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# Clinical outcomes of dental procedures in patients with hereditary angioedema

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ABSTRACT

Objective: To investigate the relationship between angioedema (AE) attacks and dental procedures in patients with hereditary angioedema (HAE) and to identify potential risk factors.

Patients and Methods: Patients diagnosed with HAE between 1999 and 2024 at a tertiary adult allergy clinic were retrospectively reviewed for dental procedures and AE attacks.

Results: Of 102 HAE patients, 74 were included after excluding 28 with incomplete data. Dental procedures were performed in 47 patients (63.5%), totaling 85 interventions, most commonly tooth extractions (50.6%), restorations (34.1%), and root canal treatments (11.8%). Preprocedural prophylaxis was administered in 46 cases (54.1%), primarily with plasma-derived C1-inhibitor (pdC1-INH) (n = 36), followed by danazol (n = 7) and icatibant (n = 3). A total of 17 AE attacks (20%) were recorded, all involving the oropharyngeal region. Prophylaxis significantly reduced attack rates (p = 0.022), with no significant difference between pdC1-INH and danazol (p = 0.572). In the pdC1-INH group, attack rates were similar for 500 IU and 1000 IU doses (11.1% vs. 14.8%, p = 0.781).

Conclusion: Preprocedural prophylaxis reduced AE attack frequency in dental procedures, with similar outcomes for pdC1-INH and danazol. Similar results were also observed between 500 IU and 1000 IU pdC1-INH.

Keywords: Hereditary angioedema, Dental procedures, Angioedema prophylaxis

## 1. INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disorder primarily caused by a deficiency in C1-esterase inhibitor (C1-INH), resulting in bradykinin-mediated increased vascular permeability. HAE is classified into three types: Type I (low C1-INH levels, ~85%), Type II (normal levels but inactive C1-INH, ~15%), and HAE-nC1INH, a rare form with normal C1-INH levels and function, linked to genetic mutations such as in factor XII [1,2]. HAE types I and II together affect an estimated 1 in 50,000 individuals, although this prevalence can vary by region [3].

Hereditary angioedema can cause swelling in almost any part of the body, most commonly affecting the subcutaneous and submucosal tissues of the limbs, genitals, face, mouth, and bowels [4]. Severe upper airway swelling has been reported to be triggered by minor trauma or pressure during routine dental procedures [5]. Following tooth extraction, more than one-third of patients who do not receive preprocedural prophylaxis may develop local angioedema (AE), with 50% of these swellings occurring within 10 hours [3,6,7].

Despite the expected benefits of preprocedural short-term prophylaxis (STP) with C1-INH concentrate, evidence supporting its efficacy remains limited [3]. Case reports and series indicate that swellings may still occur even after STP, even following relatively minor procedures [6,8]. Several studies document a reduction in the incidence of swelling associated with preprocedural STP, and the response appears to be dose-dependent [3,6,8,9]. Consequently, preprocedural STP with C1-INH concentrate is recommended for all dental procedures that involve any mechanical impact to the upper aerodigestive tract [3]. STP prior to such procedures is recommended, with options including intravenous plasma-derived C1-esterase inhibitor concentrate (pdC1-INH), fresh frozen plasma, and oral attenuated androgens (e.g., danazol, oxandrolone) [8]. Given the limited data on the relationship between dental procedures and AE attacks in HAE, this study aims to assess the incidence of perioperative attacks, the impact of preprocedural STP on attack frequency, and identify associated risk factors.

## 2. PATIENTS and METHODS

### *Study design and patient selection*

This retrospective study analyzed adult patients diagnosed with HAE types I, II, and HAE-nC1-INH in accordance with the

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latest guidelines, between 1999 and 2024 at the Adult Allergy and Clinical Immunology Clinic of the University Hospital. The diagnosis of HAE-nC1-INH was made based on clinical criteria from previously published expert consensus [2]. To confirm the diagnosis and classify the subtypes, gene mutations in factor XII (F12; OMIM 610619), plasminogen (PLG; OMIM 173350), and angiopoietin 1 (ANGPT1; OMIM 601667) were screened. Additionally, level and function of C1-INH and C4 were measured at diagnosis.

### *Laboratory assessments*

C1-esterase inhibitor and C4 were quantified using the nephelometric method, while C1-INH function was assessed via an immunoenzymatic assay. The study established normal reference ranges for C4 (10–40 mg/dL), C1-INH (15–35 mg/dL), and C1 inhibitor function (70%-130%). In patients with low C1-INH levels and inhibitor function, and low C4 levels, acquired AE was suspected, and C1q levels were measured. C1q was measured nephelometrically (normal range: 15.7 – 30.6 mg/dL), and acquired AE was diagnosed in patients with values below this range. Patients with acquired C1 inhibitor deficiency were excluded from this study.

### *Data collection and definitions*

Data were collected from patient records, encompassing demographic information, follow-up details, type of HAE, attack treatment, long – and short-term prophylaxis. The onset of attacks within 48 hours following procedures has been considered the definition of periprocedural attacks. The number of procedures performed per patient was recorded. In our study, dental procedures were identified primarily from medical records and, when feasible, confirmed during follow-up visits.

### *Prophylaxis protocols*

Short-term prophylaxis was administered using pdC1-INH at 1000 or 500 IU, per guideline recommendations [3,10]. Based on the 2012 World Allergy Organization (WAO) guidelines (10–20 U/kg or 1000 U), lower-weight individuals received 500 IU [10]. More recent administrations followed the standard 1000 IU dose per the 2022 WAO/EAACI guidelines [3]. Alternatively, preprocedural STP with danazol was provided to patients who are on regular maintenance treatment with danazol, at a dosage of 600 mg, commencing at least five to seven days prior to surgery and continuing for a minimum of two to five days thereafter.

### *Study endpoints*

The primary endpoint of the study involved a retrospective analysis of patients for information regarding dental procedures and the occurrence of AE attacks. Additionally, the secondary endpoints aimed to evaluate the risk factors associated with acute AE attacks related to dental procedures and the efficacy of prophylactic treatment.

The research protocol was approved by the Ethics Committee of Hacettepe University (approval number SBA 25/015). The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

### Statistical analysis

Statistical analyses were performed using SPSS software v. 22.0 (IBM, NY, USA). After descriptive statistics were obtained, the Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to determine whether continuous data were normally distributed. The demographic and clinical characteristics of the patients were compared between groups. The Mann-Whitney U test was used to compare variables that were not normally distributed between groups. The results of these analyses were presented as median (minimum–maximum) values. The chi-square and Fisher's exact tests were used to compare categorical data between groups. The results were given as numbers and percentages. In all statistical tests, a p-value of <0.05 was considered statistically significant.

## 3. RESULTS

A total of 102 patients with HAE followed up at the Adult Allergy and Clinical Immunology Clinic of the University Hospital were evaluated. Twenty-eight patients were excluded due to incomplete questionnaire data. Among the 74 (72.5%) patients included in the study, 60 (81.1%) had HAE type I, 8 (10.8%) had HAE type II, and 6 (8.1%) were diagnosed with HAE-nC1-INH. A factor XII mutation was detected in two of the six patients (33.3%) with HAE-nC1-INH. Of the patients, 46 (62.2%) were female, and the median (interquartile range [IQR]) age was 42 (18.0–80.0) years. Nineteen (25.6%) patients were being followed up under long-term prophylaxis (LTP), three (4%) were on regular pdC1-INH concentrate, and 16 (21.6%) were on danazol (Table I). The first AE attack occurred at a median age of 12.0 years (range: 3.0–71.0 years), and the median time to HAE diagnosis was 29.0 years (IQR: 7.0–73.0 years). A comparison of the clinical characteristics of HAE Type I / II and HAE-nC1-INH revealed no statistically significant differences, except for the age at first attack (P=0.041) (Supplementary Table I).

***Supplementary Table I.*** *Comparison of clinical characteristics between HAE type I / II and HAE-nC1-INH groups*

| | HAE type I / II (n = 68) | HAE-nC1-INH (n = 6) | P value |
|---|---|---|---|
| Age (year), median (min-max) | 42.5 (18.0-70.0) | 40.0 (21.0-60.0) | 0.572 |
| Age at HAE diagnosis (year), median (min-max) | 29.0 (7.0-28.0) | 35.0 (20.0-50.2) | 0.332 |
| Sex, n (%) | | | |
| Female | 40 (58.8) | 6 (100.0) | 0.077 |
| Male | 28 (41.2) | 0 (0.0) | |
| Age at first attack, median (min-max) | 10.5 (3.0-68.0) | 19.0 (14.0-58.0) | **0.041*** |
| History of laryngeal edema, n (%) | 37 (54.4) | 2 (33,3) | 0.322 |
| Laryngeal edema (number), median (min-max) | 2.0 (1.0-20.0) | 2.5 (1.0-4.0) | 0.974 |

*Min-max = Minimum-maximum, HAE = hereditary angioedema, HAE-nC1-INH = HAE normal C1 inhibitor; *p values <0.05 are in bold*


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***Table I.*** *Evaluation of demographic and clinical characteristics of patients with hereditary angioedema (n=74)*

| Characteristics | All patients (n=74) | Undergoing Dental Procedures (n=47) |
|---|---|---|
| Age (year), median (min-max) | 42.0 (18.0–80.0) | 41.0 (18.0-68.0) |
| Sex, n (%) | | |
| Female | 46 (62.2) | 30 (63.8) |
| Male | 28 (37.8) | 17 (36.2) |
| Type of HAE, n (%) | | |
| Type I | 60 (81.1) | 34 (72.34) |
| Type II | 8 (10.8) | 8 (17.02) |
| HAE-nC1-INH | 6 (8.1) | 5 (10.64) |
| Age at first attack, median (min-max) | 12.0 (3.0–71.0) | 12.0 (3.0-35) |
| Age at HAE diagnosis (year), median (min-max) | 29.0 (7.0–73.0) | 29.0 (7.0-53.0) |
| History of laryngeal edema, n (%) | 42 (54.5) | 17 (36.1) |
| Laryngeal edema (number), median (min-max) | 2.0 (1.0–20.0) | 2.0 (1.0–10.0) |
| Obesity, n (%) | 7 (9.4) | 5 (10.6) |
| Comorbidity, n (%) | 35 (47.2) | 21 (44.6) |
| Atopic disease | 8 (10.8) | 6 (12.8) |
| Hypertension | 9 (12.1) | 4 (8.5) |
| FMF | 2 (2.7) | 2 (4.2) |
| Urticaria | 2 (2.7) | 1 (2.1) |
| Other comorbidities* | 14 (29.7) | 8 (17.0) |
| FMF diagnosis in childhood, n (%) | 6 (8.1) | 4 (8.5) |
| Smoking history, n (%) | 18 (24.3) | 10 (21.2) |
| Smoking pack/years, median (min-max) | 20 (1.0-45.0) | 20 (1.0-45.0) |
| On-demand therapy, n (%) | | |
| Icatibant | 8 (10.8) | 7 (14.9) |
| pdC1-INH | 7 (9.5) | 5 (10.6) |
| Icatibant and pdC1-INH | 59 (79.7) | 35 (74.5) |
| Long-term prophylaxis, n (%) | 19 (25.6) | 10 (21.3) |
| Long-term prophylaxis type, n (%) | | |
| pdC1-INH | 3 (4.0) | 1 (2.1) |
| Danazol | 16 (21.6) | 8 (17.0) |
| Danazol treatment dose, mg median (min-max) | 200.0 (50.0–300.0) | 150.0 (50.0-200.0) |
| Family history of HAE, n (%) | 61 (82.4) | 37 (78.7) |
| Family history of death from asphyxia, n (%) | 23 (31.0) | 16 (34.1) |

*Min-max = Minimum-maximum, HAE = hereditary angioedema, HAE-nC1-INH = HAE normal C1 inhibitor, FMF = familial Mediterranean fever, pdC1-INH = Plasma-derived C1-inhibitor. *Asthma, diabetes, atherosclerotic cardiovascular disease, hypothyroidism, autoimmune disease, immune insufficiency, malignancy, gout, chronic renal failure*

A total of 85 dental procedures were performed on 47 patients (63.8% female, 41.0 median age). The most common procedures included tooth extractions, representing 43 procedures (50.6%), restorations at 29 procedures (34.1%), and root canal treatments at 10 procedures (11.8%). Preprocedural STP was administered in 46 procedures (54.1%). The most frequently used prophylactic agent was pdC1-INH concentrate, applied in 36 procedures (78.2%), followed by danazol in 7 procedures (15.2%). In 3 (3.5%) procedures, on-demand icatibant was used as a prophylactic agent prior to dental procedures due to the unavailability of pdC1-INH concentrate, which included two tooth extractions and one restoration; none of these patients experienced an attack (Table II).

***Table II.*** *Evaluation of characteristics of dental procedures in patients with hereditary angioedema (85 procedures, 47 patients)*

| Characteristics | N (%) |
|---|---|
| **Type of Dental Procedure, n (%)** | |
| Dental restoration | 29 (34.1) |
| Tooth extraction | 43 (50.6) |
| Root canal treatment | 10 (11.8) |
| Dental implant | 2 (2.3) |
| Teeth cleaning | 1(1.2) |
| **Preprocedural Prophylaxis, n (%)** | |
| None | 39 (45.9) |
| Icatibant | 3 (3.5) |
| pdC1-INH | 36 (42.4) |
| Danazol | 7 (8.2) |
| pdC1-INH Dose, n (%) | |
| 500 IU | 9 (10.6) |
| 1000 IU | 27 (31.7) |
| **Attacks Associated with Dental Procedures, n (%)** | |
| Present | 17 (20.0) |
| Absent | 68 (80.0) |
| Attack Recovery Time, median (min-max) | 10.0 (3.0-72.0) |
| **Periprocedural Attack Treatment, n (%)** | |
| None | 8 (47.1) |
| pdC1-INH | 9 (52.9) |
| Recovery time in those using periprocedural attack treatment, median (min-max) hours | 8.0 (3.0 – 72.0) |
| Recovery time of attacks in those not using periprocedural attack treatment, median (min-max) hours | 10.0 (6.0 – 24.0) |

*Min-max = Minimum-maximum, pdC1-INH = Plasma-derived C1-inhibitor, IU = International Unit*

During 17 (20.0%) out of the 85 dental procedures AE attacks were observed, all of which occurred in the oropharyngeal region. These 17 procedures included 10 dental restorations, 5 tooth extractions, and 2 root canal treatments. Among the 43 procedures in which preprocedural prophylaxis with pdC1-INH


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concentrate or danazol was administered, 5 (11.6%) experienced an AE attack, while 12 (30.8%) out of the 39 procedures without prophylaxis exhibited attacks. There was a significant difference in attack frequency between the prophylaxis and non-prophylaxis groups (p = 0.022).

Among the 36 procedures where pdC1-INH concentrate was administered for preprocedural prophylaxis, AE attacks occurred in 5 (13.9%) procedures, while no AE attacks were observed in the 7 procedures where danazol prophylaxis was used. The difference was not significant (p = 0.572). Nine procedures were performed with 500 IU pd-C1INH, including 5 extractions (55.6%) and 4 dental restorations (44.4%). Among 27 procedures with 1000 IU pd-C1INH, 16 were extractions (59.2%), 7 dental restorations (26.0%), and 4 root canals (14.8%). Obesity was observed in three patients (11.1%) in the 1000 IU pd-C1INH group, while no cases were reported in the 500 IU pd-C1INH group. Subgroup analysis of patients receiving pd-C1INH prophylaxis showed no significant difference in attack rates between the 500 IU (11.1%) and 1000 IU (14.8%) groups (p = 0.781). Among the procedures with perioperative attacks, pdC1-INH was administered in 9 procedures (52.9%) for treatment, while 8 procedures (47.1%) did not receive treatment due to the unavailability of pdC1-INH concentrate.

Among the 11 patients who experienced periprocedural attacks, 5 were female, with a mean age of 46.8 ± 15.01 years. The risk factors associated with attacks were analyzed by comparing these 11 patients to 36 patients who did not experience periprocedural attacks during dental procedures. Univariate and multivariate logistic regression analyses revealed no significant effect of any variable on the risk of attacks (Table III).

***Table III.*** *Logistic regression analysis of risk factors for periprocedural angioedema attacks*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | %95CI | P Value | OR | %95CI | P Value |
| Age | 1.002 | 0.951-1.055 | 0.945 | | | |
| Gender<br>Male vs Female | 1.667 | 0.422-6.587 | 0.466 | | | |
| Age at first attack | 0.973 | 0.890-1.063 | 0.542 | | | |
| Age at HAE diagnosis | 1.019 | 0.960-1.081 | 0.539 | | | |
| History of laryngeal edema | 2.980 | 0.679-13.086 | 0.148 | 3.607 | 0.765-14.564 | 0.109 |
| Family history of death from asphyxia | 0,663 | 0.149-2.947 | 0.580 | | | |
| Obesity | 2.333 | 0.331-16.468 | 0.395 | | | |
| Prophylaxis | 2.570 | 0.679-11.144 | 0.157 | 3.339 | 0.765-17.002 | 0.105 |

*OR = Odds ratio, CI = confidence interval, HAE = hereditary angioedema*

## 4. DISCUSSION

The current study demonstrated that preprocedural STP effectively reduces the frequency of periprocedural attacks triggered by minor trauma or pressure during routine dental procedures. Furthermore, although limited by the small sample size, no significant difference in efficacy was observed between pdC1-INH concentrate and danazol when used as preprocedural STP.

Studies have shown that HAE type I comprises 85% of all HAE cases and is the most common type [3]. In our cohort, consistent with the literature, HAE type I represented 81%, confirming it as the most frequently observed type. Previous studies have indicated that the age at onset of AE attacks is a key differentiating factor between the types [11-14]. It has been shown that individuals with HAE – I / II experience attacks at an earlier age compared to those with HAE-nC1-INH. In HAE type I, the majority of patients manifest symptoms of AE before the second decade of life. In contrast, those with HAE-nC1-INH tend to show symptoms after the second decade [11-14]. In our study, we also observed a significant difference in the age of first attack between individuals with HAE I / II and those with HAE-nC1-INH, a finding that has similarly been described in earlier studies. In a study examining 64 patients, a history of laryngeal edema and mortality within the family was identified in 18.7% of cases [14]. In our study, this rate was observed to be significantly higher at 31.0%. These heterogeneous findings are certainly multifactorial but may be partially explained by varying exposure to triggers around the world, as well as by genetic differences among these populations. The high mortality rate in this region further suggests that awareness of this disease may be insufficient in our country. According to the latest international WAO/EAACI guideline, on-demand therapy is recommended for all patients. In the study conducted by Varandas et al., it was observed that seventy-six percent of HAE patients received on-demand treatment [11]. In our cohort, all patients had access to on-demand treatment, with 66 (89.2%) using pd-C1-INH, while only 8 (10.8%) patients were using only icatibant due to challenges in procuring pd-C1-INH concentrate.

Several reports indicate that severe upper airway swelling can be triggered by minor trauma or pressure during routine dental procedures; however, evidence supporting the efficacy of preprocedural treatment remains limited in the literature [3,5,8,9]. Guidelines for the management of patients with HAE recommend the intravenous administration of 10–20 IU/kg or 1,000 IU of pd-C1-INH concentrate one hour before dental procedures to prevent HAE-related laryngeal attacks [3,10,15]. The recommendation for short-term prophylactic treatment prior to dental procedures in the 2021 WAO/EAACI guideline is assigned an evidence level C [3,6,16]. In our cohort, preprocedural prophylaxis was administered in 39 (45.9%) procedures, and the high rate of patients not receiving prophylaxis was associated with these procedures being performed prior to diagnosis. Additionally, the pd-C1-INH concentrate was administered in doses of 500 or 1000 IU, with a median of 1000 IU, in line with current guideline recommendations. The number of studies in the literature comparing two doses of 500–1000 IU is highly

limited [6]. In our study, despite the small sample size, the absence of a significant difference in attack frequency between these two groups ($p = 0.781$) is a noteworthy finding.

In uncontrolled studies, increased doses of up to 1,000 units of C1-INH concentrate administered intravenously at least one hour before dental and surgical procedures have demonstrated successful outcomes; however, breakthrough attacks still occur [6]. The effectiveness of STP with pdC1-INH was demonstrated in a retrospective study by Bork, which analyzed clinical records of C1-INH-HAE patients undergoing tooth extractions. The study found that AE attacks occurred in 21.5% (124/577) of tooth extractions without STP, compared to 12.5% (16/128) of tooth extractions with STP, indicating a 41.9% reduction in AE attacks when using pdC1-INH concentrate prior to the procedure ($p < 0.05$) [6]. In our study, the incidence of attacks in patients not receiving prophylaxis was 30.8%, compared to 11.6% in those receiving prophylaxis with pd-C1-INH concentrate or danazol. These findings strengthen the evidence that prophylaxis significantly reduces the risk of perioperative attacks. Although icatibant is not recommended in the guidelines for preprocedural prophylaxis, three patients in our cohort received icatibant due to limited access to pd-C1-INH therapy. Notably, two of these procedures were tooth extractions, and no AE attacks were observed. A case report in the literature has also described the prophylactic administration of icatibant prior to tracheal intubation, which was effective in preventing intubation-induced laryngeal edema in a patient with HAE [17]. Current data advise against the use of icatibant for STP because of its short half-life and limited supporting evidence; moreover, icatibant acetate does not reduce bradykinin release but only blocks the B2 receptor [1,18,19]. Nevertheless, our findings suggest that icatibant may provide protection against procedure-related attacks in selected cases.

Previous analyses have indicated a significant dose-response effect of prophylactic pdC1-INH concentrate [6,9]. In a study conducted by Bork et al., patients receiving 500 IU of pdC1-INH concentrate experienced an attack rate of 16.0%, while those receiving 1,000 IU had an attack rate of 7.5% [6]. A trend toward a dose-response effect of pdC1-INH concentrate is also suggested by Magerl and colleagues in their analysis of the Berinert® Registry [9]. However, despite the recommendation for higher doses of pdC1-INH concentrate, our study did not observe a difference in attack rates between the 500 IU and 1,000 IU groups. The absence of a significant difference between the two doses is noteworthy. Given the heterogeneity of the dental procedures evaluated in our study and the small sample size, we recommend conducting further clinical research to substantiate these findings.

Another retrospective study involving 24 HAE patients who underwent 66 dental procedures (ranging from dental extractions to orthodontic treatment) demonstrated the efficacy of preprocedural prophylaxis with pd-C1-INH concentrate or treatment with attenuated androgens [20]. While the efficacy of androgens and pd-C1-INH concentrate has been shown in prophylaxis, to our knowledge, there is no study comparing their effectiveness. In our study, it is noteworthy that the efficacy of danazol and pd-C1-INH concentrate in prophylaxis was similar, although the number of patients in the danazol group was small ($n = 7$). This suggests that despite its side effect profile, danazol may be preferred in circumstances where pd-C1-INH concentrate is not available or in elective procedures, due to its greater availability in some countries.

However, since different procedures may carry varying levels of AE risk, a major limitation of this study is the wide variety of dental procedures included, which precluded meaningful comparisons across specific types of interventions. Another important limitation is the lack of precise information on the timing of adverse events, preventing a clear distinction between immediate intra-procedural reactions and those occurring within 48 hours after the procedure. To address this, a predefined 48-hour at-risk interval was applied, in line with previous reports and guideline recommendations [3,6,9]. As a retrospective real-world study, it is also subject to recall and reporting bias, emphasizing the need for confirmation through future prospective investigations. Despite these limitations, the study provides a valuable contribution to the limited literature on adverse events during dental procedures and suggests that even low doses of pd-C1-INH concentrate may be effective as prophylaxis in this context. These findings have practical implications for both dentists and allergists. Even minor dental procedures may precipitate life-threatening oropharyngeal edema in patients with HAE, highlighting the importance of preprocedural prophylaxis and interdisciplinary collaboration. While pd-C1-INH concentrate remains the first-line option in accordance with international guidelines, danazol may be a viable alternative in settings where pd-C1-INH is not available. The comparable efficacy observed between 500 IU and 1000 IU doses suggests that lower doses may be sufficient in selected cases, though prospective validation is required. Awareness of these strategies can optimize patient safety and support evidence-based decision-making in routine dental practice.

## Conclusion

Preprocedural prophylactic treatment significantly reduces the frequency of AE attacks associated with dental procedures. In our cohort, there was no demonstrated superiority between pdC1-INH concentrate and danazol in prophylactic treatment for preventing AE attacks. Notably, the efficacy of 500 IU and 1000 IU of pdC1-INH concentrate in preventing attacks related to dental procedures was found to be comparable, though limited by the small sample size.

### Compliance with Ethical Standards

**Ethical approval:** The research protocol was approved by the Ethics Committee of Hacettepe University (approval number SBA 25/015). The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

**Conflict of interest:** The authors declare that there is no conflict of interest.


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