Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study

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Objective. Tooth extractions may trigger clinical symptoms of hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH). The aim of this study was to determine how many tooth extractions were followed by symptoms of HAE-C1-INH in patients with and without preoperative short-term prophylaxis with C1 inhibitor concentrate.

Study design. Tooth extractions and clinical symptoms of HAE-C1-INH were determined from clinical record files of 171 patients with HAE-C1-INH.

Results. Facial swelling or potentially life-threatening laryngeal edema, or both, occurred in 124/577 tooth extractions (21.5%) without prophylaxis. Similar symptoms occurred in a fewer proportion of patients undergoing extractions (16/128; 12.5%) after short-term prophylaxis with C1 inhibitor concentrate. The graded dose-response relationship was significant at \( P < .05 \).

Conclusions. Short-term prophylaxis with C1 inhibitor concentrate significantly reduces the risk of HAE-C1-INH symptoms after tooth extraction. In some patients, however, facial swellings and laryngeal edema symptoms may occur despite prophylaxis. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:58-64)

Hereditary angioedema (HAE) is an important topic in dentistry because tooth extractions may trigger laryngeal edema and thus may cause death by asphyxiation.¹ HAE types I and II are associated with functional deficiency of C1 inhibitor (C1-INH) in plasma due to mutations of the C1-INH gene.² The low plasma concentration of functionally active C1-INH permits the activation of the kallikrein-kinin system, the early steps of the classical complement pathway, and the fibrinolytic system, causing the release of vasoactive peptides. Recent data suggest that bradykinin is the most important mediator of HAE attacks.³ HAE due to C1-INH deficiency (HAE-C1-INH) is a rare disease; the prevalence is estimated to be ~1:50,000. Clinically, it is characterized by relapsing episodes of edema at various body sites, lasting 1-7 days, followed by disease-free intervals of variable duration. Skin swelling is disfiguring and in the case of facial edema bears the risk of being followed by laryngeal edema. Abdominal attacks are characterized by severe cramping pain. Episodes of upper airway obstruction (usually laryngeal edema) are potentially life threatening, and cases of death by asphyxiation have been reported. Mechanical trauma, psychological stress, and infections may, among others, provoke acute attacks. However, the majority of attacks occur unpredictably, without any recognizable trigger factors. C1-INH concentrates derived from human plasma, icatibant, and ecallantide are used for treatment of acute attacks in patients with HAE-C1-INH.⁴⁻⁸

Numerous case reports in patients with HAE-C1-INH have shown that dental surgery may provoke episodes of angioedema, such as swelling of the lips, facial edema, tongue edema, and laryngeal edema with...
upper airway obstruction.\textsuperscript{1,9-13} Seven cases with fatal outcomes have been reported.\textsuperscript{1,14,15} Additionally, abdominal swelling and peripheral angioedema after tooth extraction have been observed.\textsuperscript{9} However, not all dental surgery procedures, including tooth extraction, are followed by an acute attack in patients with HAE-C1-INH. To date there has been no systematic study quantifying the risk of angioedema attacks after dental surgery in these patients.

Prophylaxis before dental surgery has been performed to varying degrees with fresh frozen plasma, antifibrinolytics, attenuated androgens, and C1-INH concentrate with varying degrees of success.\textsuperscript{10,16-23} Fresh frozen plasma has been used for prophylaxis before dental surgery in a number of patients, some of whom still developed edema attacks.\textsuperscript{10,17,21} Antifibrinolytics, such as epsilon-aminocaproic acid\textsuperscript{24} and tranexamic acid,\textsuperscript{11,25} have also been used for preoperative prophylaxis in some patients. Prophylaxis with attenuated androgens has been commonly used before dental surgery,\textsuperscript{9,10,15,26,27} although some patients developed edema despite this treatment.\textsuperscript{17,22} In contrast, prophylaxis with C1-INH concentrate has been used in only a few patients.\textsuperscript{28-32} However, because HAE symptoms occur only after a minority of tooth extractions without short-time prophylaxis, it cannot be concluded from these reports that the prophylaxis regimens used were effective in preventing postsurgical swelling. To prove the efficacy of short-term prophylaxis, the first step is to ascertain the frequency of swellings after dental surgery in patients without prophylaxis, which has not yet been established. Subsequently, the frequency of postsurgical swellings in patients who receive prophylaxis with C1-INH concentrate or other agents before dental surgery has to be determined. The comparison of these results in a large patient series would enable an evaluation of the effectiveness of short-term prophylaxis before tooth extraction.

The aim of the present study was therefore to perform such a systematic investigation in a large number of patients with HAE-C1-INH to assess: 1) how many tooth extractions are and are not followed by HAE symptoms; 2) which symptoms are triggered by tooth extraction; 3) the time interval between tooth extraction and the beginning of the symptoms; and 4) how effective and safe pasteurized C1-INH concentrate is as short-term prophylaxis before tooth extraction.

**Materials and Methods**

Patients with HAE-C1-INH were surveyed in the Angioedema Outpatient Service at the Department of Dermatology, University of Mainz, Germany. Diagnosis of HAE-C1-INH was made on the basis of patient history, clinical examination, and laboratory results, including deficiency of functional C1-INH and C4 in plasma. The local medical Ethics Committee (Mainz) approved the study. Each subject in the project signed a detailed informed consent form. When the patients were seen for the first time, they were asked about the affected organs in all episodes they had experienced to date. Then, for each individual organ, they were asked about the onset of the first episode and the frequency of edema episodes per year. The visit included a physical examination. Later, the patients were seen for follow-up every 4-6 months during the first year and at least yearly thereafter. At each contact, the frequency of angioedema episodes and affected body sites of the symptoms experienced were assessed by questioning the patients and by analyzing a “swelling diary” that the patients filled out at home, noting time, duration, and severity of their angioedema episodes and the organs involved. Patients were asked specifically to inform the clinic of any tooth extractions they were due to undergo. The number and localization of HAE symptoms after tooth extractions were documented during personal interviews using standardized questionnaires. Information was stored in the clinical record files.

The outcome of short-term prophylaxis with pasteurized C1-INH concentrate was studied by comparing patients who had received prophylaxis with 500 U or 1,000 U of C1-INH concentrate (Berinert P; CSL Behring, Marburg, Germany) with a patient series that had not received prophylaxis. Some patients received 500 U C1-INH concentrate and others received 1,000 U because there were different dosing recommendations over time: Initially 500 U were recommended, whereas later on, owing to swellings occurring despite treatment with 500 U of C1-INH concentrate, we recommended a dose of 1,000 U. The patients received C1-INH concentrate intravenously 1 hour before surgery.

Statistical analysis was performed using Fisher exact test to compare single versus multiple tooth extractions and $\chi^2$ test for attack after surgery (yes versus no) by type of prophylaxis (none, 500 U, 1,000 U) with 2

| Table I. Patients with hereditary angioedema who underwent tooth extractions |
|-----------------------------|------------------|-------------------|------------------|-------------------|------------------|------------------|
| No. of patients              | 171              |
| Gender [male/female], n      | 68/103           |
| Age [y], mean ± SD           | 43.6 ± 15.1      |
| No. of extracted teeth       | 801              |
| No. (%) of sessions with ≥ 1 tooth extraction | 705 (100) |
| No. (%) of tooth extractions without preoperative prophylaxis | 577 (81.9) |
| No. (%) of tooth extractions preceded by a prophylactic dose of 500 U C1 inhibitor concentrate | 75 (10.6) |
| No. (%) of tooth extractions preceded by a prophylactic dose of 1000 U C1 inhibitor concentrate | 53 (7.5) |
degrees of freedom based per surgery. A $t$ test was performed for the time lag between tooth extraction and start of HAE symptoms for the conditions of “no prophylaxis” and “prophylaxis with 500 U”; the 4 attacks that occurred after prophylaxis with 1,000 U were not included. No significance tests were performed on a per-person basis.

RESULTS

One hundred seventy-one caucasian patients with HAE-C1-INH underwent $\geq 1$ tooth extractions after they had first experienced HAE symptoms. Basic data on these patients are shown in Table I. The number of extracted teeth in these patients was 801, which occurred during 705 separate extraction sessions. In the following, we use the term “tooth extraction” to refer to the surgical procedure regardless of the number of teeth that were extracted during a given session. In none of the patients was the first clinical symptom of HAE-C1-INH a swelling induced by tooth extraction.

Symptoms of HAE-C1-INH after tooth extraction without prophylaxis

One hundred forty-eight patients (86.5%), comprising 59 men and 89 women, did not receive prophylaxis before all or some of their tooth extractions (123 patients did not receive prophylaxis for any tooth extractions, 123 patients did not receive prophylaxis for any tooth extractions, 25 patients received prophylaxis on $\geq 1$ occasions and did not receive prophylaxis on other occasions). In 55 of 148 (37.2%) patients, comprising 21 men and 34 women, tooth extraction was followed by HAE symptoms (Fig. 1). Prophylaxis was not administered before 577 of the 705 extraction sessions. In 453 (78.5%) of these sessions, no HAE symptoms occurred after tooth extraction. The other 124 extractions (21.5%) were followed by HAE symptoms (Fig. 2). These attacks included 88 attacks of isolated facial edema in 39 patients, 8 attacks of isolated laryngeal edema in 6 patients, and 28 facial swellings associated with laryngeal edema in 16 patients (the number of patients exceeds 55 because some patients had varying combinations). The total number of sessions triggering facial swellings was 116. The total number of sessions triggering laryngeal edema was 36. None of the laryngeal edema was fatal. Skin swellings at other body sites or abdominal attacks related to tooth extractions were not observed. The mean time between tooth extraction sessions and the onset of symptoms was 14.3 hours (SD 10.0 h, range 1-72 h) for all HAE attacks (Fig. 3).
In a subgroup of 11 patients without prophylaxis, 2/23 sessions (8.7%) with 1 extraction and 4/13 sessions (30.7%) with ≥2 extractions (range 2-32) were followed by HAE symptoms (Table II). However, the difference between the groups was not statistically significant (Fisher exact test: \(P = .33\)). The 2 patients who each had 32 tooth extractions in 1 session under general anesthesia had no subsequent HAE symptoms.

Symptoms of HAE-C1-INH after tooth extractions after prophylaxis with C1-INH concentrate

Prophylactic treatment was administered before 128 tooth extraction sessions in 48 of the 171 patients, in 15 men and 33 women (Table III). Thirty-three patients received 500 U C1-INH concentrate as prophylaxis before 75 tooth extraction sessions, and 18 patients received 1,000 U before 53 tooth extraction sessions. Three patients received 500 U C1-INH concentrate before some of their tooth extractions and 1,000 U before others.

Table II. Hereditary angioedema (HAE) attacks in a subgroup of 11 patients after ≥1 sessions with tooth extractions per patient

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>No. of tooth extraction sessions</th>
<th>No. of extracted teeth</th>
<th>No. of sessions with 1 tooth extraction followed by HAE symptoms</th>
<th>No. of sessions with ≥2 tooth extractions</th>
<th>No. of extracted teeth in sessions with ≥2 tooth extractions</th>
<th>No. of sessions with ≥2 tooth extractions followed by HAE symptoms</th>
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<tr>
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<td>6</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>117</td>
<td>23</td>
<td>2</td>
<td>13</td>
<td>94</td>
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</table>

Table III. Number of hereditary angioedema (HAE) attacks according to body site after tooth extraction with and without short-term prophylaxis with C1 inhibitor concentrate

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of tooth extractions</th>
<th>No. of HAE attacks</th>
<th>Facial edema (isolated)</th>
<th>Laryngeal edema (isolated)</th>
<th>Both facial and laryngeal edema</th>
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<tr>
<td>Prophylaxis with 500 U</td>
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<td>12</td>
<td>8</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Prophylaxis with 1000 U</td>
<td>53</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total with prophylaxis</td>
<td>128</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Without prophylaxis</td>
<td>577</td>
<td>124</td>
<td>88</td>
<td>8</td>
<td>28</td>
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</tbody>
</table>

In a subgroup of 11 patients without prophylaxis, 2/23 sessions (8.7%) with 1 extraction and 4/13 sessions (30.7%) with ≥2 extractions (range 2-32) were followed by HAE symptoms (Table II). However, the difference between the groups was not statistically significant (Fisher exact test: \(P < .33\)). The 2 patients who each had 32 tooth extractions in 1 session under general anesthesia had no subsequent HAE symptoms.

Symptoms of HAE-C1-INH after tooth extractions after prophylaxis with C1-INH concentrate

Prophylactic treatment was administered before 128 tooth extraction sessions in 48 of the 171 patients, in 15 men and 33 women (Table III). Thirty-three patients received 500 U C1-INH concentrate as prophylaxis before 75 tooth extraction sessions, and 18 patients received 1,000 U before 53 tooth extraction sessions. Three patients received 500 U C1-INH concentrate before some of their tooth extractions and 1,000 U before others.

In 10/48 patients (20.8%), comprising 4 men and 6 women, HAE symptoms were reported despite prophylaxis (Fig. 1). After 128 extraction sessions, 16 episodes (12.5%) of edema occurred (Table III), comprising facial swelling (9), nonfatal laryngeal edema (4), or both (3). Twelve attacks (8 facial, 3 laryngeal, 1 combined) occurred after prophylaxis with 500 U C1-INH concentrate (12/75 attacks [16%]). Four attacks (1 facial, 1 laryngeal, 2 combined) occurred despite prophylaxis with 1,000 U C1-INH concentrate (4/53 attacks [7.5%]). When these numbers are compared with the rate of attacks without prophylaxis, i.e., 124 attacks among 577 extractions (21.5%), the difference was significant (\(\chi^2 = 6.71; P < .035\)). Moreover, a graded dose-response relationship is seen (Fig. 2). There were no drug-related side effects.

The mean time between tooth extraction and onset of HAE symptoms was 8.4 hours (SD 8.8 h, range 4-36 h) for all HAE attacks. Mean time lags between tooth extraction and onset of attack were 14.3 hours (SD 10.0 h) for attacks without prophylaxis (124 attacks), 6.6 hours (SD 5.6 h) for prophylaxis with 500 U C1-INH concentrate (12 attacks), and 13.3 hours (SD 15.3 h) for prophylaxis with 1,000 U (4 attacks). A test for the time lags between no prophylaxis and 500 U was significant at \(P < .001\) (\(t_{143} = 2.62\)). No test for 1,000 U was made, because the number of attacks was too small. Taken together, these data indicate that the time lag under prophylaxis is shorter than without prophylaxis.

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Efficacy of prophylaxis

Our findings showed that angioedema attacks occurred in 37.2% of patients who did not receive prophylaxis and in 20.8% of patients who received prophylaxis with C1-INH concentrate. Therefore, on a per-patient basis, prophylaxis led to a 44.1% reduction in angioedema attacks. Angioedema attacks followed 21.5% of tooth extractions without prophylaxis and 12.5% with prophylaxis. Therefore, on a per-attack basis, prophylaxis with C1-INH concentrate led to a 41.9% reduction in angioedema attacks.

DISCUSSION

We investigated a relatively large number of patients with HAE-C1-INH for the occurrence of clinical symptoms of HAE following tooth extraction. The results show that even without prophylaxis no swelling due to HAE-C1-INH occurred in the majority of patients (62.8%) and in the majority of tooth extractions (78.5%). In the remaining patients (37.2%) and tooth extractions (21.5%), either isolated facial swellings, facial swellings associated with laryngeal edema, or isolated laryngeal edema occurred.

C1-INH concentrate was chosen for short-term prophylaxis because it was known to control acute attacks highly effectively and its half-life is long enough to provide expected protection for 1 or 2 days. Furthermore, the intravenous application 1 hour before tooth extraction ensured a sufficiently high plasma level of C1-INH during the time period when the patient was at most risk of an HAE attack. In patients receiving prophylaxis with C1-INH concentrate before tooth extraction, the percentage reporting swelling was considerably lower when evaluated on a per-patient basis (20.8% vs. 37.2%) as well as on a per-attack basis (12.5% vs. 21.5%). These comparisons clearly demonstrate some efficacy of this type of prophylaxis. Based on the properties of the C1-INH concentrate used (high concentration, high in vivo recovery, short time to reach the maximal plasma concentration, and long half-life time) this efficacy was to be expected.

In some patients, however, facial and laryngeal edema occurred despite prophylaxis. This happened in patients who received 500 U C1-INH concentrate and even in some patients who received 1,000 U. However, an almost linear decrease in attack occurrence could be observed: 21.5% for no prophylaxis, 16.0% for 500 U, and 7.5% for 1,000 U.

The pathogenesis of swellings after tooth extraction seems to be as follows. Physiologically, C1-INH controls the activation of the kallikrein-kinin system by inhibiting factor XIIa, factor XIIif, and kallikrein. If functional C1-INH levels are low, in the case of HAE- C1-INH due to a defect in 1 allele of the gene coding for C1-INH, the kallikrein-kinin cascade can become activated and, in acute attacks of HAE, the release of bradykinin at the end of this cascade leads to increased vascular permeability via binding of bradykinin to the bradykinin B2 receptor on the endothelial cells. It is well known that the kallikrein-kinin system is activated by damage to endothelial cells, e.g., by trauma. Dental surgery, such as tooth extraction, involves considerable tissue damage. Therefore, the association between tissue damage and a lowered C1-INH level may lead to activation of the kallikrein-kinin cascade and result in an edema attack. It is not clear why this process occurs only with some tooth extractions. A hitherto unknown protective mechanism might also play a role. Obviously, in some tooth extractions the local activation arising from tissue damage is so high that a dose of 500 U or even 1,000 U C1-INH concentrate, which in the past has been shown to be effective in the treatment of acute HAE attacks, was insufficient to control the local kallikrein-kinin activation.

We are aware that, in addition to tooth extractions, other types of oral manipulations, such as noninvasive dental procedures or intubation may lead to HAE symptoms. Eight patients in our study also reported HAE symptoms after drilling or filling of 1 tooth without anesthesia. However, we focused on tooth extractions because these are probably the most frequent triggering factors for HAE attacks in the head region.

One further finding from this study is that the time between tooth extraction and onset of facial or laryngeal edema varied between 1 hour and 72 hours. Many of the attacks started within 12 hours after tooth extraction (Fig. 3). This implies that there is a high risk of an attack during the night after a tooth extraction. If the initial symptoms occur while asleep they are probably recognized later than if the patient is awake. By then, the attack will already have progressed and treatment may start too late. In all 4 HAE patients described in 2003 who died by asphyxiation after tooth extraction, the fatal laryngeal edema occurred at night and the patients asphyxiated in the early hours of the morning (between 3:30 and 6:00 a.m.). In the patients who received prophylaxis with C1-INH concentrate in our study, the time lag between tooth extraction and onset of HAE symptoms was shorter than without prophylaxis. However, the reason for this remains unclear.

Our results do not suggest that the invasiveness of tooth extraction is decisive for the development of HAE symptoms. Thus, as mentioned, patients can develop HAE attacks following minor dental procedures. On the other hand, 2 of our patients each had an extraction of all 32 teeth in one single session that was not followed by HAE symptoms. Furthermore, some patients had HAE symptoms after some tooth extractions but not...
after others. Therefore, we assume a certain disposition to HAE symptoms after tooth extraction that can vary within the same patient.

This study has the following limitations. First, it is based on observational data and not on a randomized controlled design. Therefore, it is possible that our estimate of a 40% reduced risk for HAE attacks after tooth extraction accompanied by prophylaxis with C1-INH concentrate is biased. However, there is little cause for concern that this is an upward bias. It is more likely that those patients who requested prophylaxis had a higher risk of developing symptoms, e.g., they may have previously experienced symptoms after tooth extraction. Such a bias would be most obvious if the reduction calculated on a per-patient basis was much higher than on a per-attack basis. The observed difference here of 44% versus 42% is too small to assume an underestimation of the risk; on the other hand an underestimation cannot be discounted. Second, the number of attacks observed despite prophylaxis was relatively small, leaving additional uncertainty in the quantification of the risk reduction. Third, because this was a retrospective study, we did not consider factors, such as age at tooth extraction, degree of facial edema, type and amount of anesthesia or sedation, or invasiveness of tooth extraction. We think that the potential benefit of considering such details in our analysis is debatable. A strength of our study is that the number of tooth extractions, which constituted the denominator in our analyses, was sufficiently large in both groups.

In spite of these limitations, the results of our study reveal a number of new and important issues: 1) They enable us for the first time to quantify the risk of facial and laryngeal edema following tooth extraction; 2) we have shown for the first time that short-term prophylaxis with C1-INH concentrate reduces this risk; 3) we have shown that HAE symptoms can occur in some patients despite prophylaxis with 500 U or 1,000 U C1-INH concentrate. The percentage of attacks was higher after extractions with prophylaxis with 500 U (16.0%) compared with 1,000 U (7.5%). The difference was statistically significant and showed a clear trend. On the basis of this result, we now recommend prophylaxis with 1,000 U of C1-INH concentrate to our patients 1 hour before tooth extraction. This recommendation is also based on a controlled study, which showed that 20 U C1-INH concentrate per kg body weight controlled acute HAE attacks, whereas 10 U/kg body weight was statistically not effective. Additionally, our patients keep 1,000 U of C1-INH concentrate (2 vials of 500 U Berinert P) at home, which could be used as an initial measure if an emergency situation occurs.

Patients should be informed about the risks of facial and laryngeal edema occurring after tooth extraction and that these symptoms may occur in the night after tooth extraction.

REFERENCES


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