



RESEARCH ARTICLE

Comparative Evaluation of Alprazolam and Hydroxyzine for Anxiolysis: Effects on Cardiac Autonomic Activity and Physiological Parameters

Alprazolam ve Hidroksizin Anksiyete Üzerine Etkilerinin Karşılaştırmalı Değerlendirmesi

Selen Adiloğlu¹ , Gülin Acar² , Alper Aktaş³ 

¹DDS, PhD, Assistant Professor, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry Hacettepe University, Ankara, Turkey,

²DDS, Specialist, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry Hacettepe University, Sıhhiye, Ankara, Turkey,

³DDS, PhD, Professor, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry Hacettepe University, Ankara, Turkey,

ABSTRACT

Objective: This observational retrospective study aims to compare the effects of alprazolam and hydroxyzine on cardiac autonomic activity and physiological parameters in dental anxiety.

Methods: This study included 90 participants, divided into three groups: alprazolam (n=30), hydroxyzine (n=30), and control (n=30). Each group consisted of 15 males and 15 females, with mean ages of 37.68 ± 4.32 years, 38.53 ± 3.98 years, and 37.38 ± 4.15 years, respectively. Alprazolam and hydroxyzine groups received 0.5 mg of their respective medications one hour before oral surgical procedures. Blood pressure, heart rate, and oxygen saturation were measured at: preoperatively, intraoperatively (at 30-minute intervals), and postoperatively. Uniform surgical protocols were followed across all groups, and data were analyzed using ANOVA.

Results: In the control group, there was a significant increase in systolic and diastolic blood pressure and heart rate from preoperative to intraoperative measurements and a significant decrease in postoperative measurements compared to intraoperative values. In the hydroxyzine group, intraoperative systolic blood pressure and heart rate decreased compared to preoperative values, while postoperative values showed no significant change compared to intraoperative values. Diastolic blood pressure did not significantly change over time. In the alprazolam group, all values decreased significantly over time. Also, the alprazolam group showed a statistically significant decrease in all values compared to the hydroxyzine group. Conclusion: Both medications are effective compared to a control group for cardiovascular values. These findings may indicate that alprazolam and hydroxyzine may be viable options for preventing anxiety, with alprazolam being the more potent medication.

Keyword: Benzodiazepines, Hydroxyzine, Dental Anxiety, Blood Pressure, Cardiac Rate

ÖZET

Amaç: Bu gözlemsel çalışmanın amacı alprazolam ve hidroksizin dental anksiyetede kardiyak otonomik aktivite ve fizyolojik parametreler üzerindeki etkilerini karşılaştırmaktır.

Yöntemler: Çalışmaya alprazolam, hidroksizin ve kontrol olmak üzere 3 grupta 90 katılımcı katılmıştır. Her grupta 30 katılımcı bulunmaktadır. Çalışma grupları işlemden bir saat önce 0,5 mg ilaç almışlardır. Kan basıncı, kalp hızı ve oksijen saturasyonu işlemden önce, işlem sırasında ve işlemden sonra ölçülmüştür.

Sonuçlar: Kontrol grubunda, sistolik ve diyastolik kan basıncı ve kalp hızında ameliyat öncesi ve ameliyat sırasındaki ölçümlerde anlamlı bir artış ve ameliyat sonrası ölçümlerde ameliyat sırasındaki değerlere kıyasla anlamlı bir azalma görülmüştür. Hidroksizin grubunda, ameliyat sırasındaki sistolik kan basıncı ve kalp hızı ameliyat öncesi değerlere kıyasla anlamlı bir değişiklik göstermemiştir. Diyastolik kan basıncı zamanla anlamlı bir şekilde değişmemiştir. Alprazolam grubunda, tüm değerler zamanla anlamlı bir şekilde azalmıştır. Ayrıca, alprazolam grubu hidroksizin grubuna kıyasla tüm değerlerde istatistiksel olarak anlamlı bir düşüş gösterdi. Sonuç: Her iki ilaç da kardiyovasküler değerler açısından bir kontrol grubuna kıyasla etkilidir. Bu bulgular, alprazolam ve hidroksizin anksiyeteyi önlemede uygulanabilir seçenekler olabileceğini, alprazolamın daha etkili ilaç olduğunu gösterebilir.

Anahtar Kelimeler: Benzodiazepin, Hidroksizin, Dental Anksiyete, Kan Basıncı, Kardiyak Aktivite

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Corresponding author: Gülin Acar

Address: Faculty of Dentistry Hacettepe University, Sıhhiye, 06100 Ankara, Turkey

Phone: +905387455533

Email: gulin.acar@hacettepe.edu.tr

Selen Adiloğlu

Gülin Acar

Alper Aktaş

0000-0002-5007-9867

0000-0002-4414-9662

0000-0002-1977-4431



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INTRODUCTION

Despite the advancements in technology in the field of dentistry, fear and anxiety remain common problems among patients, which affect their overall dental experience. Anxiety is a complex emotional state that affects both the physiological and psychological aspects of an individual. This problem often leads to the postponement of appointments and difficulties during dental procedures, which may worsen the patient's existing pathological conditions. The physical symptoms of anxiety are the result of overactivity of the sympathetic nervous system and intensified muscle tension.^{1,2} Dry mouth, difficulty swallowing, tenderness in the epigastrium, a feeling of tightness in the chest, difficulty breathing and excessive breathing may occur. In the cardiovascular system, patients may experience symptoms such as palpitations, chest pain or discomfort, tinnitus, blurred vision, tingling sensations, and dizziness. There may also be complaints due to muscular tension.³

Consequently, the use of sedative techniques is on the rise, mainly due to patient demand and the surgeon's recognition that procedures are performed more effectively when the patient is relaxed and cooperative.⁴

Alprazolam is a medication that belongs to the benzodiazepine class, commonly used to treat anxiety and panic disorder.⁵ Since its introduction in the 1960s, it has been one of the most widely used drugs due to its rapid relief of anxiety and minimal adverse effects.⁵⁻⁷ It binds to specific sites on the γ -aminobutyric acid (GABA) receptor and works by slowing down the movement of chemicals in the brain, which may become unbalanced, reducing anxiety.⁶ Alprazolam is most effective for diminishing abnormal excitement in the brain.⁷

Hydroxyzine, a derivative of the di-phenylethane group of drugs, is classified as an antihistamine or histamine (H1) blocker. It is a regular prescription agent with wide safety margins.⁸ It is known as one of the safest sedative agents used in dentistry. It has been used frequently and for many years in combination with different agents in conscious sedation methods.⁹ The physical effect of hydroxyzine does not cause true sleepiness. It relaxes the patient while creating a favorable environment, especially for dentistry, and the patient gives fully conscious and balanced responses to stimuli that cause fear.¹⁰

It is crucial to assess the effectiveness of these widely accessible drugs in clinical settings by monitoring vital signs.

The main hypothesis of the study is that alprazolam will lead to a more significant reduction in anxiety-induced cardiovascular changes compared to hydroxyzine.

This study compared the effects of alprazolam and hydroxyzine on cardiac sympathetic and parasympathetic activities using changes in heart rate variability (HRV), systolic-diastolic blood pressure, and oxygen saturation in their use as sedatives.

MATERIALS AND METHODS

The present study investigated a cohort of patients who underwent minor surgical procedures, such as impacted teeth surgery, odontogenic cyst/tumor excision, and implant surgery, under local anesthesia at the Hacettepe University Faculty of Dentistry and the Faculty of Oral and Maxillofacial Surgery between January 2019 and September 2021.

The ethical approval of the retrospective study with project number GO 22/965 was approved by Hacettepe University Non-Interventional Research Ethics Committee with decision number 2022/ 15-35. Patient data were obtained from the archival resources of our university. Once the required number of patients who met the study criteria was reached, the archival search was completed. During the inclusion of patients in the study, their personal information was carefully preserved and reviewed to mitigate the risk of bias. Attention was given to ensuring age and gender compatibility between the groups.

The study was conducted in accordance with the Declaration of Helsinki guidelines. Informed consent was obtained from the participants so that the data could be used for study purposes.

Vital signs of each patient, including heart rate, systolic and diastolic blood pressure, oxygen saturation levels, and encountered side effects, are assessed before, during (at half-hourly intervals), and after the procedure, until the patients are considered suitable for discharge. Since January 2020, our hospital has followed a routine practice of randomly administering either alprazolam or hydroxyzine to patients before surgical procedures for sedation.

The control group comprises patient data obtained in January 2020, before sedation implementation began.

The study included a total of 90 participants, divided equally into three groups: the alprazolam group, the hydroxyzine group, and the control group. Each group consisted of 30 individuals, with 15 males and 15 females in each group to ensure gender



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balance. The mean ages and standard deviations of the participants were as follows: the alprazolam group had a mean age of 37.68 ± 4.32 years, the hydroxyzine group had a mean age of 38.53 ± 3.98 years, and the control group had a mean age of 37.38 ± 4.15 years.

Participants were selected retrospectively from archival records, ensuring age and gender compatibility across all groups to minimize bias. Inclusion criteria included patients aged 18–80 years who underwent minor oral surgical procedures under local anesthesia, such as impacted tooth extractions, odontogenic cyst or tumor excision, or implant placement. Patients with systemic or mental health issues, those taking medications that could interfere with cardiovascular responses, or those with incomplete or missing data were excluded from the study.

The alprazolam and hydroxyzine groups received 0.5 mg of their respective medications one hour before the procedure, while the control group did not receive any preoperative sedation. All groups underwent similar surgical procedures performed under the same local anesthetic protocol to ensure uniformity in the study conditions. The alprazolam and hydroxyzine groups received a dose of 0.5 mg of the respective drug one hour before the procedure, as determined based on the prospectus information. Vital signs were measured 30 minutes after the start of the procedure and again 30 minutes after its completion. Systolic blood pressure, diastolic blood pressure, oxygen saturation, pulse rate, and encountered side effects were evaluated in the study.

Throughout the procedure, the vital signs of all patients were monitored at half-hourly intervals. The procedure site was completely anesthetized with the same local anesthetic for all patients to ensure a painless procedure. The duration of the procedure was recorded following established protocols. The study included patients whose procedure time ranged from 30 to 60 minutes. All patients received standard information and were requested to provide informed consent by signing a consent form.

The analyses were conducted using IBM SPSS Statistics V25 software. Numerical variables were summarized using the mean and standard deviation. The distribution of numerical values was assessed through normality tests (Kolmogorov-Smirnov and Shapiro-Wilk tests) and graphical methods such as histograms and QQ plots. Repeated Measures ANOVA with One Fixed Factor was employed to examine differences

between time points, drug groups, and the interaction between time and group. In case a significant interaction was detected, pairwise comparison tests were conducted to identify the source of the difference. The significance level for the analyses was set at 0.05.

The study was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.

RESULT

Each group consisted of 30 participants, with an equal gender distribution (15 males and 15 females). The mean age and standard deviations of the participants were as follows: the alprazolam group had a mean age of 37.68 ± 4.32 years, the hydroxyzine group had a mean age of 38.53 ± 3.98 years, and the control group had a mean age of 37.38 ± 4.15 years. Age and gender compatibility were ensured across all groups to minimize bias.

No adverse effects were encountered in patients, and their vital signs remained within the acceptable range.

The control group exhibited time-dependent changes in systolic and diastolic blood pressure values, as well as heart rate values, as described below: There was a statistically significant increase observed between preoperative and intraoperative measurements. And a statistically significant decrease was observed between intraoperative and postoperative measurements. While there was an increase between preoperative and postoperative measurements, this difference did not reach statistical significance. (Table 1).

During the analysis of time-dependent changes in the hydroxyzine group, it was observed that all intraoperative values showed a decrease compared to the preoperative values. However, the postoperative values did not demonstrate a statistically significant change compared to the intraoperative values. Additionally, when examining the preoperative and postoperative values, it was found that diastolic pressure values did not exhibit a statistically significant change, whereas systolic pressure and heart rate values displayed a statistically significant decrease. (Table 1).

Upon analyzing the time-dependent values of the group treated with alprazolam, it was observed that all values (i.e. systolic pressure, diastolic pressure, and heart rate) displayed a statistically significant decrease over time (Table 1).



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Table 1. Demographic information of the individuals included in the study and descriptive statistics.

		Hydroxyzine	Alprazolam	Control
N		30	30	30
Age (Mean)		38.53	37.68	37.38
Sex	Male	15	15	15
	Female	15	15	15
Procedure				
	Implant	12	10	9
	Impacted Teeth	11	10	13
	Cyst/Tumor	7	10	8
Procedure Time (Minute) (mean)		37.83	36.2	38.45
Pre-operative				
Systolic	Mean	141.81	145.21	122.16
	Std. Deviation	23.214	15.407	14.138
Diastolic	Mean	77.81	85.55	68.78
	Std. Deviation	12.576	11.882	10.779
Heart Rate	Mean	99.45	96.17	86.56
	Std. Deviation	14.731	17.929	16.150
Saturation	Std. Deviation	3.393	1.771	1.4
Intra-operative				
Systolic	Mean	126.29	122.83	136.78
	Std. Deviation	21.734	14.170	19.245
Diastolic	Mean	72.26	70.86	75.91
	Std. Deviation	13.677	10.763	12.678
Heart Rate	Mean	87.32	81.48	96.91
	Std. Deviation	13.227	12.880	16.257
Saturation	Std. Deviation	3.243	2.485	1.437
Post-operative				
Systolic	Mean	123.52	115.45	123.94
	Std. Deviation	14.774	13.289	11.706
Diastolic	Mean	73.16	67.59	70.84
	Std. Deviation	13.616	10.655	11.399
Heart Rate	Mean	85.84	75.66	87.28
	Std. Deviation	17.48	01.125	13.274
Saturation	Std. Deviation	2.242	1.769	1.008

Std. Deviation: Standard Deviation



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Table 2 presents the descriptive statistical analysis of the measured values of Alprazolam and Hydroxyzine, excluding the control group. The right side of the table displays the F value and p value obtained from the time-dependent, group-dependent, and group-time-dependent ANOVA analyses.

When the variations related to the administered drugs were examined using ANOVA, it was observed that the drug containing the active substance alprazolam demonstrated a

statistically significant decrease in both systolic and diastolic pressure compared to the drug containing the active substance hydroxyzine. No significant differences were found in heart rate and saturation values when considering changes over time and between groups (Table 2).

Descriptive analyses did not reveal any statistical changes in the saturation variable within any group or at any time interval. Consequently, further statistical analysis calculations could not be performed (Table 3).

Table 2. Group-time interactions of systolic and diastolic pressure changes and heart rate in the control, hydroxyzine, and alprazolam group.

Groups			Mean Difference (I-J)	Std. Error	p		
Sistolic	Control	Preoperative	Intraperative	-14.625	1.886	<0.001*	
		Postoperative	Intraperative	-1.781	2.12	1	
	Hydroxyzine	Preoperative	Intraperative	-12.844	2.082	<0.001*	
		Postoperative	Intraperative	15.516	1.916	<0.001*	
	Alprazolam	Preoperative	Intraperative	18.290	2.154	<0.001*	
		Postoperative	Intraperative	-2.774	2.115	0.579	
		Preoperative	Intraperative	22.379	1.981	<0.001*	
		Postoperative	Intraperative	29.759	2.227	<0.001*	
	Diastolic	Control	Preoperative	Intraperative	-7.125	1.908	0.001*
			Postoperative	Intraperative	-2.063	2.061	0.959
Hydroxyzine		Preoperative	Intraperative	-5.063	1.767	0.016*	
		Postoperative	Intraperative	5.548	1.938	0.016*	
Alprazolam		Preoperative	Intraperative	4.645	2.094	0.087	
		Postoperative	Intraperative	0.903	1.795	1	
		Preoperative	Intraperative	14.690	2.004	<0.01*	
		Postoperative	Intraperative	17.966	2.165	<0.01*	
Heart Rate		Control	Preoperative	Intraperative	-3.276	1.856	0.243
			Postoperative	Intraperative	-10.344	2.311	<0.001*
	Hydroxyzine	Preoperative	Intraperative	-0.719	2.55	1	
		Postoperative	Intraperative	-9.625	2.141	<0.001*	
	Alprazolam	Preoperative	Intraperative	12.129	2.348	<0.001*	
		Postoperative	Intraperative	13.613	2.591	<0.001*	
		Preoperative	Intraperative	-1.484	2.175	1	
		Postoperative	Intraperative	14.690	2.427	<0.001*	
		Preoperative	Intraperative	20.517	2.679	<0.001*	
		Postoperative	Intraperative	-5.828	2.249	0.034*	

*: <0.05, Preoperative: Pre-operative value, Intraoperative: Intra-operative value, Postoperative: Post-operative value



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Table 3. Descriptive Statistics, Tests of Between- Drugs Effects and Tests of Within-Drugs Effects.

	Time Zone	Grups	Mean	Std. Deviation	Time	Time- Group			
Sistolic	Preoperative	Hydroxyzine	129.68	18.201	F=117.563 p<0.001*	F=7.556 p<0.001*			
		Alprazolam	131.62	14.683					
		Total	130.62	16.484					
	Intraoperative	Hydroxyzine	126.29	21.734					
		Alprazolam	122.83	14.170					
		Total	124.62	18.399					
	Postoperative	Hydroxyzine	123.52	14.774					
		Alprazolam	115.45	11.816					
		Total	119.62	13.920					
	Diastolic	Preoperative	Hydroxyzine	73.55			11.254	F=29.046 p<0.001*	F=9.065 p<0.001*
			Alprazolam	76			13.628		
			Total	74.73			12.412		
Intraoperative		Hydroxyzine	72.26	13.677					
		Alprazolam	70.86	10.763					
		Total	71.58	12.271					
Postoperative		Hydroxyzine	73.16	13.616					
		Alprazolam	67.59	10.655					
		Total	70.47	12.492					
Heart Rate		Preoperative	Hydroxyzine	93.87	12.927	F= 53.481 p<0.001*	F=2.102 p=0.116		
			Alprazolam	85.97	14.386				
			Total	90.05	14.109				
	Intraoperative	Hydroxyzine	87.32	13.227					
		Alprazolam	81.48	12.88					
		Total	84.5	13.28					
	Postoperative	Hydroxyzine	85.84	17.48					
		Alprazolam	75.66	10.125					
		Total	80.92	15.177					
	Saturation	Preoperative	Hydroxyzine	96.32	4.4			F=0.452 p=0.685	F=1.033 p=0.372
			Alprazolam	96.83	1.794				
			Total	96.57	3.382				
Intraoperative		Hydroxyzine	96.58	3.243					
		Alprazolam	96.03	2.485					
		Total	96.32	2.891					
Postoperative		Hydroxyzine	96.81	2.242					
		Alprazolam	96.72	1.888					
		Total	96.77	2.061					

*: <0.05, Preoperative: Pre-operative value, Intraoperative: Intra-operative value, Postoperative: Post-operative value



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DISCUSSION

Oral anxiolytics are cost-effective medications that are easy to take, have a high degree of patient acceptance and compliance, and reduce the severity of adverse reactions without the need for additional medical intervention. These drugs provide short procedure times for surgical procedures under local anesthesia.¹¹ Preoperative anxiety is a common issue among outpatients, highlighting the need for oral premedication with potent anxiety-reducing effects and minimal psychomotor impairment. No studies have been published evaluating the impact of drugs containing the active ingredients alprazolam and hydroxyzine, administered as oral tablets, on vital signs in relation to anxiety. The primary objective of this study was to evaluate the effectiveness of commonly used drugs, alprazolam and hydroxyzine, before oral surgical procedures and to compare their efficacy with a control group.

According to current study results, as expected, the intraoperative values in the control group were statistically significantly higher than the preoperative and postoperative values. In this situation, it may be concluded that patients may experience high levels of anxiety and tension during dental procedures, which can lead to physical reactions such as increased heart rate and blood pressure. This can be attributed to various factors, including fear of pain, discomfort, or loss of control, as well as the general discomfort of being in a clinical setting.

In the groups receiving premedication, the highest values were observed preoperatively, and the lowest values were recorded postoperatively, decreasing over time.

Alprazolam and hydroxyzine are often used in premedication due to their anxiolytic effects, as reported in the literature. In the present study, the anxiolytic effects of the drugs were indirectly examined through the cardiovascular system.

Midazolam is a potential candidate due to its short duration of action and is the most widely used,¹² making it a recommended benzodiazepine for outpatient surgical procedures.¹³ However, it should be noted that the oral formulation of midazolam is not approved in certain countries.^{14,15} Therefore, oral alprazolam was used in our study. Studies have shown that alprazolam may be a viable option for managing anxiety in countries where oral midazolam is not approved. One study¹⁵ demonstrated that while a dose of 7.5mg of midazolam caused amnesia, a

0.5mg dose of alprazolam was equally effective in treating anxiety without such side effects.

It has been reported that anxiety can cause an increase in blood pressure, particularly in individuals with high blood pressure.¹⁶ The use of alprazolam has been shown to reduce the cardiovascular effects of anxiety and lower the risk of ischemic stroke, hemorrhagic stroke, and myocardial infarction events. Thus, it has been recommended to use it to reduce anxiety, especially in patients with high blood pressure.^{17,18}

Studies focusing on alprazolam for anxiety management in premedication have shown that alprazolam is more effective than a placebo for anxiety management, with doses ranging from 0.25 to 1 mg having similar efficacy.¹⁹

In 2022, Hanna et al.^{1,11} updated that alprazolam can be used in the control of panic-type anxiety by giving a single dose at a range of 0.25-1 mg before dental procedures.

Therefore, the dose of alprazolam was determined as 0.5 mg in the present study.

In the present study, hydroxyzine was less effective than alprazolam in reducing cardiovascular values. Thus, when comparing the cardiovascular values, it was found that alprazolam was more effective than hydroxyzine.

While certain studies have posited that hydroxyzine is ineffective in preventing anxiety, other research has suggested that the drug may be efficacious. Studies indicate that hydroxyzine may prevent anxiety-induced cardiovascular changes but with lower efficacy than benzodiazepines.²⁰ A study evaluating the efficacy of oral midazolam and midazolam-hydroxyzine combination in premedication for anxiolysis showed that combination therapy was more effective than midazolam alone.²¹

In a double-blind, randomized, prospective, controlled study by Boon et al., a statistically significant decrease in anxiety values was recorded in the group using hydroxyzine, but no statistical difference was observed against placebo. In addition, there was no difference in hemodynamic values (blood pressure, heart rate, respiratory rate) for the study and control groups.²² A study was conducted to evaluate the effectiveness of different doses of hydroxyzine. The researchers found that administering the drug 24 hours before and on the day of surgery was just as effective as giving a single dose only on the day of surgery.²³



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No studies show the optimal dose and time of hydroxyzine premedication; hence, the current study has followed the routine clinical practice in our hospital.²⁰

Oral surgical procedures can cause a high level of anxiety among patients, as they are typically performed while the patient is awake. The surgeon stays in the patient's field of vision, and local anesthetics don't effectively reduce the sensation of pressure. By effectively managing anxiety, the patient and physician can have a smoother and shorter procedure, which can significantly impact the success of the surgical procedure.

The observed differences between alprazolam and hydroxyzine can be attributed to their distinct biological mechanisms of action. Alprazolam, a benzodiazepine, enhances the inhibitory effect of gamma-aminobutyric acid (GABA) on the central nervous system, resulting in a significant reduction in sympathetic nervous system activity and a more pronounced anxiolytic effect.^{6,7} In contrast, hydroxyzine, an H1 receptor antagonist, exerts its anxiolytic effects primarily through histamine receptor blockade and mild sedative properties.⁸⁻¹⁰ This difference likely explains alprazolam's superior ability to attenuate anxiety-induced cardiovascular changes, as it directly modulates the central mechanisms responsible for heightened sympathetic arousal.⁵

One of the limitations of this study is that it did not involve patient feedback. Future studies that incorporate patient evaluation would be valuable additions to the literature. Although all participants underwent minor oral surgical procedures, the variability in procedure types (e.g., impacted tooth extractions, odontogenic cyst or tumor excisions, and implant placements) may have influenced the physiological responses and anxiety levels. The lack of subgroup analyses based on procedure types limits the ability to assess the specific effects of each procedure on cardiovascular parameters and anxiety levels. And, the study compared only a single dose (0.5 mg) of alprazolam and hydroxyzine. Exploring different doses and their effects could provide a broader understanding of the dose-response relationship.

Another major limitation of the present study is the indirect evaluation of the effect of the given drugs. The study primarily evaluated the anxiolytic effects of alprazolam and hydroxyzine through changes in cardiovascular parameters, rather than directly measuring anxiety levels via validated psychological scales. While cardiovascular changes are well-documented

indicators of anxiety, direct patient-reported outcomes could provide a more comprehensive understanding of the medications' anxiolytic effects.

CONCLUSION

Both alprazolam and hydroxyzine demonstrated efficacy in reducing anxiety-induced cardiovascular changes compared to the control group, with alprazolam showing a more pronounced effect. These findings suggest that alprazolam may be a superior option for managing dental anxiety in patients undergoing minor oral surgical procedures. However, further studies incorporating direct anxiety assessments and subgroup analyses based on procedure types are needed to validate and expand upon these results.

CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ETHICS

The study was approved by the Hacettepe University Non-Interventional Research Ethics Committee with the decision number "GO 22/965".

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