



ELSEVIER

www.obstetanesthesia.com

CASE REPORT

Pulseless electrical activity during caesarean delivery under spinal anaesthesia: a case report of severe anaphylactic reaction to Syntocinon

D. Pant, V. K. Vohra, S. S. Pandey, J. Sood

Department of Anaesthesiology, Pain & Perioperative Medicine, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India

ABSTRACT

Anaphylactoid reaction to Syntocinon is rare, but has been described in the literature. The reactions described include patchy erythema, hypotension, bronchospasm and oxygen desaturation, but pulseless electrical activity following Syntocinon has not been reported. We present the case of a 34-year-old primigravida with essential hypertension, gestational diabetes and hypothyroidism with a twin pregnancy following in vitro fertilization. During elective caesarean delivery she developed a severe anaphylactic reaction to Syntocinon leading to pulseless electrical activity.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Anaphylactic reaction; Syntocinon; Intradermal testing; Pulseless electrical activity; Caesarean delivery

Introduction

The incidence of anaphylactic and anaphylactoid reactions under anaesthesia is estimated to be between 1 in 4000 to 1 in 25 000.¹ Not uncommonly, these are related to anaesthetic agents. Anaphylactic reactions under anaesthesia have been attributed to muscle relaxants (58.2%), latex (16.7%), antibiotics (15.1%), colloids (4%), induction agents (3.4%), opioids (1.3%) and others (1.3%).² A high incidence of latex anaphylaxis (1:310) has recently been observed during obstetrical and gynaecological surgical procedures.³ In the pregnant patient, the fetus poses additional problems. Fortunately, maternal IgE does not cross the placenta, but maternal haemodynamic instability can jeopardize placental perfusion.

Perianaesthetic anaphylaxis may be severe and potentially associated with adverse outcomes unless promptly recognized and treated. Approximately 10% of anaphylactic reactions are fatal.¹ Accurate diagnosis and treatment are essential, but equally important is a careful review of the events and predisposing factors to avoid recurrence. We report an anaphylactic reaction to Syntocinon (synthetic oxytocin) leading to pulseless electrical

activity (PEA) during caesarean delivery under spinal anaesthesia.

Case report

A 34-year-old primigravida with a body mass index of 37.5 kg/m² (150 cm, 85 kg) was admitted at 37 weeks of gestation for elective caesarean delivery. She had twin pregnancy from *in-vitro* fertilization, with one fetus in an oblique lie and the other longitudinal. She also had essential hypertension, gestational diabetes and hypothyroidism. Her blood pressure was controlled with α -methyldopa 500 mg three times daily and labetalol 100 mg twice daily. From 26 weeks of gestation she used insulin injections and had a glycosylated haemoglobin level of 6.0%. Her thyroid hormone profile was normal on thyroxine 50 μ g daily. She had no history of asthma or allergic reactions to any food, latex condoms or gloves nor any adverse reaction to drugs during previous operations (e.g. diagnostic laparoscopy and oocyte retrieval).

Upon arrival in the operating room, our standard routine monitoring: electrocardiogram (ECG), non-invasive blood pressure and pulse oximetry was started. After preloading with 0.9% normal saline 500 mL, 1.4 mL of 0.5% hyperbaric (80 mg/mL dextrose) bupivacaine hydrochloride (Neon Laboratories Ltd, Mumbai) was given intrathecally. This low dose was used because

Accepted September 2008

Correspondence to: Dr. Deepanjali Pant, Department of Anaesthesiology, Pain & Perioperative Medicine, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India. Tel.: +919818271871.

E-mail address: deepanjali pant@gmail.com

of her short height, obesity, twin pregnancy and hypertension. A T6 block to cold, touch, pinprick was established and associated with a transient decrease in blood pressure, which recovered with rapid infusion of normal saline 300 mL. The twins were delivered uneventfully within one minute. The mother was fully conscious, oriented and extremely happy on seeing both the babies. Following delivery of the second twin, i.v. methylergometrine maleate 0.2 mg was injected followed by a slow i.v. bolus of Syntocinon 5 units and an infusion of Syntocinon 10 units in normal saline 200 mL. Within a minute, the blood pressure decreased from 126/80 mmHg to 86/50 mmHg with a heart rate of 86 beats/min and oxygen saturation of 98%; an infusion of 6% pentastarch was started.

The patient started sneezing continuously and simultaneously complained of severe itching in her throat and upper body. Marked flushing appeared rapidly, particularly on her left arm (the arm with intravenous access) followed by flushing of the face and upper body. Intravenous hydrocortisone 200 mg and Deriphylline (etophylline 170 mg + theophylline 50 mg) were given despite no obvious laryngospasm or stridor. The patient's face became swollen, her conjunctiva turned bright red, and suddenly the monitors demonstrated no recordable pulse, blood pressure or pulse oximeter readings; the ECG tracing noted sinus tachycardia. There was increased salivation which appeared as frothing. As the clinical features were suggestive of a major allergic reaction, Syntocinon and pentastarch infusions were discontinued. After rapid administration of normal saline and a bolus of ephedrine, no improvement in blood pressure was noted. Oxygen 5 L/min by face mask was administered with the patient in a head-down tilt position, followed by orotracheal intubation with succinylcholine. Intravenous epinephrine (1:10 000) was injected through a peripheral venous line (initially 4 mL followed by 6 mL). There were no secretions in the endotracheal tube and lung compliance to ventilation appeared normal.

At this time, the end tidal CO_2 was 1.3–1.6 kPa (10–12 mmHg) indicating a low cardiac output state. Although the ECG tracing showed regular sinus rhythm of 120–130 beats/min, no major pulses were felt. In the presence of pulseless electrical activity, external cardiac massage was started along with an epinephrine infusion at a rate of 4–6 $\mu\text{g}/\text{min}$. Resuscitation was continued with rapid i.v. crystalloid and colloid (modified gelatin), 7.5% sodium bicarbonate 60 mL, calcium chloride 1 g and external cardiac massage for approximately an hour until spontaneous circulation was restored. During this time, a second peripheral intravenous access was obtained followed by right subclavian central venous catheterization, which showed a CVP of 0.4–0.5 kPa (3–4 mmHg). As the blood pressure did not respond to epinephrine over 30 min, even after titrating it up to

15 $\mu\text{g}/\text{min}$, it was replaced by a norepinephrine infusion at 30 $\mu\text{g}/\text{min}$.

Arterial cannulation in the arms proved difficult because of severe obesity along with impalpable peripheral pulses; consequently, the femoral artery was cannulated with Doppler ultrasound guidance. The arterial wave tracing showed a blood pressure of 120/80 mmHg despite the absence of peripheral pulses by palpation. Oxygen saturation gradually increased to 100%. The norepinephrine infusion was tapered gradually to 10 $\mu\text{g}/\text{min}$. After the initial resuscitation, the abdomen was closed, only the uterus having been sutured while she was in PEA. Intravenous mannitol (40 g) and dexamethasone (16 mg) were given to reduce cerebral oedema. A portable echocardiogram demonstrated an under-filled right atrium and ventricle with no regional wall motion abnormality and a left ventricular ejection fraction of 70%. Normal saline 3–4 L was rapidly infused and arterial blood gas analysis showed a pH 7.24, PaCO_2 6 kPa (44.9 mmHg), PaO_2 12.5 kPa (94 mmHg), HCO_3^- 18.8 mmol/L and SaO_2 98%. The patient was paralysed with vecuronium and transferred to the intensive care unit (ICU) for ventilatory support and further management.

In the ICU the patient was electively ventilated and sedated with a midazolam and fentanyl infusion. Her pupils were mildly dilated with a normal reaction to light. Her 12-lead ECG was normal. Her troponin I level was $<0.1 \mu\text{g}/\text{L}$ (normal: $<0.1 \mu\text{g}/\text{L}$; possible myocardial infarction 0.1 to 0.8; acute myocardial infarction >0.8). Over the next 6 h her condition improved significantly, with her blood pressure being maintained with minimal norepinephrine support and urine output averaging 60 mL/h. Because of transcapillary fluid loss, the preoperative haematocrit of 33% increased to 42% 4 h after the allergic reaction but returned to baseline 12 h later. The uterus remained well contracted throughout and any bleeding per vagina was continuously monitored and remained within normal limits. The next morning the patient was fully conscious, oriented, following commands, off norepinephrine infusion and haemodynamically stable with good respiratory effort. Her chest X-ray showed bilateral pleural effusions. After 12 h her facial and whole body oedema started to subside. She was extubated 24 h after the episode but required assistance with non-invasive BiPAP for the next 24 h.

On day three, the patient developed deranged liver enzymes and renal function tests but coagulation tests were normal [fibrinogen: 2.8 g/L (normal range 2–4 g/L), FDP (D-dimer) $<0.5 \text{ mg}/\text{L}$ (normal $<0.5 \text{ mg}/\text{L}$), APTT 35.8/32.6 s and prothrombin time 14.6/12.2 s with INR 1.4]. The serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels increased from 226 and 112 units/L respectively on day 1 to 1766 and 1739 units/L on day 3 (normal range SGOT 0–42 units/L and SGPT

0–60 units/L) whereas serum bilirubin remained normal. She also developed blood-stained urine with an increase in serum creatinine from a baseline value of 1 mg/dL to 4.1 mg/dL (normal range 0.6–1.3 mg/dL). By day 5, her liver and renal function tests improved, SGPT 64 units/L, SGOT 45 units/L and serum creatinine 1.6 mg/dL. She was discharged after day 10 without any sequelae.

A blood sample collected about 4 h after the anaphylactic episode was sent for serum tryptase and IgE levels. Serum IgE level was increased at 48.7 units/mL (normal <20.4 units/mL). Serum tryptase could not be estimated as the serum had not been separated before storage at –20°C and the sample was haemolysed.

After 8 weeks, with informed consent, the patient underwent allergy testing for methylethylamine, Syntocinon and pentastarch (from the same batch) with saline as negative control and histamine as positive control, in an environment with appropriate rescue equipment and medication stand-by. Syntocinon produced a positive wheal and flare response within 20 min but there was no reaction to methylethylamine or pentastarch. The patient was given an identification tag indicating that she is allergic to Syntocinon.

Discussion

The term *anaphylaxis* includes immune- and non-immune mediated allergic reactions (previously known as anaphylactoid reactions). Immune-mediated anaphylaxis is a life-threatening systemic immediate hypersensitivity reaction that results from IgE-mediated release of mediators from mast cells and basophils in response to a range of triggers. Non-immune-mediated allergic reactions occur due to direct mast cell degranulation.

Clinical recognition of perianaesthetic anaphylaxis is not straightforward. Changes associated with the surgical procedure, anaesthesia, drug interaction or underlying pathology overshadow the event. Moreover, anaesthesia often involves the administration of numerous drugs in rapid succession, making the subsequent determination of the responsible agent difficult. In addition, the clinical syndrome associated with anaphylaxis may be variable. IgE-mediated reactions cannot be distinguished from non-IgE-mediated reactions on clinical grounds alone, although IgE-mediated reactions often occur with severe cardiovascular and pulmonary events, whereas non-IgE-mediated events have predominantly cutaneous manifestations.² In this present case, the IgE-mediated reaction mainly manifested as cardiovascular collapse leading to persistent PEA.

IgE is the least abundant immunoglobulin in the body, but is capable of triggering the most powerful type-1 hypersensitivity immune reaction. IgE elicits an immune response by binding to high-affinity receptors

(FcεRI) on the surface of mast cells and basophils.⁴ This IgE binding causes degranulation, release of preformed mediators and later release of membrane-derived lipid mediators; at the same time, basophils cross-linked with IgE release type-2 cytokines (e.g. interleukin-4, interleukin-13) and other inflammatory mediators.⁴ These mediators in turn cause urticaria, angioedema, severe bronchospasm, laryngospasm and cardiovascular collapse. Pharmacological prophylaxis with antihistamines and corticosteroids may minimize non-immune mediated reactions but does not affect sensitized mast cells and basophils. This may result in a diminished early immune response, but in consequence a severe response such as cardiovascular collapse may be the only presenting sign. Similarly, in our case involving an immune-mediated reaction, i.v. corticosteroids did not help.

The earlier administration of i.v. epinephrine might have been helpful in our case. Because our patient was on labetalol and under spinal anaesthesia, the anaphylactic reaction produced intractable vasodilatation leading to PEA unresponsive to epinephrine. Intravenous glucagon 1–5 mg administered over 5 min followed by an infusion of 5–15 µg/min may be helpful in anaphylaxis in the presence of concomitant β-adrenergic blockade.¹ Increased vascular permeability in anaphylaxis allows transfer of as much as 50% of the intravascular volume into the extravascular space within 10 min. Normal saline in large volumes should be the i.v. fluid of choice, because lactated Ringer's solution may contribute to metabolic acidosis and dextrose is rapidly extravasated from the intravascular circulation to interstitial tissue. Early placement of an arterial cannula is vital for correct dosing of vasopressors, because peripheral pulses may be missed; invasive blood pressure monitoring allowed for the titration of vasopressor infusions in our case.

Every patient presenting with a hypersensitivity reaction during anaesthesia must undergo immediate as well as secondary investigations. The level of serum tryptase, a mast cell specific protease, can clarify the diagnosis of anaphylaxis in ambiguous circumstances (i.e. vasovagal response versus anaphylaxis or other causes of intraoperative hypotension). Tryptase levels peak 20–60 min after an anaphylactic or anaphylactoid reaction and remain elevated for approximately 6 h; as such, serum should be collected within 6 h after an anaphylactic episode. Serum can be stored at 2 to 8°C for up to 5 days, or at –20°C if the sample needs to be stored for longer periods of time. An elevated serum tryptase supports a diagnosis of anaphylaxis (immune- or non immune-mediated), whereas a negative tryptase test does not exclude anaphylaxis.⁵ For example, in some cases of food-induced anaphylaxis, basophil-mediated histamine release may be associated with a normal tryptase level as it is specific only for mast cell degranulation. Tryptase

has a 95% sensitivity and a 95% specificity for clinically significant mast cell mediated anaphylactic or anaphylactoid events. Mertes et al. reported a significantly elevated tryptase in 64% of IgE-mediated and 10.7% of non-IgE-mediated reactions.² Higher levels are relatively specific for immune mediated reactions. In our case, since serum was not separated before storage and a haemolysed sample would give an incorrect value, serum tryptase was not determined, but the elevated serum IgE level suggested immune-mediated anaphylaxis.

An agent responsible for an adverse reaction can be precisely identified only in the case of immune-mediated anaphylaxis. Attempts at identifying the causative agent retrospectively by both *in vitro* allergy tests (serum IgE level) or *in vivo* allergy tests (skin prick/intradermal testing) are controversial; nonetheless, skin testing after a delay of at least 6 weeks remains the current gold standard for detection of IgE-dependent allergies.⁶ Before 6 weeks there may be an associated increased risk of false negative results due to refractoriness of the effector cell or temporary depletion of IgE antibody. A prick or scratch test should precede an intradermal skin test, with histamine used for a positive control and normal saline for negative control. This *in vivo* allergy testing protocol was followed in our case with methylethylergometrine, Syntocinon and pentastarch, as these drugs were used in rapid succession before the event.

There have been rare isolated reports of anaphylaxis to methylethylergometrine without a proven causal relationship to the product.⁷ Hypersensitivity to oxytocin has been reported and may result in hypertonicity, spasm and tetanic contraction of the uterus;⁸ in our case, the uterus remained well contracted with only 5 units of Syntocinon. Pentastarch has also been associated with anaphylactic episodes.⁹ The skin testing in our patient revealed negative prick as well as intradermal testing to methylethylergometrine and pentastarch. By contrast, a wheal and flare response to Syntocinon of 2 × 2 mm with a negative saline control within 20 min was considered indicative of IgE-mediated mast cell degranulation.

Latex anaphylaxis is also frequently reported in obstetric and gynaecological procedures.^{3,10} In our case, since the triggering allergen by intradermal skin testing was revealed, we did not consider latex as a possible cause as there was no obvious history of any fruit allergy or intolerance to materials containing latex rubber.

In conclusion, the present case demonstrates a life-threatening anaphylaxis in a parturient receiving Syntocinon. Standard anaphylaxis management should be rapidly provided to avoid compromise of the fetus and mother. Further investigations using allergy tests and other laboratory analyses can often provide diagnostic clarification to prevent future exposure and recurrence. Unfortunately, a negative test does not exclude a response to a systemic challenge.

References

1. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005; 115 (3 Suppl 2): S483–S523.
2. Mertes P, Laxenaire M, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003; 99: 536–45.
3. Draisci G, Nucera E, Pollastrini E et al. Anaphylactic reactions during caesarean section. *Int J Obstet Anesth* 2007; 16: 63–7.
4. http://en.Wikipedia.org/wiki/Immunoglobulin_E.
5. Clancy R, Reeves G, de Malmanche T, Lemmert K. Tryptase and anaphylaxis (Hunter Area Pathology Service (HAPS)) *Communiqué* 1, May 2006.
6. Fischer S. Anaphylaxis in anaesthesia and critical care. *Curr Allergy Clin Immunol* 2007; 20: 136–9.
7. Methergine Official FDA information, side effects and uses.htm.
8. Syntocinon Official FDA information, side effects and uses. htm.
9. Laxenaire M, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanism: a French multicentre prospective study. *Ann Fr Anesth Reanim* 1994; 13: 301–10.
10. Ogata J, Minami K. Synthetic oxytocin and latex allergy. *Br J Anaesth* 2007; 98: 845–6.