Anaphylaxis to topical bovine thrombin used for hemostasis during surgery for herniated nucleus pulposus - A case report -

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Anaphylaxis is a type I allergic reaction and its clinical features occur after re-exposure to the same allergen. Numerous types of drugs can cause anaphylaxis during general anesthesia. Topical bovine thrombin (TBT) is usually used for hemostasis during surgery. However, TBT can cause interruption of the normal blood coagulation pathways, delay wound repair, and lead to uncontrolled bleeding, anaphylaxis, or death. Anaphylaxis caused by TBT during the perioperative period is very rare. We report the case of a patient who developed severe hypotension, tachycardia, and bronchospasm while undergoing discectomy for herniated nucleus pulposus. Based on the symptoms and signs, anaphylaxis was considered most likely. Identification of the causative agents is important in these cases because it can be very helpful for the management and prevention of anaphylaxis. (Anesth Pain Med 2015; 10: 187-191)

Key Words: Anaphylaxis, Epinephrine, Topical bovine thrombin.

Anaphylaxis and anaphylactoid reactions are relatively rare, with an incidence of 1:6,000 to 1:20,000 [1]. Anaphylaxis requires immediate diagnosis and treatment because it is a severe, life-threatening allergic reaction. In addition, the causative agents should be removed immediately. Neuromuscular blocking agents are the most common antigens that cause intraoperative anaphylaxis, and latex, antibiotics, hypnotics, local anesthetics, and colloids are also associated with anaphylaxis [1,2]. Furthermore, some agents that are used in the field of surgery can cause anaphylaxis. If identification of the antigen that causes anaphylaxis is delayed, a poor prognosis can be expected due to delayed removal of the causative antigen.

When surgical ligation of bleeding vessels or electrocautery of small vessels fails, the surgeon relies on hemostatic aids. The use of topical hemostatic agents is common, and they have been shown to reduce bleeding in a wide variety of surgical procedures. Topical bovine thrombin (TBT) is a hemostatic agent that is commonly and successfully used for the control of hemorrhage in numerous surgeries. However, TBT can cause thrombosis, uncontrolled bleeding, and, rarely, anaphylaxis [3]. Anaphylaxis caused by TBT during the intraoperative period is quite rare. To the best of our knowledge, there are no reports of intraoperative anaphylaxis due to TBT in this country. We report a case of intraoperative anaphylaxis associated with the application of bovine thrombin powder as a hemostatic agent.

CASE REPORT

A 48-year-old woman, 155 cm tall and weighing 57 kg was scheduled for discectomy for herniated nucleus pulposus. She had a history of hypertension and diabetes mellitus, and had undergone neurosurgery for a cerebral aneurysm about 6 years ago. She had no previous history of allergic reactions to drugs or foods.

In the operating room, routine anesthetic monitoring including noninvasive blood pressure measurement, pulse oximetry, and electrocardiography (ECG) was initiated. The initial vital signs were a blood pressure of 100/70 mmHg, a
heart rate of 95 beats/min, and peripheral oxygen saturation of 99%. For induction of anesthesia, 1% propofol 90 mg with rocuronium 40 mg were administered intravenously. Anesthesia was maintained with desflurane with 50% O2 and remifentanil infusion under volume-controlled ventilation. The tidal volume was adjusted to 450 ml and peak inspiratory pressure was set at 18 cmH2O.

Approximately 140 minutes after induction of anesthesia, the blood pressure dropped to 50/30 mmHg and the heart rate increased to 130 beats/min. The tidal volume was decreased to 80–90 ml with a high peak inspiratory pressure of greater than 30 cmH2O. Lung sounds were significantly reduced in both lung fields through auscultation and peripheral oxygen saturation was decreased to 80%. Ephedrine 8 mg was administered to raise the blood pressure, but the blood pressure did not increase. In spite of the administration of an additional dose of ephedrine 8 mg as well as phenylephrine 100 µg, the blood pressure did not increase. The volatile agent and remifentanil were stopped immediately. Surgery was halted and the patient’s position was changed from prone to supine. Tracheal suctioning was performed and FiO2 was immediately adjusted from 50 to 100%. In addition, salbutamol sulfate and corticap 250 mg were administered. There were no mechanical problems with the endotracheal tube, breathing circuit, or ventilator. Arterial blood gas analysis showed pH 7.13, PaCO2 71 mmHg, PaO2 83 mmHg, HCO3− 23.6 mM, SaO2 92%, K+ 2.5 mM, Na+ 139 mM, Ca2+ 0.98 mM, and blood glucose 225 mg/dl. Because the patient continued to show unstable vital signs, with a blood pressure 60/40 mmHg, heart rate 140 beats/min, in spite of absence of massive bleeding in the surgical field, epinephrine 300 µg was administered intravenously and an epinephrine infusion 0.05 µg/kg/min was subsequently initiated.

Following epinephrine infusion, the patient’s vital signs gradually stabilized with blood pressure 100/40 mmHg, heart rate 110 beats/min, and peripheral oxygen saturation 99%. A central line was placed and femoral artery catheterization was performed for continuous arterial blood pressure monitoring. After the patient’s position was changed to supine and the surgical drapes were removed, we observed significant diffuse erythematous rashes over the entire body. While discussing about the patient’s condition with the doctor who was performing the operation, we found that the surgeon had used bovine thrombin powder for hemostasis 15 minutes before the development of clinical manifestations described above. Therefore, we had a clinical suspicion of anaphylaxis or an anaphylactoid reaction, based on the combination of the patient’s signs and symptoms. Phenylamine 4 mg and dexamethasone 5 mg were intravenously administered and immunologic blood evaluation was performed. After the patient’s vital signs were stabilized, the arterial blood gas analysis at FiO2 0.5 showed pH 7.30, PaCO2 45 mmHg, PaO2 230 mmHg, HCO3− 22.1 mM, SaO2 100%, Na+ 136 mM, K+ 2.2 mM, and Ca2+ 0.89 mM. Then, surgery was resumed, and it was performed as planned. Following surgery, the patient was transferred to the intensive care unit in an intubated state. Her vital signs were continuously stable, and on the following day, the endotracheal tube was removed without any complications.

When anaphylaxis occurred, a sample of the patient’s blood was obtained and sent to the laboratory for IgE and complement (C3c, C4) level analysis. The reported values showed an increase in total IgE to 156.6 kU/L (normal value < 100), a decrease in C3c to 53 (normal value 90–180), and a C4 level of 15, on the lower end of the normal range (normal value 10–40). After discharge, the patient underwent skin prick testing four weeks later to confirm anaphylaxis to the thrombin powder. The skin prick test was performed using solutions of the diluted TBT, normal saline as the negative control, and histamine (10 mg/ml of histamine) as the positive control. The bovine thrombin powder was diluted 1 in 10 (100 IU/ml) and 1 in 100 (10 IU/ml). The solutions were dropped on the anterior aspect of the patient’s left forearm at interval of 3 cm and injected subcutaneously by pricking the skin with a pin. The patient’s reactions which represented wheals or erythematous lesions or a systemic response were then observed for 20 minutes. After those 20 minutes, the diameters of any wheals were recorded. A positive reaction is defined as the appearance of a wheal that has a diameter 3 mm greater than that of the negative control or a diameter of at least half the diameter of the positive control wheal [4]. During the patient’s skin prick test, blood pressure, pulse oximetry, and ECG were monitored and emergency drugs including epinephrine were prepared in case of anaphylaxis. The positive control revealed a wheal of 8 mm diameter with erythema. There was also a wheal of 8 mm diameter with an erythematous lesion at the site of the 1 in 10 (100 IU/ml) thrombin diluted solution. In contrast, there was a wheal of 7 mm diameter with no erythematous lesion at the site of the 1 in 100 (10 IU/ml) thrombin diluted solution (Fig. 1). The patient displayed no unusual systemic response. After confirmation of stable vital signs, she recognized hypersensitivity to thrombin powder and returned home.
DISCUSSION

Anesthetized patients are exposed to various foreign substances including anesthetics, analgesics, neuromuscular blockers, antibiotics, antiseptics, blood products, heparin, latex, and intravascular volume expanders, which have the potential to produce a variety of predictable and unpredictable life-threatening adverse reactions. Anaphylaxis is generally an unanticipated severe allergic reaction, often explosive in onset that can occur perioperatively, especially during a surgical procedure. We experienced a case of intraoperative anaphylaxis to TBT which was accompanied by severe hypotension, tachycardia, bronchospasm, and cutaneous change.

Anaphylaxis should be considered in any case of cardiovascualar collapse, acute respiratory distress, and cutaneous change [5,6]. However it is not easy to diagnose anaphylaxis because these symptoms can occur during any type of surgery under general anesthesia. Because patients are under drapes and generally unconscious or sedated, the early cutaneous signs, such as flushing, urticaria, and edema, are often unrecognized. In addition, a large number of drugs and substances are administered during anesthesia and the operation, making it very difficult to suspect which substance caused the reactions. In regard to our patient’s clinical course, timely diagnosis and management were initially delayed, primarily due to the clinicians’ incognizance of the use of thrombin and the patient’s prone position.

The antigen presumed to be the cause of the anaphylaxis in this case, thrombin, is a serine protease that cleaves fibrinogen into fibrin. There are three types of thrombin, purified from different sources: bovine thrombin, human thrombin, and recombinant human thrombin [7]. Nowadays, bovine thrombin is the most commonly used, and it is used alone as a powder or in combination with other hemostatic aids such as fibrin or gelatin. Bovine thrombin has a long history of more than 70 years of use in surgical hemostasis. However, since 1989, clinical studies and case reports have proposed that certain postoperative and intraoperative adverse events were due to thrombin use in surgery [8]. According to a 21-year review of TBT case safety reports submitted to the FDA’s adverse event reporting system, from 1986 to 2006, 41 TBT spontaneous adverse event reports were submitted to the US FDA. Nineteen cases were classified as anaphylactic or anaphylactoid reactions, 5 cases as hemorrhagic complications, and 5 cases as infection [3].

The time of drug administration can be an important clue to the etiology of an adverse reaction such as anaphylaxis. However, it is difficult to determine the causative agent if various drugs are administered between the induction of anesthesia and the onset of anaphylaxis. In this case, anaphylaxis arose 140 minutes after the induction of anesthesia. No drugs except the anesthetic induction drug, inhalation agent, remifentanil, and neuromuscular blocking agent (NMBA) were administered during that period. The NMBA could be suspected as the causative agent of the anaphylaxis because the most common cause of anaphylaxis is NMBAs. However, the NMBA had been administered at the induction of anesthesia, and moreover was also administered periodically during the intraoperative period. There were no abnormal reactions. For this reason, it was concluded that the NMBA had no significant important role in the occurrence of anaphylaxis in this case. The majority of cases of anaphylaxis in reaction to intravenous induction agents and antibiotics occur within minutes of administration, as a large bolus of the allergen is given intravascular. However, allergy-causing substances which are administered via other routes, e.g., on the skin and mucosa, in contact with the peritoneum, or subcutaneously, may take some time to be absorbed and may trigger reactions after more than 15 minutes. In this case, TBT took time to produce a systemic reaction because the solution containing TBT was not directly given intravascular but was instead absorbed through mucosa or connective tissue.

IgE-mediated anaphylaxis is a type I allergic reaction in which, after sensitization on initial exposure to an allergen, re-exposure to the same antigen results in anaphylaxis. In a case reported in 2003, a patient who had chronic kidney
Skin testing should be performed 4-6 weeks after the anaphylactic episode. When skin prick testing is done in the early period after anaphylaxis, a severe allergic reaction can occur due to re-exposure to the allergen, or mast cell depletion can result in a false negative reaction [4]. The authors in this case conducted skin prick testing 4 weeks after the occurrence of anaphylaxis. Compared to the positive control group (histamine administration), both the 1/10 and 1/100 diluted solutions of thrombin revealed positive results. The vital signs should be monitored carefully during skin testing because severe allergic reactions could occur. In addition, cardiopulmonary resuscitation may be necessary when a severe allergic reaction occurs due to re-exposure to an allergen.

Management must be immediate, because anaphylaxis is life-threatening and may produce cardiovascular collapse. The causative drugs or products should be immediately stopped to discontinue further allergic reactions. Epinephrine is the drug of choice in the treatment of anaphylaxis, because its α1 effects help to support the blood pressure while its β2 effects provide bronchial smooth-muscle relaxation. However, it is not always given promptly, because anaphylaxis can be difficult to diagnose while patients are undergoing anesthesia. In a retrospective study [13], 45.2% of patients developed intraoperative anaphylactic shock with circulatory instability or cardiac arrest, yet only 83% of these patients received epinephrine. Intravenous corticosteroids early in the course of therapy can decrease the airway swelling and prevent recurrence of symptoms, as seen in biphasic or protracted anaphylaxis. Therefore, their effects play role of secondary treatment for anaphylaxis [14]. In this case, ephedrine and phenylephrine were injected for treatment of hypotension in the early period of anaphylaxis. However the blood pressure did not increase. Following some doubt about whether the patient’s condition in fact represented anaphylaxis,
epinephrine was administered, and after that the severe hypotension and bronchospasm gradually improved. According to the severity of clinical symptoms, anaphylaxis is divided into 5 grades (Table 1) [1]. Our patient was categorized as grade III, which is defined as severe clinical symptoms leading to death. A patient in this case requires immediate administration of epinephrine.

Patients who have had previous uninvestigated severe immediate reactions during anesthesia are at increased risk of a recurrence during subsequent administrations of anesthesia [11,13]. If a patient has a history of a hypersensitivity reaction during previous anesthesia, the anesthesiologist should search the previous anesthesia record. Because no preemptive therapeutic strategies exist, the most important thing to do to prevent anaphylaxis is to avoid the antigen. Avoidance of drugs that produced anaphylaxis and positive tests during a prior period of anesthesia has been demonstrated to prevent an episode of anaphylaxis from recurring [15]. When a specific allergen was not identified, it is necessary to test the agents used during the previous anesthesia by using the skin prick test and the antigen-specific IgE assay [4]. In addition, it is important to diagnose and treat the clinical symptoms that the anesthesiologist considered complications, such as anaphylaxis, when a patient who has a history of thrombin use is scheduled for another operation.

In conclusion, we suggest that patients with a history of repeated exposure to TBT during previous operations are at increased risk of anaphylaxis. Therefore, we recommend that our patients undergo skin prick testing using solutions with varying concentrations of thrombin before the use of TBT in subsequent surgeries. Alternatively, other hemostatic materials may also be considered in patients with a history of repeated exposure to TBT. In patients who develop unexpected, sudden, or severe hypotension during anesthesia accompanied by respiratory compromise and reactive skin lesion, anaphylaxis should be suspected and treatment with epinephrine should be considered.

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