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A cross-sectional questionnaire assessing patient and physician use of short-term prophylaxis for hereditary angioedema

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ABSTRACT

Background: Current guidelines recommend short-term prophylaxis (STP) before invasive procedures to prevent hereditary angioedema (HAE) attacks; however, adherence to these guidelines may be variable because this indication lacks Food and Drug Administration approval in the United States.

Objective: To ascertain the STP experiences of patients with HAE and HAE-treating physicians.

Methods: Online questionnaires focusing on STP experiences were distributed by the US Hereditary Angioedema Association to the first 250 patients with HAE and to registered HAE-treating physicians. SAS 9.3 was used to perform descriptive statistics and to test the difference between patients who underwent procedures and those who did not using Pearson χ^2 test, Fisher exact test, and 2-sample *t* test.

Results: For the patient survey, 219 respondents met the criteria for HAE type 1 and 2; 37 (17%) underwent 66 invasive procedures, and all reported receiving STP. Eight patients (22%) reported failed STP, but only 3 required on-demand therapy. For STP, anabolic steroids and plasma-derived C1 inhibitor were the most and second-most commonly used, respectively. For the physician survey, 37 physicians reported caring for 433 patients with HAE. Depending on the procedure, 19% to 54% of physicians used STP and 30% to 86% prescribed on-demand therapy; 69% and 78% of physicians prescribed plasma-derived C1 inhibitor as STP for minimally invasive and invasive procedures, respectively. Physicians reported excellent efficacy for the STP treatments used.

Conclusion: Physicians reported excellent outcomes using primarily newer STP therapies, namely plasma-derived C1 inhibitor, which was discordant to patient-reported outcomes using older STP therapies, namely anabolic steroids. Well-controlled STP studies are needed to clarify use for patients with HAE in the United States.

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Introduction

Hereditary angioedema (HAE) attacks are frequently triggered by trauma such as dental work, elective medical procedures, or surgery.^{1–3} The presence of angioedema after a procedure without prophylaxis was 5.7% in 144 patients with HAE who underwent 335 invasive procedures, which shows the risk for these patients is

significant.⁴ Various medications have been used for short-term prophylaxis (STP) before procedures with varying degrees of success. Before 2009, when novel HAE therapeutic agents first became available in the United States, STP consisted of using preparations of fresh frozen plasma for 1 to 2 hours within 12 hours before the procedure or using high-dose 17 α -alkylated androgens (6–10 mg/d per kilogram of patient weight in divided doses up to a maximum of 200 mg of danazol or equivalent 3 times per day) for 5 to 10 days before the procedure and 2 days afterward, with varying degrees of success.^{5–8} Since the approval of nanofiltered plasma-derived C1 inhibitor (pdC1INH) replacement therapy in the United States for prophylactic and acute on-demand therapy (ODT) of HAE attacks, pdC1INH administered as 1,000 to 2,000 units 1–2 hours before the procedure has been increasingly used for STP, with low post-procedure attack rates reported.⁹

The evidence for advocating STP is based on case reports, case series, and several retrospective or cross-sectional questionnaire surveys showing fewer angioedema attacks during and after the

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procedure when STP is used. For example, Leimgruber et al¹⁰ reported a favorable outcome for a patient with HAE provided with STP using pdC1INH for a dental procedure. Farkas et al⁶ also reported favorable outcomes when androgen therapy was used as STP before and after dental procedures in 12 patients with HAE. Codispote et al¹¹ reported excellent outcomes in a 51-year-old man with HAE who received pdC1INH as STP before mitral valve annuloplasty on a balloon pump. Bernstein et al¹² subsequently reported a similar favorable outcome in the same patient who received pdC1INH as STP for surgical revision of the original mitral valve, which had developed an annular leak. Larger studies have shown similar results; Grant et al⁹ analyzed data across all completed pdC1INH replacement therapy studies in which pdC1INH was administered within 24 hours before a medical, dental, or surgical procedure. Forty-one patients (8 children, 33 adults) received pdC1INH for 91 procedures (40 in children, 51 in adults); approximately 56% of the procedures involved dental work and 44% involved surgeries or interventional diagnostic procedures. A single 1,000-unit dose was administered for 96% of procedures; 2 separate 1,000-unit doses were used for 2 coronary artery bypass surgeries, 1 gastrointestinal endoscopy, and 1 labor and delivery. Only 2 HAE attacks were reported within 72 hours after dosing—1 for a genitourinary attack after dental work and 1 for a laryngeal attack after laparoscopy, which resolved after an additional dose of pdC1INH. No significant adverse events were reported. The investigators concluded that preprocedure administration of pdC1INH was effective in preventing HAE attacks related to medical, dental, or surgical procedures.⁹

As a result, international consensus guidelines recommend that all patients with HAE receive STP with pdC1INH or alternative medications to prevent patients from developing an acute attack during an invasive medical or surgical procedure (ie, dental work other than routine teeth cleaning, surgical procedures, and endoscopy); however, during a minor procedure, STP is not recommended if pdC1INH is immediately available.⁵ Currently, STP is not approved in the United States by the Food and Drug Administration for use before traumatic procedures; thus, the current usage of STP and medications likely varies considerably by physician practice despite recommendations and the potential increased risk of swelling associated with these procedures. Given the lack of evidence supporting uniform STP for all patients undergoing any medical, surgical, or dental procedures, a larger double-blinded, placebo-controlled study investigating the benefit of presurgical prophylaxis with pdC1INH or other currently approved ODTs is warranted. To substantiate such a study, a questionnaire study was designed with the primary objective of ascertaining the STP experiences of patients with HAE and HAE-treating physicians. The authors hypothesized that the 2 surveys would reflect the widely variable use of pre-procedure STP and STP medications by physicians in patients with HAE, which would further substantiate the need for a double-blinded, placebo-controlled study.

Methods

Patient and physician surveys were administered online and anonymously; therefore, this study was exempt from approval by the institutional review board.

Patient Survey

In 2012, e-mail invitations were sent to 960 randomly selected patients from the United States Hereditary Angioedema Association (US HAEA) patient database using the US HAEA e-mail server containing a 1-time use only link to the survey form, which resided on the US HAEA server; the first 250 respondents with self-reported HAE were recorded and included in this study. The purpose of this survey was to obtain information about patients' experiences

with STP used before invasive medical and surgical procedures and their current experience with long-term prophylaxis (LTP) and/or ODT (eSupplement 1). Information was collected regarding age, age at symptom onset, attack triggers, frequency of attacks, severity of attacks (emergency department [ED] visits, hospitalizations, intubations), burden of disease (missed work, missed school), and presence of prodromes. Information also was collected regarding medications taken for STP, LTP, and ODT. Medications listed included Cinryze (Shire, Dublin, Ireland), Berinert (CSL Behring, King of Prussia, Pennsylvania), Kalbitor (ecallantide; Dyax, Burlington, Massachusetts), Firazyr (icatibant; Shire), anabolic steroids (Winstrol [stanozolol], Sanofi Aventis, Paris, France; danazol; Oxandrine [oxandrolone], Savient Pharmaceuticals, Inc), and fresh frozen plasma.

The respondents were asked to "please specify which medication you are/were taking" and then the reason for using this medication. Those who chose "prevention of attacks resulting from a surgical/invasive procedure" were defined as receiving STP. The next question asked about the "type of surgery/procedure," and those who chose "dental work," "surgical procedure," "endoscopy (colonoscopy, esophagoduodenostomy, bronchoscopy)," "laparoscopy," or "pregnancy/delivery" were defined as patients who underwent a procedure (eSupplement 1). Those whose STP had failed were defined as those patients who answered "yes" to "used as a prevention of an attack before a surgery/invasive procedure, were there any attacks after your procedure?" The 114 patients with HAE who affirmatively answered the question "my HAE attacks are triggered by (please check all that apply)" with "dental procedures, surgery, endoscopies, or labor/delivery" are referred to as the procedural trigger group in the analysis of this dataset (eSupplement 1). Figure 1 provides an overview of patients included in this study and how they were grouped.

Physician Survey

Physicians who treat HAE also were surveyed using an online questionnaire on STP. In 2012, e-mail invitations were sent to 650 randomly selected HAE-treating physicians from the US HAEA database using the US HAEA e-mail server containing a 1-time use only link to the survey form, which resided on the US HAEA server; 37 physicians responded and were included in this study. The purpose of this survey was to obtain information about physicians' experiences with STP used before invasive medical and surgical procedures (eSupplement 2). The physician respondents were not linked to patient respondents in this analysis. Information was collected on the total number of patients with HAE treated, treatment of laryngeal attacks requiring intubation in patients with HAE, number of ED visits that patients with HAE had in the past year, number of hospitalizations that patients with HAE had in the past year, and medications (same as those listed in the patient questionnaire) used for LTP in patients with HAE, medications used for ODT in patients with HAE, medications used for STP in patients with HAE, and the effectiveness of STP medications as preventive therapies for invasive procedures in patients with HAE.

Definitions for medications used for STP and ODT were based on the series of questions from the physician survey that asked "please specify which medication you prescribed"; after choosing the type of medication, the physicians were asked "how do you prescribe this drug?" Physicians could choose from a list of 13 options, including use of STP and ODT for minimally invasive procedures, invasive procedures, vaginal delivery, or cesarean-section delivery and accounting for whether or not the patient had a history of attacks with a procedure (eSupplement 2). Minimally invasive procedures were defined as "endoscopy, dental work, etc." Invasive surgical and medical procedures were defined as "laparoscopy, tracheotomy, other procedures requiring incision, etc." Efficacy was

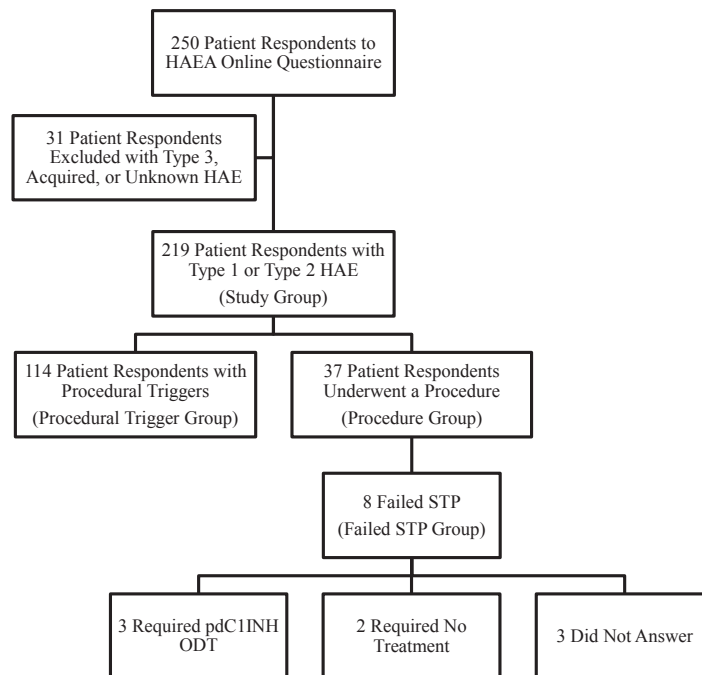


Figure 1. Number of patient respondents included in the study group, procedural trigger group, procedure group, and failed STP group. The procedural trigger group and procedure group are not mutually exclusive. Of the 8 patients with failed STP, 3 received pdC1INH, 4 received an anabolic steroid, and 1 received a bradykinin receptor antagonist. HAE, hereditary angioedema; HAEA, United States Hereditary Angioedema Association; ODT, on-demand therapy; pdC1INH, plasma-derived C1 inhibitor; STP, short-term prophylaxis.

defined as an affirmative response to the question “if prescribed as a prevention of an attack resulting from surgery/invasive procedures, was this drug effective in preventing an HAE attack?”

Statistical Analysis

Questionnaire data were analyzed using SAS 9.3 (SAS Institute, Cary, North Carolina) to obtain descriptive statistics on all 219 patient respondents with type 1 and type 2 HAE and 37 physician respondents. Pearson χ^2 test, Fisher exact test, and 2-sample *t* test were used to examine the relation between patients who underwent procedures and those who did not with respect to type of HAE, age at onset of disease, current age, and current LTP. Pearson χ^2 test, Fisher exact test, and 2-sample *t* test also were used to examine the relation between patients in the procedural trigger group and those without a procedural trigger with respect to type of HAE, age at onset of disease, current age, and current use of LTP. Descriptive statistics on the types of medications used for STP, LTP, and ODT from patient and physician perspectives were performed.

Results

Patient Survey

In total, 219 patient respondents with type 1 and type 2 HAE were included in this analysis. Thirty-one respondents were excluded because they did not have a definitive diagnosis of HAE type 1 or 2. Table 1 presents the characteristics of patients with HAE with respect to HAE type, triggers, prodromes, frequency of attacks, severity of attacks, and type of medication used. The predominant triggers for patients with HAE were emotional stress (87%), physical stress (79%), and physical trauma (77%). Prodromal warnings were present in 74% of patients, with the most common prodrome being fatigue (32%). Almost half the patients who provided information about the frequency of prodromes indicated that prodromes occur “most times” (*n* = 58 of 117) and indicated “75–100%” accuracy of the prodromes in predicting an impending attack (*n* = 57 of 117).

The median number of HAE attacks per year in the past 2 years was 12 (interquartile range 4–30), the mean number of ED visits for HAE attacks in the past year was 2.1 (range 0–70), and the mean number of hospitalizations in the past year was 1.2 (range 0–90). A significant number of respondents reported missing work (74%) and school (35%) because of HAE attacks. Most respondents (62%) reported using LTP; anabolic steroids and pdC1INH were used for LTP in 66% and 65% of respondents, respectively. There were 136 patient respondents with 180 affirmative responses to the LTP question, indicating that many patients were using multiple medications.

Of the 219 patients with HAE type 1 and 2, 37 (17%) underwent 66 invasive procedures; the types of procedures included dental (33%), invasive surgical (38%), endoscopy (20%), laparoscopy (8%), and pregnancy and delivery (1%). The characteristics of patients who underwent procedures (procedure group) and patients who reported procedural triggers (procedural trigger group) are presented in Table 2. The difference between these 2 groups is that the procedure group only includes patients who specifically reported use of STP during a procedure, whereas the procedural trigger group includes only patients who responded affirmatively to the initial question that procedures trigger attacks; therefore, STP use could not be analyzed in the procedural trigger group. A significantly larger number of patients with HAE type 1 vs type 2 underwent procedures (*P* = .02); however, there was no difference in reporting attacks secondary to procedures between the HAE types. There was no difference in mean age, proportion of children (<18 years of age), age at HAE symptom onset, and LTP use in patients within the procedure group or within the procedural trigger group.

For each type of procedure (dental, surgical, endoscopy, or laparoscopy), the type of medication used for STP and the rate of STP failure are reported in Figure 2. Anabolic steroids were the most commonly used medication reported by patients with HAE, with pdC1INH therapy being the second-most common, irrespective of the type of procedure. Of the 37 patients who underwent 66 procedures, all 37 received STP, and 8 (22%) reported failed STP. Of these 8 patients with failed STP, 3 received pdC1INH, 4 received an

Table 1Patient-reported HAE disease characteristics of patients with HAE type 1 or type 2 (n = 219^a)

Characteristics	Patients, n (%)	Characteristics	Patients, n (%)	Characteristics	Patients, n (%)
HAE classification		Prodromal symptom		Attack frequency in past 5 y	
Type 1	182 (83)	Present	162 (74)	Increased	68 (31)
Type 2	37 (17)	Absent	57 (26)	Decreased	65 (30)
Attack triggers		Frequency of prodromes (n = 117 ^b)		Same	38 (17)
Emotional stress	190 (87)	Sometimes	49 (42)	Variable	48 (22)
Physical stress	173 (79)	Most times	58 (50)	Severity and frequency of attacks	
Physical trauma	169 (77)	Always	10 (9)	Attacks per year in past 2 y, median (IQR)	12 (4–30)
Spontaneous	161 (74)	Type of prodromal warning		Number of hospitalizations in past year, mean (range)	1.2 (0–90)
Hormones	118 (54)	Fatigue	70 (32)	Number of ED visits in past year, mean (range)	2.1 (0–70)
Dental	87 (40)	Nausea	60 (27)	Ever had laryngeal attack requiring intubation	42 (19)
Work	85 (39)	Tingling	58 (27)	Missed work due to HAE attack	161 (74)
Infection	86 (39)	Soreness	51 (23)	Missed school due to HAE attack	76 (35)
Surgery	83 (38)	Rash	48 (22)	LTP responses ^c	
Sports	68 (31)	Muscle ache	35 (16)	Total respondents using LTP	136 (62)
Allergy	61 (28)	Loss of appetite	25 (11)	C1 inhibitor replacement	88 (65)
School	43 (20)	Diarrhea-constipation	46 (21)	Anabolic steroid	90 (66)
Medications	41 (19)	Flushing	24 (11)	Bradykinin receptor antagonist	1 (0.7)
Pregnancy	39 (18)	Throbbing	20 (9)	Kallikrein inhibitor	0 (0)
Alcohol	28 (13)	Lightheadedness	20 (9)	Fresh frozen plasma	0 (0)
Labor-delivery	18 (8)	Numbness	15 (7)	ε-Aminocaproic acid	1 (0.7)
Endoscopies	11 (5)				

Abbreviations: ED, emergency department; HAE, hereditary angioedema; IQR, interquartile range; LTP, long-term prophylaxis.

^aThirty-one of the original 250 patient respondents were excluded from this study for their condition not meeting diagnostic criteria for HAE type 1 or 2.^bOne hundred two of the 219 patient respondents with HAE type 1 or 2 did not answer this item on the questionnaire.^cOf the 136 patient respondents with HAE type 1 or 2, there were 180 responses to questions regarding LTP because of multiple medications used per patient. Thus, the sum of the percentages of individual medications in this category is larger than 100.

anabolic steroid, and 1 received Firazyr (ie, bradykinin receptor antagonist; Fig 2). All 8 with failed STP also were receiving LTP therapy. Of these 8 patients with failed STP, 3 reported requiring ODT with pdC1INH, 2 reported no required treatment, and 3 did not respond to this question (Fig 1).

Physician Survey

Thirty-seven physicians responded to the online survey and reported caring for 307 patients with type 1 HAE, 53 with type 2 HAE, 34 with type 3 HAE, 34 with acquired HAE, 4 with mutated genes, and 1 unknown. These 37 physicians treated a total of 177 patients who required ED visits for acute HAE attacks during the past year. These patients had an average of 4.8 ED visits per year, 1.2 hospitalization per year, and 9 attacks treated in the office per year. Thirty percent of physicians reported ever having treated a laryngeal attack that required intubation.

For patients with a history of HAE attacks from a specific procedure, only 19% of physicians reported pretreatment for vaginal and cesarean-section deliveries, 37% for pretreatment of an invasive surgical procedure, and 54% for pretreatment of a minimally invasive procedure. Similar rates of pretreatment were reported for patients regardless of whether they reported

having a history of HAE attacks with the procedure. Most physicians reported using ODT for procedures; 89% of physicians gave ODT for minimally invasive procedures, 76% for invasive procedures, and only 30% to 32% for vaginal and cesarean-section deliveries.

The most commonly used STP medication reported by physicians was pdC1INH, and the second-most common was anabolic steroids (Fig 3). When physicians prescribed STP, pdC1INH replacement therapy was used for 69% and 78% of patients for pretreatment of all minimally invasive and all invasive procedures, respectively. When STP was prescribed at time of delivery, pretreatment with pdC1INH was used in 100% and 91% of all vaginal and all cesarean-section deliveries, respectively. Anabolic steroids were used as STP in 25% and 17% of all minimally invasive and all invasive procedures, respectively. The greatest variability in types of medications prescribed was for those patients receiving ODT. The most commonly prescribed medication for ODT was pdC1INH, which was used in 52%, 50%, 73%, and 83% of patients undergoing a minimally invasive procedure, an invasive procedure, vaginal delivery, or cesarean-section delivery, respectively. Physicians reported that the medications used for pretreatment of minimally invasive procedures, invasive procedures, vaginal deliveries, and cesarean-section deliveries were very effective (89%–100%). For a given procedure

Table 2

Characteristics of patients with HAE in procedure group and procedural trigger group according to patient survey responses

Characteristics (n = 219 ^a)	Procedures (n = 201 ^b)			Procedures as HAE attack triggers (n = 219)		
	Undergoing procedures (n = 37)	Not undergoing procedures (n = 164)	P value	Reported as trigger (n = 114)	Not reported as trigger (n = 105)	P value
HAE type 1 (n = 182), n (%)	26 (70)	142 (87)	.02	97 (85)	85 (81)	NS
HAE type 2 (n = 37), n (%)	11 (30)	22 (13)	.02	17 (15)	20 (19)	NS
Age (y), mean (range)	42.6 (19–65)	40.4 (7–82)	NS	41.8 (9–82)	39.3 (7–77)	NS
Age <18 y, n (%)	0	12 (7)	NS	5 (4)	10 (10)	NS
Age at HAE symptom onset (y), mean (range)	12.8 (1–48)	13.3 (0–67)	NS	12.6 (0–51)	14.4 (1–67)	NS
LTP use, n (%)	27 (73)	109 (67)	NS	78 (69)	58 (66)	NS

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; NS, not significant.

^aThirty-one of the original 250 patient respondents were excluded from this study for their condition not meeting diagnostic criteria for HAE type 1 or 2.^bEighteen of the 219 patient respondents with HAE type 1 or 2 did not answer this item on the questionnaire.

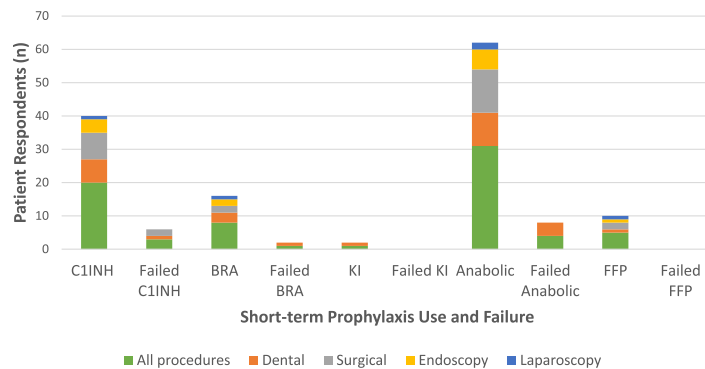


Figure 2. Patient-reported use of short-term prophylaxis type and failure by procedure type. The 66 procedures that patients reported undergoing is the total denominator used. Anabolic, anabolic steroids; BRA, bradykinin receptor antagonist; C1INH, C1 inhibitor; FFP, fresh frozen plasma; KI, kallikrein inhibitor.

(minimally invasive, invasive, vaginal delivery, caesarean delivery), there was no significant difference in physician-reported pretreatment efficacy between all patients with HAE and patients with HAE and a history of a swelling episode.

Discussion

Physicians reported excellent efficacy of preprocedure STP, whereas patients receiving preprocedure STP reported a 22% ($n = 8$ of 37) breakthrough attack rate. In the patient survey, 114 respondents reported procedures as a trigger for an HAE attack; however, only 37 patients went on to report details of the STP used in a specific procedure. Eight patients (22%) reported developing a breakthrough attack, and 3 reported requiring ODT with pdC1INH. Physicians reported low rates of prescribing pretreatment for procedures; however, the rate of pretreatment efficacy reported by physicians was excellent, ranging from 89% to 100% ($n = 33$ –36 of 37). Physicians reported prescribing predominantly pdC1INH for ODT and STP, whereas most patients reported using anabolic steroids for STP. This discordance between patient- and physician-reported experiences with STP is likely due to the different medications used for STP, with physicians

reporting more pdC1INH use. Approximately 6% of physicians ($n = 37$ of 650) responded to this survey and these physicians are likely HAE specialists. Therefore, the difference in medications prescribed may reflect the difference in prophylaxis prescribed by seasoned allergists vs HAE specialists, where the HAE specialists are using newer medications for prophylaxis with better efficacy reported. PdC1INH has been shown to be an effective STP agent before dental, medical, and surgical procedures, with no HAE attack occurring in 98% of patients in 1 study.⁹ Use of pdC1INH for STP has been shown to be more efficacious in decreasing the number of postprocedure edema episodes compared with danazol¹³ and in decreasing the number of facial and laryngeal edema episodes in a dose-responsive manner after tooth extraction compared with a control group.² This observed discordance between patient and physician reporting would have been of greater significance if the treating physicians of the patients in the patient survey had been identified and responded; however, this cross-sectional query of randomly selected HAE-treating physicians and patients with HAE is still representative of current practice and perspectives.

Rates of STP prescribed by physicians in this study are variable, indicating the lack of consensus among HAE specialists regarding

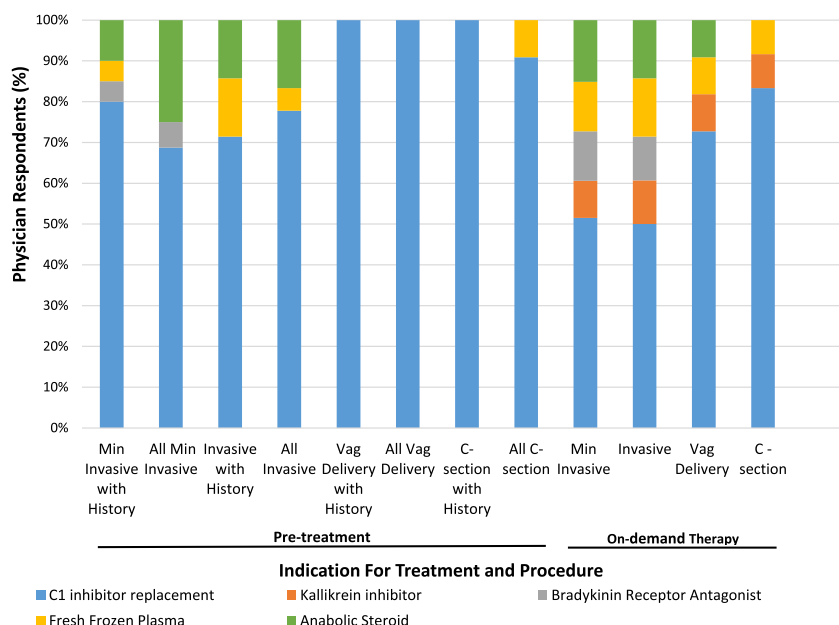


Figure 3. Medication types that physicians reported using for pretreatment and on-demand therapy for minimally invasive procedures, invasive procedures, vaginal delivery, and caesarean-section delivery. C-section, caesarean-section delivery; History, history of attack with prior procedure; All, all patients regardless of history; Min, minimally; Vag, vaginal.

indications for STP vs ODT. Physicians reported pretreatment in approximately half of minimally invasive and invasive surgical procedures, whereas ODT was provided for more than 75% of minimally invasive and invasive surgical procedures. Prescription rates of pretreatment and ODTs for vaginal and surgical deliveries were low (19%–32%). The international consensus guidelines recommend providing pdC1INH replacement therapy for STP before major procedures (eg, surgery and/or intubation) and providing no STP before minor procedures (eg, dental work) if pdC1INH is immediately available.⁵ Alternatives to pdC1INH replacement for minor and major procedures include anabolic androgens or antifibrinolytic prophylaxis (tranexamic acid preferred to ϵ -aminocaproic acid).⁵ The lack of consensus in the United States for STP makes adherence to these guidelines difficult and likely reflects the variability in the use of STP by physician respondents.

The major limitations of this survey-based study include the small sample, recall and respondent bias, low physician response rate, inability to verify responses, and possible respondent misinterpretation of questions. The respondent bias refers to the physician survey reflecting the practices of HAE experts using newer therapies and the patient survey reflecting the practices of less experienced treating physicians who may be still using older therapies. This difference likely accounts for the discordance between the effectiveness of STP between the patient- and physician-reported outcomes. In addition, the patient and physician surveys were formatted to ask about patient medication use first and then prompted for indications of the treatment. Although this emphasis on medications used for STP, LTP, and ODT is valuable in determining current prescribing trends, the drawback is the inability of patients and physicians to report procedures that patients underwent without STP or ODT. The procedural trigger group consisted of 114 patients, and further questioning of this group to elaborate on their experiences with and without treatment may have been beneficial. Furthermore, this study was unable to compare the rates of procedure-induced attacks in those receiving STP vs those not receiving STP; however, other studies have cited a significant decrease (ie, from 40.4% to 9.7%) in postprocedure attacks with STP use¹³ and a significantly smaller number of attacks precipitated by dental work in STP-treated vs untreated groups.¹⁴

Surgical and dental procedures are proven triggers of swelling episodes.^{1,5,15} The presence of angioedema after a procedure without prophylaxis has been reported to be 5.7%, which demonstrates that the risk for patients with HAE is significant.⁴ The need for prevention of these episodes is clear; however, there is a lack of consensus regarding how to use STP in at-risk patients. Furthermore, there is a lack of evidence supporting uniform STP for all patients undergoing any medical, surgical, or dental procedures, especially if the patient historically reports no swelling in response to physical trauma. This study is unique because it summarizes and compares the current usage of STP in the United States from patient and physician perspectives. The findings of this study emphasize the lack of consensus among HAE specialists leading to the heterogeneous preprocedure use of STP and/or ODT

and types of medications used. It also highlights the discordance between physician and patient experiences regarding STP efficacy. Collectively, these results demonstrate an unmet need for elucidating the role of preprocedure STP and thus support conducting a larger controlled study to investigate the benefit of proactively using preprocedure STP vs having ODT readily available.

Acknowledgments

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.05.009>.

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

HAE History

Date of Diagnosis:

Your age now (years):

Age when Hereditary Angioedema (HAE) signs and symptoms began (years):

Please select your type of C1-Inhibitor Deficiency

- ☐ Type I - Insufficient or low levels of C1-Inhibitor
- ☐ Type II - Defective or disfunctioning C1-Inhibitor
- ☐ Type III - HAE with normal level and normal function of C1-Inhibitor
- ☐ Acquired C1-Inhibitor Deficiency
- ☐ Mutated Gene
- ☐ Unknown

My HAE attacks are triggered by *(Please check all that apply)*

- ☐ Dental Procedures
- ☐ Physical Stress
- ☐ Pregnancy
- ☐ Hormones
- ☐ Alcohol
- ☐ Sports

- ☐ Infection
- ☐ Emotional Stress
- ☐ Labor/ Delivery
- ☐ Endoscopies
- ☐ Work
- ☐ Allergy

- ☐ Surgery
- ☐ Physical Trauma
- ☐ Spontaneous
- ☐ Medications/ Drug use
- ☐ School
- ☐ Other:

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

Hereditary Angioedema (HAE) History

Estimate the average number of HAE attacks per year for the past 2 years:

In the past 5 years, the frequency of your attacks has:

- ☐ increased ☐ decreased ☐ stay the same ☐ variable from year to year

Estimate the number of HAE attacks triggered by any invasive medical procedures (i.e: dental work, endoscopies, surgeries) in the past year:

Estimate the number of HAE attacks triggered by any invasive medical procedures (i.e: dental work, endoscopies, surgeries) in the past 5 years:

Estimate the number of HAE attacks triggered by trauma (i.e physical injuries or prolonged physical pressure from sitting, typing, pushing a lawn mower, etc) in the past year:

Estimate the number of HAE attacks triggered by trauma (i.e physical injuries or prolonged physical pressure from sitting, typing, pushing a lawn mower, etc) in the past 5 years:

Estimate the number of HAE attacks for each location in the past year:

- 0 Extremity attacks (arms, legs, hands, feet)
- 0 Abdominal attacks (stomach)
- 0 Trunk attacks (buttocks, flank-side, back, chest)
- 0 Genitourinary attacks (scrotal, vaginal)
- 0 Facial attacks (cheeks, neck, lips, eyes)
- 0 Oropharynx attacks (throat/mouth)

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

Hereditary Angioedema (HAE) History

Have you ever had a laryngeal attack that required intubation

How many times (in entire lifetime):

What were the years of intubation:

Number of Emergency room visits for an HAE attack in the past year:

Number of Emergency room visits for an HAE attack in the past 5 years:

Number of hospitalizations for an HAE attack in the past year:

Number of hospitalizations for an HAE attack in the past 5 years:

Have you missed work due to HAE attacks?

Average number of work days missed per month due to HAE attacks?:

Have you missed school due to HAE attacks?

Average number of school days missed per month due to HAE attacks?:

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

Prodromal Reliability

Do you have prodromal warnings (tingling, nausea, rash) before an HAE attack?

What is the frequency of your prodromal warnings before an attack:

- ☐ Never ☐ Sometimes ☐ Most times ☐ Always

How accurate do your prodromals predict an impending attack?:

- ☐ 100% of the time ☐ 75% of the time ☐ 50% of the time ☐ 25% of the time
☐ 0% of the time

Average time of onset of a prodromal warning sign before an HAE attack:

- ☐ Days: days ☐ Hours: hours
☐ Varies with each attack

What type of prodromal warning signs do you have before an acute HAE attack

- | | | |
|--|---|--|
| ☐ Fatigue | ☐ Rash | ☐ Muscle Ache |
| ☐ Nausea | ☐ Tingling | ☐ Lightheadedness |
| ☐ Loss of appetite | ☐ Throbbing | ☐ Soreness |
| ☐ Numbness | ☐ Flushing | ☐ Vaginal dryness |
| ☐ Difficulty swallowing | ☐ Diarrhea or constipation | ☐ Other: <input type="text"/> |

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

HAE Treatments

Are you currently taking or have you previously taken any of the HAE medications listed below to prevent or acutely treat (treating an HAE attack after it started) HAE ATTACKS?

- **Cinryze®** - Plasma derived C1-inhibitor FDA-approved for preventing HAE attacks. Cinryze® is delivered intravenously and is approved for home infusion
- **Berinert®** - Plasma derived C1-inhibitor FDA-approved for treating acute facial, laryngeal and abdominal HAE attacks. Berinert® is delivered intravenously
- **Kalbitor®** - A plasma kallikrein inhibitor FDA-approved to treat acute HAE attacks in patients 16 years of age and older. Kalbitor® is delivered subcutaneously under the care of a trained health care professional
- **Firazyr®** -A bradykinin 2 receptor antagonist FDA-approved for treating acute HAE attacks in patients 18 years and older. Firazyr® is delivered subcutaneously and is approved for self-administration
- **Stanolzolol (Winstrol)** ♦ an anabolic steroid used to prevent HAE attacks
- **Danacrine (Danazol)** ♦ an anabolic steroid used to prevent HAE attacks
- **Oxandrolone (Oxandrine)** ♦ an anabolic steroid used to prevent HAE attacks
- **FFP (Fresh Frozen Plasma)** ♦ used to treat acute HAE attacks
- **Amicar (epsilon aminocaproic acid)** - an anti-fibrinolytic agent used to prevent HAE attacks

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

HAE Treatment Details

The next few pages will allow you to enter the details of each of the HAE treatments you have received or are receiving.

Treatment

Please specify which medication you are/ were taking:

- | | | | |
|--|---|---|--|
| ☐ Cinryze | ☐ Berinert | ☐ Kalbitor | ☐ Firazyr |
| ☐ Fresh Frozen Plasma | ☐ Stanozolol (Winstrol) | ☐ Danacrine (Danazol) | ☐ Oxandrolone (Oxandrin) |
| ☐ Amicar (epsilon aminocaproic acid) | | | |

Dose: units, every

Dose: mgs

Dose: mgs

Dose: mgs, every days

Dose: units

I am:

- ☐ currently taking this medicine ☐ previously taken this medicine

This drug is/was taken for

- ☐ Treatment of acute attacks
☐ Prevention of attacks taken on a regular basis
☐ Prevention of attacks resulting from a surgical/ invasive procedure

Type of surgery/ procedure

- ☐ Dental work
☐ Surgical procedure
☐ Endoscopy (colonoscopy, esophagoduodenoscopy, bronchoscopy)
☐ Laparoscopy
☐ Pregnancy delivery
☐ Other:

This drug was given:

- ☐ Before the surgery/procedure ☐ After the surgery/ procedure

How many hours before the surgery/ procedure were you given this drug?: hours

How many hours after the surgery were you given this drug?: hours

Used as a prevention of an attack before a surgery/ invasive procedure, were there any attacks after your procedure?

You have indicated that the drug was not effective, when after the procedure did you experience an HAE attack?

- ☐ immediately ☐ within 6 hours
☐ within 24 hours ☐ not at all

You have indicated that the drug was not effective, what (if any) other treatment did you receive?

- | | | |
|--------------------------------|-------------------------------|---|
| ☐ None | ☐ Cinryze | ☐ Berinert |
| ☐ Kalbitor | ☐ Firazyr | ☐ Fresh Frozen Plasma |

☐ Other



Was this 2nd drug effective in improving/ alleviating your HAE attack (select one response)

You have indicated that the 2nd drug was not effective, what (if any) other treatment did you receive?

- | | | |
|--|-------------------------------|---|
| ☐ None | ☐ Cinryze | ☐ Berinert |
| ☐ Kalbitor | ☐ Firazyr | ☐ Fresh Frozen Plasma |
| ☐ Other <input type="text"/> | | |

Was this 3rd drug effective in improving/ alleviating your HAE attack (select one response)

You have indicated that the 3rd drug was not effective, what (if any) other treatment did you receive?

- | | | |
|--|-------------------------------|---|
| ☐ None | ☐ Cinryze | ☐ Berinert |
| ☐ Kalbitor | ☐ Firazyr | ☐ Fresh Frozen Plasma |
| ☐ Other <input type="text"/> | | |

Was this 4th drug effective in improving/ alleviating your HAE attack (select one response)

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Short-Term Prophylaxis Questionnaire: The Patient's Experience

You've reached the end of the questionnaire

Please click on 'Submit' if you are satisfied with all of your answers. Otherwise click on the 'Previous' button to go back to the survey pages to review your answers.

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Short Term Prophylaxis Questionnaire: The Physician's Experience

HAE History

Estimate the number of HAE patients of each type you have treated to date:

- 0 Type I
- 0 Type II
- 0 Type III
- 0 Acquired C1-Inhibitor Deficiency
- 0 Mutated Gene
- 0 Unknown

Estimate the average number of HAE attacks you treat each month in your office, total for all patients:

Estimate the average number of HAE attacks you treat each year in your office, total for all patients:

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Short Term Prophylaxis Questionnaire: The Physician's Experience

HAE History

Have you ever treated a laryngeal attack that required intubation?

How many total?

Estimate the total number of Emergency Room visits your patients have had for treatment of an HAE attack in the past year:

Estimate the total number of Emergency Room visits your patients have had for treatment of an HAE attack in the past 3 years:

Estimate the total number of hospitalizations your patients have had for treatment of an HAE attack in the past year:

Estimate the total number of hospitalizations your patients have had for treatment of an HAE attack in the past 3 years:

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Short Term Prophylaxis Questionnaire: The Physician's Experience

HAE Treatments

Have you ever prescribed any of the following medications to prevent/ treat HAE attacks resulting from an invasive surgical procedure?

Select

- **Cinryze®** - Plasma derived C1-inhibitor FDA-approved for preventing HAE attacks. Cinryze® is delivered intravenously and is approved for home infusion
- **Berinert®** - Plasma derived C1-inhibitor FDA-approved for treating acute facial, laryngeal and abdominal HAE attacks. Berinert® is delivered intravenously
- **Kalbitor®** - A plasma kallikrein inhibitor FDA-approved to treat acute HAE attacks in patients 16 years of age and older. Kalbitor® is delivered subcutaneously under the care of a trained health care professional
- **Firazyr®** - A bradykinin 2 receptor antagonist FDA-approved for treating acute HAE attacks in patients 18 years and older. Firazyr® is delivered subcutaneously and is approved for self-administration
- **Stanozolol (Winstrol)** - an anabolic steroid used to prevent HAE attacks
- **Danacrine (Danazol)** - an anabolic steroid used to prevent HAE attacks
- **Oxandrolone (Oxandrine)** - an anabolic steroid used to prevent HAE attacks
- **FFP (Fresh Frozen Plasma)** - used to treat acute HAE attacks
- **Amicar (epsilon aminocaproic acid)** - an anti-fibrinolytic agent used to prevent HAE attacks

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Short Term Prophylaxis Questionnaire: The Physician's Experience

HAE Treatment Details

The next few pages will allow you to enter the details of each of the HAE treatments you have prescribed to your patients for attacks due to invasive procedures/ surgeries.

Treatment

Please specify which medication you prescribed:

- | | | | |
|--|---|---|--|
| ☐ Cinryze | ☐ Berinert | ☐ Kalbitor | ☐ Firazyr |
| ☐ Fresh Frozen Plasma | ☐ Stanozolol (Winstrol) | ☐ Danacrine (Danazol) | ☐ Oxandrolone (Oxandrin) |
| ☐ Amicar (epsilon aminocaproic acid) | | | |

Dose: units, **how often** days

Dose: mgs

Dose: mgs

Dose: mgs, **how often** days

Dose: units

How do you prescribe this drug: (check all that apply)

- ☐ Prevention of attacks taken on a regular basis
- ☐ On-demand therapy for minimally invasive surgical/ medical procedure (endoscopy, dental work, etc)
- ☐ On-demand therapy for invasive surgical/ medical procedure (laparoscopy, tracheotomy, other procedures requiring incision, etc)
- ☐ On-demand therapy for routine/ normal vaginal delivery
- ☐ On-demand therapy for C-section delivery
- ☐ Pre-treatment therapy for minimally invasive surgical/ medical procedure (endoscopy, dental work, etc) only if the patient has a history of attacks resulting from the specific procedure
- ☐ Pre-treatment therapy for minimally invasive surgical/ medical procedure (endoscopy, dental work, etc) all the time, regardless of the patient's attack history
- ☐ Pre-treatment therapy for invasive surgical/ medical procedure (laparoscopy, tracheotomy, other procedures requiring incision, etc) only if the patient has a history of attacks resulting from the specific procedure
- ☐ Pre-treatment therapy for invasive surgical/ medical procedure (laparoscopy, tracheotomy, other procedures requiring incision, etc) all the time, regardless of the patient's attack history
- ☐ Pre-treatment therapy for routine/ normal vaginal delivery only if the patient has a history of attack from delivery
- ☐ Pre-treatment therapy for routine/ normal vaginal delivery all the time, regardless of the patient's attack history
- ☐ Pre-treatment therapy for C-section delivery, only if the patient has a history of attack from a C-section
- ☐ Pre-treatment therapy for C-section delivery, all the time, regardless of the patient's attack history

Prescribed as a prevention of an attack resulting from surgery/ invasive procedure, was this drug effective in preventing an HAE attack(circle one response)

You have indicated that this drug was not effective, when after the procedure did the patient experience an HAE attack?

- | | |
|---------------------------------------|--|
| ☐ immediately | ☐ within 6 hours |
| ☐ within 24 hours | ☐ not at all in the first 24 hours after procedure |

You have indicated that this drug was not effective, what (if any) other treatment did you give to the patient?

- | | |
|----------------------------|-------------------------------|
| ☐ None | ☐ Cinryze |
|----------------------------|-------------------------------|

- ☐ Berinert
- ☐ Firazyr
- ☐ Other

- ☐ Kalbitor
- ☐ Fresh Frozen Plasma



Was this 2nd drug effective in preventing an HAE attack(circle one response)

You have indicated that the 2nd drug was not effective, what (if any) other treatment did you give to the patient?

- ☐ None
- ☐ Berinert
- ☐ Firazyr
- ☐ Other

- ☐ Cinryze
- ☐ Kalbitor
- ☐ Fresh Frozen Plasma

Was this 3rd drug effective in preventing an HAE attack(circle one response)

You have indicated that the 3rd drug was not effective, what (if any) other treatment did you give to the patient?

- ☐ None
- ☐ Berinert
- ☐ Firazyr
- ☐ Other

- ☐ Cinryze
- ☐ Kalbitor
- ☐ Fresh Frozen Plasma

Was this 4th drug effective in preventing an HAE attack(circle one response)

HAE Treatment Outcomes

After the first 24 hours has elapsed, estimate how long before the patient would experience their next attack?

hours days weeks

Without Pre-Treatment

Estimate how long after the procedure, if NOT pre-treated, would the patient experience an HAE attack in the 24 hours after the procedure (circle one)?

- ☐ immediately
- ☐ within 6 hours
- ☐ within 24 hours
- ☐ not at all in the first 24 hours after procedure

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Short Term Prophylaxis Questionnaire: The Physician's Experience

You've reached the end of the questionnaire

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