Vasopressin for the management of catecholamine-resistant anaphylactic shock

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ABSTRACT

Severe anaesthetic anaphylaxis is relatively uncommon. Oxygen, fluids and epinephrine are considered to be the mainstay for treatment of cardiovascular collapse and current guidelines for the management of anaphylaxis list only epinephrine as a vasopressor to use in the event of a cardiovascular collapse. Recently, evidence has emerged in the support of the use of vasopressin in cardiopulmonary resuscitation; it is also recommended for the treatment of ventricular fibrillation, septic shock and post-cardiopulmonary bypass distribution shock. Currently, there is no algorithm or guideline for the management of anaphylaxis that include the use of vasopressin. We report a 24-year-old woman who developed severe anaphylactic shock at induction of anaesthesia while undergoing laparoscopic cholecystectomy. Circulation shock was refractory to epinephrine and high doses of pure alpha-agonist phenylephrine and norepinephrine. Single intravenous dose of two units of vasopressin re-established normal circulation and blood pressure.

Keywords: anaphylaxis, epinephrine, phenylephrine, vasopressin

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INTRODUCTION

Anaphylaxis during induction of anaesthesia is uncommon. The effects of this complication range from mild urticaria to life-threatening circulatory shock. The incidence of anaphylaxis and anaphylactoid reactions during anaesthesia are probably under-reported and are difficult to predict, but have been estimated to range from one in 3,500 to one in 13,000 cases.[1,2] Life-threatening reactions to various anaesthetic drugs have been reported in the literature. Muscle relaxants (69%) and natural rubber latex (12%) are the most frequently-reported agents to cause anaphylaxis. Other causes include drugs, such as antibiotics (8%) and induction agents (4%).[3-5] Successful management of anaphylaxis depends on prompt diagnosis and appropriate management. We report a case of anaphylaxis that was resistant to catecholamine vasoconstrictors (epinephrine, norepinephrine and phenylephrine) but responded to vasopressin.

CASE REPORT

A 24-year-old ASA grade 1 woman weighing 74 kg was scheduled for elective laparoscopic cholecystectomy. She had no known allergies and had undergone an uneventful caesarean section under subarachnoid block two months previously, during which propofol 100 mg was used for sedation. The patient was premedicated with tablet midazolam 7.5 mg one hour prior to surgery. On arrival in the operating room, the baseline noninvasive blood pressure was 128/72 mmHg, heart rate 78/min and oxygen saturation (SpO_2) 100% on room air. General anaesthesia was planned for laparoscopic cholecystectomy and coinduction was done with fentanyl 100 µg, propofol 100 mg and atracurium 30 mg given intravenously following pre-oxygenation. Immediately after administration of the induction drugs, cyanosis was noticed and SpO_2 suddenly dropped to 80%, as read by pulse oximeter. Because of severe hypotension, the pulse waveform was not displayed properly. Her blood pressure became unrecordable and there was marked reduction in end-tidal carbon dioxide concentration. Heart rate increased to 140/min and electrocardiography rhythm appeared normal. Although the blood pressure was not recordable, the femoral and carotid pulses were palpable; therefore, chest compressions were not started.

Her trachea was intubated and ventilation started with 100% oxygen, but SpO_2 did not improve. Lung auscultation was done to confirm tracheal tube position which revealed mild wheezing. No crepitations were present. A "call for help" was initiated. Wheezing resolved within minutes without any pharmacological intervention. There was no clinical evidence of pulmonary aspiration, no fluid was encountered in the pharynx and a later chest radiograph showed clear lungs. Although her heart rate dropped to 58/min, it responded to a single dose of intravenous 1 mg atropine, but blood pressure was still not recordable. Atropine

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was used as it was immediately available. Although there was no cutaneous rash, a provisional diagnosis of an anaphylactic reaction was made and resuscitation started. During resuscitation, radial arterial line and central venous access through the internal jugular vein were secured and confirmed by good waveform pattern. Arterial line showed blood pressure of 40/30 mmHg, and central venous cannulation showed central venous pressure of 3 mmHg.

Multiple boluses of 100 µg epinephrine (total 2,000 µg) were given. Since the patient had tachycardia (120/min), small bolus doses of epinephrine were used. The rationale was that with tachycardia, there is a great risk of arrhythmias, which may in themselves be fatal in a shocked patient. When the patient did not respond to epinephrine boluses, phenylephrine boluses 100–200 µg (total 4,000 µg) were given. Infusions of epinephrine and norepinephrine were started at 0.03 µg kg^{-1} min^{-1} and increased to 0.5 µg $kg^{-1}min^{-1}$. During the resuscitation effort, hydrocortisone 200 mg was also administered. We then repeated high bolus doses of phenylephrine to restore perfusion and avoid further increase in heart rate. Phenylephrine was again given in 5 mg boluses (total 20 mg). Resuscitation also included infusion of crystalloids and colloids to maintain the central venous pressure to 10 mmHg. Total resuscitation fluid given was 3,500 ml (1,500 ml of gelofusine, i.e. colloid, and 2,000 ml of Ringer's lactate).

During 40 min of resuscitative measures, heart rate varied from 120 to 130/min, but the blood pressure did not rise (systolic varied from 40 to 50 mmHg and diastolic 20 to 30 mmHg) and cyanosis was persistent (SpO_2 of 80%–84%). Arterial blood gases showed mixed metabolic and respiratory acidosis (pH 7.20; $PaCO_2$ 50 mmHg; PO_2 68 mmHg; HCO_3 11, and base deficit -14). Decision was made to add a bolus of non-adrenergic vasopressor, vasopressin. 2 units of vasopressin were then given intravenously, which resulted in a profound response, and blood pressure increased to 90/50 mmHg and SpO_2 improved to 90%.

At this point, the patient started breathing spontaneously. Midazolam was given to prevent awareness and vecuronium for muscle relaxation. The decision was made to postpone the surgery. Infusions of epinephrine and norepinephrine were continued. She was mechanically ventilated in the operating room for an additional hour until her blood pressure was stabilised to 100/60 mmHg, SpO_2 remained at 97% and pH returned to normal, as seen on arterial blood gases. Gradually, inotropic support was withdrawn over two hours. She was extubated when she required minimal inotropic support to maintain her vital parameters and SpO_2. She made good recovery without any apparent memory loss and was able to recognise her family. She was kept under observation for 24 hours in the postanaesthetic care unit, and was then discharged.

The patient was followed-up in the surgical clinic for two months for her primary pathology, and with the primary anaesthetist for any post-resuscitation residual damage and future anesthesia plan. No formal psychological evaluation was done, but during these visits, she actively participated in the discussion. She was an architect by profession and was able to continue working. Two months later, she was again scheduled for the same surgery under general anaesthesia which was uneventful. On this occasion, pre-induction intravenous tramadol 150 mg was given and induction was done with an inhalation agent (sevoflurane and nitrous oxide in oxygen) along with intravenous midazolam 5 mg. Vecuronium was used as muscle relaxant to facilitate tracheal intubation.

DISCUSSION

Anaphylaxis must be considered as a differential diagnosis for any acute-onset respiratory distress, bronchospasm, hypotension or cardiac arrest during anaesthesia. We suspected anaphylaxis in our case on a high index of suspicion. In a healthy 24-year-old subject with no other disease and who unexpectedly collapsed after the administration of anaesthetic induction drugs, the two differential diagnoses would be an allergic reaction or aspiration. Myocardial infraction was highly unlikely. At the time of tracheal intubation, no residual fluid or blood was encountered in the pharynx. Bronchospasm was not the dominant presenting feature and the chest radiograph done on the operating room table did not show any evidence of aspiration. On the other hand, all the induction agents used had the possibility of histamine release and cause various degrees of anaphylaxis. During an episode of suspected anaphylaxis, a confirmation of the diagnosis should be sought by an increase in blood histamine and tryptase concentrations, indicating a mast-cell-mediated process.[6] We did not have the facilities to do blood histamine and tryptase levels in our laboratory. The option of intradermal skin and prick tests for induction drugs was given to the patient during the follow-up period. When the procedure was explained with the advantages, disadvantages and possible complications, the patient refused to undergo testing. Therefore, she was not referred to an allergist.

It is not possible to state with confidence as to which anaesthetic drug had caused the anaphylactic reaction, and the possibility of either propofol, atracurium or fentanyl being the causative agent could

not be completely eliminated. When we inquired post-event, the patient had received propofol 100 mg for sedation two months ago in a previous anaesthesia. It is known that re-exposure to causative agents can cause a severe anaphylactic reaction. Points against propofol would be that the patient did not encounter any complication when she was given propofol the first time, as even a first exposure can cause a life-threatening reaction. Possibility of atracurium causing anaphylaxis also could not be ruled out as this is one of the most common agents which can cause anaphylaxis during anaesthesia (50%–70%). Anaphylaxis to a muscle relaxant has also been observed in patients with no previous administration. There was absence of bronchospasm and skin rashes in our case, but the possibility of atracurim causing the anaphylaxis still remained high as cardiovascular collapse is a common finding of anaphylaxis under anaesthesia without bronchospasm and skin changes. Fentanyl could also cause an anaphylactic reaction,[7] but there are few published case reports to support this. As no definite causative agents could be ruled out we avoided all three drugs when she was anaesthetised two months after this reaction.

Pathophysiological effects of anaphylaxis result from immune-mediated release of mediators including histamines, prostanoids, leukotrienes, kinins and platelet-activating factors. The predominant reasons for acute cardiovascular collapse in anaphylaxis are mediator-induced vasodilation and leakage of plasma from capillaries due to increased permeability.[2] Aims in the management of anaphylaxis should be an early return of spontaneous circulation, and maintenance of adequate coronary and cerebral perfusion. Immediate discontinuation of the offending drug, airway maintenance, 100% oxygen administration, intravascular volume expansion and epinephrine, are essential to treat the hypotension and hypoxia that result from vasodilatation, increased permeability and bronchospasm.[1,8]

Epinephrine is a catecholamine with both α- and β-adrenergic effects and remains an empirical agent in the treatment of anaphylaxis. It opposes the deleterious systemic adverse effect of released mediators through its vasoconstriction (α-mediated), positive inotropic (β_1-mediated) and bronchodilating (β_2-mediated) properties. It also reduces mast cell and basophil mediator releases. When an intravenous route is available, titrated bolus administration according to arterial pressure and pulse is advised (10–20 µg in Grade II reaction, 100–200 µg in Grade III reaction, and for Grade IV reaction, i.e. cardiac arrest, 1 mg epinephrine boluses along with external cardiac massage are recommended). Continuous infusion may be required in some cases and titrated as needed.[6] Most episodes of anaphylaxis respond to treatment with a single dose of epinephrine, but anaphylactic cardiovascular collapse can be resistant to treatment with this drug, as seen in our case.[9] Heytman and Rainbird reported two cases in which return of spontaneous circulation was refractory to epinephrine.[2] Waldhausen et al reported 49 patients with anaphylaxis who did not respond adequately to epinephrine.[10] Konarzewski and De'Ath reported an anaphylactic reaction which was treated with standard cardiopulmonary resuscitation (CPR) including cardiac massage, ventilation of the lungs with 100% oxygen, atropine 3 mg and epinephrine 2 mg. Despite vigorous resuscitation attempts for 45 min, the patient died.[11] Similarly, in our patient, volume expansion and epinephrine were ineffective.

It has been reported that early use of alpha-agonists, along with the second dose of epinephrine, may reduce the morbidity and mortality associated with anaphylaxis and reduced unwanted sideeffects produced by high dose epinephrine.[12] This was first described by Higgins and Gayatri.[13] Heytman and Rainbird reported beneficial effects of alpha-agonist metaraminol in epinephrine-resistant anaphylactic shock.[2] McBrien et al also reported a good response to methoxamine in two anaphylactic reactions (succinylcholine, cefamandole) and one cardiovascular collapse (secondary to methylmethacrylate cement).[14] Phenylephirine 10 mg in bolus doses and norepinephrine infusions during open heart surgery have been reported successful in the treatment of anaphylaxis.[15] Bolus doses of phenylephrine and metaraminol are used in various case reports to manage anaphylactic shock. As phenylephrine is easily available at our institution, we used it for bolus doses along with infusion of norepinephrine and epinephrine. We started with minimum doses of 100–200 µg. We were reluctant to use high doses of epinephrine for fear of ventricular arrhythmias in the presence of tachycardia. In this case, as it was an emergency situation, we tried large bolus doses of phenylephrine, but our patient did not respond to norepinephrine infusion at an increasing dosage nor to phenylephrine boluses. This was similar to the case reported by William et al where hypotension was refractory to high doses of phenylephrine.[16]

Currently, trials to evaluate the effects of vasopressin in cardiac arrest, septic shock and uncontrolled haemorrhagic shock are being performed.[17] Role of vasopressin in cardiovascular haemostasis is through its non-adrenergic peripheral vasoconstriction (by direct stimulation of smooth muscle vasopressin 1 receptors) and antidiuretic

action. It produces vasoconstriction in the skin, skeletal muscle, intestine and fat, with relatively less constriction of coronary and renal vasculature, and causes cerebral vasodilatation.[15] Recent evidence has emerged for the use of vasopressin in CPR. Epinephrine and other catecholamines lose much of their effectiveness as vasopressors in a hypoxic, acidotic milieu, and this fact has stimulated efforts to identify an effective alternative to epinephrine for use in this situation. In early 1990s, endogenous vasopressin levels were found to be higher in survivors of cardiac arrest than in patients who died, suggesting that vasopressin could be beneficial in cardiac arrest. Effectiveness of vasopressin in catecholamine-resistant shock and cardiac arrest is due to the fact that it acts in an acidic environment, which exists in prolonged cardiac arrest, where epinephrine loses its potency.[18,19] American Heart Association recommends it for CPR of adults with shock- refractory ventricular fibrillation.[20] Some but not all clinical trials demonstrated improved haemodynamic variables and survival when using vasopressin as an alternative to epinephrine during resuscitation from cardiac arrest. As a placebo-controlled trial has yet to be conducted and due to insufficient evidence, the European Resuscitation Council did not include vasopressin in the universal algorithm in its published guidelines and stated that "further evidence is required before this agent can be firmly recommended".[21]

Anaphylaxis also presents as vasodilatory shock, as various case reports and series have shown a beneficial effect of using vasopressin in vasodilatory shock.[22,23] That was the reason we used vasopressin as a last resort following volume loading, use of adrenaline, noradrenaline and phenylephrine. No controlled trials of treatment in humans are currently available and recommendations for use of vasopressin for anaphylactic shock are based on case reports and summaries of experience. There are no guidelines regarding use and dosage of vasopressin in anaphylaxis refractory to adrenergic vasopressors. In different cases, report of anaphylaxis 2–5 units of vasopressin have been used.[16,24] We therefore decided to start with 2 units and then increase the dosage. The patient responded to 2 units of vasopressin, vascular tone was restored, and did not require further doses.

Based on our experience, we conclude that the complexity and severity of anaphylaxis are such that no single algorithm can adequately treat all cases. Currently, there is no guideline or algorithm for the management of anaphylaxis that includes the use of vasopressor other than epinephrine. Vasopressin should be considered early for catecholamine-resistant anaphylactic shock and before resuscitation is discontinued. Guidelines for management of anaphylactic shock should also include vasopressin in association with pure alpha-agonist in acute circulatory shock due to anaphylaxis.

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