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Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor – a long-term survey

H. Farkas[1,*], Z. Zotter[1,*], D. Csuka[1], E. Szabó[1], Z. Nébenfűhrer[1], G. Temesszentandrási[1], L. Jakab[1], L. Varga[1], G. Harmat[2] & I. Karádi[1]

[1]3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; [2]"Heim Pál" Children's Hospital, Budapest, Hungary

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Correspondence
Henriette Farkas, 3rd Department of Internal Medicine, Faculty of Medicine, Semmelweis University, H-1125 Budapest, Kútvölgyi út 4, Hungary.
Tel.: (+36 1) 212 9351
Fax: (+36 1) 225 3899
E-mail: farkash@kut.sote.hu

*These two authors contributed equally and should be regarded as joint first authors.

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Abstract

Background: Hereditary angioedema is a potentially life-threatening disorder, because edema occurring in the mucosa of the upper airways can lead to suffocation. The management of HAE consists of avoiding the triggering factors, prophylaxis, and the acute treatment of edematous episodes. Medical procedures can also provoke edematous attacks, and therefore, short-term prophylaxis (STP) is recommended before such interventions. Our aim was to evaluate the efficacy and safety of STP administered before medical procedures.

Methods: We conducted a retrospective analysis before and a prospective survey after establishing the diagnosis in a group of 137 (60 males, 77 females; 20 pediatric and 117 adult) patients with HAE. Both were implemented using questionnaires, patient diaries and hospital charts focusing on medical interventions provoking edematous attack, and the medicinal products (C1-INH concentrate, tranexamic acid, and danazol) administered for STP.

Results: Comparing surgical interventions performed without pre-event STP (in 39/89 patients before HAE was diagnosed), or after STP (in 3/55 cases after diagnosis), we found a significant ($P < 0.0001$, Fisher's exact test) reduction in the number of edematous episodes. Evaluating the efficacy of the drugs administered for STP revealed that C1-INH concentrate (Berinert®, CSL Behring, Marburg, Germany) was significantly ($P = 0.0096$, Fisher's exact test) superior to orally administered drugs in reducing the instances of postprocedural edema. None of the medicinal products caused adverse events potentially related to STP.

Conclusions: STP reduces the number of postprocedural edematous episodes. C1-INH concentrate is safe and effective for prophylaxis. When this agent is not available, danazol is a potential alternative for prophylaxis before elective medical interventions.

Hereditary angioedema (HAE-C1-INH), caused by the deficiency or dysfunction of the C1-inhibitor (C1-INH), is a potentially life-threatening disorder (1,2). In Type I HAE-C1-INH, low levels of the C1-INH protein can result from intracellular degradation, or insufficient secretion by the cells synthesizing it. In Type II HAE-C1-INH, a nonfunctional C1-INH protein is transcribed, the serum level of which is normal or even appears increased (3). Both types of HAE-C1-INH are characterized by paroxysms of edema formation in the subcutis, and/or in the submucosa of the upper airways, as well as of the gastrointestinal tract (4). Edema formation is attributed to bradykinin, released during the activation of the plasma cascade systems. Bradykinin enhances capillary permeability with the consequent seeping of intravascular fluid into the interstitium, and this leads to edema formation (5, 6).

Abbreviations
C1-INH, C1-inhibitor; pdC1-INH, plasma-derived C1-inhibitor concentrate; HAE-C1-INH hereditary angioedema due to C1-inhibitor deficiency; ETN, endotracheal narcosis; STP, short-term prophylaxis; TXA, tranexamic acid.

Mental stress, hormonal changes, infections and medicinal products (including oral contraceptives, ACE inhibitors) all can provoke edema formation; however, mechanical trauma remains the most common triggering factor (4, 7–11). Accordingly, short-term prophylaxis (STP) with a 17-alkylated androgen, an antifibrinolytic, or plasma-derived C1-INH (pdC1-INH) concentrate is recommended before diagnostic and invasive procedures involving tissue trauma (12–14). The various forms of C1-INH concentrate have widely different half-lives; it is the shortest (max. 3 h) in the case of recombinant human C1-INH (15). Only a single report has been published on the use of a bradykinin receptor antagonist for STP (16). Each of the consensus documents published so far lists STP among the treatment modalities, except for the paper of Cicardi et al. (17) on evidence-based recommendations, which focused on long-term prophylaxis. Reviewing the literature on STP yields only case reports and small-scale studies focusing on dental procedures, primarily (8, 14, 18–25). Clinical studies are lacking, and the only observation made on a large number of patients undergoing STP has been published recently by Bork et al. (26), focusing on STP administered before dental interventions.

Our objective was to conduct a retrospective analysis of the occurrence of edematous episodes provoked by medical interventions performed before establishing the diagnosis of HAE-C1-INH. These data were then compared to the information on attacks that occurred after the diagnosis of HAE-C1-INH and the use of STP before the procedure. Our further aim was to analyze prospectively the efficacy and safety of the modalities used for STP administered before medical procedures.

Methods and study design

Study design

Our retrospective analysis was conducted using a purposely designed questionnaire containing the following items: the types and times of invasive (including dental) procedures the patient had before the diagnosis of HAE-C1-INH was established, and the potential occurrence of edematous episodes after these events. The inclusion criteria comprised the presence of the known types (I or II) of HAE-C1-INH confirmed by complement studies.

The prospective study started once the diagnosis of HAE-C1-INH had been established. Upon diagnosis, the patients were warned of the potential attack-triggering effect of the medical procedures mentioned above. Then, STP was recommended as a preventive measure, to be implemented after consultation with the follow-up center. The patients were asked to record in their diaries the following: the type of the intervention, the method of STP, as well as the dose and effect of the drug administered, the postoperative course, and the occurrence of edematous episodes potentially related to the intervention. We considered edema formation related to a medical intervention, if it occurred within 48 h after the procedure. At the annual follow-up visits, the subjects underwent a laboratory screen (virus serology, such as hepatitis B and C, HIV, parvovirus B19) and the measurement of anti-C1-INH antibody titers. Our study was approved by the Institutional Review Board of Semmelweis University, and all patients gave informed consent.

The type and dosage of STP used in our practice

STP was administered using the following medicinal products before surgical or diagnostic procedures contemplated in the head and neck region (including dental procedures), and other types of major surgery:

- Danazol (Danoval; KRKA, Novo Mesto, Slovenia): 2.5–10 mg/kg/day orally (maximum daily dose: 600 mg), initiated 5 days before and continued for additional 2 days after surgery.
- Tranexamic acid (TXA, Exacyl, Sanofi-Synthelabo; Produtos Farmaceuticos, SA, Porto Salvo, Portugal): 20–40 mg/kg/day orally (maximum daily dose: 3 g in two to three divided doses), started 5 days before and continued for additional 2 days after the intervention.
- Human plasma-derived C1-INH concentrate (Berinert®; CSL Behring, Marburg, Germany): 500 IU i.v. 1 h before the procedure. During the intervention, an additional vial of this medicinal product was kept at hand for use if an emergency occurs.

Statistical analysis

The calculations were performed with the Prism 5 package (GraphPad Software, San Diego CA, USA). Fisher's exact test was used to compare the occurrence of edematous episodes with or without STP, whereas chi-square test was used to compare the efficacy of the three types of medicinal products used for STP. In all statistical analyses, $P < 0.05$ was considered statistically significant, calculating two-tailed p-values.

Results

Study subjects

One-hundred and thirty-seven HAE-C1-INH patients – 20 children (under the age of 18 years, seven boys and 13 girls, mean age: 12.2 [min. 2.2–max. 17.3] years) and 117 adults (53 men and 64 women, mean age: 41.3 [min. 18.5–max. 81.2] years) – were included in this cohort study. 126 patients (who completed the standard questionnaire correctly) were included into the retrospective stage, which focused on the period before the diagnosis of HAE-C1-INH. All the 137 patients diagnosed and followed up at our Center were included into the prospective phase of the study, which lasted from the date when HAE-C1-INH was diagnosed to December 2011. The duration of follow-up varied between 0.6 and 30 years (median and interquartile range: 11 [7–14] years). Eleven patients had not experienced any symptoms until the end of the study, although they had low C1-INH and C4 levels and tested positive by the genetic screening, all confirming the diagnosis of HAE-C1-INH. Figure 1 represents the different groups of the 137 managed HAE-C1-INH patients, according to their medical history.

Invasive or diagnostic procedures performed before the diagnosis of HAE-C1-INH was established, followed by an edematous episode

By reviewing the completed questionnaires and the medical records on the subjects, we accumulated reliable data from 126 of 137 patients, on 202 invasive procedures (including 113 dental procedures and 89 diagnostic/surgical interventions) and their clinical course from the period before establishing the diagnosis of HAE-C1-INH. Although 11 of these 126 patients remained symptom-free throughout the study period, their data were also included in the statistical analysis. Accurate retrospective data were not available for every dental procedure without consecutive edema formation, because all medical records could not be obtained afterward. Therefore, only medical records on diagnostic/surgical interventions, but not on dental procedures were used for statistical comparison. Before HAE was diagnosed, 52/126 patients had not undergone any medical intervention that triggered edema formation. On the other hand, 58.7% (74/126) of patients recorded 139 events, where an edematous episode followed within 48 h of a dental, a diagnostic, or an invasive procedure (Table 1). Of these, edema formation occurred after a dental procedure (extraction, curettage, filling, polishing, and root canal treatment) in 100 cases of 68 patients, whereas edema formation occurred after medical interventions other than dental procedures in 39 cases (Table 1). Edema formation, involving the subcutaneous tissue in 108 and the upper airway mucosa in 31 cases, was managed conservatively, most frequently by administering an antihistamine, a glucocorticosteroid, or epinephrine. According to the data excerpted from the medical records, the edema resolved slowly after conventional therapy. Specifically, subcutaneous edema disappeared within 3–7 days, whereas the regression of airway edema took 1–2 days, but required intensive care in 10 cases.

Fifty-seven patients underwent 89 different medical interventions (other than dental procedures), most frequently tonsillectomy, adenotomy, or appendectomy. An edematous episode followed 39 of the 89 medical interventions – that is, occurred after 43.8% of procedures and in 40.4% of patients (n = 23/57) (Table 1).

Of 23 patients, five children and 13 adults experienced postprocedural edema formation only once, whereas five adults on several occasions.

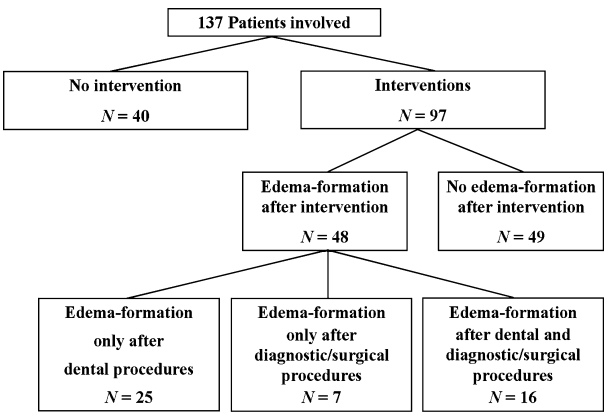

Figure 1 Flow chart representing the different groups of 137 managed HAE-C1-INH patients, according to their medical history.

Invasive/diagnostic interventions with the use of STP, during the follow-up after establishing the diagnosis of HAE-C1-INH

By reviewing the database containing prospectively collected medical records on the subjects, we accumulated reliable data from all 137 registered and followed-up patients, on 139 invasive procedures (including 84 dental procedures of which five was performed without STP and 55 diagnostic/surgical interventions) and their clinical course from the period after establishing the diagnosis of HAE-C1-INH. Once the diagnosis of HAE-C1-INH had been established, all subjects (except two patients) received STP before the invasive or diagnostic procedures set out in Table 2. The compliance of these two cases was poor. One of them failed to inform the professional performing the dental intervention about the disease. The other one forgot to have the pdC1-INH concentrate administered before four dental procedures, each of which was followed by facial edema. Remarkably, this subject underwent dental treatment on two additional occasions after STP with pdC1-INH concentrate, which prevented the edema formation in both instances.

Fifty-seven of the 137 patients (41.6%) received STP in 134 instances altogether. Of the subjects on STP, 39/57 (68%) received STP on one occasion only, whereas 18/57 patients (32%) on several occasions.

Table 2 shows the frequency of STP in our pediatric or adult patients with HAE-C1-INH. Except for the procedures performed in the head and neck region, the number of patients receiving STP was larger among the adults.

The efficacy of STP

Of the 134 (dental, diagnostic, or surgical) interventions performed after STP, edema formation occurred in 13 cases (two children and seven adults) despite the prophylaxis (Table 2). In ten of these 13 cases, postprocedural edema followed a dental, whereas in the remaining three, a surgical procedure.

The proportion of patients experiencing an edematous attack despite STP was 36% (5/14) when danazol, 50% (3/6) when TXA, and only 9% (5/54) when pdC1-INH concentrate was used with this purpose. Evaluating the efficacy of pdC1-INH concentrate or danazol administered for STP revealed that prophylaxis with pdC1-INH concentrate reduced the number of postprocedural edema significantly (P = 0.0254, Fisher's exact test) compared to danazol, when the *number of patients* who experienced edema after the intervention was considered. When we took into account the number of patients experiencing edema despite STP, as well as analyzed the efficacy of pdC1-INH concentrate, danazol, and TXA separately, then – again – pdC1-INH proved the most effective drug (P = 0.0064, chi-square test).

Table 1 The types of medical interventions followed by postprocedural edema before the diagnosis of HAE-C1-INH

	Number of patients		Number of cases	
Type of intervention	Children	Adults	Children	Adults
Dental procedures				
Dental surgery				
Dental extraction	5	19	5	62
Dental trephination	1	5	1	8
Dental cyst removal	0	2	0	2
Gingival incision	0	1	0	1
Conservative dental treatment				
Dental filling	4	7	5	11
Dental restoration	0	3	0	3
Dental polishing	0	1	0	1
Root canal treatment	0	1	0	1
Total	10 pediatric and 28 adult patients		11 pediatric cases and 89 adult cases	
Other medical diagnostic/surgical interventions				
Nasal tonsillectomy	1	2	1	2
Pharyngeal tonsillectomy	2	8	2	8
Nasal septoplasty	0	1	0	1
Reposition of fractured nasal bones	0	1	0	1
Interventions in the head and neck region (nevus excision, suture of traumatic wounds, oral surgery)	0	3	0	3
Genital-urethral procedures	2	0	2	0
Coronary artery bypass grafting	0	1	0	1
Gastroduodenoscopy	0	2	0	2
Cholecystectomy	0	2	0	2
Appendectomy	0	5	0	5
Childbirth	0	6	0	6
Artificial abortion	0	2	0	3
Total	5 pediatric and 18 adult patients		5 pediatric cases and 34 adult cases	

Prophylaxis was implemented with danazol in 38, with TXA in 9, and with pdC1-INH concentrate in 87 cases. The proportion of surgical/diagnostic interventions followed by an edema despite STP was 13% (5/38 – one episode after an artificial abortion and four after a dental procedure) when danazol, 33% (3/9) when TXA, and only 6% (5/87) when pdC1-INH concentrate was used for this purpose. Evaluating the efficacy of the medicinal products administered for STP revealed that prophylaxis with pdC1-INH concentrate reduced the number of postprocedural edema events significantly ($P = 0.0096$, Fisher's exact test) compared to oral agents (TXA, or danazol), when the *number of interventions* followed by edema formation was considered.

If we considered the number of interventions ending with edema formation, as well as analyzed the efficacy of pdC1-INH concentrate, danazol, and TXA separately, then pdC1-INH proved the most effective remedy ($P = 0.0202$, chi-square test).

Nevertheless, edematous episodes still occurred, even after the administration of pdC1-INH concentrate. A female patient experienced facial edema repeatedly, after cataract surgery on both eyes. Edema evolved after dental intervention in two additional patients, whereas a third patient had facial and upper airway edema following artificial abortion. In four of these cases, edema formation occurred within 12 h – and in the fifth one within 24 h – of the medical procedure. The prompt administration of pdC1-INH concentrate as acute treatment halted the progression of the edema in all instances and relieved the symptoms within an hour. Time to the complete resolution of symptoms was less than 12 h in upper airway edema and 1–2 days in facial edema. Of the 57 patients who were receiving STP since the time of diagnosis, 23 sustained an edematous attack after a diagnostic/surgical procedure performed before diagnosis – that is, without STP.

Accurate information from the period before establishing the diagnosis of HAE was not available in the case of dental procedures, and therefore, only the data related to surgical interventions were subjected to statistical analysis. Comparing the numbers of edematous episodes induced by diagnostic/surgical interventions (not counting dental procedures here) without/with STP – that is, before/after diagnosing HAE in 39/89 *vs* 3/55 cases – revealed a significant difference ($P < 0.0001$, Fisher's exact test). Importantly, however, a proportion of patients experienced several episodes, and this casts doubt on the independence of the data analyzed with the Fisher's exact test. Therefore, we compared the numbers of patients who had experienced edema after any type of

Table 2 The use of short-term prophylaxis before diagnostic or surgical interventions after the diagnosis of HAE-C1-INH in 57 of 137 (41.6%) registered and followed-up patients

Type of intervention	No. of patients (children/adults)	No. of cases (children/adults)	Type of STP	Edema formation (children/adults)
Dental extraction	13 (7/6)	21 (13/8)	pdC1-INH	2 cases (1/1)
	15 (2/13)	18 (3/15)	Danazol	1 case (0/1)
	4 (2/2)	4 (2/2)	TXA	0
Dental filling				
	8 (3/5)	14 (8/6)	pdC1-INH	1 case (0/1)
	8 (1/7)	10 (2/8)	Danazol	3 cases (0/3)
	2 (1/1)	3 (2/1)	TXA	3 cases (1/2)
Dental curettage				
	4 (1/3)	6 (3/3)	pdC1-INH	0
	2 (0/2)	2 (0/2)	Danazol	0
	1 (1/0)	1 (1/0)	TXA	0
ENT procedures				
	2 (1/1)	2 (1/1)	pdC1-INH	0
	1 (0/1)	1 (0/1)	Danazol	0
Interventions in the head and neck region	7 (4/3)	7 (4/3)	pdC1-INH	0
Surgery under ETN	11 (4/7)	12 (4/8)	pdC1-INH	2 cases (0/2)
	1 (0/1)	3 (0/3)	Danazol	0
Diagnostic procedures: colo-, broncho-, gastroduodenoscopy, cardiovascular catheterization	8 (2/6)	8 (2/6)	pdC1-INH	0
Childbirth	11 (0/11)	11 (0/11)	pdC1-INH	0
	1 (0/1)	3 (0/3)	Danazol	0
	1 (0/1)	1 (0/1)	TXA	0
Artificial abortion	4 (1/3)	6 (1/5)	pdC1-INH	0
	1 (0/1)	1 (0/1)	Danazol	1 case (0/1)
Total	57 (20/37)	134 (46/88)		13 cases of 9 patients

pdC1-INH = plasma-derived C1-inhibitor concentrate (Berinert®, CSL Behring, Marburg, Germany); TXA= tranexamic acid.
A patient might have had several invasive procedures and accordingly can belong to multiple groups. STP was administered on a single occasion to 39/57 patients (68%) and on multiple occasions to 18/57 patients (32%).

surgical or diagnostic (but not dental) procedure and again found a significant ($P < 0.0001$, Fisher's exact test) difference: 23/57 patients without STP (i.e., before diagnosing HAE) *vs* 3/48 patients receiving STP (i.e., after diagnosing HAE).

Table 3 shows the distribution of the 137 HAE-C1-INH patients followed up continuously, by the type and number of the interventions performed during the periods before or after diagnosis.

The safety of STP

The patients have not experienced potentially treatment-related adverse events with any of the medicinal products administered; discontinuing prophylaxis was not necessary. Viral transmission or the development of anti-C1-INH antibodies did not occur either.

Discussion

This was the first large-scale, observational study with long-term follow-up to evaluate the efficacy and safety of STP before various invasive and diagnostic procedures. The analysis of clinical data from 126 patients revealed that before the diagnosis of HAE-C1-INH – that is, when prophylaxis had not been even considered – 40.4% of the subjects reported postprocedural edema formation. This finding is in agreement with the results of Bork et al. (26), obtained in a series of dental interventions performed without STP. These episodes usually evolved within 48 h after – taking into account all the interventions (except for dental treatment) – approximately 43.8% of medical procedures. Once the diagnosis of HAE-C1-INH had been established and STP introduced, edematous episodes occurred in 7.1% of patients. Considering all the interventions, edema occurred after 9.7% of the procedures within 24 h, most commonly after surgery performed in the head and neck region. Clinically manifest edema involved the face, the neck, and the upper airways, primarily; abdominal episodes did not occur. This is probably explained by the site of the intervention: These procedures were performed in the head and neck region, under general anesthesia with endotracheal narcosis. Thus, edema in this region must have resulted from local tissue trauma. Comparing the efficacy of the three medicinal products used

Table 3 The distribution of the 137 HAE-C1-INH patients followed up continuously, by the type and number of the interventions performed during the period before or after diagnosis

Edematous attacks after dental procedures
After diagnosis

	Edema formation				Number of patients					
						Number of attacks				
	None	All	Some	Number of interventions	$\sum n$	0	1	2	3	4
Number of patients	33/40	1/40	6/40	1	22	21	1			
%	82.5	2.5	15	2	9	8	1	0		
				3	4	2	1	1	0	
				≥ 4	5	2	1	1	0	1

Edematous attacks after diagnostic/surgical procedures
Before diagnosis

	Edema formation				Number of patients					
						Number of attacks				
	None	All	Some	Number of interventions	$\sum n$	0	1	2	3	4
Number of patients	37/57	16/57	4/57	1	40	28	12			
%	65	28	7	2	11	5	3	3		
				3	5	3	1	0	1	
				≥ 4	1	1	0	0	0	0

Edematous attacks after diagnostic/surgical procedures
After diagnosis

	Edema formation				Number of patients					
						Number of attacks				
	None	All	Some	Number of interventions	$\sum n$	0	1	2	3	4
Number of patients	28/33	2/33	3/33	1	23	21	2			
%	85	6	9	2	5	4	1	0		
				3	4	3	1	0	0	
				≥ 4	1	0	1	0	0	0

The left side of the table shows the total number of patients against the number of interventions. The rows on the right side give detailed information on how many postprocedural attacks (1–4) were experienced by how many patients who underwent the given number of interventions. The number of attacks never exceeded four, even if more than four interventions had been performed. Accurate information from the period before establishing the diagnosis of HAE was not available on all cases of dental procedures. Therefore, only the data related to surgical/diagnostic interventions are shown from this period.

in this study, edematous episodes occurred significantly less frequently after STP with C1-INH concentrate (Berinert®, CSL Behring, Marburg, Germany) than following the prophylactic administration of danazol, or TXA (6%, *vs* 13%, *vs* 33% of cases, respectively). Edema formation, which occurred despite STP, always resolved after the administration of pdC1-INH concentrate; a rebound effect or exacerbation of the episode did not occur. As shown by the clinical trials conducted in recent years, a single dose increased to 20 U/kg b.w. was superior to the 10-U/kg dose when administered as acute treatment. Based on the I.M.P.A.C.T.2 study, a single dose of 20 U/kg pdC1-INH concentrate (Berinert®, CSL Behring, Marburg, Germany) is safe and provides reliable efficacy in the long-term treatment of HAE attacks at any body location (27). Additionally, another brand of C1-INH concentrate (Cinryze®; ViroPharma Inc., Exton, PA, USA) significantly reduced the number of attacks when administered for prophylaxis in a 1000-U dose (28, 29). A single, 1000-U dose was administered before 96% of the procedures (56% of which were dental, and 44% involved surgery or diagnostic intervention); HAE attacks did not occur after 72 h of C1-INH administration in 98% of the procedures (30). Investigating edema after dental procedures, Bork et al. (26) found an almost linear decrease in attack frequency, which was 21.5% without prophylaxis, 16.0% during prophylaxis with a 500-U, and 7.5% with a 1000-U dose of pdC1-INH. Considering these findings aggregately, a 1000-U dose may prove superior to 500 U for STP. However, when used for STP in both studies, C1-INH concentrate was administered in fixed doses, regardless of body

weight (26, 30). It is yet unclear why does postprocedural edema occur after STP in patients who have had several event-free medical interventions earlier after the administration of 500 U pdC1-INH concentrate (29). The background of the pathophysiological changes accompanying medical procedures includes tissue injury, during which the phospholipid molecules released from damaged cells might be able to activate the Hageman's factor (31). Under physiological circumstances, C1-INH controls the activation of the kallikrein-kinin system by inhibiting factors XIIa, XIIf, and kallikrein. In HAE-C1-INH, the diminished functional activity of C1-INH may lead to the activation of the kinin-kallikrein cascade, which can result in edema formation (6, 32, 33). In agreement with the observations of other authors, our findings confirm that medical interventions increase the chance of an edematous episode. In our study, STP proved an effective and safe treatment modality. This finding should be substantiated by appropriate evidence from randomized, placebo-controlled, multicenter trials.

Authors' contribution

HF and ZZ involved in the acquisition, analysis, and interpretation of data. HF, DC, ES, ZZ, ZN, GT, LJ, LV, GH, and IK involved in the final approval of the study. DC, ES, and LV involved in the acquisition and analysis of data. HF, ES, ZZ, ZN, GT, LJ, LV, GH, and IK involved in drafting the article. DC involved in revising the manuscript. ZN and IK involved in the analysis and interpretation of data. GT and LJ involved in acquisition and interpretation of data. LV involved in the interpretation of data. GH involved in the acquisition of data.

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Conflict of interest

Henriette Farkas has received consultancy/speaker fees and honoraria from Shire Human Genetic Therapies Inc., Pharming, Viropharma and CSL Behring. Dorottya Csuka has received travel grants from CSL Behring, Shire Human Genetic Therapies Inc and Viropharma. Lilian Varga has received travel grants from CSL Behring and Shire Human Genetic Therapies Inc.

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