ijlpr 2023; doi 10.22376/ijlpr.2023.13.4.P95-P104

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Behavioural and Physiological Effects of Oral Midazolam Premedication in Paediatric Dental General Anaesthesia: A Pilot Study

Abdul Rauf Badrul Hisham, [1,2] Noraida Mamat,[1] Ahmad Faisal Ismail,[3] Wan Muhamad Amir W Ahmad, [4] and Dr. Norsamsu Arni Samsudin[1]

[1.] *Paediatric Dentistry Unit, School of Dental Sciences, Universiti Sains Malaysia (USM), Health campus, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia.*

[2.] *Paediatric Dentistry Department, Sabah Women and Children's Hospital, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia.*

[3.] *Associate Professor Dr, Department of Paediatric Dentistry and Dental Public Health, Kulliyyah of Dentistry, International Islamic University Malaysia (IIUM), Pahang, Malaysia.*

[4] *Associate Professor Ts. Dr., Unit of Biostatistics, School of Dental Sciences, Universiti Sains Malaysia (USM), Health campus, 16150, Kubang Kerian, Kota Bharu, Kelantan, Malaysia*

Abstract: Children undergoing anesthesia, including dental treatment under general anesthesia (DGA), tend to develop severe preoperative anxiety. Oral Midazolam is one of the many premedications used in controlling behavior and reducing anxiety in children before general anesthesia. This study is aimed to evaluate the effect of oral midazolam premedication on recovery behavior and physiologic effects of children undergoing DGA. It involved thirty uncooperative children aged from 2 to 11 years old. Group I (n = 15): children received 0.5 mg/kg midazolam orally, while Group II (n = 15): children who did not receive any premedication. Their peripheral capillary oxygen saturation, respiratory rate, and heart rate were measured upon arrival at the post-anesthesia care unit. The recovery behavior was evaluated using the Modified Houpt Behavior Rating Scale. Fisher's Exact test and Mann-Whitney test were used for data analysis. There are no significant differences in both groups' post-behavior and physiologic parameters (p>0.05). However, children in Group II reported tachycardia (13.3%, n= 2), hypoxemia (13.3%, n= 2), and bradypnea (13.3%, n= 2), compared to one case of bradypnea (6.7%) in Group I at 30 minutes. Although there were no significant differences between both groups (p>0.05), Group I showed less movement and no crying reaction but was more awake—no significant association of premedication oral midazolam with successful recovery behavior (p=0.381). One child in Group II had an episode of vomiting. An interesting pattern of improved recovery behavior and physiology was identified among children receiving oral midazolam premedication. More research with a bigger sample size is needed to investigate the effect of oral Midazolam in pediatric DGA and to determine the optimal effect of premedication.

Keywords: behavior/behavior, general dental anesthesia, oral Midazolam, premedication.

***Corresponding Author**

Dr. Norsamsu Arni Samsudin , Paediatric Dentistry Unit, School of Dental Sciences, Universiti Sains Malaysia (USM), Health Campus,16150 Kubang Kerian, Kelantan, Malaysia.

Received On 8 March, 2023
Revised On 15 April, 2023
Accepted On 29 April, 2023
Published On 1 July, 2023

Funding This work is supported by Universiti Sains Malaysia short-term'sterm grant 304/PPSG/6315338.

Citation Abdul Rauf Badrul Hisham, Noraida Mamat, Ahmad Faisal Ismail,Wan Muhamad Amir W Ahmad, and Dr. Norsamsu Arni Samsudin , Behavioural and Physiological Effects of Oral Midazolam Premedication in Paediatric Dental General Anaesthesia: A Pilot Study.(2023).Int. J. Life Sci. Pharma Res.13(4), P95-P104 http://dx.doi.org/10.22376/ijlpr.2023.13.4.P95-P104

1. INTRODUCTION

Managing uncooperative or anxious pediatric patients is a huge challenge for many dental practitioners, even after years of practice. Dental anxiety and uncontrolled behavior are two main issues that dentists encounter.[1] This has been associated with numerous contributing factors, including tooth pain, previous unpleasant dental experiences, and the patient's young age.[2,3] In Malaysia, Esa et al. reported 53.9% of preschool children had high anxiety levels.[4] Similar results were found in children from different parts of the world who had high levels of dental anxiety, which ranged between 8.9% to 20.6%.[5,6] Dental treatment under general anesthesia (DGA) is one of the treatment options used in managing uncooperative pediatric patients.[7] Early childhood caries was a principal preoperative diagnosis for pediatric DGA.[8] The route of premedication administration includes oral, intramuscular, intravenous, rectal, sublingual, and intranasal. Although oral premedication eliminates the pain of injecting a needle into a small child, it has the drawback of a slower onset and lower bioavailability of the premedication medications.[9] Premedication's goals are as follows; 1) To induce drowsiness, relieve anxiety, and alleviate trauma. 2) Stop undesired autonomic reflexes (vagal). 3) Decrease the volume and acidity of the stomach contents. 4) Make anesthesia induction go more smoothly and safely. 5) To induce amnesia. 6) Add to anesthesia to lessen the general anesthesia (GA) medication requirement. 7) Preventing nausea and vomiting after surgery.[10] Children display a wide range of postoperative or recovery behavior when undergoing GA, such as crying, verbal pain, verbal resistance, and nonverbal support requests. The term emergence delirium (ED) is known in pediatric anesthesiology. It manifests as negative behavior after rapid awakening that is common in younger children and associated with poor compliance at induction, maladaptive behavior, and preoperative anxiety.[11] These behaviors were also reported to have positive associations with analgesics used during GA and postoperative pain scores.[12] Intraoral bleeding, difficulty in eating, mouth/nose/throat discomfort, nausea-vomiting, constipation, fever, and other difficulties are frequent postoperative complications reported in DGA.[13] The postoperative period is the most vital phase of a children's life. As the patient leaves the operating theatre (OT), careful supervision is essential to ensure the success of the patient's recovery. The patient's recovery behavior, vital signs, and postoperative complications are all meticulously monitored in the recovery area before the patient is transferred back to the ward. [13] There are several components in vital signs that need close observation postoperatively, such as room air oxygen saturation level, heart rate, respiratory rate, blood pressure, and body temperature.[14] Results from various study reports Midazolam is widely used as premedication sedation in pediatric patients, but its recovery behavior and physiological effects in post-DGA are still in doubt. Thus, this study assesses postoperative recovery behavioral and physiological effects of oral Midazolam as sedative premedication in pediatric patients who needed dental treatment under GA. The null hypothesis of our study was determined that oral midazolam premedication with a dosage of 0.5mg/kg would not give positive behavioral and physiological effects post-DGA. [13]

2. MATERIALS AND METHODS

2.1. Ethical Statement

This randomized control trial study was conducted on thirty uncooperative children initially recruited (March 2021 - July 2022) at the Paediatric Dentistry Specialist Clinic, Universiti Sains Malaysia, Kelantan, Malaysia, where pediatric dental specialists performed initial consultations. On this occasion, the goal and procedures of the study were explained to parents, and they were invited to participate willingly in this study. The study is part of a larger study investigating the dental anxiety of children who received oral midazolam premedication in DGA. This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (Reference Number: USM/JEPeM/20050249). Written informed consent was obtained from all parents or legal guardians before enrolling children in the study.

2.2. Inclusion/Exclusion Criteria

This study comprised thirty uncooperative children with American Society of Anaesthesiology (ASA) physical status I or II, Frankl Behavioural Rating Scale score of 1 or 2, normal body weight, and the capacity to tolerate oral Midazolam. Patients were excluded from the study if they were taking medication that may interfere with the pharmacokinetics of Midazolam, hypersensitivity or known allergy to benzodiazepines derivatives, had a history of developed side effects after taking midazolam medication, or/and refused to take the full dose of midazolam premedication. In addition, patients whose parents were absent from admission at arrival in OT and the recovery area of OT were also excluded from the study.

2.3. Sample-size Estimation

Sample-size estimation was performed on data obtained from a study by Tyagi et al. and calculated using the Sample Size Calculator Version 2.0 and PS Power. Sample Size Calculation (PS calculator) version 3.1.2.[15] Prior data indicate that the probability of exposure among controls is 0.01.[16] If the true probability of exposure among cases is 0.31, we will need to study 29 case patients and 29 control patients to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. However, due to the limitations described further in the discussion section, this study involved fifteen cases in each Group, yielding only 51.7% according to the limitations discussed further in the discussion section.

2.4. Clinical Procedures

Apart from the patient's body weight, preoperative children's anxiety was measured by the pediatric dental specialist during the first consultation using a facial image scale[17] (Figure1). Once the inclusion and exclusion criteria had been fulfilled, the child was assigned using permuted block randomization to one of two groups; Group I was given a crushed tablet of Midazolam (Dormicum Roche, Toluca, Mexico) with a dosage of 0.5 mg/kg body weight diluted in 15ml orange drink (Marigold® orange, Malaysia) in the ward around 30 minutes prior arrival at the OT. Group II received no premedication and served as the control group. The blinded research assistant would generate the list of patients with a specific identity document (ID) for each child as a reference for the primary examiner to access and evaluate the data for collection next. The flow diagram of the study participants is presented in Figure 2. A trained nurse monitored the premedication consumed by the patient and closely observed any complication post-intake. The children were supervised

in a quiet environment after being given oral Midazolam. Thirty minutes after administration, the children were transferred to OT, accompanied by their parents. Parents were asked to leave the OT during the treatment. Dental treatments under GA, such as dental extractions, tooth restorations, and minor oral surgery, were commenced in a maximum of 60 minutes by experienced pediatric dental specialists oblivious to each patient's assigned study group. Once the DGA was completed, the child was moved to the post-anesthesia care unit (PACU) for close postoperative supervision.

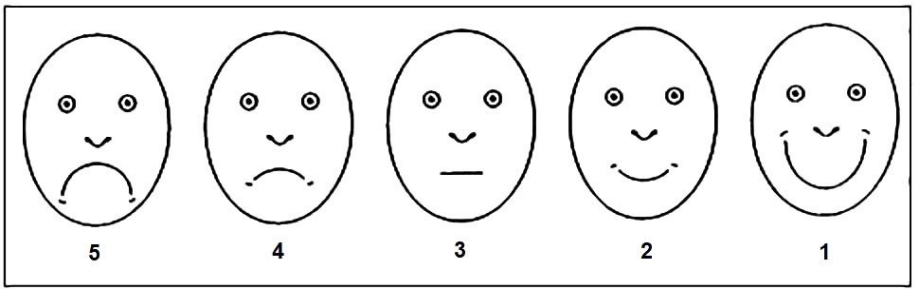

Fig 1: Facial Image Scale with image scores, 1-5

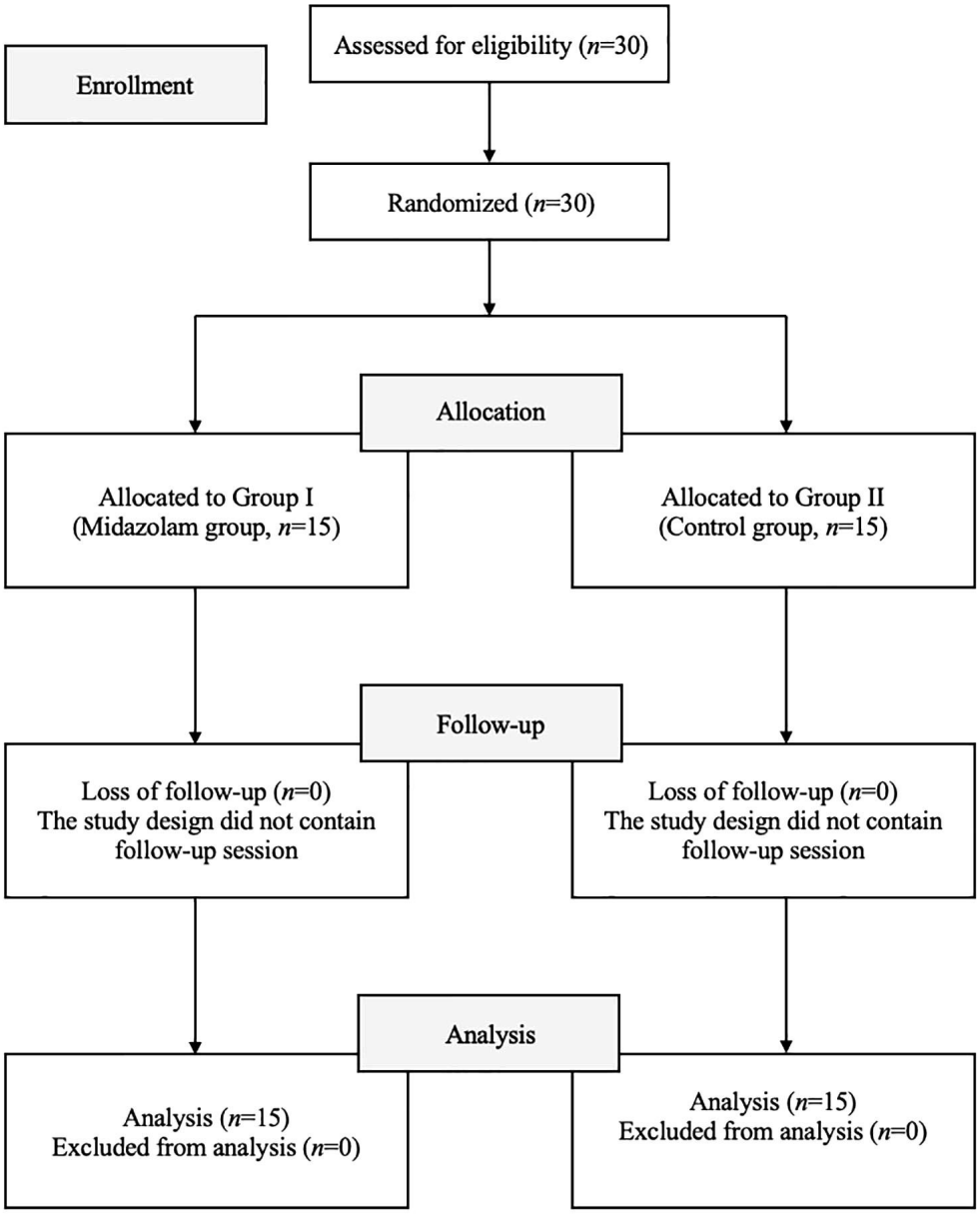

Fig 2: Consort flow diagram of the study group

2.5. *Behavior Assessment*

When the children arrived at the PACU, the same blinded research assistant used the video camera to document their condition using 2 Canon Digital Camera PowerShot SX740 HS for around 30 minutes that recorded the whole condition of the children (whole body and face seen in the video). The recorded video was later evaluated by the trained and calibrated main examiner and a pediatric dentistry specialist independently who was blind to the study group. The modified Houpt Behaviour rating scale[18] was used to evaluate the recovery behavior of children post-DGA. The percentage of

Kappa Score Agreement between the main examiner and experienced pediatric dental specialist for intra-examiners reliability was 0.912, considered an almost perfect agreement between examiners.[19] Any discrepancies in the assessment were resolved by discussion between the main examiner and a pediatric dental specialist until a consensus was achieved. Through video recording, three primary categories were evaluated: Sleep, Movement, and Crying in 3 different periods at 0,15, and 30 minutes upon arrival at PACU. They were given a score from 1 to 4 for each category. The overall behavior of children who had DGA was evaluated after 30 minutes to assess the influence of oral midazolam premedication on recovery behavior. When the Houpt Behavior Rating Scale for Sleep, Movement, and Crying received scores of 3 and 4 for each variable, the effects were considered successful; when the behavior scales for sleep, movement, and crying 30 minutes received scores of 1 and 2, the effects were considered unsuccessful. Overall behavior was dichotomized at 30 minutes, and two categories were positive, successful, negative, and unsuccessful. The positive and successful were defined as scores 4 (*good*), 5 (*very good*), and 6 (*excellent*). The negative and unsuccessful were defined as scores 3 (*regular*), 2 (*poor*), and 1 (*aborted*).

2.6. Physiologic Parameters

Physiologic parameters included peripheral capillary oxygen saturation (SPO_2), respiratory rate (RR), and heart rate (HR), which were recorded at 0, 15, and 30 minutes, starting when the patient arrived at the PACU. Reading within the normal range was considered a positive and successful outcome, while beyond and above the normal range was deemed negative and unsuccessful (Coté et al., 2019). Any abnormalities or adverse effects within 30 minutes will be recorded, such as nausea, vomiting, and fever. Tachycardia, bradycardia, hypertension, and hypotension were defined as the change in HR or BP of > or < 30% of the baseline and oxygen desaturation: fall in SPO_2< 95%.[14]

3. ASSESSMENT

3.1. Preoperative children's anxiety

The pediatric dental specialist measured preoperative children's anxiety during the first consultation using a facial image scale[17] (Figure1).

3.2. Postoperative/Recovery behavior

The modified Houpt Behaviour rating scale[18] was used to evaluate the recovery behavior of children post-DGA.

Definition of Modified Houpt Behaviour Rating Scale[18].

A rating scale for Sleep

Score 1 Anxious, excited
Score 2 Fully awake, alert
Score 3 Drowsy, disoriented
Score 4 Sleep

A rating scale for Movement

Score 1 Violent movement, interrupt treatment.
Score 2 Continuous movement making treatment difficult
Score 3 Controlled movement and does not interrupt treatment
Score 4 No movement

A rating scale for Crying

Score 1 Hysterical crying that demands attention
Score 2 Continuous, persistent crying
Score 3 Intermittent, mild crying
Score 4 No crying

A Rating for Overall Behavior

Score 1 *Aborted*, no treatment rendered.
Score 2 *Poor,* treatment interrupted, only partial treatment completed
Score 3 *Regular*, treatment interrupted but eventually completed
Score 4 *Good*, difficult, but all treatments performed
Score 5 *Very good*, some limited crying or movement,
Score 6 *Excellent*, no crying or movement

3.3. Postoperative/Recovery Physiology

Physiologic parameters included peripheral capillary oxygen saturation (SPO_2), respiratory rate (RR), and heart rate (HR), which were recorded at 0, 15, and 30 minutes, starting when the patient arrived at the PACU.

3.4. Statistical Analysis

The results obtained were subjected to statistical processing using The IBM SPSS statistical software package for Mac (version 26.0; IBM, Armonk, NY, USA) to assess the behavior and physiology of children post-dental general anesthesia. Fisher's exact and Mann-Whitney U tests were used in this study. Statistical analyses were carried out using statistical significance, defined as $p < 0.05$ was considered statistically significant.

4. RESULTS AND DISCUSSIONS

The study population comprised 30 children aged 2 to 11 who completed all procedures successfully. The sociodemographic characteristics and preoperative Facial Image Scale (FIS) of the participants are given in Table 1. The children were divided into two groups; Group I (n=15), who had oral midazolam premedication, and Group II (n=15), who had no premedication before DGA. There were 19 males and 11 females, with a mean age of 6.13 years (SD= 1.959) for Group I and 4.73 years (SD=1.668) for Group II. 29 children (96.7%) were from the Malay ethnic group, and only one child (3.3%) was from the Chinese ethnic Group. Facial Image Scale (FIS) preoperative resulted in 1 (n=1, 3.3%), 2(n=3, 10.0%), 3 (n=2, 6.7%), 4 (n=17, 56.7%), and 5 (n=7, 23.3%). The measured mean body weight of 17.99kg (SD=4.075) was for Group I and 17.97 (SD=4.514) for Group II.

Table 1: Socio-demographic profiles of the children			
Variables	***n***	**Frequency, %**	**Mean (SD)**
Age (years)			
Group I	15	50.0	6.13 (1.959)
Group II	15	50.0	4.73 (1.668)
Gender			
Male	19	63.3	
Females	11	36.7	
Ethnic			
Malay	29	96.7	
Chinese	1	3.3	
Indian	0	0	
Others	0	0	
Facial Image Scale (FIS) preoperatively			
1	1	3.3	
2	3	10.0	
3	2	6.7	
4	17	56.7	
5	7	23.3	
Mean body weight (kg)			
Group I	15	50.0	20.093 (8.387)
Group II	15	50.0	18.340 (4.204)

n: number of children; SD: Standard Deviation

Table 1 shows the socio-demographic profiles of the children who underwent dental treatment under general anesthesia. FIS evaluated preoperatively during the first visit to determine children's anxiety. [17]

4.1. Recovery behavior of pediatric DGA

The Modified Behaviour Rating Scale results from arrival, 15 minutes, and 30 minutes of children at PACU are shown in Table 2. There were no significant differences; Fisher's exact test was p>0.05 between both groups all three times, respectively. However, a pattern demonstrated that the oral midazolam group did better in behavior and physiology than the control group.

Table 2: Comparison of Modified Houpt Behavior Rating Scale in children with and without premedication oral midazolam									
Modified Houpt Rating Scale	**Group I (*n*=15)**				**Group II (*n*=15)**				***p*-value***
	Score								
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Time (minutes)	**Sleep, *n* (%)**								
0 -At arrival	-	-	5(33.3)	10(66.7)	-	1(6.7)	7(46.7)	7(46.7)	0.462
15 -After 15 minutes	-	2(13.3)	4(26.7)	9(46.7)	-	3(20.0)	5(33.3)	7(46.7)	0.791
30 -After 30 minutes	-	5(33.3)	3(20.0)	7(46.7)	-	2(13.3)	4(26.7)	9(60.0)	0.616
Time (minutes)	**Movement, *n* (%)**								
0 -At arrival	-	-	5(33.3)	10(66.7)	1(6.7)	-	7(46.7)	7(46.7)	0.462
15 -After 15 minutes	-	-	5(33.3)	10(66.7)	-	1(6.7)	6(40.0)	8(53.3)	0.710
30 -After 30 minutes	-	-	6(40.0)	9(60.0)	-	-	5(33.3)	10(66.7)	1.000
Time (minutes)	**Crying, *n* (%)**								
0 -At arrival	-	-	2(13.3)	13(86.7)	1(6.7)	2(13.3)	3(20.0)	9(60.0)	0.310
15 -After 15 minutes	-	1(6.7)	4(26.7)	10(66.7)	-	-	5(33.3)	10(66.7)	1.000
30 -After 30 minutes	-	1(6.7)	2(13.3)	12(80.0)	-	2(13.3)	3(20.0)	10(66.7)	0.727

****Fisher's exact test was applied***

Table 2 shows the comparison Modified Houpt Behavior Rating Scale in children with and without premedication oral Midazolam in three different intervals where 0 – at arrival in PACU, 15 – after 15 minutes in PACU, and 30 – after 30 minutes in PACU.

- ***Rating Scale for Sleep***

Group I showed more awake after 15 and 30 minutes, where 13.3% (n=2) and 33.3 % (n=5), respectively, compared to 20.0% (n=3) and 13.3% (n=2) in Group II at 15 minutes and 30 minutes, respectively. But there were no significant differences in rating sleep (p >0.05) between both groups at arrival, 15 minutes, and 30 minutes, whereas =0.462, p=0.791, and p=0.616, respectively.

- ***Rating Scale for Movement***

One child (6.7%) in Group II reported violent movement and interrupted treatment care given during the arrival in the

PACU. There is no significant difference in the movement for both groups, whereas p =0462, p=0.710, and p=1.000 at arrival, after 15 and 30 minutes, respectively.

- ***Rating Scale for Crying***

One child (6.7%) cried hysterically in Group II while arriving at the PACU. Group II showed persistent crying and mild crying at 13.3% (n=2) and 20.0% (n=3), respectively, compared to 13.3% (n=2) mild crying in Group I at arrival. In contrast, at 15 minutes, persistent crying showed in one child (6.7%) in Group I, while none had persistent crying in Group II. At 30 minutes, Group II showed more persistent and mild crying, with 13.3% (n=2) and 20.0% (n=3), respectively. Meanwhile, persistent and mild crying in Group I resulted in 6.7% (n=1) and 13.3% (n=2), respectively. No significant difference was reported (p=0.727) between these two groups.

- ***Rating for Overall Behaviour***

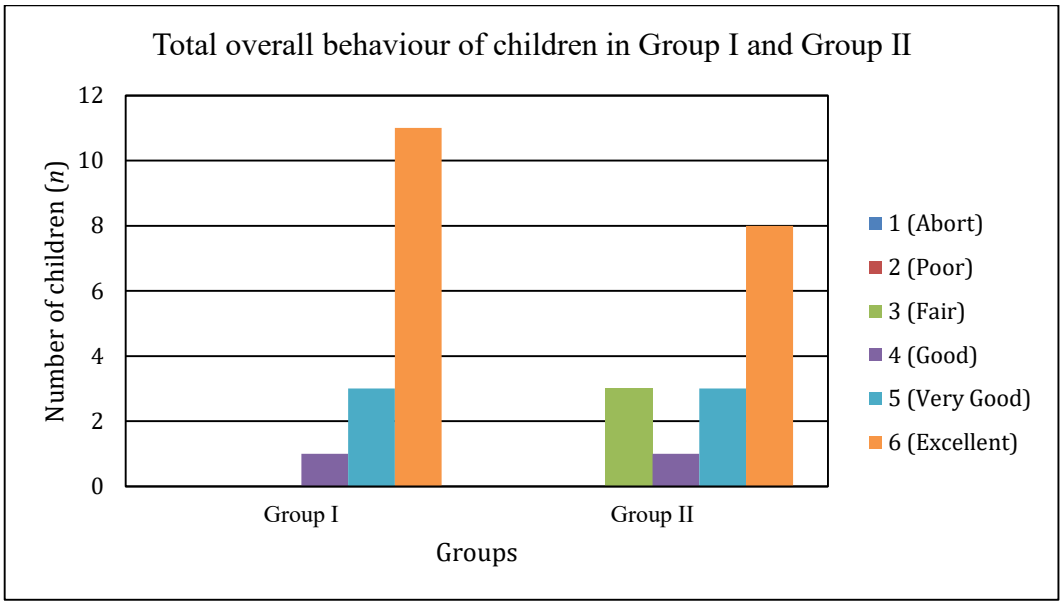

Fig 3: Total overall behavior of children in Group I and Group II

Figure 3 and Table 3 show overall behavior at 30 minutes, which was analyzed using Fisher's exact test, which gives the result of a p-value = 0.381, or > 0.05. There was no significant association between children who received oral midazolam premedication with recovery behavior of children. Although there was no significant association in both group, Group I showed more positive and successful behavior than Group II. All children (100%) in Group I showed positive and successful recovery behavior. While in Group II, three children (20.0%) exhibited negative and unsuccessful behavior.

Table 3: Total overall behavior of children in Group I and Group II

Overall Behaviour Rating	Group I *n*, (%)	Group II *n*, (%)	*p*-value*
1 (Abort)	0	0	0.381
2 (Poor)	0	0	
3 (Fair)	0	3(20.0)	
4 (Good)	1(6.7)	1(6.7)	
5 (Very good)	3(20.0)	3(20.0)	
6 (Excellent)	11(73.3)	8(53.3)	

Fisher's exact test was applied

Figure 3 and Table 3 showed the total overall behavior of children in Group I and Group II at 30 minutes in the PACU. There is a positive recovery trend in children who received oral midazolam premedication with a dosage of 0.5 mg/kg for DGA.

- ***Side Effects***

One child in Group II reported vomiting at 30 minutes in the PACU. At the same time, others showed no side effects at all three intervals.

4.2. Recovery physiological of pediatric DGA

The SPO2 (%), respiratory rate (cycles/min), and heart rate (beats/min) at intervals of 15 minutes from the arrival of children at PACU are shown in Table 4. There were no statistically significant differences in SPO2 (%), respiratory rate (cycles/min), and heart rate where p>0.05, respectively.

Table 4: Comparison of physiologic parameters between Group I and Group II						
Variables		**Median (IQR)**		**Median (IQR)**	**Z statistic**	***p*-value***
	n	**Group I**	***n***	**Group II**		
SPO_2 (%)						
0 -At arrival	15	100.00(2)	15	98.00(3)	**-1.103**	**0.345**
15 -After 15 minutes	15	99.00(3)	15	99.00(4)	**-0.652**	**0.539**
30 -After 30 minutes	15	99.00(2)	15	99.00(2)	**-0.131**	**0.902**
Respiratory rate (cycles/min)						
0 -At arrival	15	20.0(6)	15	22.00(6)	**-0.778**	**0.461**
15 -After 15 minutes	15	20.0(6)	15	22.00(6)	**-1.050**	**0.305**
30 -After 30 minutes	15	20.00(3)	15	21.00(6)	**-1.093**	**0.284**
Heart rate (beats/min)						
0 -At arrival	15	98.00(15)	15	98.00(28)	**-0.208**	**0.838**
15 -After 15 minutes	15	93.00(17)	15	96.00(14)	**-0.477**	**0.809**
30 -After 30 minutes	15	97.00(14)	15	99.00(32)	**-0.809**	**0.418**

IQR: Interquartile range; *Mann-Whitney U test was applied

Table 4 compares the physiologic parameters between Group I and Group II. The results show positive and better physiology parameters in children who received oral midazolam premedication with a dosage of 0.5 mg/kg for DGA. An unusual result was reported more in Group II. Children reported tachycardia (above 150 beats per minute) at arrival (13.3% n=2) and after 30 minutes (13.3% n=2), respectively. Two children (13.3%) in Group II and one child (6.7%) in Group I reported having bradypnea (less than 18 breaths/minute) after 30 minutes. In Group II, two children (13.3%) reported having hypoxemia (differences greater than 10%) at 15 minutes and one child (6.7%) at 30 minutes. Even though there are no significant differences in all categories, an interesting trend demonstrates greater improvement in behavior and physiology measures in children who received oral midazolam premedication with a dosage of 0.5 mg/kg for DGA.

5. DISCUSSION

The null hypothesis that oral midazolam premedication with a dosage of 0.5mg/kg would not give positive behavioral and physiological effects was accepted in our study. There is limited evidence that evaluates immediate recovery behavior and physiologic response of oral midazolam premedication in children who underwent DGA. Although there is no statistically significant difference in behavior and physiology effect between those who received oral midazolam premedication and the control group (p>0.05), our study demonstrated that oral midazolam premedication showed a positive result in providing better postoperative behavior and physiological effect in children aged 3-11 years who underwent DGA. Uncooperative pediatric patients in the dental clinic also demonstrate low cooperation in the perioperative for DGA.[20,21] As an outcome, the requirement for premedication in children who require DGA is considered.[21] The use of premedication sedation in children undergoing DGA may help to alleviate anxiety, reduce traumatic experiences, and facilitate induction of anesthesia.[20,22] Midazolam is a common and routinely used drug for oral premedication in children at a dose of 0.5mg/kg body weight.[23] Studies have shown that 0.5mg/kg of oral Midazolam effectively provided preoperative cooperation.[24,25] The oral route was more acceptable than the nasal route in children aged 2-6 years.[26] The advantages include a rapid and reliable onset and anterograde amnesia with minimal respiratory depression.[27] Some disadvantages include bitter taste, cognitive impairment, long-term behavioral disturbance, paradoxical reactions, hiccups, and respiratory depression.[21] Preoperative anxiety reduction is critical for improving preoperative cooperation among children and parents and for immediate postoperative outcomes.[23] We compared all aspects of the effect of oral Midazolam, including sleep, movement, crying, and overall behavior.

5.1. Behavioral effects of pediatric DGA

Limited published studies have investigated the recovery behavior effect of oral midazolam premedication and the control group in the PACU before its discharge. [28, 29, 30, 31] Patients' preoperative anxiety needs to be alleviated for their treatment outcomes and improved preoperative cooperation. Parnis et al. compared the postoperative behavior based on the different dosages of oral midazolam premedication. It showed that those with a dosage of 0.5 mg/kg were asleep during recovery monitoring upon arrival in the recovery room.[28] The study used a four-category behavior scale (Asleep, Awake and Calm, Awake and anxious, and crying) that showed most children who consumed oral midazolam premedication with a dosage of 0.5mg/kg were awake and calm.[28] Same as our study, children with oral Midazolam were less movement and crying but more awake. While Singh et al. reported that more children in the midazolam group were crying postoperatively compared to those in the butorphanol group using a postoperative behavioral questionnaire.[29] This study differs from the result of this study. Our study shows children with Midazolam were less crying than those who did not receive any premedication. However, both studies used different behavior assessments, which is difficult to compare, apart from other different study criteria, such as drugs used as a comparison. [28, 29] More studies reported behavior effects preoperatively before patients underwent general anesthesia for a medical procedure with premedication. Savla et al. concluded more success in laryngeal mask airway placement with low levels of sevoflurane used in children with oral Midazolam and intranasal dexmedetomidine premedication groups when compared to a placebo group.[30] Kalibatienė et al. compared oral midazolam with doses of 0.2-0.41 mg/kg and the control group by using Modified Houpt Behaviour Rating Scale.[31] The study showed children who received oral midazolam doses of 0.2-0.41 mg/kg body weight were statistically significant in sleep, movement, and crying compared with the control group 30 minutes after sedation preoperatively.[31] Tazeroualti et al. compared oral clonidine 4

g/kg body weight with oral Midazolam 0.5mg/kg body weight by using the Modified Objective Pain Scale (Movement, Tears, and Behaviours) that resulted in significantly less pain exhibited in the clonidine group (median= 3) compared to the midazolam group (median= 6.5).[32] Keles and Kocaturk also reported that children in the oral dexmedetomidine group showed a significantly lower ED score than those in the midazolam group ($p < 0.05$).[21] The study recalled data from DGA and used a different scale, the Pediatric Anesthesia Emergence Delirium Scale (PAEDS).[21] Most studies did not evaluate the immediate behavioral effect of oral midazolam premedication in DGA. A recent network meta-analysis regarding premedication drugs before GA for selective surgery summarised that dexmedetomidine, clonidine, and melatonin caused less incidence of ED post-GA compared to Midazolam.[33] Since the latter was a review that included multiple randomized control trials, it could not specify the methodology and variables involved, such as patient demographics, assessment tools, and outcomes studied.[33] Nevertheless, Midazolam is associated with significantly fewer adverse effects, similar to the finding in this study in which no adverse effects were reported in the midazolam group. Wang et. Al reported that Midazolam was not effectively superior to dexmedetomidine using Pediatric Anesthesia Emergence Delirium Scale (PAEDS).[34]

6. Physiological outcomes of pediatric DGA

This study demonstrates the better physiological effect of oral Midazolam as premedication in children who underwent DGA compared to those who did not receive any. However, no significant difference was found for the pulse oxygen saturation (SPO_2), respiratory rate, and heart rate at arrival, after 15 minutes, and after 30 minutes compared to those with oral midazolam premedication and without. However, only one (6.7%) had bradypnea in Group I at 30 minutes, although there was no significant difference ($p>0.05$). Few studies have shown physiological effects within its normal range in the midazolam group. Mountain et al. reported no side effects (blood pressure and HR fluctuation) in the midazolam group.[35] Kalibatienė et al. also reported no pharmacological significance of oral Midazolam at 0.2mg/kg – 0.6mg/kg on children's vital functions, including the respiratory, heart rate, and pulse oxygen saturation (SPO_2).[31] However, this study compared multiple doses of oral midazolam premedication.[31] Keles & Kocarturk reported that hemodynamic variables (mean HR, RR, and SPO_2) remained within normal limits in the midazolam group.[21] A systematic review by Cox et al. demonstrated that premedication with oral midazolam 0.5 mg/kg has minimized the effect on recovery time.[36] Another systematic review by Matharu et al. showed weak evidence that oral Midazolam is an effective sedative agent for dental treatment children.[37] Ashley et al. reported moderate evidence regarding the effectiveness of sedative agents using oral Midazolam for children undergoing dental treatment.[38] The authors also recommended monitoring side effects on recovery time in the recovery room before discharging the patient.[38] Current systematic review by Hisham et al. stated that oral midazolam 0.5 mg/kg body weight produces the most desirable postoperative behavior. However, there is still insufficient evidence for good behavioral outcomes with oral midazolam premedication.[39] The outstanding limitation of this study is the small sample size. It is due to the reduction of operation theatre sessions, albeit the case for DGA during the COVID-19 pandemic. Covid-19 has resulted in the cancellation of DGA for children, extended waiting lists, swab testing and self-isolation challenges, and the need to re-organize dental services.[40] Midazolam's bitter taste also challenges a child to consume the whole dosage. This study excluded four potential sample sizes due to refusal to take or complete the oral midazolam premedication. Since no syrup midazolam preparation is available in Malaysia, the tablet form has been used in this study. These findings also identify the need to explore immediate postoperative behavior in the recovery room as a pilot study. Immediate post-analgesic is mandatory to prevent postoperative pain and negative behavior postoperatively. Therefore, further future studies are highly suggested with larger sample sizes, different dose comparisons, and longer follow-up periods. It is also strongly advised to expand this investigation to a multi-center study.

7. CONCLUSION

In the current pilot study, oral midazolam premedication at a 0.5 mg/kg dose produces a favorable behavioral outcome in children with DGA. However, no significant differences are found in postoperative behavior and physiology parameters. It has been demonstrated that 0.5 mg/kg body weight has a beneficial postoperative effect and significantly improves postoperative behavior in children undergoing DGA. A postoperative adjunct analgesic is highly advised to prevent postoperative distress and pain. Further research with more sample size is needed to establish the effect of oral Midazolam as premedication sedation in pediatric DGA to discover optimum premedication sedation.

8. CLINICAL RELEVANCE

- Scientific rationale for the study: The safety and efficacy of oral Midazolam as a premedication sedation in pediatric general dental anesthetic on behavioral outcomes is insufficient to offer firm clinical recommendations.
- Principal finding: Despite reports of adverse effects in physiologic measures, oral midazolam premedication at 0.5 mg/kg body weight produces better behavioral and physiological effects than those without premedication.
- Practical implication: Oral premedication, such as Midazolam, is reported to be less intrusive when administered before surgery. According to the findings of this study, pediatric patients who received oral midazolam premedication in DGA had better behavioral and physiologic outcomes than those who did not.

9. FUNDING ACKNOWLEDGEMENT

We acknowledge the Anaesthesiology department, School of Medical Sciences and Medical Record Unit, Hospital Universiti Sains Malaysia (USM), Kubang Kerian, Kelantan, Malaysia, for assisting during data collection. This research was supported by Universiti Sains Malaysia short-term's term grant 304/PPSG/6315338.

10. AUTHORS CONTRIBUTION STATEMENT

Abdul Rauf Badrul Hisham and Norsamsu Arni Samsudin designed and conceived the study. Abdul Rauf Badrul Hisham and Norsamsu Arni Samsudin collected the data. Abdul Rauf Badrul Hisham, Norsamsu Arni Samsudin, and Wan Muhamad Amir W Ahmad analyzed and interpreted the data. Abdul Rauf Badrul Hisham drafted the manuscript. Norsamsu Arni Samsudin, Noraida Mamat, Ahmad Faisal Ismail, and Wan Muhamad Amir W Ahmad Dam provided administrative,

technical, and material support. All authors contributed to the article and approved the submitted version.

11. CONFLICTS OF INTEREST

Conflict of interest declared none.

12. REFERENCES

1. Klingberg G. Dental anxiety and behavior management problems in pediatric dentistry—a background factors and diagnostics review. Eur Arch Paediatr Dent. 2008 Feb;9;Suppl 1:11-5. doi: 10.1007/BF03262650, PMID 18328243.
2. Ramos-Jorge ML, Marques LS, Pavia SM, Serra-Negra JM, Pordeus IA. Predictive factors for child behavior in the dental environment. Eur Arch Paediatr Dent. 2006 Dec 1;7(4):253-7. doi: 10.1007/BF03262561, PMID 17164071.
3. McNeil DW, Helfer AJ, Weaver BD, Graves RW, Kyle BN, Davis AM. The memory of pain and anxiety associated with tooth extraction. J Dent Res. 2011 Feb;90(2):220-4. doi: 10.1177/0022034510385689, PMID 21149859.
4. Esa R, Jamaludin M, Yusof ZYM. Impact of maternal and child dental anxiety on oral health-related quality of life of 5-6-year-old preschool children. Health Qual Life Outcomes. 2020 Dec;18(1):319. doi: 10.1186/s12955-020-01565-z, PMID 32993663.
5. Lee CY, Chang YY, Huang ST. Prevalence of dental anxiety among 5- to 8-year-old Taiwanese children. J Public Health Dent. 2007 Jan;67(1):36-41. doi: 10.1111/j.1752-7325.2007.00006.x, PMID 17436977.
6. Kilinç G, Akay A, Eden E, Sevinç N, Ellidokuz H. Evaluation of children's dental anxiety levels at a kindergarten and a dental clinic. Braz Oral Res. 2016 Aug 18;30(1). doi 10.1590/1807-3107BOR-2016.vol30.0072, PMID 27556551.
7. Savanheimo N, Sundberg SA, Virtanen JI, Vehkalahti MM. Dental care and treatments are provided under general anesthesia in the Helsinki Public Dental Service. BMC Oral Health. 2012 Dec;12(1):45. doi: 10.1186/1472-6831-12-45, PMID 23102205.
8. Samsudin NA, Ahmad W. WMA, Nashir MNM. Awang Nawi MA, Ibrahim MSM, Aleng, NA, Ghazali FMM, Akbar NAN, Noor NFM, Ghazali PL, Rahman NA. The common dental diagnosis under general anesthesia in Hospital Universiti Sains Malaysia: A four years pediatric case study. Sapporo Medical Journal. 2021 55 (2). 1-9.
9. Phaltankar J, Shah M. Oral midazolam as a pre-medication in pediatric patients. MVP J Med Sci. 2017 May 1;4(1):30-54. doi: 10.18311/mvpjms/0/v0/i0/12464.
10. Gregory DF, Koestner JA, Tobias JD. Stability of Midazolam prepared for oral administration. South Med J. 1993 Jul 1;86(7):771-2. doi: 10.1097/00007611-199307000-00010, PMID 8322084.
11. Bong CL, Ng AS. Evaluation of emergence delirium in Asian children using the Pediatric Anesthesia Emergence Delirium Scale. Paediatr Anaesth. 2009 Jun;19(6):593-600. doi: 10.1111/j.1460-9592.2009.03024.x, PMID 19645978.
12. Chorney JM, Tan ET, Martin SR, Fortier MA, Kain ZN. Children's behavior in the postanesthesia care unit: the development of child behavior coding system-PACU (CBCS-P). J Pediatr Psychol. 2012 Apr 1;37(3):338-47. doi: 10.1093/jpepsy/jsr101, PMID 22167123.
13. Cantekin K, Yildirim MD, Delikan E, Çetin S. Postoperative discomfort of dental rehabilitation under general anesthesia. Pak J Med Sci. 2014 Jul;30(4):784-8. doi: 10.12669/pjms.304.4807, PMID 25097517.
14. Coté CJ, Wilson S, American Academy of Pediatrics, American Academy of Pediatric Dentistry. Guidelines for monitoring and managing pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. Pediatrics. 2019 Jun 1;143(6). doi 10.1542/peds.2019-1000, PMID 31138666.
15. Ahmad WM, Samsudin NA, Adnan MM, Husein A. Sample size calculations (study design based) using PS software and sampling selection (penerbit USM). Penerbit USM; 2019 Aug 9.
16. Tyagi P, Tyagi S, Jain A. Sedative effects of oral Midazolam, intravenous Midazolam, and oral diazepam in the dental treatment of children. J Clin Pediatr Dent. 2013 Apr 1;37(3):301-5. doi 10.17796/jpg.37.3.6u482603r0388558, PMID 23855176.
17. Buchanan H, Niven N. Validation of a Facial Image Scale to assess child dental anxiety. Int J Paediatr Dent. 2002 Jan;12(1):47-52. doi: 10.1046/j.0960-7439.2001.00322.x, PMID 11853248.
18. Houpt MI, Weiss NJ, Koenigsberg SR, Desjardins PJ. Comparison of chloral hydrates with and without promethazine in the sedation of young children. Pediatr Dent. 1985;7(1):41-6. PMID 3857559.
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar 1;33(1):159-74. doi: 10.2307/2529310, PMID 843571.
20. Knapp R, Gilchrist F, Rodd HD, Marshman Z. Change in children's oral health-related quality of life following dental treatment under general anesthesia for managing dental caries: a systematic review. Int J Paediatr Dent. 2017 Jul;27(4):302-12. doi 10.1111/ipd.12259, PMID 27531644.
21. Keles S, Kocaturk O. Comparison of oral dexmedetomidine and Midazolam for premedication and emergence delirium in children after dental procedures under general anesthesia: a retrospective study. Drug Des Devel Ther. 2018 Mar 28;12:647-53. doi: 10.2147/DDDT.S163828, PMID 29636599.
22. Dave NM. Premedication and induction of anesthesia in pediatric patients. Indian J Anaesth. 2019 Sep;63(9):713-20. doi: 10.4103/ija.IJA_491_19, PMID 31571684.
23. Sheta SA, AlSarheed M. Oral midazolam premedication for children undergoing general anesthesia for dental care. Int J Pediatr. 2009 Apr 13;2009:274380. doi: 10.1155/2009/274380, PMID 19946418.
24. Kaviani N, Shahtusi M, Haj Norousali Tehrani MH, Nazari S. Effect of Oral Midazolam Premedication on Children's Co-operation Before General Anesthesia in Pediatric Dentistry. J Dent (Shiraz). 2014 Sep;15(3):123-8. PMID 25191661.
25. Kumari S, Agrawal N, Usha G, Talwar V, Gupta P. Comparison of oral clonidine, oral dexmedetomidine, and oral Midazolam for premedication in pediatric patients undergoing elective surgery. Anesth Essays Res. 2017 Jan;11(1):185-91. doi: 10.4103/0259-1162.194586, PMID 28298782.

26. Verma RK, Paswan A, De A, Gupta S. Premedication with midazolam nasal spray: an alternative to oral midazolam in children. Anesth Pain Med. 2012;1(4):248-51. doi: 10.5812/aapm.4567, PMID 24904809.
27. Becker DE. Pharmacodynamic considerations for moderate and deep sedation. Anesth Prog. 2012;59(1):28-42. doi: 10.2344/0003-3006-59.1.28, PMID 22428972.
28. Parnis SJ, Forte JA, Van der Walt JH, Short T, Crowe CE. Oral Midazolam is an effective premedication for children having day-stay anesthesia. Anaesth Intensive Care. 1992 Feb;20(1):9-14. doi: 10.1177/0310057X9202000102, PMID 1609951.
29. Singh V, Pathak M, Singh GP. Oral Midazolam and oral butorphanol premedication. Indian J Pediatr. 2005 Sep;72(9):741-4. doi: 10.1007/BF02734144, PMID 16186674.
30. Savla JR, Ghai B, Bansal D, Wig J. Effect of intranasal dexmedetomidine or oral midazolam premedication on sevoflurane EC50 for successful laryngeal mask airway placement in children: a randomized, double-blind, placebo-controlled trial. Paediatr Anaesth. 2014 Apr;24(4):433-9. doi 10.1111/pan.12358, PMID 25229980.
31. Kalibatienė L, Kalibatas V, Macas A, Trepenaitis D. An evaluation of the effectiveness and safety of Midazolam in children undergoing dental surgery. Medicina (Kaunas). 2015 Jun;51(3):180-6. doi: 10.1016/j.medici.2015.04.001, PMID 28705481.
32. Tazeroualti N, De Groote F, De Hert S, De Villé A, Dierick A, Van der Linden P. Oral clonidine vs. Midazolam in preventing sevoflurane-induced agitation in children. A prospective, randomized, controlled trial. Br J Anaesth. 2007 May 1;98(5):667-71. doi: 10.1093/bja/aem071, PMID 17416907.
33. Yang CQ, Yu KH, Huang RR, Qu SS, Zhang JM, Li YL. Comparison of different sedatives in children before general anesthesia for elective surgery: A network meta-analysis. J Clin Pharm Ther. 2022 Oct;47(10):1495-505. doi: 10.1111/jcpt.13763, PMID 36029118.
34. Wang L, Huang L, Zhang T, Peng W. Comparison of intranasal dexmedetomidine and oral Midazolam for premedication in pediatric dental patients under general anesthesia: a randomized clinical trial. BioMed Res Int. 2020 Apr 24;2020:5142913. doi: 10.1155/2020/5142913, PMID 32382556.
35. Mountain BW, Smithson L, Cramolini M, Wyatt TH, Newman M. Dexmedetomidine as a pediatric anesthetic premedication to reduce anxiety and to deter emergence delirium. American Association of Nurse Anesthesiology [journal]. AANA J. 2011 Jun 1;79(3):219-24. PMID 21751690.
36. Cox RG, Nemish U, Ewen A, Crowe MJ. Evidence-based clinical update: does premedication with oral Midazolam lead to improved behavioral outcomes in children? Database of abstracts of reviews of effects (DARE): quality-assessed reviews [internet]; 2006 [cited 21/4/2023].
37. Lourenço-Matharu L, Ashley PF, Furness S. Sedation of children undergoing dental treatment. Cochrane Database Syst Rev. 2012;2012(3): CD003877. doi 10.1002/14651858.CD003877.pub4, PMID 22419289.
38. Ashley PF, Chaudhary M, Lourenço-Matharu L. Sedation of children undergoing dental treatment. Cochrane Database Syst Rev. 2018;12(12): CD003877. doi 10.1002/14651858.CD003877.pub5, PMID 30566228.
39. Hisham AR, Mohamad F, Ali I, Nik Abdul Ghani N, Wan Ahmad WM, Samsudin N. Behavioral outcome of oral midazolam premedication in pediatric dental general anesthesia: A systematic review. J Int Oral Health. 2022 Nov 1;14(6):531. doi: 10.4103/jioh.jioh_161_22.
40. Elsherif N, Lewney J, John JH. Impact of Canceled General Anaesthetic dental extraction appointments on Children Due to the COVID-19 Pandemic. Community Dent Health. 2021 Aug 31;38(3):209-14. doi: 10.1922/CDH_00015Elsherif06, PMID 34218535.