Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Dental Procedures for Hereditary Angioedema Patients: What Happens in Real Life?

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Abstract

Objective: Dental procedures are known to be potential triggers for attacks in hereditary angioedema (HAE). Therefore, we aimed to demonstrate the potential of dental procedures to trigger HAE attacks through real-life experiences. **Methods:** The files of 57 patients diagnosed with HAE-I/II and followed up at the Immunology Allergy Diseases Outpatient Clinic between January 1, 2018, and April 4, 2025, were examined. **Results:** The study included 44 patients, and short-term prophylaxis (STP) was administered to 27.3%, 26.7%, and 8.3% of those who underwent tooth extraction, filling, and root canal treatment, respectively. The frequency of attacks after tooth extraction was reduced in patients who received STP compared to those who did not receive STP, but this reduction was statistically insignificant (33.3% in those who did not receive STP vs. 22.2% in those who did). When comparing patients who experienced attacks without STP after tooth extraction with those who did not receive STP, it was observed that the group experiencing attacks was predominantly female (p=0.079). Attacks occurring after tooth extraction were not statistically significantly associated with attack triggers. **Conclusion:** Most HAE patients do not receive STP before dental procedures. Given the risk of fatal laryngeal attacks, albeit rare, it is important to carefully assess patients for their STP needs before dental procedures, and to raise awareness among both patients and dentists regarding the risk of attacks despite STP.

Keywords: Hereditary angioedema, prophylaxis, attack, real-world data

1. Introduction

Hereditary angioedema (HAE) is a rare inherited condition characterized by recurrent episodes of skin or submucosal swelling. According to current international guidelines, HAE is classified based on C1-inhibitor (C1-INH) antigenic levels and functional activity. Most cases are associated with C1-INH deficiency, defined by reduced antigenic levels and/or impaired functional activity, leading to excessive bradykinin production and subsequent activation of bradykinin B2 receptors. The disease most commonly presents with attacks affecting the skin, abdomen, and upper respiratory tract[1]. Attacks involving upper airway obstruction (supraglottic edema; laryngeal attacks) are less common but potentially life-threatening. Asphyxia during a laryngeal attack is a risk, and this can lead to death[2]. Physical stress, infections, psychological stress, medical and surgical procedures (e.g., dental procedures), medications (such as ACE inhibitors and estrogen-

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containing birth control pills), or endogenous hormonal fluctuations (including menstruation, menopause, and pregnancy) are known as potential triggers for attacks[3,4]. Because swellings often occur near the site of surgical trauma, dental procedures can potentially cause fatal laryngeal attacks due to anatomical proximity[5,6]. When the risk of HAE attacks is elevated due to known triggers, short-term prophylaxis (STP) is recommended. This may include a single dose of C1-INH (1000 units or 20 units/kg) administered 1–12 hours before the event, or short-term treatment with anabolic steroids initiated 5–7 days prior to the event and continued for 2–5 days afterward[1,7]. Fresh frozen plasma (FFP) is an alternative for STP management, but is considered a second-line treatment due to its lower safety profile compared to intravenous C1-INH concentrate[1]. The objective of this study was to evaluate whether dental procedures may precipitate HAE attacks and to analyze the relationship between these factors based on real-world experiences.

2. Materials and Methods

2.1. Study Population

Dental procedures of adult patients diagnosed with HAE and followed up at the Immunology Allergy Diseases Outpatient Clinic between January 1, 2018 and April 4, 2025 were evaluated. Files of 57 patients diagnosed with HAE due to C1-INH deficiency were reviewed; patients who had not received dental treatment or for whom detailed information about dental treatment was unavailable were excluded from the study. The study flow is shown in Figure 1.

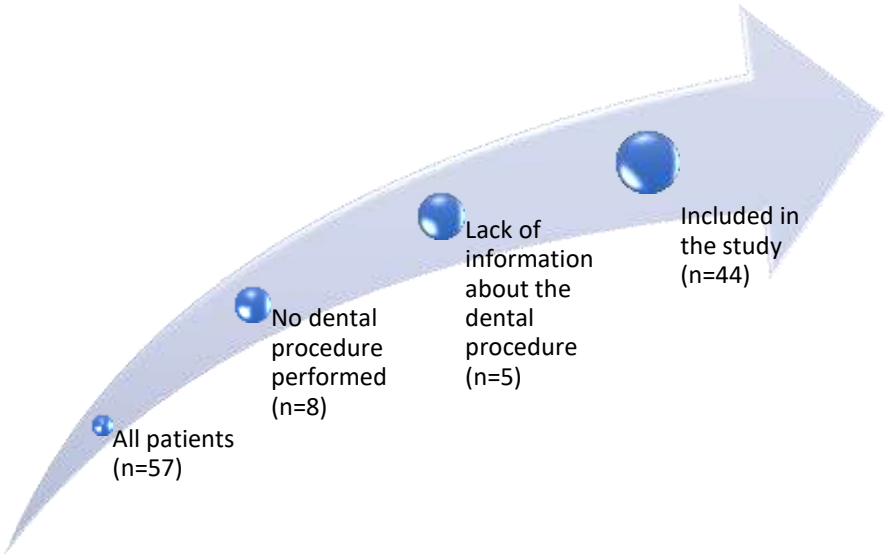

Figure 1. Study design

HAE was diagnosed in accordance with current international guidelines, including those of the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI). Laboratory evaluation included measurement of C1-INH antigenic levels, C1-INH functional activity, and complement component C4 levels for each patient. HAE with C1-INH deficiency was defined by low C1-INH levels and/or decreased functional activity, typically accompanied by low C4 levels. For descriptive purposes, those with low C1-INH levels and function were classified as HAE-1, while those with only decreased function and high and/or normal C1-INH levels were classified as HAE-2[1]. Patients' demographic characteristics, information about their illnesses, and

treatments received were recorded. Information regarding attack triggers was specifically included. The type of dental procedure performed (tooth extraction, dental filling, root canal treatment, dental crown replacement, implant, or dental cleaning), whether STP was received, and whether there were any attacks after the procedure were also recorded. All data, including dental treatment data, were obtained retrospectively from patients' medical records. The study protocol was approved by the local Ethics Committee.

2.2. Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (Statistical Package for Social Sciences). Descriptive and categorical data were summarized as frequencies and percentages. Data normality was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were expressed as mean ± standard deviation, while variables with a non-normal distribution were expressed as median (minimum-maximum). Due to the small sample size and the expectation of fewer than five cells, Fisher's exact test was used to analyze the relationships between categorical variables. Statistical significance was defined as a p-value < 0.05.

3. Results

A total of 44 patients were included, 65.9% (n=29) of whom were female, with a mean age of 41.0 ± 15.2 years. Seventy-seven point three percent (n=34) of the patients had HAE-1, 38.6% (n=17) had parental consanguinity, and 90.9% (n=40) had a family history. Sixty-three point six percent (n=28) of patients reported emotional stress, 52.3% (n=23) reported cold, 27.3% (n=12) reported trauma, and 20.5% (n=9) reported infection as attack triggers. For long-term prophylaxis (LTP), 15 patients (34.1%) received danazol, 4 patients (9.1%) received tranexamic acid, and the remaining 24 patients (56.8%) were not receiving any LTP. Patient demographics and clinical characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics of patients

	All patients (n=44)
Age (years) mean±SD	41.0±15.2
Gender Male / Female n (%)	15 (34.1) / 29 (65.9)
Age at symptom onset (years) median (min-max)	10 (4-50)
Age at diagnosis (years) mean±SD	24.6±13.5
Diagnostic delay (years) median (min-max)	5 (0-45)
Parental consanguinity n (%)	17 (38.6)
Family history n (%)	40 (90.9)
Death in the family due to HAE n (%)	32 (72.7)
Laryngeal attack n (%)	24 (54.5)
C1-INH-HAE subtype, HAE-1/HAE-2 n (%)	34 (77.3) / 10 (22.7)

SD: Standard deviation, HAE: Hereditary angioedema, C1-INH-HAE: HAE due to C1 inhibitor deficiency

Of the patients who underwent tooth extraction, 27.3% received STP, while 33.3% of those who did not receive STP experienced an attack. The incidence of tooth extraction attacks decreased with STP compared to without STP, but this decrease was not statistically significant (33.3% without STP vs. 22.2% with STP). Table 2 presents the results of prophylaxis and attacks in patients who have undergone tooth extraction. In the dental filling group, STP was administered to 26.7% of patients, whereas attacks occurred in 18.2% of patients who did not receive STP. Facial swelling has been observed in patients who experienced attacks following tooth extraction or dental fillings, and laryngeal edema occurred in only one patient who underwent tooth extraction. Among patients who underwent root canal treatment, 91.7% (n=11) did not receive STP, and no attacks were observed. Detailed illustration of STP in dental procedures is shown in Figures 2a-b.

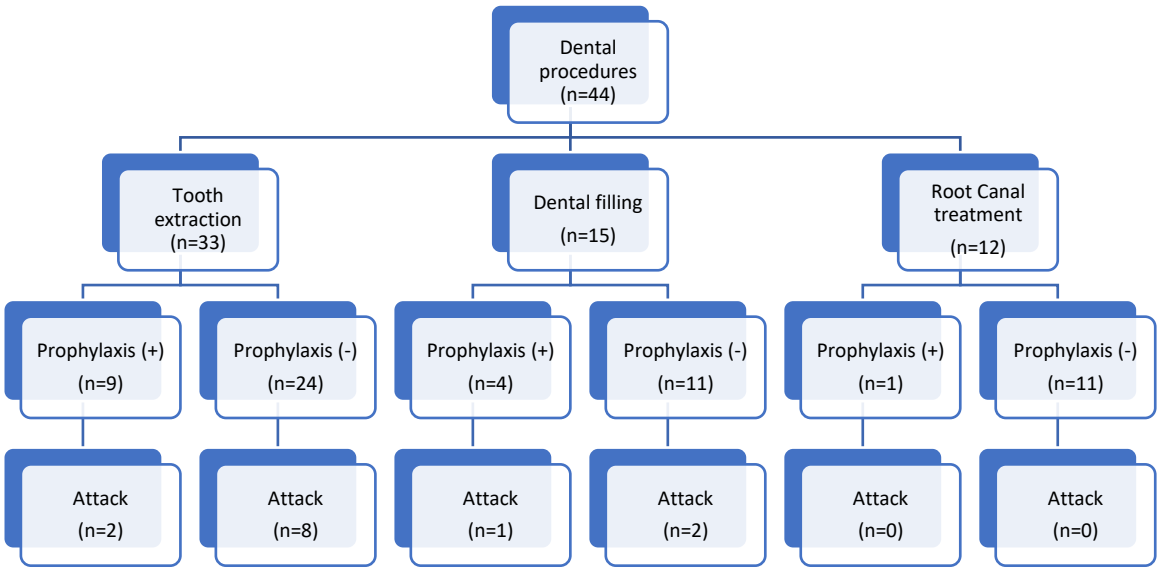

Figure 2a. Detailed Presentation of Prophylaxis and Attack in Dental Procedures

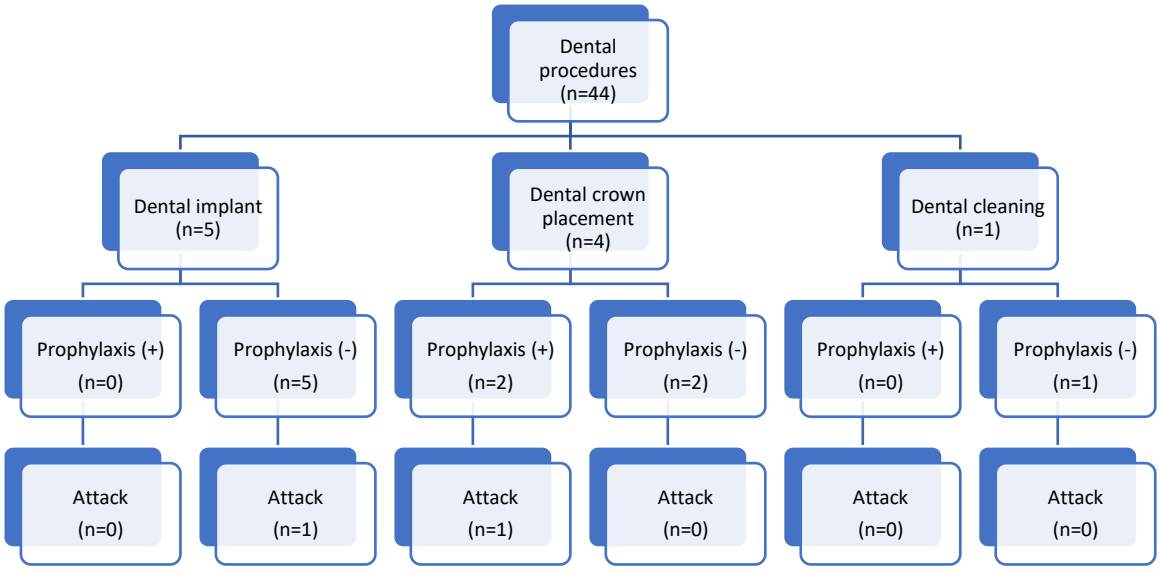

Figure 2b. Detailed Presentation of Prophylaxis and Attack in Dental Procedures

Table 2. Presentation of prophylaxis and attack outcomes in patients undergoing tooth extraction

	Attack (+) n (%)	Attack (-) n (%)	Total n
Short-term prophylaxis (-)	8 (33.3)	16 (66.7)	24
Short-term prophylaxis (+)	2 (22.2)	7 (77.8)	9
Total	10 (30.3)	23 (69.7)	33

P = 0.686 (Fisher's exact test).

Five patients underwent dental implant surgery without receiving STP, and one patient developed facial swelling. Of the four patients who underwent dental crown placement, two received STP (one with C1-INH, the other with attenuated androgen). The patient who received C1-INH concentrate developed facial swelling. No attack occurred in the single patient who underwent dental cleaning without STP. Comparison of patients undergoing tooth extraction without STP showed that those who developed attacks were mainly female (p = 0.079). No statistically significant relationship was found between attack triggers and attacks experienced after tooth extraction. Table 3 summarizes the characteristics of patients who did and did not experience attacks after tooth extraction without STP.

Table 3. Characteristics of patients who experienced and did not experience attacks after tooth extraction without prophylaxis

	With Attack (n=8)	Without Attack (n=16)	P
Gender Female n (%)	7 (87.5)	7 (43.8)	0.079
Parental consanguinity n (%)	4 (50.0)	5 (31.3)	0.412
Family history n (%)	8 (100.0)	15 (93.8)	1.000
Death in the family due to HAE n (%)	7 (87.5)	9 (56.3)	0.189
Laryngeal attack n (%)	5 (62.5)	6 (37.5)	0.390
C1-INH-HAE subtype, HAE-1/HAE-2 n (%)	6 (75.0) / 2 (25.0)	12 (75.0) / 4 (25.0)	1.000
Attack Triggers - Emotional stress n (%)	4 (50.0)	11 (68.8)	0.412
Attack Triggers - Cold n (%)	3 (37.5)	8 (50.0)	0.679
Attack Triggers - Trauma n (%)	2 (25.0)	2 (12.5)	0.578
Attack Triggers - Infection n (%)	1 (12.5)	1 (6.3)	1.000

SD: Standard deviation, C1-INH-HAE: HAE due to C1 inhibitor deficiency, HAE: Hereditary angioedema. Fisher's exact test was used.

4. Discussion

The present study reports real-world data regarding the administration of STP during dental procedures and its relationship with attack development in patients with HAE-1 and HAE-2. While certain patients remained attack-free after dental procedures without STP, there were also cases of attacks despite STP administration. Fortunately, only one patient experienced a laryngeal attack during dental treatment, and it was not fatal. Although not statistically significant, it was observed that applying STP before tooth extraction tended to reduce the frequency of attacks, and that female gender may also be associated with the frequency of attacks.

There are series in the literature showing patients with HAE who did not receive STP before dental procedures; in one study, 70.7% of patients, and in another, 71.9% of patients who underwent tooth extraction had never received pharmacological treatment to prevent attacks related to dental procedures[8,9]. In a different study, 52% of patients did not receive STP before dental procedures[10]. The proportion of patients who did not receive STP was 72.7% for tooth extraction, 73.3% for dental fillings, and 91.7% for root canal treatment in our study. It is crucial in HAE to investigate why the rate of patients not receiving STP before dental procedures is so high, and to enhance both patient and physician knowledge and awareness on this issue.

The literature reports cases of laryngeal edema, asphyxia, and death in patients with angioedema symptoms but without a diagnosis of HAE, and in patients diagnosed with HAE who did not receive STP after tooth extraction[5,11]. Conversely, there are also reports of HAE patients who received STP prior to dental procedures and underwent them without complications[12,13,14,15]. Furthermore, another patient with a history of tracheostomy due to laryngeal edema who underwent tooth extraction was discharged without complications after receiving STP prior to the tooth extraction and completing the observation period[16]. Most patients included in our study did not develop attacks after STP treatment. In addition to patients who did not experience attacks after receiving prophylaxis, there are

also patients who experienced attacks despite receiving STP. In one series, 47.5% of HAE patients who received STP reported a history of attacks during/after dental procedures[10]. In another series, attacks were observed in 20.8% of patients who received STP with C1-INH concentrate[9]. Studies have shown that STP treatment before dental procedures significantly reduces the risk of acute attacks, but may not completely prevent them[9,10,17]. In our study, patients were prophylactically treated with C1-INH by our clinic prior to dental procedures; however, if access to C1-INH was difficult outside of our clinic, attenuated androgen and FFP prophylaxis may have been administered instead. Although few in number, no attacks were observed in patients receiving C1-INH concentrate during procedures other than dental crown treatment. However, attacks were observed in patients receiving attenuated androgens and FFP. This situation demonstrates that attack development is a multifactorial process. As our study supports, attacks can still occur despite STP. Accordingly, it is essential for dentists to recognize the clinical presentation of acute attacks, identify early warning signs, and initiate appropriate and timely interventions during emergencies. Patients should also be informed that attacks may occur up to 24–48 hours after dental procedures and reassured that acute attack treatment is available in the event of a possible attack[18].

In real-world data, 66.7% of patients who underwent tooth extraction without STP did not experience an attack, while this rate is reported as 78.5% in the literature[9]. Considering different dental procedures, 81.8% of patients who underwent dental fillings and 100% of patients who underwent root canal treatment did not experience an attack if STP was not applied. These findings suggest that the risk of HAE attacks following dental procedures without STP may vary according to the type and invasiveness of the procedure. Tooth extraction appears to carry a relatively higher risk, whereas less invasive procedures, such as fillings and root canal treatments, are associated with a lower likelihood of triggering attacks. Nevertheless, considering the limited number of patients and the retrospective design of this real-world study, these results should be viewed cautiously.

Although a relationship between female gender and acute attacks associated with pre-diagnostic dental interventions has been reported in previous literature[17], in our study, although not statistically significant, a higher proportion of women was observed among patients who experienced attacks after tooth extraction without prophylaxis. In the same study[17], tooth extraction - especially wisdom tooth extraction and difficult surgical procedures - was identified as a risk factor with a higher annual attack frequency and lower C1-INH function, and the importance of pre-procedure prophylaxis was emphasized. Additionally, the results did not reveal a direct link between emotional stress and attacks. However, anxiety, a separate but related concept, may be overlooked in current recommendations regarding anesthesia practices in HAE patients in preventing acute attacks. Effective management of anxiety may contribute to the prevention or reduction of acute angioedema attacks[19,20].

From another perspective, many patients with C1-INH- deficient angioedema have reported difficulties in accessing dental care due to dentists' limited knowledge of the disease and its management[21]. It was also observed that a significant portion of HAE patients are denied access to dental care by their dental professionals, with half of the patients reportedly not seeking dental care due to HAE attacks or fear of rejection[8]. Although avoidance of dental procedures by both patients and physicians is common in individuals with HAE, one study reported that a considerable percentage (21.05%) of patients with angioedema due to C1-INH deficiency experienced a reduction in the frequency of angioedema attacks following dental care[21]. This issue may be addressed by improving dentists' knowledge of HAE and educating patients about the role of STP in reducing the risk of attacks before dental procedures. This can make dental care more accessible and potentially reduce HAE attacks by improving oral hygiene.

The retrospective design of the study, the small sample size, and the inclusion of a relatively high number of independent variables limited statistical power and hindered robust regression analyses. Furthermore, the exclusion of patients may have led to selection and information bias. These methodological limitations should be considered, and the results should be interpreted with caution.

5. Conclusions

In conclusion, the vast majority of real-world HAE patients do not receive STP before dental procedures, and most of these patients do not experience attacks. However, attacks have occurred in a small number of patients despite STP, and a laryngeal attack has been observed in a rare case in a patient not receiving STP. Therefore, although rare, the risk of potentially fatal laryngeal attacks in HAE patients should not be ignored. The need for STP should be carefully assessed individually before dental procedures, and awareness of the possibility of attacks despite STP should be increased among both patients and dentists. Furthermore, improving dentists' knowledge about HAE can help provide safer and more effective dental care for these patients.

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Data Availability Statement: The datasets generated and/or analyzed in this study are not publicly available, but may be obtained from the corresponding author upon reasonable request.

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