Comparison of Behavior and Dental Anxiety During Intranasal and Sublingual Midazolam Sedation – A Randomized Controlled Trial

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Objectives: *The objective of the study was to assess the behavioral effects and the changes in the anxiety level of children after intranasal and sublingual midazolam sedation using Venham's clinical anxiety scale and salivary cortisol level.* ***Study Design:*** *Twenty children aged 3 to 7 years were randomly assigned to Group A (n=10) intranasal or Group B (n=10) sublingual midazolam (0.2mg/kg) sedation. The anxiety levels at various time periods were assessed using Venham clinical anxiety scale and corresponding changes in salivary cortisol levels were assessed before and after the drug administration. The anxiety levels were assessed independently by two pediatric dentists from recorded videos. Wilcoxon signed rank test and Mann Whitney U test were used for statistical analysis using SPSS version 19.0.* ***Results:*** *There was a significant decrease in anxiety level from baseline to 20 minutes after drug administration in group A (p=0.004) and group B (p=0.003). There was no significant change in salivary cortisol levels before and after the drug administration in group A (p=0.07) and group B (p=0.38).* ***Conclusions:*** *Both intranasal and sublingual administration of midazolam was equally effective in reducing the child's anxiety. However, there was no significant difference in the salivary cortisol levels in both groups.*

INTRODUCTION

Dentists face more challenges and difficulty in treating young children. Treating a child is an art rather than just science. Children are more anxious and uncooperative between 3and 7 years[1] of age and this anxiety decreases with age.[2] The factors which have been proven to make children more anxious about dental care include syringe carpules,[3] extraction forceps, rubber dam punch, dental explorer[4] and first dental visit[1]. The child's behavior can never be stated as a reason for a shoddy dental care. It is the responsibility of pediatric dentist to perform dental treatment effectively and instill positive attitude to the child.[5] Anxiety is a systemic response. The body via the Hypothalamus-Pituitary-Adrenal (HPA) produces various mediators responsible for stress such as glucocorticoids, catecholamines, adrenocorticotropic hormone and corticotrophin releasing hormone. These mediators in turn can increase the blood pressure, heart rate, mental activity and cellular metabolism. It takes about 15 to 20 minutes for the cortisol to reach blood after a stress exposure. An additional 2 minutes (22 minutes) is required to reach saliva.[6]

Simple behavior management techniques such as tell-show-do, modeling, positive reinforcement can be used for familiarization of the child to the dental environment during initial examination. In situations where uncooperative children require more invasive procedures, these simple measures alone might not help the pediatric dentist. Moderate sedation bridges gaps between the child and the dentist in managing children with fear and anxiety, while meeting the desires of parents. Transmucosal routes such

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as intranasal, sublingual and rectal have gained attention mainly as a pre anesthetic medication. The high vascularity of the nasal mucosa[7] and high permeability of the sublingual mucosa[8] coupled with avoidance of first pass metabolism ensures higher systemic drug absorption and bioavailability than drugs administered through parenteral routes. Among the medications available, midazolam has the following advantages: rapid onset, faster action, excellent safety profile, anterograde amnestic effect, dose dependent anxiolysis.[9]

Research is limited on the anxiety control in Indian children after transmucosal sedation. The purpose of the study was to assess the behavioral effects and the change in dental anxiety level of children after intranasal and sublingual midazolam sedation using Venham's clinical anxiety scale and salivary cortisol level.

MATERIALS AND METHOD

The study protocol (figure 1) was analyzed and approved by the institutional review board of KSR Institute of Dental Science and Research (KSRIDSR). This randomized controlled trial with parallel design and allocation ratio of 1:1 was carried out in the Department of Pedodontics, KSRIDSR between June 2014 and September 2014. Healthy children (ASA I or ASA II) aged 4 to 7 years who reported with Venham's clinical anxiety scale score ≥ 3 during the first visit and required treatment under local anesthesia were selected for the study. After obtaining written consent from the parents/ guardians, the children were physically examined by the anesthetist for sedation fitness. The parents were instructed to ensure that their children followed the fasting criteria of 4 hours for semisolid food and 6 hours for solid food (AAPD 2011). Sample size calculated with type I error 5% and power of test 80% was around 7. On the day of sedation the children were assigned to either Group A (intranasal 0.2mg/kg) (n=10) or Group B (sublingual 0.2mg/kg) (n=10) based on the randomization pattern generated with computer software.

Group A: Undiluted midazolam (5mg/ml) was sprayed using a Mucosal Atomizing Device (MAD 100, Wolfe Tory Medical, Inc, USA) into both the nostrils with the child in semi reclined position.

Group B: The children were asked to touch the incisor teeth with the tip of the tongue and the undiluted midazolam (5mg/ml) was sprayed using the Mucosal Atomizing Device (MAD 100, Wolfe Tory Medical, Inc, USA) below the tongue. The children were instructed not to swallow the drug during the initial 30 seconds after which they were instructed to swallow the drug. [10]

Single operator blinded to the routes of drug administration performed the dental treatment procedures 20 minutes after drug administration. Topical gel (Precaine, Pascal International, USA) application was done prior to the local anesthetic (LA) injection procedure. The injection was given using cartridge syringe (Septodont, France) which consisted of 2% lignocaine with 1:80,000 adrenaline. One of the following treatments was rendered: extraction, pulpectomy, pulpotomy, restoration. All the procedures were planned to be completed within 20 to 30 minutes.[5] Behavior management techniques such as tell-show-do, voice control and restraints were used based on the behavior of the child. Vital signs such as blood pressure, heart rate, oxygen saturation were periodically monitored throughout the study. The children were evaluated every ten minutes using Post Anesthetic Aldrette Recovery Score for discharge which assessed the patient's airway, color, respiration, movement and the level of consciousness (each scale of 0-2). When the score was greater than 9 the children were discharged after obtaining written consent from the parents/guardians.

The whole procedure was videotaped from the time the child was brought into the dental operatory till the procedure was completed. The recorded videos were assessed using Venham's clinical anxiety[11] by two trained pediatric dentists. The anxiety assessments was scored from 0 to 5 (Score 0- Relaxed, smiling, willing and able to converse; Score 5- General loud crying, unable to listen to verbal communication makes no effort to cope with the threat. Actively involved in escape behavior) at the following time intervals: baseline (before sedation), S (20 minutes after drug administration), LA (during local anesthetic administration) and every five minutes till the end of the treatment procedure (T_1,T_2,T_3,T_4).

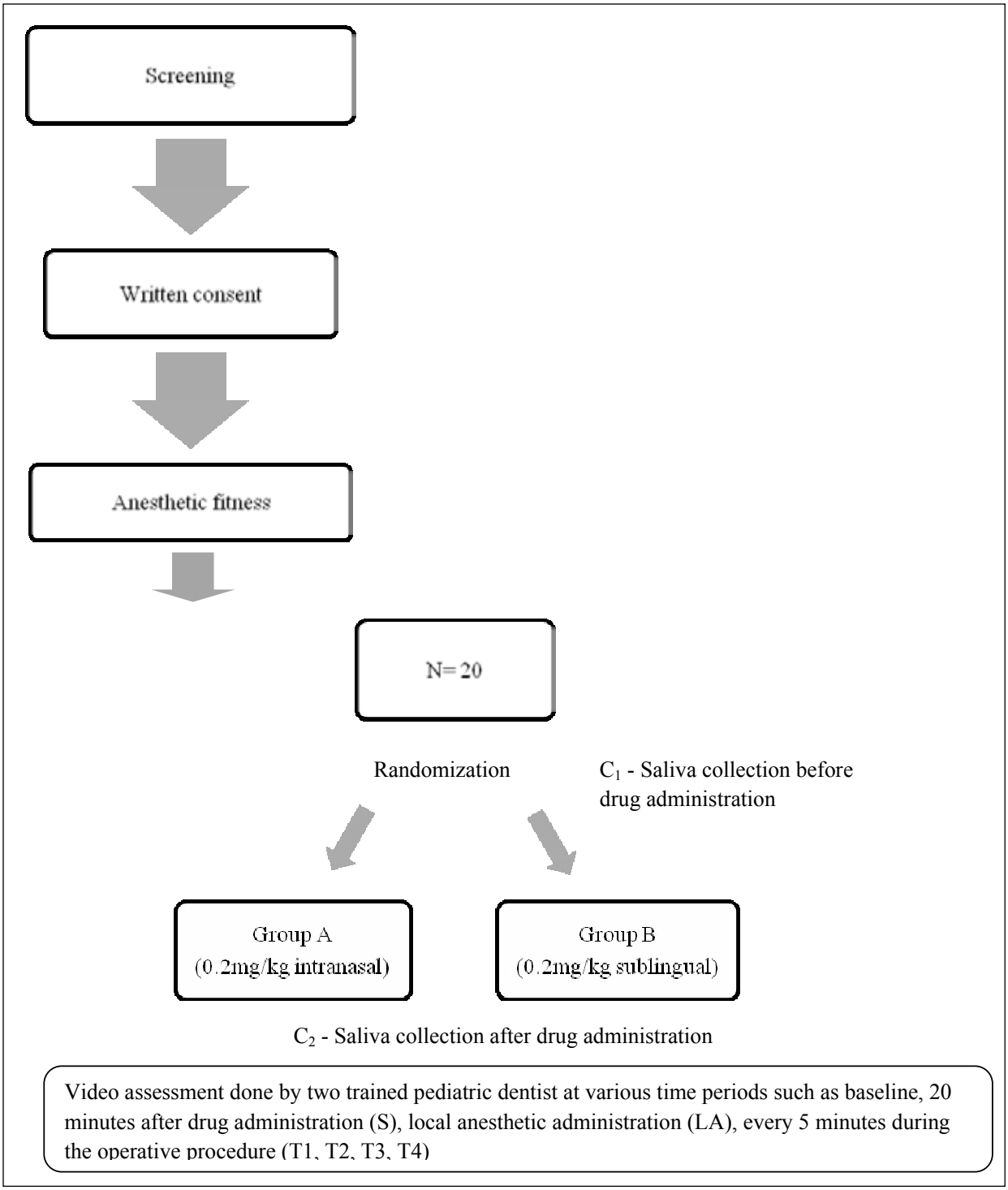
Salivary Analysis

Salivary samples were collected in the morning time between 9 am to 12 noon to minimize the effect of diurnal variation of salivary cortisol. The saliva was collected by means of syringe aspiration technique. The children were instructed to touch the upper incisor teeth with the tongue and not to swallow the saliva. The pooled saliva was aspirated using a 2ml sterile disposable syringe. The samples were collected at two different time intervals: C_1- before drug administration and C_2- 20 minutes after the drug administration. The collected salivary samples were transported to the laboratory immediately in a vaccination box packed with dry ice. The samples were centrifuged and the salivary cortisol levels were measured using ELISA (enzyme linked immunoassay, Diametra, Italy) at Roentgen's Scans World, Chennai. The obtained values were multiplied by 2.76 to convert the units to nmol/l.[6]

Statistics

The results were tabulated and analyzed statistically using SPSS version 19.0 (SPSS Inc., IBM, USA) with a 5% significance level ($p < 0.05$). Since the data was non-normal in distribution as suggested by Shapiro Wilk test ($p < 0.05$), non-parametric tests of significance were chosen. Descriptive statistics were chosen accordingly and expressed as Median and range. Wilcoxon signed rank test was used to compare the anxiety levels at different time periods to baseline and salivary cortisol levels before and after drug administration. Mann Whitney U test was used to compare the anxiety level between the two groups at various time periods. To obtain the difference in the clinical anxiety level, the anxiety level at 20 minutes after the drug administration (S) was subtracted from the baseline anxiety level. Similarly, the difference in the salivary cortisol levels was obtained by subtracting the salivary cortisol level after the drug administration (C_2) from salivary cortisol level before the drug administration (C_1). Positive value indicates a decrease and negative value indicates an increase in the clinical anxiety and the cortisol levels. The decrease in the clinical anxiety level was correlated with the change n the salivary cortisol level by means of spearman correlation test.

Figure 1: Flow chart of the study protocol.



RESULTS

Table 1 shows the comparison of the clinical anxiety levels at various time periods to baseline anxiety levels in group A and B. There was a significant decrease in anxiety from baseline to 20 minutes after drug administration in both group A (p=0.004) and B (p=0.003). Group A showed statistically significant decrease in anxiety at T_1, T_2, T_3 and T_4 time periods also. There was no significant difference in the salivary cortisol level before and after the drug administration in group A (p=0.07) and group B (p=0.38) as shown in figure 2. There was no significant correlation between the decrease in clinical anxiety and the difference in salivary cortisol level in group A (r_s=+0.213, p=0.554) and group B (r_s=+0.265, p=0.457) as shown in figure 3 and 4 respectively.

Table 1: Comparison of baseline anxiety levels to the clinical anxiety levels at various time periods in Group A and B.

Time Period	Baseline	S	LA	T1	T2	T3	T4
Group A	1.4	0	0.7	0.6	0.4	0.3	0.2
p value		0.004**	0.053	0.033**	0.020**	0.015**	0.006**
Group B	1.3	0	0.9	0.6	0.4	0.6	0.375
p value		0.003**	0.317	0.058	0.075	0.153	0.050**

Group A, 0.2mg/kg midazolam, intranasal admiinistration.

Group B, 0.2mg/kg midazolam, sublingual administration.

Baseline, anxiety level assessed when no procedure was done.

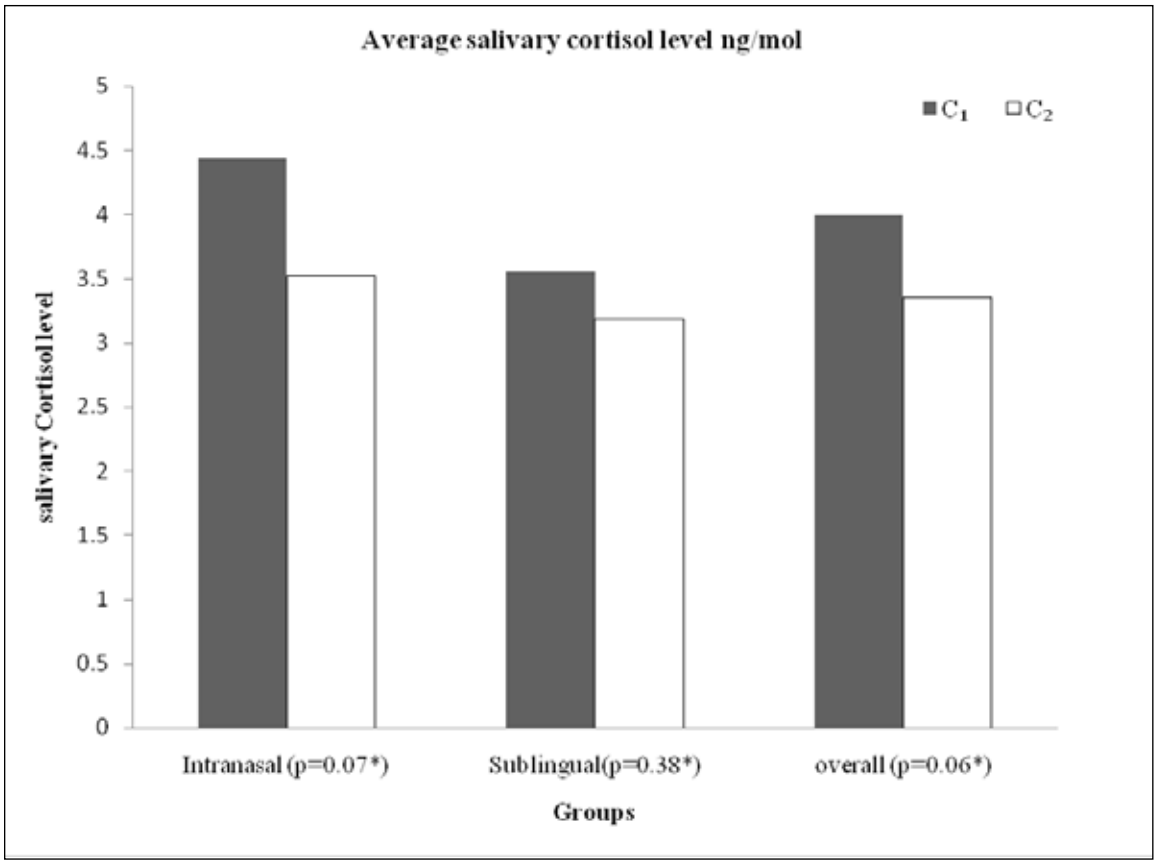
S, anxiety level assessed 20 minutes after the drug administration.

LA, anxiety level assessed during local anesthetic administration.

T1, T2, T3, T4 – anxiety level assessed at 5, 10, 15, 20 minutes during the operative procedure.

** P<0.05 significant (Wilcoxon test)

Figure 2:Comparison of the salivary cortisol levels before and after administration of midazolam in Group A and Group B.



Group A, 0.2mg/kg midazolam, intranasal admiinistration.

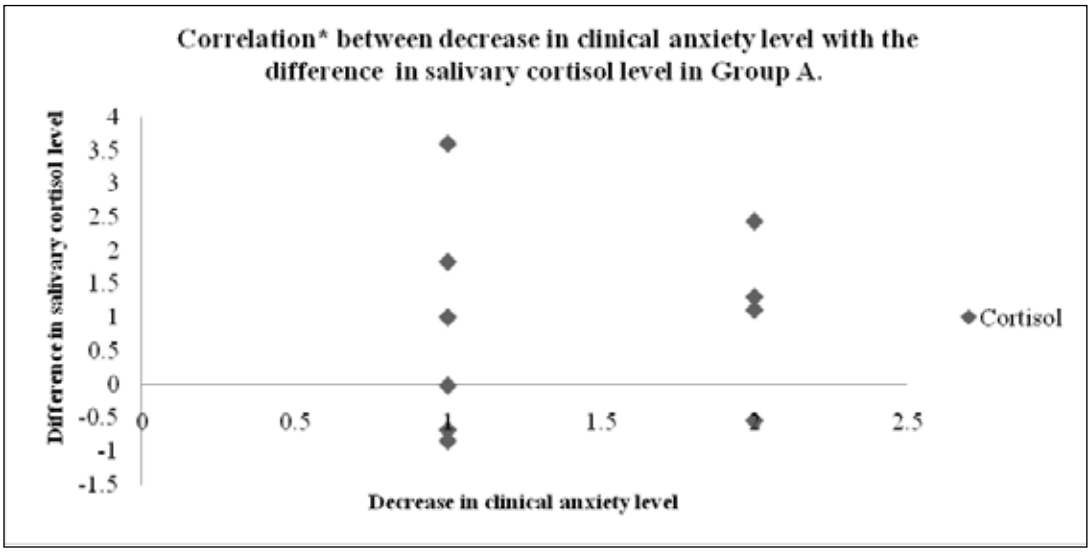
Group B, 0.2mg/kg midazolam, sublingual administration.

C_1 and C_2, before and 20 minutes after the drug administration respectively.

Overall, combined cortisol level in group A and group B.

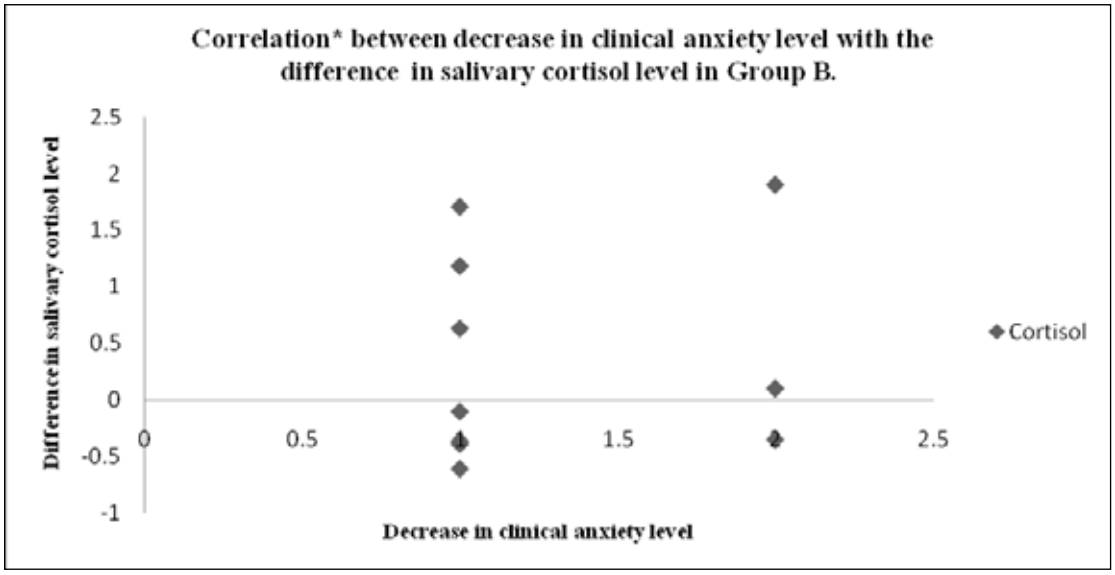
* p value (wilcoxon test used to compare the salivary cortisol levels before and after the drug administration).

Figure 3: Scattered diagram showing the correlation between decrease in clinical anxiety levels with the difference in salivary cortisol levels in Group A.



*Spearman correlation test (r_s=+0.213, p=0.554).

Figure 4: Scattered diagram showing the correlation between decrease in clinical anxiety levels with the difference in salivary cortisol levels in Group B.



*Spearman correlation test (r_s=+0.265, p=0.457)

DISCUSSION

The word anxiety emerged from the German word "Angst" which means a non-directional and unmotivated emotion. Anxiety can be assessed by objective and subjective means.[12] The objective method of assessing anxiety includes physiological parameters such as heart rate, electrodermal activity, salivary cortisol[12] and salivary alpha amylase levels.[13] The subjective method of anxiety assessment includes the use of scales such as Venham picture scale, Children's Fear Survey Schedule- Dental Subscale (CFSS-DS), Corah's Dental Anxiety scale, Modified Dental Anxiety Scale, State Trait Anxiety Inventory for Children.[12] Since these scales are mostly self reporting scales and are less reliable for usage in children, Venham's clinical anxiety scale (1980) has been used in this study. This is a 6 point scale (scores from 0 to 5) scored by the dentist on visualizing child's anxiety during the procedure. This scale is simple, reliable, valid,[11] easily recodable[14] and has high inter observer reliability.[11] In this study, the whole procedure was videotaped and rated independently by two trained pediatric dentists with inter observer reliability of 85.3% (kappa=0.755). There is limited literature assessing child's clinical anxiety after sedation. This study is first of its kind in an Indian scenario, to correlate the clinical anxiety assessment (Venham's clinical anxiety scale) with a biological stress

marker (salivary cortisol level). Evidence has stated that 0.2mg/kg of midazolam by intranasal administration provides adequate sedation with no significant clinical advantage over 0.3mg/kg intranasal or 0.5mg/kg oral administration.[15,16,17,18] Hence a dose of 0.2mg/kg of midazolam by intranasal and sublingual route was planned in this study.

There was no significant difference between the anxiety scores during the initial examination (first dental visit) and base line recorded on the day of sedation between two groups A and B. Around 44% (3 in the intranasal group and 5 in the sublingual group) of the children in this study had a Frankl negative score in their first dental visit. In spite of the negative behavior, the baseline anxiety (before sedation) had reduced considerably in most of the children in both groups. This could have been due to the positive attitude instilled in the child during their first dental visit. In intranasal group, Venham's clinical anxiety scale revealed a statistically significant decrease at various time intervals (S, T_1, T_2, T_3, T_4) compared to the baseline. In sublingual group, there was significant decrease in anxiety score from baseline to S (20 minutes after drug administration) and T_4. Similar results were shown by Kapur *et al* [9] from baseline to 15minutes after oral midazolam sedation. There was no significant difference in the physiological parameters assessed at various time periods. However, a slight decrease in heart rate and blood pressure was noted from baseline to 20 minutes after the drug administration.

Local anesthetic injection[19] and extraction[20] are the most anxiety producing threat which can affect the child's co-operative behavior in the dental office. In this study the anxiety reduced significantly 20 minutes after the drug administration. However, during local anesthetic administration the anxiety level of the children increased significantly in both group A (p= 0.038) and group B (p=0.024). In both the groups the increase in anxiety score was below the baseline anxiety. The prick during the LA injection should have been the reason for the increased anxiety.

Behavior management techniques such as tell show do, tender love care, distraction were used in both the groups during LA administration and operative procedures. The operative procedures done were pulpectomy, pulpotomy, restoration, and extraction. Two out of the three (67%) children in sublingual group who underwent extraction required physical restraints to manage them. The type operative procedure played a vital role in the child's anxiety and behavior. No significant difference in the anxiety was found between the two groups at various time periods. This implies that intranasal and sublingual (0.2mg/kg) midazolam sedation along with simple behavior management techniques can be equally effective in managing anxious children.

The salivary cortisol levels can be used as a biomarker for stress[6] and dental anxiety in children.[21] The salivary cortisol level has a circadian rhythm with peak in the early morning and decreases 30 minutes after awakening[21]. The normative value of salivary cortisol for children ranges from 5.52 to 28.92 nmol/l in the morning and 1.10 to 11.32 nmol/l in the afternoon.[6] Salivary cortisol level assessments are non-invasive, easy and not affected by flow rate.[6] In this study there was no significant difference in the salivary cortisol levels before and after drug administration. The changes in salivary cortisol levels were within the normal limits. This study showed no significant correlation between the reduction in clinical anxiety levels and the change in the salivary cortisol levels in group A (r_s=+0.213, p=0.554), group B (r_s=-+0.265, p=0.457) and in the combined group irrespective of sedation used (r_s=+0.227) (p=0.335). In contrast, Hsu AA *et al* [22] reported that sedation itself is a stressful procedure and can cause a significant increase in salivary cortisol. Kanagne *et al* [23] stated that it is the pain rather than the anxiety alone which is needed to increase the salivary cortisol level. Brand *et al* [24] and sadi *et al* [25] have also shown that no significant correlation was observed between dental anxiety score (DAS) and salivary cortisol levels.

Though it is beyond the scope of this study, it was observed that the acceptance was better with sublingual route and the depth of sedation was better in intranasal route. No adverse effects were noted in this study in both the groups.

CONCLUSIONS

1. There was significant decrease in clinical anxiety level after midazolam administration in both the groups.
2. There was no significant difference between the two groups A and B.
3. There was no significant difference in the salivary cortisol levels before and after the drug administration.
4. There was no significant correlation between the decrease in the clinical anxiety and the change in the salivary cortisol levels.
5. There was no significant difference between the physiological parameters within the group at various time periods.

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