Anesthetic Management of a Patient With Hereditary Angioedema for Oral Surgery

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Hereditary angioedema (HAE) is a rare genetic disease that results from deficiency or dysfunction of C1 inhibitor (C1-INH). This disease is characterized by sudden attacks of angioedema. When edema occurs in the pharynx or larynx, it can lead to serious airway compromise, including death. Physical and/or psychological stress can trigger an attack. Dental treatment, including tooth extraction, is also a recognized trigger. We report a case of a 20-year-old male with HAE who required impacted third molar extractions. C1-INH concentrate was administered 1 hour before surgery, which was completed under deep intravenous sedation. This report describes the anesthetic management of a patient with HAE and reviews treatment options and concerns.

Key Words: Hereditary angioedema; Intravenous sedation; Dental surgery; Oral surgery.

Hereditary angioedema (HAE) is a rare genetic disorder clinically characterized by episodic attacks of angioedema, and is found in 1:10,000 to 1:50,000 persons.¹ It is caused by a mutation of the gene for the plasma protein C1 inhibitor (C1-INH) generally causing a deficiency or dysfunction of C1-INH.² C1-INH is a member of the serpin family of protease inhibitors, which includes alpha-1 antitrypsin, antithrombin III, and angiotensinogen.³ C1-INH inhibits the classical complement pathway including the kinin-generating system. The major mediator of angioedema attacks is bradykinin, which is released during activation of the kinin-generating system. The release of bradykinin results in capillary leakage, and subsequently in attacks of edema.² Although plasma-derived C1-INH also inhibits plasma kallikrein, some coagulation factors, and plasmin, these systems do not appear to be affected by C1-INH administration.

Common sites for edema include subcutaneous tissues of the face, hands, arms, and legs; abdominal organs such as the stomach, intestines, bladder, and urethra; and the upper airway, including the larynx and tongue.

Patients commonly have episodic swelling of the bowel wall including severe abdominal pain. In many patients, vomiting is a main feature of an episode. Physical and/or emotional stress can be a trigger. In general, the swelling itself is not life threatening, except when involving the airway.²

As dental and oral surgical procedures are close to the airway, careful surgical, anesthetic, and emotional stress management is important.¹ Patients with HAE should receive prophylactic treatment to prevent attacks of angioedema. The most common prophylactic treatment for HAE is administration of plasma-derived C1-INH before the operation. Other prophylactic therapies include androgens, which can increase the levels of C4 and C1-INH. Fresh-frozen plasma has been used for prophylaxis, although it has not been approved by the Food and Drug Administration in the United States for acute attacks. Fresh-frozen plasma may supply substrate for bradykinin formation and may worsen angioedema but has been used when no other options exist.

Although the treatment of choice for acute management of angioedema is C1-INH concentrate, 2 novel medications were recently approved in the United States. One is ecallantide (Kalbitor, Dyax Corporation), which inhibits plasma kallikrein. The other is icatibant (Firazyr, Shire Orphan Therapies Incorporated), which is a bradykinin B2 receptor antagonist.^{4,5}

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CASE REPORT

The patient was a 20-year-old male, 180.0 cm in height and 61.5 kg in weight. His mother had been diagnosed with HAE. He complained of abdominal pain several times and was hospitalized with a diagnosis of acute gastroenteritis. Eventually, he was diagnosed with HAE by examination of C1-INH levels. His 3 siblings did not have the disease. After the diagnosis of HAE, acute HAE episodes did not occur. He has had routine dental treatment without any complications. He reported no medical conditions other than HAE.

He was scheduled for extraction of 2 horizontally impacted mandibular third molars and 2 maxillary third molars because of persistent pain. As the procedure is invasive and potentially stressful for the patient, it was scheduled under deep intravenous sedation. The results of preoperative laboratory examination were within normal limits, except for a low C1-INH level with 25% function (normal: 70–130%). The immunologist in our hospital suggested administering 1500 units of C1-INH prior to the operation and administering an additional 1000 units of C1-INH if angioedema appeared.

The patient was admitted to our dental hospital on the day of surgery. One hour before arrival in the operating room, he received 1500 units of plasma-derived C1-INH concentrate intravenously. Prior to the patient entering the operating room, emergency airway equipment, including endotracheal tubes, various laryngoscopes, fiber-optic bronchoscope, and tracheostomy set, was verified to be present and functional. In the operating room, an intravenous infusion of acetated Ringer solution containing 1% glucose was started. Oxygen (3 L/min) was supplied via nasal cannula. After administration of 1 mg of midazolam, the patient received a propofol target-controlled infusion with Marsh pharmacokinetic model via a Terufusion TCI pump (TE-371, Terumo) at 1 mcg/mL blood concentration level. During intravenous sedation, his cardiovascular condition maintained stable: electrocardiogram (sinus rhythm), blood pressure (100–140/40–60 mm Hg) and heart rate (62–70 bpm). His oxygen saturation as measured by pulse oximetry varied between 98 and 100% and his bispectral index value ranged from 58 to 80. A total of 12.6 mL of 2% lidocaine containing 1:200,000 epinephrine was injected for the extractions. Extraction of teeth was completed uneventfully in 50 minutes without any surgical or anesthetic complications. There was minimal blood loss. The patient emerged from sedation 7 minutes after propofol infusion was stopped. During recovery, his respiratory and hemodynamic conditions were stable. As no airway obstruction or edema occurred, he was transferred to

the general ward. He developed no complications and was discharged the next day.

DISCUSSION

HAE is a rare genetic disorder that causes a deficiency of C1-INH. Many parts of the body may be affected. However, when the upper airway is involved, HAE can be life threatening because of serious airway obstruction.

There are several reports that invasive dental procedures, such as tooth extraction, could be a trigger for HAE.^{6–12} Maeda et al¹⁰ found that laryngeal edema occurred in 2 of 36 cases with HAE after tooth extraction. Several cases with fatal outcomes have been reported. There is a report that a woman with HAE died of fatal airway obstruction following dental extraction.⁷ Bork and Barnstedt⁹ also reported that 4 patients with HAE died of laryngeal edema after tooth extraction. Even nonsurgical dental procedures may be a trigger for edema. Aziz and Tin¹¹ reported spontaneous perioral angioedema after taking a dental impression for a prosthesis.

It has been reported that preoperative administration of C1-INH for the prevention of HAE is important, even for dental treatments. Bork et al¹³ reported that facial swelling and/or laryngeal edema appeared in 124 of 577 tooth extractions (21.5%) without prophylaxis, whereas similar symptoms appeared in 16 of 128 extractions (12.5%) with C1-INH concentrate prophylaxis. The graded dose-response relationship was significant. Grant et al⁶ reported that HAE attacks did not occur within 72 hours after administration of C1-INH concentrate in 89 of 91 procedures (98%) including medical, surgical, and dental interventions. Administration of C1-INH concentrate prior to dental/oral procedures may be effective, but does not reliably prevent laryngeal attacks in all cases. Bork et al¹³ found that many of the attacks occurred within 12 hours after tooth extraction. Importantly, Bork and Barnstedt⁹ reviewed one patient with HAE who died on the second night after tooth extraction. The risk of an attack continues at least until the night after extraction, and might continue for longer.¹³ Because of the need for increased attention in the postoperative period, careful patient observation during the first 12–24 hours following oral surgery seems prudent. The patient should be informed of the rare possibility of angioedema for 24–72 hours after surgery and seek treatment immediately if there are any concerns of edema developing.

In addition to surgical stress, psychological stress can also trigger attacks. Rosa et al¹ reported that control of

anxiety with the use of nitrous oxide sedation for dentistry was effective for preventing edema in a small series of patients. In our case presentation, sedation with propofol reduced physical and psychological stress. Therefore, an attack of angioedema was likely prevented not only by preoperative C1-INH administration, but also by careful anesthetic management with propofol sedation, which was guided by BIS and hemodynamic parameters.

Amemiya et al¹⁴ reported that edema of the face and lips appeared during insertion of a bridge under local anesthesia with prilocaine containing felypressin. They postulated that the administration of vasoconstrictors could cause an attack of HAE. However, we could find no other alert on the use of vasoconstrictors than this one Japanese report. We therefore chose to use low-dose epinephrine, as sufficient analgesia was deemed more important to avoid an attack of HAE.

In conclusion, we present a case of a patient with HAE who required impacted third molar surgery. Preoperative management with C1-INH concentrate, intraoperative management with deep sedation, and overnight postoperative monitoring resulted in an uncomplicated perioperative course.

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