

## A Review of 25 Patients with Hereditary Angioedema Requiring Surgery

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Hereditary angioedema (HAE) is a periodic swelling disorder due to decreased functional activity of a plasma protein, the C<sub>1</sub> esterase inhibitor (C<sub>1</sub> INH).<sup>1</sup> This protein acts to inhibit the activity of C<sub>1</sub> in the complement system as well as in all of the mediator pathways activated by Hageman factor and its fragments. Thus, the C<sub>1</sub> inhibitor protein acts in the clotting, fibrinolytic, and kinin-generating systems as well. HAE is inherited as an autosomal dominant trait. Patients either have low levels of protein (common form, 85% of cases) or have normal levels of a circulating nonfunctioning protein (variant form, 15% of cases). HAE is characterized by the development of episodic edema, usually of the extremities, face, neck, airway, and/or gastrointestinal tract. In about half the patients, edema formation is precipitated by trauma, emotional upset, or anxiety. Why trauma precipitates attacks in some patients is unclear. One theory is that trauma leads to local clot formation and plasmin generation and this plasmin activates C<sub>1</sub> to initiate attacks. Laboratory confirmation of HAE involves obtaining specific assays of proteins (C<sub>4</sub> and C<sub>1</sub> INH) in the complement system. Therapy for HAE includes long-term prophylaxis (antifibrinolytic agents, hormonal agents), short-term prophylaxis (antifibrinolytic agents, hormonal agents, fresh frozen plasma), and the treatment of acute attacks. Reports of mortality due to HAE have been as high as 15–33%, with most deaths being attributed to laryngeal edema.<sup>2</sup>

The few case reports that have appeared in the anesthesia literature have suggested that management of pa-

tients with a history of HAE is either avoidance of an initiating stimulus for upper airway edema (*i.e.*, irritation from an oral airway or endotracheal tube, or traumatic intubation) or prophylactic elevation of functional C<sub>1</sub> esterase inhibitor prior to the procedure.<sup>3–7</sup> Abada *et al.* advocated the use of regional techniques, where applicable, to avoid trauma to the upper airway. They successfully used a subarachnoid block for a urological procedure in a patient with HAE.<sup>3</sup> Gibbs *et al.* used local anesthesia and prophylactic pretreatment of a patient with two units of FFP prior to three dental extractions without complications.<sup>4</sup> The incidence of fatal laryngeal edema following dental extractions in patients with HAE has been significant.<sup>5,6</sup> Schär reported successfully administering general anesthesia to a patient with HAE. However, the author advocated the use of a mask without any form of artificial airway.<sup>7</sup> Poppers reported a case of extensive dental surgery accomplished with general anesthesia using an endotracheal tube. The author elected to use an oral endotracheal tube rather than a nasal tube because of the lower likelihood of associated trauma. Prophylactic pretreatment with danazol, a hormonal agent, and FFP were used for this case.<sup>8</sup>

This is a review of the anesthetic management of 41 surgeries on 25 patients with HAE. Specific clinical guidelines are offered.

## MATERIALS AND METHODS

Patients with HAE have been treated at the Warren G. Magnuson Clinical Center since 1970. A retrospective chart review examined the preoperative, intraoperative, and postoperative courses of 25 patients with the diagnosis of HAE who underwent 41 surgical procedures. All 25 patients had laboratory confirmation of HAE and exhibited typical clinical attacks including extremity swelling and abdominal pain. Eighteen patients were female and seven were male. The ages ranged from 10–75 yr. Nine patients had more than one surgical procedure. Twenty-five of the 41 surgical procedures were cystoscopies. Cystoscopies were frequent because of the need to document possible bladder toxicity (presenting as hematuria) secondary to danazol therapy.

Twenty-two patients (88%) had a positive past history for airway compromise secondary to edema from HAE. Symptoms ranged from a feeling of tightness in the throat to complete upper airway obstruction. Four (16%) of these patients had required tracheal intubation to treat airway compromise, and three others (12%) had received trach-

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TABLE 1. Data on Three Perioperative Complications

Age	Race/Sex	Airway History	Preoperative Prophylaxis	FFP	Operation	Anesthesia	Intubation	Complications		
								Intra-op	RR	Postop
27	WF	Yes	Oxymethalone	Yes	Laparoscopy, tubal ligation	General	Yes	No	Yes	No
56	WM	Yes	Danazol	No	Cystoscopy, transrectal prostate biopsy	General	Yes	No	No	Yes
27	WF	Yes	Epsilon aminocaproic acid	Yes	Elective tracheostomy	General	Yes	No	No	Yes

eostomies. Three patients (12%) had no history of airway involvement.

Long-term pretreatment with hormonal agents or antifibrinolytic agents was present preoperatively for 37 of the 41 (90%) surgical procedures. Hormonal agents (*i.e.*, danazol, oxymethalone, stanazolol, or methyltestosterone) accounted for 32 (86%) of the cases while antifibrinolytic agents (*i.e.*, epsilon aminocaproic acid [EACA] and tranexamic acid) accounted for five (14%). Only one short-term pretreatment course with a hormonal or antifibrinolytic agent was noted. In this case intravenous EACA was used. On three occasions (7%), patients did not receive a long-term or short-term pretreatment course of hormonal agents or antifibrinolytic agents; one patient was too young (age 10 yr), one patient had a prior history of being unresponsive to all therapies, and a third patient for reasons that could not be determined from the records.

Short-term prophylaxis with FFP was instituted preoperatively in 30 of the 41 cases (73%). Two units of FFP were given the night before surgery. Eleven procedures (27%) were not preceded by the prophylactic administration of FFP. Where there was no anticipated trauma to the airway, and when the surgical site was sufficiently remote so that local swelling was unlikely to compromise the airway, FFP was not administered if the condition was satisfactorily controlled by medication. Often the dose of hormonal or antifibrinolytic agent was increased for 1 week prior to surgery. One of these 11 procedures was performed in 1973, before FFP was suggested as a prophylactic measure. In five of the other ten cases, regional techniques or monitored anesthesia care (monitoring with or without intravenous sedation and/or intravenous analgesia) were used. In one case, there was no documented pretreatment with either drug therapy (hormonal or antifibrinolytic) or FFP. This case involved a patient undergoing cystoscopy with a bladder biopsy receiving monitored anesthesia care with no intraoperative or postoperative complications noted.

## RESULTS

General anesthesia was administered for 30 of the 41 cases (73%). Spinal anesthesia was administered for two cases (5%) and nine cases (22%) were done with monitored

anesthesia care. Of the 30 general anesthetics, in 15 cases (50%) tracheal intubation (11 orotracheally, four nasotracheally) was performed, whereas anesthesia was delivered *via* mask for the other 15. Two of the 30 general anesthetics had been converted to general anesthesia after insufficient analgesia from one spinal anesthetic and one case of monitored anesthesia care. All tracheal intubations were facilitated by the use of muscle relaxants. In 13 cases, succinylcholine was used and, in two cases, atracurium was administered for muscle relaxation.

Of the 15 cases in which tracheal intubation was employed, 11 had received long-term pretreatment and FFP, one received FFP only (10 yr old), and three received long-term pretreatment, but no FFP.

Complications involving the airway, either intraoperatively or postoperatively, occurred in three of the 41 cases (7%) (see table 1). In all cases, no postoperative intensive care stay was necessary.

Below is a brief account of each complication.

*Case 1.* A 27-yr-old white woman underwent a laparoscopy with tubal ligation. She had received long-term pretreatment with oxymethalone (15 mg/day) and received two units of FFP the night before surgery. She received a general anesthetic along with tracheal intubation and had an uncomplicated intraoperative course. In the recovery room she experienced "shortness of breath and throat tightness" which responded within 30 min to the inhalation of vaporized racemic epinephrine.

*Case 2.* A 27-yr-old white woman presented for elective tracheostomy. She had required tracheal intubation on three occasions in the past for airway compromise, the most recent being 1 week prior to this surgery. Because of the rapid onset of airway compromise in the past, and the difficulty in securing an airway by tracheal intubation (*i.e.*, near fatal outcomes), it was recommended to this patient that she consider tracheostomy. Her disease had been unresponsive to all therapies. Despite refractoriness to past therapies, she received short-term pretreatment with intravenous epsilon amino caproic acid (EACA) 8–10 g/day and two units of FFP the night prior to surgery. A general anesthetic with tracheal intubation was administered. No intraoperative or immediate postoperative problems occurred. On the second postoperative day, the patient complained of pharyngeal swelling which resolved over several hours without specific treatment.

*Case 3.* A 56-yr-old white man presented for a cystoscopy and transrectal prostate biopsy. He was receiving long-term pretreatment with danazol (600 mg/day), but did not receive FFP preoperatively for reasons which were not documented. He received a general anesthetic by mask, but due to excessive secretions and mild laryngospasm intraoperatively, required tracheal intubation. The remainder of the intraoperative course and recovery room stay were uneventful. Five hours postoperatively, the patient developed significant lip and facial swelling that responded to subcutaneous epinephrine (0.3 mg), intravenous diphenhydramine (0.5 mg/kg), and the administration of two units of FFP. He experienced no airway compromise secondary to the swelling.

#### DISCUSSION

The medical management of patients with HAE includes long-term prophylaxis, short-term prophylaxis, and the treatment of acute attacks. Long-term prophylaxis is not required for all patients. Fortunately, most attacks are sufficiently mild or infrequent and do not require long-term therapy. Long-term therapy is indicated if the patient has a history of repeated laryngeal obstruction or swelling of the face and neck, or frequent debilitating attacks. Children and pregnant women are treated rarely because of the harmful drug side effects. The two classes of drugs for long-term treatment include antifibrinolytic agents (*i.e.*, EACA and tranexamic acid) and hormonal agents (*i.e.*, methyltestosterone, stanazolol, oxymethalone, and danazol). Antifibrinolytic agents are reported to act by inhibiting plasmin activation. Hormonal agents are believed to increase the hepatic synthesis of C<sub>1</sub> INH. Several days of treatment are needed with each of these classes of drugs to achieve a therapeutic effect. Toxic side effects may be limiting. Short-term prophylactic therapy is indicated for patients with HAE undergoing traumatic procedures to the airway (*i.e.*, dental surgery, endotracheal intubation, etc.). Such therapy can be provided by a 2–3 day course of antifibrinolytic or hormonal therapy before surgery and/or the use of fresh frozen plasma (FFP). FFP is a source of C<sub>1</sub> INH and two units given on the day before surgery can prevent airway swelling in the intraoperative and immediate postoperative period. Unfortunately, the treatment of acute attacks leaves much to be desired. Patients with HAE often do not respond to epinephrine, steroids, or antihistaminics. No controlled studies using these drugs have been performed. However, the drugs continue to be used because of subjective and anecdotal patient reports of their ability to alter the course of an attack. Antifibrinolytic and hormonal agents are of no major benefit during acute attacks. FFP contains C<sub>1</sub> INH and components of complement and occasionally may exacerbate an acute attack.

The development of airway edema in patients with HAE is often precipitated by periods of trauma, emotional upset, or anxiety. Each of these initiating events can occur with an anesthetic and surgical experience. The key to safe anesthetic management of these patients appears to be adequate prophylaxis. Administration of two units of FFP on the evening before surgery to all patients in whom there is anticipated airway trauma is recommended. The potential for airway trauma is an individual determination made by the anesthesiologist. We consider endotracheal intubation to be associated with a high potential for producing airway trauma and therefore recommend FFP preoperatively when this form of airway management is chosen. The insertion of an oral or nasal airway and suctioning of the airway may or may not be traumatic and the potential for such trauma should be determined preoperatively. Others have advocated androgen therapy or tranexamic acid prophylaxis without FFP.<sup>8</sup> We have not limited our therapy to these agents since attacks can occur despite long-term prophylactic regimens, especially at the lowest tolerated dose, and once acute attacks start, they may be very difficult to treat. However, if long-term prophylactic therapy (*i.e.*, antifibrinolytic agent or hormonal agent) has been ongoing, we generally continue it preoperatively and postoperatively. If no long-term therapy is ongoing, short-term prophylactic therapy with an antifibrinolytic or hormonal agent for a 2–3-day course is preferred if time permits.

Monitored, regional, and general anesthesia can be safely administered to patients with HAE if adequate prophylaxis is prescribed. Postoperative intensive care management is not necessary unless the surgical procedure dictates such care.

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