Perioperative management for patients with hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant disease that results from mutations in the C1-esterase inhibitor (C1-INH) gene. HAE is characterized by recurrent episodes of angioedema of the skin (face, extremities, genitalia, trunk), the gastrointestinal tract, and respiratory tract. Symptoms experienced can be debilitating, may impact quality of life, and can be life threatening. Preventing attacks particularly for patients undergoing procedures is critical. Patients with HAE may now treat acute attacks or prevent attacks with medications that have recently become available in the United States; however, these same medications can be used for perioperative management for patients undergoing medical, surgical, and dental procedures. Periprocedural planning is important for patients to reduce the incidence of acute attacks. Education is critical and increasing awareness of short-term prophylaxis options will allow providers to develop an appropriate action plan for their patients. The goal of this review is to increase awareness for HAE treating physicians, surgeons, anesthesia, and emergency room physicians by examining the available treatment options, researching the literature, and summarizing available data for periprocedural management. The availability of treatment options has increased over the past few years, expanding options for physicians and patients living with HAE and improve safety during the perioperative period and at the time of other procedures.

Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency of C1-esterase inhibitor (C1-INH) resulting in sudden episodes of edema.[1–4] It is often debilitating and potentially life threatening[5] and is characterized by recurring and often spontaneous angioedema of the skin (face, extremities, genitalia, trunk), the gastrointestinal tract, and respiratory tract[1,2,6] The extremities, genitals, trunk, face, bowels, and larynx are the areas most commonly affected; however, any area or multiple sites can be affected during a given attack.[7–9] HAE has an estimated prevalence of between 1:10,000 and 1:50,000 in the United States.[2,3,10,11] In many patients, symptoms typically manifest between the ages of 4 and 11 years, but the age of diagnosis may not be until 10–22 years.[7] It is an inherited autosomal dominant disorder, with a 50% chance of inheritance when one parent has HAE.[4,7] However, similar to other autosomal dominant diseases, a family history is not always present,[10] and it has been estimated that 25% of HAE arise from spontaneous mutations.[7,12] HAE can affect patients irrespective of race, sex, or ethnicity; however, more women than men have been seen to be severely impacted.[7,11] This gender difference, in combination with the increased occurrence after puberty, decrease after menopause, and exacerbations with the use of estrogens, suggests that estrogen plays a significant role in HAE symptoms.

The most common types of HAE are type I HAE and type II HAE caused by either low levels or low functioning of C1-INH. Type I, now referred to as HAE with deficient C1 inhibitor, results from low levels of C1 inhibitor (C1-INH) and accounts for approximately 85% of cases.[7,13–16] Type I is also characterized by low C4 levels and normal C1q level.[5] Type II is characterized by normal or elevated dysfunctional C1-INH and, for this reason, is properly termed HAE with dysfunctional C1 inhibitor, and accounts for approximately 15% of cases.[7,13–16] Type II, much like type I, is also characterized by low C4 and normal C1q level.[5,10] A third type of HAE, type III, is characterized with normal C1 inhibitor, is very rare, and is seen mainly in women with normal C1-INH, function, and C4. Some data suggest that HAE with normal C1-INH may be associated with activation mutations in the gene for factor XII; however, this is neither a sensitive nor specific marker for the disease, and at this time, there are no diagnostic tests to confirm the diagnosis of HAE with normal C1 inhibitor.[5,15,16]

HAE attacks make up an estimated 30,000 emergency department visits per year in the United States, significantly impacting quality of life.[5,7,17] Patients

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with HAE can experience an average of 20 attacks annually with laryngeal attacks occurring in approximately 50% of patients.[5,18] Moreover, 34% of patients who present with abdominal attacks to the emergency department undergo unnecessary surgical or medical procedures due to misdiagnosis by physicians unfamiliar with HAE.[7,19,20]

During HAE attacks, plasma proteolyctic cascades are activated, and several vasoactive substances are generated.[4,12] In particular, bradykinin, is over produced by activation of the contact system secondary to the loss of inhibition of the system from low or dysfunctional C1-INH.[4,11] Bradykinin is the mediator of enhanced vascular permeability, resulting in vasodilation, nonvascular smooth muscle contraction, and edema formation, thus resulting in the acute symptoms of HAE.[4,11–13] Therefore, reducing or preventing bradykinin production or its effect is of paramount importance in the treatment of HAE as well as preparing a patient for a procedure.

Gastrointestinal attacks are frequently associated with abdominal pain and vomiting often from intestinal obstruction that is caused by edema of the bowel wall, sometimes leading to unnecessary abdominal surgeries due to the similarity of symptoms with other acute surgical conditions.[20,21] Pain associated with gastrointestinal attacks is usually slowly progressive over a day and can last for three to five days.[22] Upper airway edema is documented by 50%–79% of patients and has an estimated 15%–33% mortality rate when untreated resulting most commonly from airway obstruction during laryngeal edema.[23–26] Studies show that asphyxiation can occur in 20 minutes to 14 hours after the onset of edema in patients, and it has occurred in patients with no previous history of respiratory symptoms nor previous angioedema.[27]

HAE is characterized by substantial variability among patients with regards to severity, provoking factors, impact of comorbid conditions, and response to treatment.[23,28,29] This notable variability in the duration, frequency, and severity of HAE attacks seen in individuals, leads to variable treatment needs for long-term prophylaxis, short-term prophylaxis, and acute attacks.[30] It is important for patients to have access to treatments that will be effective and reflective of their needs. The rarity of HAE makes it unfamiliar to many physicians and results in a delay in diagnosis as well as an inadequate treatment plan and management by many physicians.[3,30]

HAE attacks are often unpredictable without recognizable triggers; however, in many reported cases, risk factors leading to HAE attacks include physical trauma such as dental procedures and surgery as well as psychological stress, acute illness, and tonsillectomy.[5,6,23,31–33] Dental procedures have been a reported trigger of up to 50% of attacks with the potential to lead to asphyxiation approximately 4–30 hours after dental procedures.[26] Several case studies have shown that dental surgery and tooth extractions have provoked episodes in patients, including swelling of the lips, face, tongue, and laryngeal edema as well as abdominal swelling.[29] Laryngeal edema often leads to upper airway obstruction, making it the most important concern when caring for these patients.

The unpredictable onset of attacks, impact on school, work, and social interactions, and overall decreased quality of life can impose a significant disease burden.[3,18,30,34] Furthermore, a survey for patients living with HAE without therapies reported that at least 85% of respondents live their lives constantly fearing sudden airway closure, fear that can potentially intensify from dental, medical, and surgical procedures.[34] Therefore, an appropriate management plan for patients undergoing physical trauma and surgical and dental procedures is critical to minimize the morbidity and mortality associated with HAE. With this goal, we searched the literature using search engines PubMed, Google, and Ovid with HAE and cross terms perioperative, operative, prophylaxis, operation, surgery, and procedures. We did not include studies that were based on only a few case reports and also discarded studies that did not make sense based upon the mechanism of action or half-life of the drug.

PERIOPERATIVE MANAGEMENT

A perioperative management plan and multispecialty collaboration for patients undergoing dental procedures, surgery, and pregnancy or delivery can reduce the likelihood of a patient experiencing postoperative HAE attacks or premature mortality.[35] Dental surgery, even if considered minor surgery, may be associated with swelling of the oral cavity that can progress and cause airway constriction, which can be life threatening.[1,12,31,33,36] Currently, short-term prophylaxis, typically with danazol or C1-INH, is indicated for HAE patients before major medical, surgical, or dental procedures.[7,9] There are currently no universal guidelines regarding perioperative management of a patient with HAE; however, recommendations of administration of C1-INH before procedures, starting or increasing doses of attenuated androgens and administering fresh frozen plasma (FFP), have been recommended (Table 1).[12,33] Studies have reported success in preventing angioedema with no complications and insignificant adverse events.

TREATMENTS FOR SHORT-TERM OR PREPROCEDURAL PROPHYLAXIS

Observational studies have shown that short-term prophylaxis before dental procedures, medical procedures, and surgeries with antifibrinolytics, attenuated

Table 1 Reducing risk of procedural induced HAE attacks

Avoid intubation if possible

Avoid general anesthesia and use local therapy if possible

Pretreat with androgens, C1-INH, or if neither is available with FFP

Have two doses of rescue therapy available to include ecallantide, icatibant, C1-INH, recombinant C1-INH, or FFP

During delivery use vaginal delivery when possible

Always have capability to protect the airway during perioperative period

Ensure that the patient has therapy available and has been educated to treat or present for care if an attack occurs after discharge

androgens, FFP, and C1-INH concentrates have been successful in preventing HAE attacks.[6,33] Unfortunately, there are no comparative studies; nonetheless, most experts consider C1 inhibitor or androgens to be the most effective because other therapies have shelf-lives that are too short. Although there are no specific perioperative therapies approved by the Food and Drug Administration, short-term prophylaxis for patients undergoing dental and surgical procedures have been recommended and are noted in Table 2.[16] Despite preprocedural prophylaxis, some patients still experienced episodes and rescue medication is essential to have for this reason.[23]

Antifibrinolytics are less effective in long-term prevention than attenuated androgens and are prescribed to patients with HAE that cannot tolerate attenuated androgens, especially when other therapies are not available, such as in developing nations.[5,13] Long-term prophylaxis use results in potential adverse effects, including nausea, diarrhea, muscle weakness, fatigue, impaired vision, prolonged menstruation, and thrombosis, but these adverse events are rare in short-term therapy. Despite the minimal risks, use before a procedure is not thought to be effective enough to suggest its use in this situation.[5,9,13]

Historically, since the 1970s, attenuated androgens, most commonly danazol, have been considered the main medication for long-term prophylaxis.[28] Androgens are well tolerated by many patients and were for many years the only available chronic prophylactic therapy for treating HAE in the United States.[16,37] Studies show that increasing attenuated androgens such as danazol to doses of 600 mg at least five to seven days before surgery and at least two to five days after surgery can reduce the number of attacks in the periprocedural period with minimal side effects.[16,29] In contrast, when used for long-term prophylaxis, at least

80% of patients reported adverse side effects, including weight gain, nausea, acne, headache, anxiety, hypertension, myalgia, depression, hematuria, or liver toxicity.[5,8,12] For this reason, most experts suggest limiting the long-term prophylactic dose to no more than 200 mg of danazol per day.[38] The lack of controlled studies for danazol with short-term prophylaxis is the main limiting factor in its use for preprocedural therapy; however, most consider it very effective.[38]

FFP has frequently been used for attacks and short-term prophylaxis. C1-INH is in FFP, and the use for attacks is probably effective, but controlled studies have not been done.[12,23] FFP has also been used as short-term prophylaxis for patients undergoing surgical procedures such as tooth extractions, dental restorations, and other procedures, but again, controlled studies have not been performed.[1] FFP has typically been administered the night preceding surgical procedures or just before the procedure. However, because attacks may follow a trigger by two to three days, use of FFP immediately before the procedure seems a more rational approach to extend protection.[39,40] In a review of medical and dental records for 53 patients seen at the Dental Clinic of the National Institutes of Health, patients treated with two units of FFP experienced postprocedural attacks in 6.7% of cases after dental surgery.[1] This percentage of postprocedural angioedema is lower than anticipated, suggesting efficacy, which approaches the reduction of the attacks in the Bork *et al.* study where patients received 1000 units of C1 inhibitor.[29]

Unlike anecdotal reports of FFP worsening acute attacks, similar reports of this paradoxical response is not available using FFP for short-term prophylaxis.[40] FFP has also been successfully used during pregnancy and cesarean delivery.[40] Although few adverse effects have been reported when using FFP for preprocedural therapy, the major concern of transmission of blood-borne pathogens has limited its use with the advent of C1INH becoming available. The manufacturing steps for producing plasma derived C1INH reduce the chance of viral transmission when compared with FFP.[2,12,38] Another consideration is the large volume necessary for prophylaxis.[5] For these reasons, when available, the preferred treatment for short-term prophylaxis is currently C1-INH.[5,9]

C1-INH concentrate has been used in many patients and reports indicate success in preventing postsurgical swelling episodes after dental, medical, and surgical procedures.[4,9] Many experts consider C1-INH as the preferred and first-line therapy for chronic prophylaxis, but cost limits access to the majority of countries throughout the world.[5,9] In uncontrolled studies, increased doses of up to 1000 units of C1-INH concentrate administered intravenously at least one hour before dental and surgical procedures have shown

Table 2 Therapy for short-term prophylaxis

Drug	Dose	Cautions
Androgens	Danazol 200 mg 3 times a day for 5 days before and 3 days after; however, the duration before and after the procedure varies from study to study.	Few adverse effects for short-term use, but controlled data are limited.
FFP	Two units 1 hour before procedure. Adjust dose for children.	Few adverse effects should be anticipated, but controlled data to support use are limited.
C1-INH	1000 units or 20 units/kg 1 hour before procedure. Units per kg is preferred in children.	No known concerns. Approved in Europe.
Ecallantide, icatibant, rcC1-INH, C1-INH, FFP	Have 2 doses of therapy available if angioedema occurs. Dose appropriate for acute attacks.	Cautions based on drug used.

successful outcomes, but breakthrough attacks still occur and approximate the breakthrough after FFP as noted above.[29] C1-INH has been shown to be effective in reducing the number of angioedema attacks when administered 1000 units twice per week in a prospective double-blind, placebo-controlled trial, but again, absolute reduction of attacks was not accomplished.[27] Multiple case reports suggest effectiveness in preprocedural use; however, Bork et al.[29] demonstrated break through attacks even at 1000 units given before the procedure, suggesting that higher doses may be necessary.[4,33,35,36,41,42] Because break through attacks occur even at 1000 units, many believe that dosing 20 units/kg may be more effective. An alternative would be using 1500 or 2000 units, but data are not available for set dosing above 1000 units. Dosing by weight allows dose adjustment for size and for an average size adult would be 1500 units. Also, the option of dosing at 20 units/kg allows dose adjustment for pediatrics and other extremes of weight. Data for treatment of attacks suggests that 20-units/kg C1-INH is more effective than lesser doses, and the same may be true for short-term and preprocedural prophylaxis.[17] During pregnancy and lactation and in children, C1-INH is the preferred medication for preprocedural prophylaxis; however, for others, androgens may be an adequate option.[6,38]

An alternate approach is to have two doses of therapy available to treat postprocedural angioedema. In this approach, many therapies appear to be beneficial. This would include ecallantide, recombinant C1-INH, C1-INH, icatibant, and possibly FFP. For major procedures, especially involving the upper airway or mouth, and those that require intubation or the possibility of significant fluid loss, preprocedural therapy is indicated, but for other procedures, having two rescue doses if swelling occurs is an appropriate alternative,

especially for minor dental procedures such as cleaning and cavity restoration.[38]

CONCLUSION/RECOMMENDATIONS

Short-term prophylaxis should now be included in a treatment plan for perioperative care for dental procedures, medical procedures, and surgeries for every HAE patient, even if asymptomatic before the procedure. The prevention of potentially life-threatening complications during procedures is critical and minimizing the risk of angioedema is key for appropriate patient outcomes. Patients who been denied routine dental care or medical or surgical procedures due to their HAE diagnosis can now receive care with perioperative planning using short-term prophylaxis treatments such as C1-INH and abiding by other suggestions in Tables 1 and 2.[4,12]

Improving the patient outcomes of HAE patients should be our primary concern, and increasing awareness of this unique disease is the first step. Once this is recognized, treatments such as C1-INH administered one to six hours before, two units of FFP administered within one to six hours of surgery, or 600 mg of attenuated androgens five days before and two to three days after the procedure should be considered.[9,12,39] In addition, all patients should have a periprocedural action plan for treatment of acute attacks, and the plan should include two doses of therapy for a postprocedure attack. Although attenuated androgens such as danazol are potential alternatives for prophylaxis and FFP has been used before elective medical interventions, C1-INH concentrate is the preferred treatment based on its safety that has been demonstrated for many years in Europe.[5] The only controversy is the dose. Should the dose be 500, 1000, 1500, or 2000 units or 20 units/kg? Research is necessary to clarify this question.

Educating patients, physicians, and emergency rooms on HAE management for upcoming dental, medical, and

surgical procedures can improve patient outcomes. Despite this statement, data suggest that we as healthcare providers have room for improvement. A 2009–2010 survey of United States physicians reported that 84% of physicians administered short-term procedural prophylaxis with 35% prescribing FFP, 30% prescribing C1-INH, and 19% prescribing high-dose attenuated androgens.[43] Of the respondents, 16% of United States physicians reported that they do not prescribe short-term procedural prophylaxis, suggesting increased need for awareness and need for education of treatment options.[38,42,44]

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