Safety of Premedication with Oral Midazolam before Rhinoplasty as Indicated by Intraoperative Levels of Blood Oxygen Saturation

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ABSTRACT: **Background:** The use of oral midazolam as premedication to induce anxiolysis before surgical procedures under local anesthesia is widely accepted in plastic surgery. Rhinoplasty performed under local anesthesia is known to generate high levels of perioperative anxiety, thus the use of appropriate premedication is important. Oral midazolam has been shown to be safe in various procedures. However, the safety of oral midazolam before rhinoplasty has not been evaluated.

Objectives: To evaluate the safety of premedication with oral midazolam prior to rhinoplasty by analyzing the intraoperative blood oxygen saturation levels as predictors of adverse respiratory events.

Methods: We retrospectively reviewed the anesthesia records of 62 patients who underwent rhinoplasty under local anesthesia and received premedication with oral midazolam for anxiolysis between March 2017 and December 2017. The median age of the patients was 25.4 years, and they were all classified as American Society of Anesthesiologists class 1. The patients received 10 mg midazolam hydrochloride orally 1 hour prior to the procedure. Oxygen blood saturation was monitored using a pulse oximeter and recorded every 15 minutes.

Results: All the patients maintained blood oxygen saturation levels above 95% (median peripheral capillary oxygen saturation 99%) on room air, and they did not require supplemental intraoperative oxygen. There were no transient hypoxemic events during and following the procedure.

Conclusions: Our study confirmed the safety of oral midazolam premedication to reduce perioperative anxiety when performing rhinoplasty under local anesthesia.

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KEY WORDS: anxiolytics, local anesthesia, midazolam, oxygen saturation, septorhinoplasty

Proper control of patient anxiety during surgery performed under local anesthesia is critical [1]. Anxiety might alter a patient's cardiovascular physiology, leading to syncope, elevated blood pressure, or increased risk of intraoperative and postoperative bleeding [2]. Anxiety also might negatively affect how the patient experiences the surgery. Patients who underwent surgery for cutaneous malignancy and had a local recurrence delayed seeking a new procedure due to the negative experience [3]. A significant increase in sympathetic activity attributed to preoperative anxiety was observed in patients waiting to undergo rhinoplasty [4]. Previous studies that measured perioperative cardiovascular and hemodynamic parameters confirm that cosmetic surgery patients experience a distinct preoperative anxiety [4,5-7].

Anxiolysis is defined as the use of pharmacological agents to reduce anxiety. Perioperative anxiety prior to certain plastic surgery operations performed under local anesthesia can be controlled by pharmacological premedication [2,3,8-10]. Benzodiazepines are the most commonly used anxiolytic agents. Midazolam is a short-acting benzodiazepine that provides anxiolysis within 20 minutes, at a dose of 5 mg to 10 mg and has the shortest half-life of all benzodiazepine [11]. Oral midazolam administered before procedures performed under local anesthesia is accepted as the anxiolytic treatment of choice [2-10,12]. In a phase 1 clinical trial, midazolam was reported as safe and efficacious for patients undergoing Mohs surgery [2]. Numerous studies have reported the efficacy and safety of premedication with oral midazolam for diagnostic, as well as surgical procedures [2,3-15].

Rhinoplasty is performed either under general or local anesthesia. Due to the high level of anxiety that precedes this operation; adequate premedication is recommended for patients operated under local anesthesia. Although widely accepted as a safe treatment, at extremely high doses midazolam can lead to complications and even to respiratory depression. The current study evaluated the safety of premedication with 10 mg oral midazolam prior to rhinoplasty, analyzing the intraoperative oxygen blood saturation as a predictor of adverse respiratory events. To the best of our knowledge, this is the first study that evaluated the safety of oral midazolam when used as premedication before rhinoplasty.

PATIENTS AND METHODS

This retrospective study comprised 62 patients who underwent rhinoplasty under local anesthesia and received premedication with oral midazolam for anxiolysis between March 2017 and December 2017. The anesthesia records were reviewed and blood oxygen saturation data during the procedure was obtained. This data was used to evaluate the safety of oral midazolam as related to the patient's respiratory status. The main goal of the study was to analyze the safety of oral midazolam when used as premedication to reduce preoperative anxiety.

The patients included in the study were classified as American Society of Anesthesiologists (ASA) class 1, and were 17 to 58 years-old. Exclusion criteria were ASA class 2, 3, or 4; a history of chronic illness, alcoholism, or myasthenia gravis; or recorded prescriptions for psychiatric medications. Additional exclusion criteria were allergy to midazolam or refusal to receive premedication with oral midazolam.

All patients were monitored using a pulse oximeter. Oxygen saturation was monitored constantly and recorded every 15 minutes. Hypoxemia was defined as peripheral capillary oxygen saturation (SpO2) of less than 93% [16]. Patients received 10 mg midazolam hydrochloride (intravenous solution, Teva, Israel) to be taken orally one hour before the procedure. All the patients underwent primary closed rhinoplasty after a local anesthetic injection of lidocaine 1% 35 ml, normal saline 15 ml, and adrenaline 0.5 ml solution by the same surgeon (MH). Average duration of the procedure was 73 minutes.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test. All continuous variables deviated significantly from normal, so non-parametric methods were used. Continuous variables were described using median (range). Nominal variables were described using frequency counts and are presented as n (%). Correlations between continuous variables were calculating using Spearman's correlation coefficient. The effect of gender on differences between continuous variables was assessed using the Mann-Whitney U test. All tests were two-sided, and $P \leq 0.05$ was considered statistically significant.

RESULTS

The study comprised 62 patients with ASA 1 who underwent rhinoplasty under local anesthesia. The median age was 25.4 years (range 17–53.1 years) and 57 were female (91.9%). All patients received premedication with 10 mg oral midazolam one hour before surgery.

All changes in SpO_2 were within normal parameters with median blood oxygen saturation of 99%, (range 96.75%–100%) [Table 1]. There were no transient hypoxemic events. All patients maintained SpO_2 levels above 95% on room air and did not require supplemental perioperative oxygen. There was no respiratory distress of any kind. Average duration of surgery was 73 minutes. Spearman correlation did not find any association between age and saturation [Table 2]. In addition, there was no significant difference in age and saturation according to the gender of the patient (P =1) [Table 3].

Table 1. Descriptive statistics for age and saturation

	Age	Saturation
Number	62	62
Median	25.4500	99.0000
Minimum	17.00	96.75
Maximum	53.10	100.00

Table 2. Comparative statistics between patient's age and saturation

			Saturation	Age
Spearman's rho	Saturation	Correlation coefficient	1.000	0.190
		Significance (2-tailed)		0.138
		N	62	62
	Age	Correlation coefficient	0.190	1.000
		Significance (2-tailed)	0.138	
		N	62	62

Table 3. Comparative statistics between patient's age and saturation to gender

		Age	Saturation
Female	Mean	29.5844	98.6368
	Standard deviation	10.25934	0.78533
	Median	25.4000	99.0000
	Minimum	17.00	96.75
	Maximum	53.10	100.00
Male	Mean	26.1600	98.7600
	Standard deviation	5.35752	0.43359
	Median	26.8000	99.0000
	Minimum	17.70	98.00
	Maximum	30.80	99.00
Total	Mean	29.3082	98.6468
	Standard deviation	9.96958	0.76136
	Median	25.4500	99.0000
	Minimum	17.00	96.75
	Maximum	53.10	100.00

DISCUSSION

The use of oral benzodiazepines as anxiolytics before surgery is widely accepted in surgical practice. Diazepam, lorazepam, and other benzodiazepines have been used for decades as anxiolytics with varying rates of efficacy. Midazolam is the preferred benzodiazepine due to its superior amnesic activity, rapid metabolization, and consequent short-acting properties [11].

The use of oral midazolam to reduce perioperative anxiety has gained extensive popularity among the surgical community for procedures performed under local or general anesthesia. Oral midazolam was first used as premedication for children undergoing surgical or dental procedures to achieve effective anxiolysis without painful intravenous injections. The effectiveness and safety of oral midazolam have made it the treatment of choice in pediatric premedication [17].When performing surgical procedures under local anesthesia, reducing patient perioperative anxiety is extremely important. It is widely accepted that untreated perioperative anxiety raises blood pressure and heart rate and is directly responsible for intraoperative complications such as excessive bleeding, leading to poor surgical performance and postoperative hematomas [2]. A traumatic experience could negatively affect the readiness of patients to undergo additional procedures, if required.

Studies have shown the benefits of premedication with oral midazolam before plastic surgery operations [2,3,8-10,12]. In this study, we examined the safety of oral midazolam when given one hour before rhinoplasty performed under local anesthesia. Adverse respiratory effects are the main possible complication of midazolam and we used oxygen saturation as a predictor of those effects.

Although in other studies, physiological parameters such as heart rate and blood pressure were also included in the evaluation of midazolam safety, we chose to focus on oxygen saturation values to eliminate possible extrinsic influences, such as pain which can cause elevated heart rate and blood pressure. Another reason was the infiltration of the local anesthesia solution that includes adrenaline for vasoconstriction, which is an essential step in every rhinoplasty. The infiltration is done at the beginning of the operation, and includes all of the subcutaneous tissues surrounding the nose. Intraoperatively, it is applied directly to the nasal septum. The use of subcutaneous infiltration of adrenaline, especially to the septum, can cause tachycardia and changes in blood pressure. We concluded that additional hemodynamic indicators other than oxygen blood saturation could bias the study.

We showed that there were no significant changes in oxygen saturation levels during the surgeries. The median blood oxygen saturation was 99%, substantially higher than 93%, which is the limit above hypoxemia.

Our findings are consistent with the works of Ravitskiy et al. [2], Kreicher and colleague [3], and Studer et al. [18], who have shown the safety of using midazolam as premedication before surgical or diagnostic procedures performed under local anesthesia.

LIMITATIONS

The findings are limited due to the retrospective study design. The study population was small and from a single center. Different drugs were not compared; however, the population was closely monitored. The homogeneity of the results obtained strengthens the conclusion that oral midazolam is safe for use before rhinoplasty under local anesthesia.

CONCLUSIONS

Local anesthesia is increasingly being used in plastic surgery. Local anesthesia is safer than general anesthesia, has reduced intraoperative bleeding, leads to faster and easier recovery, and results in earlier discharge from the surgical facility. However, high levels of anxiety ameliorate the advantages of local anesthesia. The use of oral premedication with midazolam has proven to be an excellent facilitator of anxiolysis and is largely preferred to other benzodiazepines such as diazepam, lorazepam, and bromazepam, due to its short half-life and better retrograde amnesia. Our study shows that the use of oral midazolam as a premedication to reduce perioperative anxiety is safe when performing a rhinoplasty under local anesthesia.

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References

1. Rankin M, Borah GL. Anxiety disorders in plastic surgery. *Plast Reconstr Surg* 1997; 100 (2): 535-42.
2. Ravitskiy L, Phillips PK, Roenigk RK, et al. The use of oral midazolam for perioperative anxiolysis of healthy patients undergoing Mohs surgery: conclusions from randomized controlled and prospective studies. *J Am Acad Dermatol* 2011; 64 (2): 310-22.
3. Kreicher KL, Bordeaux JS. Addressing practice gaps in cutaneous surgery: advances in iagnosis and treatment. *JAMA Facial Plast Surg* 2017; 19 (2): 147-54.
4. Demirtas Y, Ayhan S, Tulmac M et al. Hemodynamic effects of perioperative stressor events during rhinoplasty. *Plast Reconstr Surg* 2005; 115 (2): 620-6.
5. Agelink MW, Majewski TB, Andrich J, Mueck-Weymann M. Short-term effects of intravenous benzodiazepines on autonomic neurocardiac regulation in humans: a comparison between midazolam, diazepam, and lorazepam. *Crit Care Med* 2002; 30 (5): 997-1006.
6. Gostimir M, Hussain A. A systematic review and meta-analysis of methods for reducing local anesthetic injection pain among patients undergoing periocular surgery. *Ophthalmic Plast Reconstr Surg* 2019; 35 (2): 113-25
7. Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; 78 (4): 400-6.
8. Beer GM, Spicher I, Seifert B, Emanuel B, Kompatscher P, Meyer VE. Oral premedication for operations on the face under local anesthesia: a placebo-controlled double-blind trial. *Plast Reconstr Surg* 2001; 108 (3): 637-43.
9. Lanz E, Schäfer M, Brünisholz V. Midazolam (Dormicum) as oral premedication for local anesthesia. *Anaesthesist* 1987; 36 (5): 197-202.
10. De Alencar VM, Gonçalves RD, Cruz AA. Oral medication with diazepam or

midazolam associated or not with clonidine for oculoplastic office surgery under local anesthesia. *Ophthalmic Plast Reconstr Surg* 2010; 26 (4): 269-72.

11. Papineni A, Lourenço-Matharu L, Ashley PF. Safety of oral midazolam sedation use in pediatric dentistry: a review. *Int J Paediatr Dent* 2014; 24 (1): 2-13.
12. Otley CC, Nguyen TH, Phillips PK. Anxiolysis with oral midazolam in pediatric patients undergoing dermatologic surgical procedures. *J Am Acad Dermatol* 2001; 45 (1): 105-8.
13. Mui LM, Teoh AY, Ng EK, et al. Premedication with orally administered midazolam in adults undergoing diagnostic upper endoscopy: a double-blind placebo-controlled randomized trial. *Gastrointest Endosc* 2005; 61 (2): 195-200.
14. Salem K, Khoshrang H, Kousha M, et al. Efficacy and safety of orally administered intravenous midazolam versus a commercially prepared syrup. *Iran J Pediatr* 2015; 25 (3): e494.
15. Sebghatollahi V, Tabesh E, Gholamrezaei A, Zandi AR, Minakari M, Shavakhi A. Premedication with benzodiazepines for upper gastrointestinal endoscopy: Comparison between oral midazolam and sublingual alprazolam. *J Res Med Sci* 2017; 22: 133.
16. Conway A, Rolley J, Sutherland JR. Midazolam for sedation before procedures *Cochrane Database Syst Rev* 2016; (5): CD009491.
17. Manoj M, Satya Prakash MVS, Swaminathan S, Kamaladevi RK. Comparison of ease of administration of intranasal midazolam spray and oral midazolam syrup by parents as premedication to children undergoing elective surgery. *J Anesth* 2017; 31 (3): 351-7.
18. Studer FR, Grätz KW, Mutzbauer TS. Comparison of clonidine and midazolam as anxiolytic premedication before wisdom tooth surgery: a randomized, double-blind, crossover pilot study. *Oral Maxillofac Surg* 2012; 16 (4): 341-7.

Capsule

Dietary salt promotes cognitive impairment through tau phosphorylation

Dietary habits and vascular risk factors promote both Alzheimer's disease and cognitive impairment caused by vascular factors. Furthermore, accumulation of hyperphosphorylated tau, a microtubule-associated protein and a hallmark of Alzheimer's pathology, is also linked to vascular cognitive impairment. In mice, a salt-rich diet leads to cognitive dysfunction associated with a nitric oxide deficit in cerebral endothelial cells and cerebral hypoperfusion. **Faraco** and colleagues reported that dietary salt induced hyperphosphorylation of tau followed by cognitive dysfunction in mice, and that these effects were prevented by restoring endothelial nitric oxide production. The nitric oxide deficiency reduced neuronal calpain nitrosylation and resulted in enzyme activation, which, in turn, led to tau phosphorylation by activating cyclin-dependent kinase 5. Salt-induced cognitive impairment is not observed in tau-null mice or in mice treated with anti-tau antibodies, despite persistent cerebral hypoperfusion and neurovascular dysfunction. These findings identify a causal link between dietary salt, endothelial dysfunction and tau pathology, independent of haemodynamic insufficiency. Avoidance of excessive salt intake and maintenance of vascular health may help to stave off the vascular and neurodegenerative pathologies that underlie dementia in the elderly.

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Capsule

Five-year survival with combined nivolumab and ipilimumab in advanced melanoma

Nivolumab plus ipilimumab or nivolumab alone resulted in longer progression-free and overall survival than ipilimumab alone in a trial involving patients with advanced melanoma. **Larkin** and colleagues reported on 5-year outcomes in the trial. The authors randomly assigned patients with previously untreated advanced melanoma to receive one of the following regimens: nivolumab (at a dose of 1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram every 2 weeks); nivolumab (3 mg per kilogram every 2 weeks) plus ipilimumab-matched placebo; or ipilimumab (3 mg per kilogram every 3 weeks for four doses) plus nivolumab-matched placebo. The two primary endpoints were progression-free survival and overall survival in the nivolumab-plus-ipilimumab group and in the nivolumab group, compared to the ipilimumab group. At a minimum follow-up of 60 months, the median overall survival was more than 60.0 months (median not reached) in the nivolumab-plus-ipilimumab group and 36.9 months in the nivolumab group, compared to 19.9 months in the ipilimumab group (hazard ratio for death with nivolumab plus ipilimumab vs. ipilimumab, 0.52; hazard ratio for death with nivolumab vs. ipilimumab, 0.63). Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, compared with 26% in the ipilimumab group. No sustained deterioration of health-related quality of life was observed during or after treatment with nivolumab plus ipilimumab or with nivolumab alone. No new late toxic effects were noted. Among patients with advanced melanoma, sustained long-term overall survival at 5 years was observed in a greater percentage of patients who received nivolumab plus ipilimumab or nivolumab alone than in those who received ipilimumab alone, with no apparent loss of quality of life in the patients who received regimens containing nivolumab.

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