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Investigating The Effect of Midazolam on Pediatric's Sedation and Anxiety

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Abstract

Introduction and Aim: One of the essential experiences in life is surgical events anesthesia. This experience may cause physiological and psychological disorders such as anxiety and stress, especially in children. The anxiety problem appears without appropriate treatment, and many cause impactive physical or psychological complications in children. Procedural sedation methods for children and adults are different, and a successful method for anxiety control in adults may not be effective in children. Few studies have specifically studied performing the preoperative midazolam therapy and method of consumption on post-operative children's anxiety. Hence, this study was conducted to compare intranasal and sublingual midazolam as premedication for sedation and reduction of anxiety in pediatric patients. Material and method: This study was conducted as a randomized controlled trial study. A list of patients was prepared from the clinical part of the Nasiriyah hearth center. The list was inputted into the software randomly, and 107 persons were selected. The type of administration was randomly chosen for each patient prescribed midazolam. Participants who have general anesthesia and midazolam prescribed for them between July 2022 in the Nasiriyah Cardiac heart center will be included in this study. Half of the participants (n=107) received sublingual midazolam, and others (n=107) received intranasal midazolam. This study's outcome is the anxiety score in children (quantitative and qualitative). The exposure of the study is the consumption of midazolam before general anesthesia. The measurement for all participants was in the same method. Result: Totally, of 214 patients were included in this study. Among them, 50.9% (n=109) were male, and 49.1% (n=105) were female. The mean age was 10.15 ± 1.87 years (95% Confidence Interval 9.90 - 10.40 years). Our result showed that the anxiety of patients who received intranasal midazolam was significantly lower than patients who received sublingual midazolam at 10 (P=0.006) and 20 (P=0.020) minutes. However, this difference was not statistically significant in min 30 (P=0.644) and 60 (P=0.655). In addition, the pain of participants who received intranasal midazolam was significantly lower than patients who received sublingual. While this difference was not statistically significant, it was borderline significant (p=0.078). In addition, our results showed that the mean time for sedation of participants in the nasal midazolam intervention group was 9.47±2.01years. In the sublingual midazolam intervention group, it was 16.38±2.99 years. The difference was statistically significant (p<0.001), which means the mean sedation time in patients who received sublingual midazolam was significantly higher than in those who received intranasal midazolam. Discussion: We concluded from our study that intranasal midazolam has superiority compared with sublingual midazolam in premedication in children for sedation and anxiety score and some other factors, including pulse rate and o2 saturation before anesthesia. The anxiety scores after premedication are significantly lower in the intranasal compared are sublingual. In addition, the onset time

for sedation was significantly lower in intranasal inter, which nation group means this method may have a faster effect. The adverse effect was similar in both groups. Thus, intranasal midazolam is a fallow-danger, low-danger method for children undergoing anesthesia.

Keywords

Intranasal, Sublingual, Midazolam, Anxiety, Pediatric.

About 10-20% of pediatric admission (patients under 18 years old) are undergoing surgery for congenital anomalies, wound-related injuries, etc. (1). One of the essential experiences in life is surgical events and anesthesia. This experience may cause physiological and psychological disorders such as anxiety and stress, especially in children. Risk factors such as unfamiliar settings (hospital setting), fear of separation in children, child scaring of doctors and medical tools, and feeling of loss of control may cause stress and anxiety in patients. In addition, changes in patients' hormones due to treatment or anesthesia also may cause human response to anxiety response to having secondary effects on hormone secretion from other organs (2-3).Due to definition of the American Society of Anesthesiologists, general anesthesia is defined as a reversible loss of consciousness usually induced by drugs. During the anesthesia, the patient is not arousable. In addition, some organs, such as the ventilator and cardiovascular function, may be impaired (4). Also, general anesthesia was associated with adequate analgesia and amnesia, rapid induction, muscle relaxation, depression of the autonomic nervous system, rapid emergence, and avoidance of undesirable side effects, usually administered with intravenous or inhalational methods (5). In addition, large amounts of nitrous oxide mixture were used to prepare adequate anesthesia. Therefore, some new inhaled or volatile anesthetics drugs were synthesized. These other drugs included halogenated vapors of halothane, isoflurane, desflurane, and sevoflurane (6). Also, in recent years, xenon was used, and it was a favorite method since it has rapid induction and emergence times due to the low blood-gas coefficient of the body (5).

Additionally, a large mixture of nitrous oxide was required to provide adequate anesthesia. New inhaled or volatile anesthetics were synthesized, including the halogenated vapors of halothane, isoflurane, desflurane, and sevoflurane (6). Xenon has recently been favored as a general anesthetic due to its low blood-gas coefficient and rapid induction and emergence time (5). Intravenous general methods were introduced in 1872, and chloral hydrate was the first prod-produced intravenous anesthetic. In addition, using barbiturates, including sodium thiopental, increased after using chloral hydrate. However, cardiovascular and respiratory depressant risks were one of the risks of barbiturates; hence, other suitable intravenous anesthetics with low risk of cardiovascular depressant effects, for example, etomidate, were popular (6). In a similar process, benzodiazepines, including diazepam and midazolam, have been popular for sedative aims in anesthesia (7, 8). In addition, Ketamine was common only and introduced in the induction agent role (9).

Another example is propofol as the substitute for the etomidate role due to post-operative nausea due to etomidate exposure (10,11). All of the general anesthetics, either positive or negative allosteric, modulate the ligand-gated ion channel in the dose of clinically effective (12). For example, some molecular targets are glycine receptors, N-methyl-D-aspartate (NMDA) receptors, potassium channels, and voltage-gated sodium channels. However, most inhaled and intravenous anesthetics targets are GABAA receptors (12-13).

In 1950, Dr. Pearson published an article that determined the effects of anesthesia that can have traumatic consequences in children's lives (14). However, the reported consequences reported by the Pearson et al. study were rare. The publication of this article led the researchers to recognize that the anesthesia experience in children is very different compared to adults. This experience may be due to anesthesia, hospitalization, and surgery. As Jessner et al. (15) reported and described, four anxiety domains exist in children with a history of ear-nose-throat ENT surgery. 1. First of that'sthatear of hospitalization, 2. Anticipation of anesthesia and narcosis (threat of death, punishment, execution, fear of murder or sexual assault, loss of control), 3. The fear from theofrations and 4. Fear of needles, knifes or other imagine of imagesy in the child's mind. In addition, subsequent studies have shown that induction of anesthesia is one of the most stressful experiences a child can have during a hospital encounter (3-6), also often involving the insertion of a needle. There can be significant differences in perception during childhood (7-11 years old). A medical procedure can be viewed as punishment by children in the preoperative stage, as they actively switch from relying solely on their perceptions to more rational thinking (16). On the other hand, those children who have reached the concrete operational stage can think logically and comprehend a series of events. In addition, Erikson found that the needs of children at the initiative stage compared with

those of children at the guilt stage (3-6 years old), as well as those at the industry stage compared with those at inferiority (5-12 years old), were vastly different psychosocially from one another (16). There is a significant difference between the initiative and guilt stages in children, and children in this stage want and need control over the environment around them. In the hospital setting, this can be extremely challenging to accomplish (17). During this stage, children build a sense of competence, nurture the desire to succeed in tasks, and remain cooperative throughout the procedures, such as staying still during medical procedures and working with the doctor (16).In this regard, the effects presented in the original study may differ by age based on the perceptual and psychosocial differences between younger and older children. It is essential to keep this in mind when evaluating the effectiveness of interventions that involve electronic distractions. There is some difficulty in generalizing research results in order to make them more useful. The use of global instruments by some researchers differs from the use of structured observational behavioral tools by others. It is possible to define different words differently based on their meanings. Among the frequently used terms are anxiety, distress, disruptive behavior, behaviors, and cooperation. In addition to these differences, children are also treated differently in different countries regarding how they are met and anaesthetized.

Methodology

This study was conducted as a randomized controlled study. In this study, we tried to collect representative data from a representative sample size. Hence, our inclusion and exclusion criteria will not be considered as difficult to reduce the probability of selection bias and increase the sample size of patients (power of the study). This study's participants will be children who had general anesthesia for surgery in Nasiriya city (south of Iraq). The included criteria were age in childhood years), general anesthesia for any surgery, and physicians prescribing midazolam for them in the pre-operation stage for anxiety control. Finally, patients or their guardians have informed consent to include in the study. Also, the patient should be in ASA Physical status I and II. The patient should undergo elective surgery under general anesthesia or general anesthesia combined with regional anesthesia. Suppose the patients or their guardians refuse to include the patient study. Suppose the patient has an allergy to midazolam and a history of psychological disease. In that case, they will be excluded from the study if they are on another psychotherapy method to control the stress and anxiety. If the patients had a history of psychiatric disorders or they were on antipsychotic medications, sleep disorders, renal derangements, mental retardation, an allergy to midazolam, and color blindness were excluded from the study.

This study was a hospital/clinical center-based and experimental study. The clinics selected to be included in the study have various referents (Nasiriyah Cardiac heart center), and the sample from these clinics is representative of the whole Nasiriyah and Thiqar population according to a variety of independent variables such as educational level, socio-economic status, etc.

A list of patients was prepared from the clinical part of the Nasiriyah hearth center. The list was inputted into the software, and randomly, 107 persons were selected. The type of administration was randomly chosen for each patient prescribed midazolam. Participants who have general anesthesia and midazolam prescribed for them between July 2022 in the Nasiriyah Cardiac heart center will be included in this study. Patients were selected with the Convenience sampling method to be included in the study. Trained research assistants spoke with each eligible child's parents and explained the study's details. All examinations were performed in private. Written parental consent was obtained before any assessment or interventions. In the second step, the researcher assistance examined the inclusion and exclusion criteria of the participants. Children with inclusion criteria were selected to take informed consent from the child and parent and collect the data.

This study's outcome is the anxiety score in children (quantitative and qualitative). The exposure of the study is the consumption of midazolam before general anesthesia. The patients were randomly assigned to the group of intranasal and midazolam subgroup. The randomization method will be conducted as block randomization with the block of 2-4-6 or 8 persons. Since the intervention method is obvious (intranasal and sublingual), the blinding or masking of participants or health-care workers will be omitted. During the pre-anesthesia assessment, a detailed clinical history was taken, a thorough physical examination, and an evaluation of the patient's general and systemic health. Routine hematological and, Following the institutional protocol, biochemical investigations were performed. An anesthesiologist used the same scales during the operation room to assess the level of sedation and behavior according to the hospital protocol at the time of induction of anesthesia. It strictly adhered to all the standard monitors and safety protocols recommended for pediatric anesthesia. The choice of anesthesia (intravenous versus inhalational/general anesthesia with/without regional anesthesia) was left to the discretion of the attending anesthesiologists during the procedure.

Additionally, other sedatives like benzodiazepines and drugs like Ketamine were avoided. Anaesthesia was terminated at the end of the surgery, and the child's behavior was recorded when awake. Continuous non-invasive blood pressure and pulse oximetry monitored

the patient's vitals throughout the procedure. Patients were assessed for wake-up behavior after surgery. The researcher conducted an assessment of the variables using a questionnaire. These studies used a questionnaire adapted for Iraqi culture (Arabic language) to collect information without bias. This study's data contained demographic variables, absence/present, gender, age, history of surgery, comorbidity with other diseases, and weight and height. In addition, the SEDATION SCORE checklist, including criteria and scores of Moving, Tearful status, Calm status, and Easily arousable, were assessed. Also, anxiolytics were evaluated by standards of afraid and crying, fearful, slightly fearful, and No fear and the venham questionnaire'. In addition, cooperation, including refusing intervention, required to achieve intervention, accepting intervention reluctantly, and Accepting intervention readily for Parental separation, venipuncture, and Mask application was assessed. The acceptability of the drug administration was also evaluated with no defense action, defense action/weeping, or refusing vehement criteria. Moreover, facial pain evaluation questionnaires were used to assess patients' pain after cardiac surgery. In addition, secondary outcomes such as comfortability and side effects of this treatment (such as headache, sleepy condition, etc.) were collected 10 and 20 minutes after surgery.

The sample size of this study was calculated using formula 1 to calculate the power of the study. The α level in this formula represents the potential risk of an incorrect rejection of a zero hypothesis since 0.05 is the risk level, the study's power is 80%, the prevalence is calculated, and the margin of error is considered. The prevalence of the outcome is about 30% (p=0.30), and we will consider 0.05 as our level of significance, so 107 individuals will be considered as the sample size.

Formula 1:

P of anxiety in intranasal method= 20.3%

P of anxiety in Sublingual method= 37.5%

$$n = \frac{2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \times (\bar{p}\,(1-\bar{p}))}{(p_1 - p_0)^2}$$

Results

Table 1: demographic and clinical characteristics of patients in both intervention groups and total population

Variable	Intranasal	Sublingual	Total	P-value
Age (mean±SD)	10.17±1.83	10.14±1.91	10.15 ± 1.87	0.679
Height (mean±SD)	147.48±13.93	145.34±15.20	146 ± 14.58	p=0.370
Weight (mean±SD)	34.45±6.67	32.55±7.68	33.5 ± 7.2	0.147
BMI (mean±SD)	15.82±2.18	15.34±2.42	15.58± 2.3	0.284
Time for sedation (mean±SD)	9.47±2.01	16.38±2.99	12.92±4.30	<0.001
O2 saturation (mean±SD)	99.06±0.26	99.01±0.34	99.04%±0.30	0.004
pulse rate (mean±SD)	109.86±4.53	118.16±3.46	114.01±5.79	0.006
Gender				0.999
Male	54 (50.47)	55 (51.40)	109 (50.93)	
Female	53 (49.53)	52 (48.60)	105 (49.07)	

Table 2: sedation score of participants.

			intranasal	sublingual	Total
sed_score_10	Alert /Active − agitated	Count	8	79	87
		The percentage for each intervention group	7.50%	73.80%	40.70%
	Upset/ Worried	Count	34	25	59
		The percentage for each intervention group	31.80%	23.40%	27.60%
	Relaxed	Count	60	2	62
		The percentage for each intervention group	56.10%	1.90%	29.00%
	Drowsy	Count	5	1	6
		The percentage for each intervention group	4.70%	0.90%	2.80%
sed_score_20	Alert /Active − agitated	Count	0	18	18
		The percentage for each intervention group	0.00%	16.80%	8.40%
	Upset/ Worried	Count	10	81	91
		The percentage for each intervention group	9.30%	75.70%	42.50%
	Relaxed	Count	65	7	72
		The percentage for each intervention group	60.70%	6.50%	33.60%
	Drowsy	Count	32	1	33
		The percentage for each intervention group	29.90%	0.90%	15.40%
sed_score_30	Alert /Active − agitated	Count	0	4	4
		The percentage for each intervention group	0.00%	3.70%	1.90%
	Upset/ Worried	Count	3	45	48
		The percentage for each intervention group	2.80%	42.10%	22.40%
	Relaxed	Count	45	51	96
		The percentage for each intervention group	42.10%	47.70%	44.90%
	Drowsy	Count	59	7	66
		The percentage for each intervention group	55.10%	6.50%	30.80%
sed_score_60	Alert /Active − agitated	Count	0	2	2
		The percentage for each intervention group	0.00%	1.90%	0.90%
	Upset/ Worried	Count	1	30	31
		The percentage for each intervention group	0.90%	28.00%	14.50%

Table 3: anxiety status of patients with anxiolysis score checklist

			intranasal	Sublingual	Total
Anxiolysis_score_10	Afraid and crying, restrained	Count	8	0	8
		The percentage for each intervention group	7.50%	0.00%	3.70%
	Fearful, moderate apprehension	Count	29	43	72
		The percentage for each intervention group	27.10%	40.20%	33.60%
	Slightly fearful	Count	67	61	128
		The percentage for each intervention group	62.60%	57.00%	59.80%
	No fear or apprehension	Count	3	3	6
		The percentage for each intervention group	2.80%	2.80%	2.80%
Anxiolysis_score_20	Fearful, moderate apprehension	Count	13	20	33
		The percentage for each intervention group	12.10%	18.70%	15.40%
	Slightly fearful	Count	55	66	121
		The percentage for each intervention group	51.40%	61.70%	56.50%
	No fear or apprehension	Count	39	21	60
		The percentage for each intervention group	36.40%	19.60%	28.00%
Anxiolysis_score_30	Fearful, moderate apprehension	Count	6	9	15
		The percentage for each intervention group	5.60%	8.40%	7.00%
	Slightly fearful	Count	36	38	74
		The percentage for each intervention group	33.60%	35.50%	34.60%
	No fear or apprehension	Count	65	60	125
		The percentage for each intervention group	60.70%	56.10%	58.40%
Anxiolysis_score_60	Fearful, moderate apprehension	Count	3	6	9
		The percentage for each intervention group	2.80%	5.60%	4.20%
	Slightly fearful	Count	23	22	45
		The percentage for each intervention group	21.50%	20.60%	21.00%
	No fear or apprehension	Count	81	79	160
		The percentage for each intervention group	75.70%	73.80%	74.80%

Table 4: The anxiety status of patients with Venham score checklist

		Intranasal	sublingual	Total	
Venham score min 10	Relaxed and smiling	Count	10	10	20
		The percentage for each intervention group	9.30%	9.30%	9.30%
	Uneasy and concerned	Count	21	15	36
		The percentage for each intervention group	19.60%	14.00%	16.80%
	Scared	Count	50	45	95
		The percentage for each intervention group	46.70%	42.10%	44.40%
	Crying	Count	23	31	54
		The percentage for each intervention group	21.50%	29.00%	25.20%
	Crying and struggling	Count	1	5	6
		The percentage for each intervention group	0.90%	4.70%	2.80%
	Out of proportion to the threat	Count	2	1	3
		The percentage for each intervention group	1.90%	0.90%	1.40%
Venham score min 20	Relaxed and smiling	Count	20	18	38
		The percentage for each intervention group	18.70%	16.80%	17.80%
	Uneasy and concerned	Count	35	29	64
		The percentage for each intervention group	32.70%	27.10%	29.90%
	Scared	Count	33	37	70
		The percentage for each intervention group	30.80%	34.60%	32.70%
	Crying	Count	17	23	40
		The percentage for each intervention group	15.90%	21.50%	18.70%
	Crying and struggling	Count	2	0	2
		The percentage for each intervention group	1.90%	0.00%	0.90%
Venham score min 30	Relaxed and smiling	Count	33	29	62
		The percentage for each intervention group	30.80%	27.10%	29.00%
	Uneasy and concerned	Count	36	41	77
		The percentage for each intervention group	33.60%	38.30%	36.00%
	Scared	Count	28	27	55
		The percentage for each intervention group	26.20%	25.20%	25.70%
	Crying	Count	10	10	20

		The percentage for each intervention group	9.30%	9.30%	9.30%
Venham score min 60	Relaxed and smiling	Count	54	59	113
		The percentage for each intervention group	50.50%	55.10%	52.80%
	Uneasy and concerned	Count	31	27	58
		The percentage for each intervention group	29.00%	25.20%	27.10%
	Scared	Count	17	16	33
		The percentage for each intervention group	15.90%	15.00%	15.40%
	Crying	Count	5	5	10
		The percentage for each intervention group	4.70%	4.70%	4.70%

Discussion

This study's main aim was to compare intranasal and sublingual midazolam as premedication for sedation and reduction of anxiety in pediatric patients under general anesthesia.

Our result showed that the anxiety of patients who received intranasal midazolam was significantly lower than patients who received sublingual midazolam at 10 and 20 minutes. However, this difference was not statistically significant in min 30 and 60. In addition, the pain of participants who received intranasal midazolam was significantly lower than patients who received sublingual. While this difference was not statistically significant, it was borderline significant (p=0.078), and it may be changed to important with increasing the sample size.

Researchers have been exploring different types of pediatric premedication agents and the best routes of administration to find the most suitable agent for pediatric premedication (19). A pediatric premedical must also be able to administer a drug in a non-traumatic and acceptable way in addition to the other characteristics that can be expected from such a medication (20, 21). Several drugs have been recommended previously for premedication in children, including Ketamine and midazolam, which can be administered nasally (22). Oral midazolam remains the most commonly used premedication in pediatric outpatients (23).

It has become part and parcel of the role of every pediatric anaesthesiologist to calm children's anxieties before surgery (24). In addition, they need to prescribe optimal and appropriate premedication (25). As a result of pharmacological premedication, patients are prepared for induction, and the hypnotic effect of general anesthesia is enhanced. Pharmacological premedication is primarily used to produce amnesia and anxiolysis, decrease secretions and vagal reflexes after intubation, and prepare patients for anesthesia induction (26).

The use of midazolam in anesthetic practice has been extensively documented since it was introduced in 1982, and the pharmacodynamics and pharmacokinetics of midazolam are well known. A common use of midazolam is for the premedication of children, and it is usually administered orally rather than intravenously (27). It was first described and advocated by Wilton et al. (28) as intranasal midazolam for premedication in preschoolers. Premedication children undergoing surgery with midazolam has many desirable properties as a premedication agent. In addition to its dose-dependent anxiolytic effect, midazolam doesn't cause excessive sedation or cardiopulmonary effects and exerts a reliable anxiolytic effect without causing excessive sedation. Anesthesia and surgery can cause a great deal of psychological trauma for people, and midazolam can reduce this trauma through the anterograde amnesia it produces. Midazolam has a half-life of 1.5 - 2 hours, during which it is eliminated from the body, which is noticeably shorter than other drugs. In addition, intranasal midazolam has a similar elimination half-life to intravenous midazolam. No significant complications have been reported due to intranasal midazolam administration, which can be compared to intravenous administration. Some pharmacokinetic studies have examined the effect of midazolam at varying doses intranasally and in varying plasma concentrations, with the most common dosage of 0.1-0.3 mg/kg intranasally being used in most studies (29-30). There are different methods of administering midazolam, the most common one being the administration of drops. Still, these are difficult for the awake patient to keep in their noses and are susceptible to being swallowed and ending up in the liver as a first-pass drug (31).

Compared to drops, aerosols allow for more contact with absorbent surfaces and are less unpleasant to apply than drops. According to several studies, nasal sprays have a high bioavailability (83%) and virtually complete absorption with a high bioavailability, which means that they provide a high level of bioavailability (32). Neither the 0.5 mg/kg group nor the 1.0 mg/kg group showed a significant difference, nor did the 0.5 mg/kg group and the 0.25 mg/kg group in previous studies (33). There was a satisfactory level of sedation for 99% of participants after taking study medication, and 97.5% showed an adequate anxiolytic response (score >3). Moreover, a positive correlation was found between the dose, and the onset of anxiolysis (p=0.001) was reported; it was found that the higher the dose, the more significant

the proportion of children who achieved satisfactory anxiolysis within 10 minutes of taking medicine. >90% maintained satisfactory anxiolysis for up to 45 minutes (34, 35). Various reasons made the intranasal route for sedation the optimal suggested from our study, including its rapid onset of action, greater bioavailability, and quick recovery time, making it more appropriate for use in an emergency for preoperative children (36). The only drawback of administering intranasal sedation is that, in children, it has been reported that the nasal mucosa burns following intranasal sedation (37). However, an intranasal sedation study conducted by Chiareitti et al. (2011) included intranasal sedation with midazolam (34), followed by the administration of a local anesthetic spray (Lignocaine) to anesthetize the nasal mucosa before the intranasal sedation. Based on the study results, they found that 100 percent of the patients had no burning sensation at all. Several conclusions can be drawn from the results of this study, some of which will be discussed further in this article. According to the researcher, a literature search using some search engines such as PubMed did not reveal any randomized clinical trials conducted to compare different doses of IN midazolam in the setting of an emergency that has been undertaken so far. To determine which dosage would be the most appropriate for use in an emergency setting where time and recovery space are of the essence, two doses were investigated for their safety, effectiveness, and recovery times to determine which dosage would be appropriate for use in such setting (38, 39).

As demonstrated in prior literature(40, 41), doses of 0.3 mg/kg and 0.5 mg/kg midazolam resulted in satisfactory sedation at the dosage levels (0.3 mg/kg and 0.5 mg/kg). It is important to note that the doses were not compared in a pediatric dental emergency clinic in these studies. A pediatric dental emergency clinic undergoing emergency treatment with midazolam would benefit significantly from comparing the doses of this medication used intranasally to reduce anxiety. Continuous monitoring of the oxygen saturation levels of the children, as well as the safety of the participants, was ensured. In a study by Narendra, PL et al. (42). midazolam was given intranasally at a dose of 0.25 mg/kg, and ketamine (5 mg/kg) was given nasally at a dose of 1 mg/kg. In this study, midazolam was found to be equally effective as a premedication for sedative symptoms in both groups of patients, and nasal delivery of midazolam was well accepted. Also, it has been reported that Tushar Patel et al. (43) found that midazolam produced more sedation than placebo or melatonin, respectively. A similar study conducted by Naguib et al. (44) revealed that at 60 and 90 minutes after premedication, the midazolam groups showed higher levels of sedative effects than the placebo and melatonin groups. The intergroup comparison revealed that midazolam provided the most favorable degree of sedation; In contrast, a study by Eloisa et al. (45) found that preoperative sedation levels were not significantly different between the melatonin and midazolam groups in their study. In addition, our results showed that the mean time for sedation of participants in the intranasal midazolam intervention group was 9.47±2.01years and in the sublingual midazolam intervention group, it was 16.38±2.99 years. The difference was statistically significant ($p<0.001$), which means the mean sedation time in patients who received sublingual midazolam was significantly higher than in those who received intranasal midazolam. It was found in the study by Sunny Alex et al. (46). that the mean time for onset of sedation and satisfactory sedation for nasal midazolam was 8.63 minutes and 11.3 minutes, respectively.

In contrast, the mean time for oral midazolam was 14.03 minutes and 18.3 minutes, respectively. P values of 0.001 were extremely significant, indicating a significant difference between the two groups that was consistent with our results. In the study by Lam et al. (47), it has been demonstrated that midazolam given intranasally to patients before intravenous conscious sedation is more effective than midazolam given intramuscularly to patients before intravenous conscious sedation. The age range of the patients ranged from 2-9 years old (mean age 5.13 years old), and midazolam was administered intramuscularly or intranasally at a dose of 0.2 mg/kg to the patients, and it is essential to point out that the patients were from 2-19 years old (mean age 5.13 years old). According to the study, 23 patients received intramuscular midazolam, while those who received intranasal midazolam appeared to be more deeply sedated than those given intramuscular midazolam. As Karl HW et al. (48) reported, the oral mucosa has a rich blood supply, which allows drugs to be absorbed rapidly directly into the systemic circulation as a direct result of its high blood supply. There are several factors influencing the absorption of the drug. They include the time during which the drug is adjacent to the mucosal surface (Resident time), the local pH (6-7), as well as the presence of secretions (respiratory tract infections), the drug's physicochemical properties, and the physicochemical properties of the route of administration of the drug are also taken into consideration. Drug absorption is also influenced by the methods and techniques used for administering the medication. Because midazolam is soluble in aqueous solutions at an acidic pH (3.5), it can maintain a high concentration within the nasal mucosa (pH 6-7) for a prolonged period. Ionized and non-ionized forms of midazolam are absorbed from the nasal mucosa due to the pKa of midazolam 6.15, which is close to the local pH(49). The effects of midazolam at the oral, rectal, and

nasal levels were studied by Kogan et al. (50). A significant difference was found between the children's acceptance of the oral route compared to the nasal or rectal route. As a result of the rectal administration of midazolam, the onset of sedation was the fastest. The oral midazolam effect was good in many children, but the result was less predictable.

A study conducted by Sunny Alex et al. (46) showed that nasal sedation scores were significantly higher than those of the nasal group 20 minutes after premedication, suggesting that nasal sedation was more effective than oral sedation. A high P value of 0.006 was found at the 10-minute, and a P value of 0.028 was found at 20 minutes, which was significantly significant. However, the P-value at min 30 and higher was not statistically significant, which was consistent with our results. Our study showed that the sedation score was significantly higher in intranasal midazolam groups.

Our result showed that the anxiety of patients who received intranasal midazolam was significantly lower than patients who received sublingual midazolam at 10 and 20 minutes. However, this difference was not statistically significant in min 30 and 60. There are, however, clear discrepancies between the findings of Sunny Alex et al. (46) during the study period of sunny et. Al, the anxiolysis scores of both groups (oral and nasal) were similar within each of the two groups, with a p-value of >0.05, meaning that it was not statistically significant.

Conclusion

we concluded from our study that intranasal midazolam has superiority compared with sublingual midazolam in premedication in children for sedation and anxiety score and some other factors, including pulse rate and o2 saturation before anesthesia. The anxiety scores after premedication are significantly lower in the intranasal group compared with the sublingual. In addition, the onset time for sedation was significantly lower in the intranasal intervention group, which means this method may have a faster effect. The adverse effect was similar in both groups. Thus, intranasal midazolam is a quick, effective, and low-danger method for children undergoing anesthesia.

Ethical Approval

The ethical consideration of the study was examined by the ethical committee of the Tehran university of medical sciences, and ethical approval for the study was obtained (ethical code: IR.TUMS.SPH.REC.1401.196). The Declaration of Helsinki was observed in all study procedures (18). As mentioned above, Written and verbal informed consent was obtained from the participant's guardians before any data collection, intervention, or examinations.

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