutions; (b) unclear standing of third-party payers (insurance coverage) in regards to these tests; and (c) lack of clear-cut mandated enforced institutional guidelines for appropriate work-up and follow-up of suspected PAA. Many (but not all) tertiary healthcare institutions (possibly with research aptitude and acumen) around the world including some in the United States have specialized clinics for allergy skin testing for anesthetic medications with appropriate follow-up mechanisms. It is our humble opinion that all tertiary hospital settings (with collective-cumulative peri-anesthesia patient catchment areas covering the whole population within the societies exposed to peri-anesthesia periods on regular basis) should have the facilities for allergy skin testing of anesthetic medications to definitely delineate the causative agents for PAA events.

**Conclusion**

Management of allergic reactions during anesthesia requires emergent diagnosis and immediate treatment. Post-event laboratory investigation and post-discharge outpatient follow-up are crucial for identifying causative anaphylactic peri-anesthesia agents. However there is still a long way to go to ensure that these suspected peri-anesthesia allergic reactions do get investigated and anaphylactic agent do get identified so that specific agents (and not the general class of “anesthetics” as such) can be avoided in future anesthetic administrations to prevent the expected PAA events.

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*TOF: train-of-four
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