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A Cross-Sectional Questionnaire Assessing Patient and Physician 1 Use of Short-Term Prophylaxis for Hereditary Angioedema

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Keywords

hereditary angioedema; short-term prophylaxis; medical; surgical; dental; labor/delivery procedures; anabolic steroids; C1INH replacement therapy

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 HAE patients who underwent 335 invasive procedures, which shows the risk for these patients is significant⁴. Various medications have been reported as short term prophylaxis (STP) prior to procedures with varying degrees of success. Prior to 2009, when novel HAE therapeutic agents first became available in the US, STP consisted of using preparations of fresh frozen plasma (FFP) for 1–2 hours within 12 hours before the procedure or using high-dose 17 α -alkylated androgens (6–10 mg / patient kg / day in divided doses up to a maximum of 200 mg of Danazol or equivalent 3 times per day) for 5–10 days before the procedure and 2 days afterwards with varying degrees of success^{5–8}. Since the approval of nano-filtered, 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 1,000–2,000 units 1–2 hours before the procedure has also been increasingly used for STP with low post-procedural attack rates reported⁹.

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The evidence for advocating STP is based on case reports, case series, and several retrospective or cross-sectional questionnaire surveys showing reduced angioedema attacks during and after the procedure when STP is used. For example, Leimgruber *et al.* reported a favorable outcome for an HAE patient provided STP with pdC1INH for a dental procedure¹⁰. Farkas *et al.* also reported favorable outcomes when androgen therapy was used as STP before and after dental procedures in 12 HAE patients⁶. Codispote *et al.* reported excellent outcomes in a 51-year-old man with HAE who received pdC1INH as STP prior to mitral valve annuloplasty on a balloon pump¹¹. Bernstein *et al.* 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 leak¹². Larger studies show similar results; Grant *et al.* analyzed data across all completed pdC1INH replacement therapy studies in which pdC1INH was administered within 24 hours prior to a medical, dental, or surgical procedure.⁹ Forty-one subjects (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; two separate 1,000-unit doses were used for two coronary artery bypass surgeries, one GI endoscopy, and one child labor/delivery. Only 2 HAE attacks were reported within 72 hours after dosing — one for a genitourinary attack after dental work and one for a laryngeal attack after laparoscopy, which resolved after an additional dose of pdC1INH. No significant adverse events were reported. The authors concluded that pre-procedure administration of pdC1INH was effective in preventing HAE attacks related to medical, dental, or surgical procedures⁹.

As a result, the international consensus guidelines recommends that all HAE patients receive STP with pdC1INH or alternative medications to prevent patients from experiencing an acute attack during an invasive medical or surgical procedure (i.e. dental work other than routine teeth cleaning, surgical procedures, endoscopy); however, during a minor procedure STP is not recommended if pdC1INH is immediately available⁵. Currently STP is not approved in the United States 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 pre-surgical prophylaxis with pdC1INH or other currently approved ODTs is warranted. In order to substantiate such a study, a questionnaire study was designed with the primary objective of ascertaining the STP experiences of HAE patients and HAE-treating physicians. We hypothesized that both surveys would reflect the widely variable use of pre-procedural STP and STP medications by physicians in HAE patients, 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 IRB approval.

Patient Survey

In 2012, email invites were sent to 960 randomly selected patients from the United States Hereditary Angioedema Association (US HAEA) patient database using the HAEA email server containing a one-time use only link to the survey form, which resided on the 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 the patients' experiences with STP used prior to invasive medical and surgical procedures, as well as their current experience with long-term prophylaxis (LTP) and/or ODT (E-supplement1). Information was collected regarding age, age at symptom onset, attack triggers, frequency of attacks, severity of attacks [emergency room (ER) visits, hospitalizations, intubations], burden of disease (missed work, missed school), and presence of prodromes. Information was also collected regarding medications taken for STP, LTP, and ODT. Medications listed included Cinryze®, Berinert®, Kalbitor® (Ecallantide), Firazyr® (Icatibant), anabolic steroids (Winstrol, Danazol, Oxandrine), and FFP.

The respondents were asked 'Please specify which medication you are/were taking' and then the reason for this medication was chosen. Those who chose 'Prevention of attacks resulting from a surgical/invasive procedure' were defined as receiving STP. The next question asked 'Type of surgery/procedure' and those who chose 'Dental Work', 'Surgical Procedure', 'Endoscopy (Colonoscopy, Esophagoduodenoscopy, Bronchoscopy)', 'Laparoscopy', or 'Pregnancy/Delivery' were defined as patients who underwent a procedure (E-supplement1). Those who failed STP 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 HAE patients 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 (E-supplement1). Figure 1 provides an overview of patients included in this study and how they were grouped.

Physician Survey

Physicians who treat HAE were also surveyed using an online questionnaire regarding STP. In 2012, email invites were sent to 650 randomly selected HAE treating physicians from the US HAEA database using the HAEA email server containing a one-time use only link to the survey form, which resided on the HAEA server; 37 physicians responded and were included in this study. The purpose of this survey was to obtain information about the physicians' experiences with STP used prior to invasive medical and surgical procedures (E-supplement2). The physician respondents were not linked to patient respondents in this analysis. Information was collected regarding the total number of HAE patients treated, treatment of laryngeal attacks requiring intubation in HAE patients, number of emergency room visits that HAE patients had in the past year, number of hospitalizations that HAE patients had in the past year, and medications (same as listed above in the patient questionnaire) used for LTP, medications used for ODT, and medications used for STP in HAE patients, as well as the effectiveness of STP medications as preventive therapies for invasive procedures in HAE patients.

Definitions for medications used for STP and ODT was based on the series of questions from the physician survey which asked ‘Please specify which medication you prescribed,’ after choosing the type of medication, the physicians were asked ‘How do you prescribe this drug’. Physicians were able to choose from a list of 13 options including use for 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 (E-supplement2). 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 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 was analyzed using SAS 9.3 to obtain descriptive statistics on all 219 HAE type I and type II patient respondents and 37 physician respondents. Pearson’s χ^2 , Fisher’s exact test, and a two-sample t-test were used to examine the relationship between patients who underwent procedures compared to those who did not with respect to the type of HAE, age at onset of disease, current age, and current LTP. Pearson’s χ^2 , Fisher’s exact test, and a two-sample t-test were also used to examine the relationship between patients in the procedural trigger group versus those without a procedural trigger with respect to the 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

A total of 219 patient respondents with type 1 and type 2 HAE were included in this analysis. Thirty-one respondents were excluded as they did not have a definitive diagnosis of HAE type 1 or 2. Table 1 summarizes the characteristics of the HAE patients with respect to HAE type, triggers, prodromes, frequency of attacks, severity of attacks, and type of medication used. The predominant triggers for the HAE patients 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 of the patients who gave information about the frequency of prodromes indicated that prodromes occur ‘most times’ ($n = 58/117$) and indicated ‘75–100%’ accuracy of the prodromes in predicting an impending attack ($n = 57/117$). The median number of HAE attacks per year in the past two years was 12 (interquartile range 4–30), the mean number of emergency room 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. The majority of 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 HAE type 1 and 2 patients, 37 (17%) underwent 66 invasive procedures; the types of procedures included dental (33%), invasive surgical (38%), endoscopy (20%), laparoscopy (8%), and pregnancy/delivery (1%). The characteristics of patients undergoing procedures (procedure group) and patients who reported procedural triggers (procedural trigger group) are summarized in Table 2. The difference between these two 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 greater number of HAE type 1 versus type 2 patients underwent procedures ($p = 0.02$); however, there was no difference in reporting attacks secondary to procedures between the HAE patient 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 is reported in Figure 2. Anabolic steroids were the most commonly used medication reported by HAE patients 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 failing STP. Of these 8 patients who failed STP, 3 received pdC1INH, 4 received anabolic steroid, and 1 received Firazyr (i.e. bradykinin receptor antagonist) (Figure 2). All 8 who failed STP were also receiving LTP therapy. Of these 8 patients who failed STP, 3 reported requiring ODT with pdC1INH, 2 reported no required treatment, and 3 did not respond to this question (Figure 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 emergency room visits for acute HAE attacks during the past year. These patients had an average of 4.8 emergency room 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 30–32% 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 (Figure 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 or 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, 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 (minimally invasive, invasive, vaginal delivery, caesarean delivery), there was no significant difference in physician-reported pretreatment efficacy between all HAE patients and HAE patients with a history of a prior swelling episode.

Discussion

Physicians reported excellent efficacy of pre-procedure STP, whereas patients receiving pre-procedure STP reported a 22% (n=8/37) 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 (22%) patients 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 89–100% (n=33–36/37). Physicians reported prescribing predominantly pdC1INH for ODT and STP, whereas the majority of 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. About 6% (n=37/650) of physicians 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 versus 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 prior to dental, medical, and surgical procedures, with no HAE attack occurring in 98% of subjects in one study⁹. Use of pdC1INH for STP has been shown to be more efficacious in reducing the number of post-procedural edema episodes compared to danazol¹³ and in decreasing the number of facial and laryngeal edema episodes in a dose-responsive manner after tooth extraction compared to a control group². 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 physicians and patients 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 indications for STP versus 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 prior to major procedures (e.g. surgery and/or intubation) and providing no STP prior to minor procedures (e.g. dental work) if pdC1INH is immediately available.⁵ Alternatives to pdC1INH replacement for minor and major procedures includes anabolic androgens or anti-fibrinolytic prophylaxis (tranexamic acid preferred to epsilon 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 small sample size, 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. While 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 was 114 patients, and further questioning of this group to elaborate on their experiences with and without treatment may have also been beneficial. Furthermore, this study was unable to compare the rates of procedure-induced attacks in those receiving STP versus those not receiving STP; however, other studies have cited a significant reduction (i.e. from 40.4% to 9.7%) in post-procedural attacks with STP use¹³ and a significantly lower number of attacks precipitated by dental work in STP-treated versus untreated groups¹⁴.

Surgical and dental procedures are proven triggers of swelling episodes^{1, 5, 15}. The presence of angioedema after a procedure without prophylaxis has been previously reported to be 5.7% which demonstrates that the risk for HAE patients is significant⁴. 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 US from both the patient and physician perspective. The findings of this study emphasize the lack of consensus among HAE specialists leading to the heterogeneous pre-procedural 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 pre-procedural STP and thus support conducting a larger controlled study to investigate the benefit of proactively using pre-procedural STP versus having ODT readily available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Number of patient respondents included in the study group, procedural trigger group, procedure group, and failed short-term prophylaxis group

The procedural trigger group and procedure group are not mutually exclusive. Of the 8 patients who failed STP, 3 received pdC1INH, 4 received anabolic steroid, and 1 received a bradykinin receptor antagonist. HAE, hereditary angioedema; HAEA, United States Hereditary Angioedema Association; ODT, on-demand therapy; pdC1INH, plasmaderived C1 inhibitor; STP, short-term prophylaxis.

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.

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.

Table 1

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

Characteristics	Patients (n, %)	Characteristics	Patients (n, %)	Characteristics	Patients (n, %)
HAE Classification		Prodromal Symptom		Attack Frequency in Past 5 Years	
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**)		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 Years (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 ER 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)	Long-term Prophylaxis Responses***	
Sports	68 (31)	Muscle ache	35 (16)	Total respondents Using Long-term Prophylaxis	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: ER, emergency room; HAE, hereditary angioedema; IQR, interquartile range

* 31 of the original 250 patient respondents were excluded from this study for their condition not meeting diagnostic criteria for HAE type 1 or 2.

** 102 of the 219 patient respondents with HAE type 1 or 2 did not answer this item on the questionnaire.

*** From the 136 patient respondents with HAE type 1 or 2, there were 180 responses to questions regarding long-term prophylaxis because of multiple medications used per patient. Thus, the sum of the percentages of individual medications in this category is over 100.

Table 2
Characteristics of HAE patients* in procedure group and procedural trigger group per patient survey responses.

Characteristics (n = 219*)	Procedures (n = 201**)		Procedures as HAE Attack Triggers (n = 219)	
	Undergoing Procedures (n = 37)	Not Undergoing Procedures (n = 164)	Reported as Trigger (n = 114)	Not Reported as Trigger (n = 105)
HAE type 1 (n = 182)	26 (70%)	142 (87%)	97 (85%)	85 (81%)
HAE type 2 (n = 37)	11 (30%)	22 (13%)	17 (15%)	20 (19%)
Age, yrs (mean, range)	42.6 (19–65)	40.4 (7–82)	41.8 (9–82)	39.3 (7–77)
Age <18 years	0	12 (7%)	5 (4%)	10 (10%)
Age at HAE Symptom Onset, yrs (mean, range)	12.8 (1–48)	13.3 (0–67)	12.6 (0–51)	14.4 (1–67)
LTP Use	27 (73%)	109 (67%)	78 (69%)	58 (66%)

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis; yrs, years

* 31 of the original 250 patient respondents were excluded from this study for their condition not meeting diagnostic criteria for HAE type 1 or 2.

** 18 of the 219 patient respondents with HAE type 1 or 2 did not answer this item on the questionnaire.