Effect of oral-transmucosal midazolam sedation on anxiety levels of 3-4 years old children during a Class II restorative procedure

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Abstract

Aim: A double-blind randomized control trial was conducted to assess the effect of oral-transmucosal midazolam sedation on changes in anxiety levels of precooperative children during a Class II amalgam restorative procedure. **Methodology:** A sample of 40 healthy, American Society of Anesthesiologists I, children aged 3-4 years having at least one carious primary mandibular molar requiring a Class II amalgam restoration with no previous dental history were randomly divided into experimental and control groups comprising of 20 children each. The children in the experimental group (Group I) received 0.5 mg/kg body weight of midazolam mixed in strawberry syrup and those in the control group (Group II) received the same syrup mixed in saline, 15 min prior to the restorative procedure. Routine nonpharmacological behavior management techniques were used in both groups. The anxiety levels were recorded using Venham's anxiety scale at the start and end of each procedural step. **Results:** There was a significant ($P < 0.001$) reduction in the anxiety levels of children in the experimental group on entry into the operatory compared with the control group. Introduction of each fear evoking stimuli showed a somewhat similar increase in anxiety levels in the two groups. In spite of a similar trend, the anxiety levels remained much lower in Group I than in Group II. **Conclusion:** Midazolam in conjunction with behavior management is more helpful in relaxing the child initially than behavior management alone, thus increasing the chances of successful and easy accomplishment of further treatment steps.

Keywords: Anxiety levels, oral midazolam, restorative procedure

Introduction

A pleasant and pleasurable first dental visit of the child is important in establishing a bond of trust between him and the dentist, thus ensuring a successful outcome of the ensuing treatment. Achieving a child's co-operation to deliver the required dental care always remains a challenge for a pediatric dentist. Children avoid dental treatment mainly due to fear and anxiety resulting from anticipated pain, fear of unfamiliar surroundings, bright lights, loud noises, sharp instruments etc., and it is more so at the time of the first visit.[1,2] Since young children are curious by nature, simple methods like tender love and care (TLC), modeling and tell show and do (TSD), in which a pediatric dentist is well trained, can be successfully used on a majority of children for an introduction to the operatory and familiarization.[3] These methods, however, may not prove to be as successful in the very young potentially un-cooperative children <4 years of age, leaving a large number of procedures, many a times, unaccomplished or compromised. This group makes up a sizeable number of pediatric dental patients visiting the out-patient department for treatment. A handful of other cases, which also remain outside this domain, are children with inherent behavioral problems and young, anxious children reporting with dental emergencies requiring immediate attention.

The obvious alternative to management of such children remains sedation or general anesthesia. General anesthesia, apart from being an expensive procedure, requires a hospital set-up and is sometimes a poor compromise between the extent of treatment and difficulties associated with it.[4] It therefore, remains a good choice for children requiring extensive treatment or children not found fit for sedation usually due to an underlying medical problem or sometimes, parental demand. For the majority of the cases, sedation/anesthesia remains the first choice.

The various agents currently being used, the world over, for sedation/anesthesia in pediatric dentistry, are propofol,[5-7] ketamine,[8,9] midazolam,[10-13] N_2O-O_2 analgesia[14-17] and sevofluorane.[18] These drugs/agents can be administered via, intravenous, oral, rectal, intranasal, and inhalation routes. Out of various routes, it is the oral route, which is considered

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the most acceptable and convenient. Midazolam, via the oral/oral-transmucosal route is currently a popular agent among pediatric dentists for sedating young children as it is a short acting benzodiazepine, which is efficacious,[10,12] has a rapid onset of action,[19] an excellent safety profile,[11] a reliable dose dependent anxiolysis[20] and a low-grade anterograde amnestic effect.[21,22] The limitations of oral midazolam include a poor depth of sedation,[23] poor analgesia,[24] respiratory depression[24,25] and a short duration of action. Moreover, it is not always successful for all types of cases and procedures. There is no study in the literature, which has studied the effect of midazolam sedation on common anxiety provoking stimuli in dentistry. The purpose of this study was to evaluate if 0.5 mg/kg midazolam via the oral-transmucosal route is efficacious in significantly reducing the child's anxiety at different procedural steps of a Class II restorative procedure compared with placebo, as measured by the Venham's Clinical Anxiety Scale.

Methodology

A sample of 40 healthy, American Society of Anesthesiologists I, children aged 3-4 years having at least one carious primary mandibular molar requiring a Class II amalgam restoration and no previous dental history were selected from the out-patient Department of Oral Health Sciences Centre, Postgraduate Institute of Medical Education and Research. The children were randomly divided into experimental and control groups comprising of 20 children each, using block randomization technique. Written informed consent was obtained from the parents of children involved in the study. On the day of the procedure, the children in the experimental group (Group I) received 0.5 mg/kg body weight of midazolam (Ranbaxy, 1 mg/ml vial) mixed in strawberry syrup and those in the control group (Group II) received the same syrup mixed in saline, 15 min prior to having been taken inside the operatory by the principal investigator (PI). The solutions were administered by the PI in increments, using a bowl and spoon. The study was double-blind in nature with both the investigator and the parents/child not aware of the group to which they belonged. To maintain the blind nature of the study the test and control solutions were prepared by a co-investigator and were of similar consistency. The clinical procedure for both groups comprised of the following steps: Entry into operatory (OE); 15 min after administration of the test solution the child was brought into the operatory accompanied by the anesthetist and the chief investigator to be seated in the dental chair, administration of local anesthesia (LA); local anesthetic gel (xylocaine gelly) was applied on the site of injection on the side of the tooth being restored, followed by a classical inferior alveolar nerve block in that region with 2% lignocaine hydrochloride having 1: 80,000 dilution of adrenaline, using a 26 gauge sterile needle, rubber dam application (RDA); amalgam being a technique sensitive material all cases were treated under rubber dam. In most cases clamp no. 8a was used for primary second molars and premolar clamps no. 1 and 2 for primary first molars, operative procedure (OP); in the selected carious mandibular molars, a Class II mesio-occlusal or disto-occlusal cavity was prepared depending on the location of carious lesion followed by restoration with amalgam, by a single investigator (PI). The anxiety levels were evaluated by the PI using the Venham's Clinical Anxiety Scale (1977) [Table 1], first at baseline as the "pretreatment anxiety scores" and then at the beginning and termination of each one of the treatment steps as "during treatment anxiety scores." Behavior management techniques (BMT) such as TLC, TSD, distraction were used in both groups, voice control and physical restraint were used only when the child showed extremely un-coperative behavior corresponding to Venham's score of ≥4, leading to interference in treatment. The parameters such as total treatment time, depth of sedation and acceptability of the drug were also recorded and have been shared in a previously published part of the same study. A trained anesthetist, at baseline and subsequently at every 15 min interval monitored all children for blood pressure, respiratory rate, and oxygen saturation during the entire procedure. Student's *t*-test at 5% significance level was used for analysis. For intragroup analysis, paired *t*-test was used, and for inter group analysis independent *t*-test was used.

Table 1: Venham's Clinical Anxiety Rating Scale (1977)

0.	Relaxed, smiling, willing, able to converse, best possible working conditions. Displays the behaviour desired by dentist spontaneously, or immediately upon being asked
1.	Uneasy concerned. During stressful procedures may protest briefly and quietly to indicate discomfort. Hands remain down or partially raised to signal discomfort . child willing and able to interpret experience as requested. Tense facial expression and breathing is sometimes held in (high chest). Capable of cooperating well with treatment
2.	Tense tone of voice, questions and answers reflect anxiety. During stressful procedures, verbal protest, hands tense and raised but not interfering much. Child interprets situation with reasonable accuracy and continues to cope with his/her anxiety. Protest more distracting and troublesome. Child still complies with request to cooperate. Continuity is undisturbed
3.	Reluctant to accept the treatment situation, difficulty in assessing situational threat. Pronounced verbal protest, crying. Using hands to try to stop the procedures. Protest out of proportion to threat or is expressed vehemently before the threat. Copes with situation with great reluctance. Treatment proceeds with difficulty
4.	Interference of anxiety and ability to assess situation. General crying not related to treatment. Prominent bodily movements, sometimes needing physical restraint. Child can be reached through verbal communication, and begins eventually to cope. Though with reluctance and great effort. Protest disrupts procedure
5.	Out of contact with the reality of threat. Hard, loud crying, screaming, swearing. Unable to listen to verbal communication. Regardless of age, reverts to primitive flight responses. Actively involved in escape behaviour. Physical restraint required

Results

Changes in anxiety levels

The two groups were found to be relatively well matched according to the baseline anxiety levels assessed using the Venham's scale. Though the baseline anxiety levels were slightly greater in the midazolam group, the difference was statistically not significant [Table 2]. There was a highly significant ($P < 0.001$) reduction in anxiety levels in the midazolam group from the baseline levels till the time the child was brought into operatory 15 min after administration of the test solution. In the behavior management group, there was a slight increase in anxiety from baseline until OE. The increase, however, was statistically not significant [Table 2].

The baseline and final values corresponded to the anxiety levels at the start and end of each procedural step. It can be appreciated that the majority of the times the mean final values were always lower than the baseline values in both groups [Table 3]. This trend was seen for all steps in Group I. The Group II showed a similar pattern for step "LA" and "RDA." The opposite of this pattern was seen only in "OE" step of Group II where the final anxiety levels were higher than baseline, and a difference was also seen in the step "OP" where both values were same. The differences were not statistically significant for any step in either group. Though a somewhat similar trend was seen in the two groups in terms of reduction from the baseline anxiety levels to the final anxiety levels, it was, however, noted that both baseline and final anxiety levels remained lesser in Group I throughout the clinical procedure as compared to Group II [Table 3 and 3a]. This intergroup difference was significant for OE, and LA administration ($P < 0.01$) and statistically not significant for RDA and OP.

It was interesting to note that in both the groups the baseline anxiety levels of the succeeding stage always exceeded the final values of the previous stage until the step "RDA" [Table 3 and 3b]. This trend was, however, reversed in case of the OP step in both groups where the baseline anxiety levels were lower than the final levels after RDA ($P > 0.1$).

Further, difference in anxiety levels was derived by subtracting the final values from baseline values for each clinical step in the two groups. The mean values for OE were found to be 0.10 for Group I and - 0.20 for Group II respectively. The negative value for Group II indicated that instead of a decrease in anxiety score from baseline to final there was an increase in anxiety [Table 3 and 3c]. This discrepancy was statistically not significant ($P > 0.1$). In the steps that followed, that is, LA and RDA, the decrease in anxiety was found to be of a greater degree in Group II than in Group I ($P > 0.1$). The children in Group II did not show any change in the anxiety level during the start and end of OP compared with a 0.26 decrease in Group I ($P > 0.1$).

Unaccomplished procedural steps in children of the two groups

In Group I; bringing the child into operatory and administration of LA, could be accomplished in all the cases compared with Group II where it was not possible to bring two children inside the operatory, and another five children refused LA administration, making a total of seven children in whom this step could not be accomplished. One child in Group I refused RDA (never reached the next clinical step) and one more did not allow the OP to be completed, thus having unaccomplished procedures in two cases. In Group II, the total number of children in whom RDA could not be accomplished were 12, and there was one child who refused the OP making a total of 13 children in whom cavity cutting and filling remained unaccomplished [Table 4].

Behavior management techniques used for successfully completed procedural steps

It was observed that almost all children in Group I could be managed using TSD only, except for two children who required use of voice control and physical restraint during RDA. On the contrary, in Group II, two children required restraint even during OE, three during administration of LA and two during RDA. None of the children in this group, however, required restraint for the OP [Table 5].

Table 2: Comparison between baseline anxiety and anxiety level on entry into operatory 15 minutes after administration of the test solution

	Baseline ($\bar{\chi}$±SD)	On entry ($\bar{\chi}$±SD)	*P* value
Midazolam+BMT	2.05 1.43	0.35 0.49	<0.001
BMT	1.85 0.98	1.95 1.67	>0.1
P value	>0.1	<0.01	

Midazolam+BMT (Behavior management): Group 1 BMT (Behavior management alone): Group 2, SD: Standard deviation, BMT: ???

Table 3: Mean anxiety scores during treatment

	Midazolam+BMT			BMT		
	Baseline (B1) ($\bar{\chi}$±SD)	Final (F1) ($\bar{\chi}$±SD)	*P* value	Baseline (B2) ($\bar{\chi}$±SD)	Final (F2) ($\bar{\chi}$±SD)	*P* value
On entry till patient sits on chair	0.35 0.49	0.25 0.44	>0.1	1.95 1.67	2.15 1.93	>0.1
Local Anaesthesia	1.35 0.87	1.0 0.86	>0.5	2.78 1.39	2.31 1.70	>0.1
Rubber dam application	1.55 1.32	1.40 1.57	>0.1	2.62 1.90	2.18 2.23	>0.1
Operative procedure	1.15 1.31	0.89 0.1	>0.1	1.38 1.92	1.38 1.85	>0.1

SD: Standard deviation

Table 3a: Comparison of baseline and final value

	B_1 vs B_2 (*P* value)	F_1 vs F_2 (*P* value)
OE	<0.01 (S)	<0.01 (S)
LA	<0.01 (S)	<0.01 (S)
RDA	>0.05	>0.05
OP	>0.05	>0.05

OE: On entry, LA: Local anaesthesia, RDA: Rubber dam application, OP: Operative procedure

Table 3b: Comparison of the final value of one step with baseline of next step

	Midazolam+BMT (*P* value)	BMT (*P* value)
OE - F vs LA - B	<0.01 (S)	<0.01 (S)
LA - F vs RDA - B	<0.05 (S)	<0.05
RDA - F vs OP - B	>0.1	>0.1

OE: On entry, LA: Local anaesthesia, RDA: Rubber dam application, OP: Operative procedure, BMT: ???

Table 3c: Intergroup comparison of 'difference of final and baseline anxiety levels', for each step

	Midazolam+BMT	BMT	*P* value
OE	0.10	−0.20	>0.1
LA	0.35	0.47	>0.1
RDA	0.15	0.44	>0.1
OP	0.26	0.00	>0.1

OE: Entry into operatory, LA: Local anaesthesia, RDA: Rubber dam application, OP: Operative procedure, BMT: ???

Table 4: Number of unaccomplished procedural steps in children with incompatible treatment

Groups	*n*			
	OE	LA	RDA	OP
Midazolam+BMT	-	-	01	02
BMT	02	07	12	13

OE: Entry into operatory, LA: Local anaesthesia, RDA: Rubber dam application, OP: Operative procedure, BMT: ???

Table 5: Behavior management techniques used for successfully completed procedural steps

Groups	Midazolam+BMT				BMT				*P* value
	TSD		Restrain		TSD		Restrain		
	n	%	*n*	%	*n*	%	*n*	%	
OE	20	100	00	00	16	89	02	11	>0.1
LA	20	100	00	00	10	77	03	23	>0.1
RDA	17	90	02	10	06	75	02	25	>0.5
OP	18	100	00	00	07	100	00	00	>1

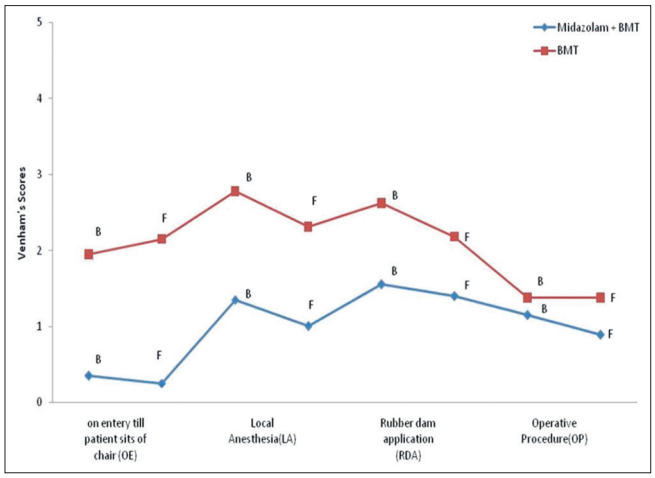
OE: Entry into operatory, LA: Local anaesthesia, RDA: Rubber dam application, OP: Operative procedure, BMT: ???

The differences in the use of type of BMT between the two groups were, however, not found to be statistically significant ($P > 0.1$).

Discussion

The Class II amalgam restoration was a moderate time duration procedure and therefore performed in a single sitting. The categorization of clinical procedures into different stages enabled evaluation of the changes in anxiety levels due to the introduction of different stimuli during a particular stage, e.g. "OE until patient sits on chair," represented a situation where child was exposed to a new environment, but not yet exposed to any procedure, "administration of LA," which is known to be the most feared dental procedure, "application of rubber dam," which represented a noninvasive but new and anxiety - provoking procedure by virtue of its appearance, and "restorative procedure," which involved a moderately lengthy procedure with some painful moments.

The final anxiety levels at the end of each step in the experimental group were always found to be lower or same in comparison with the baseline levels recorded at the start of that step. The trend was also seen in all procedural steps in the control group except "on entry," showing that children in the two groups were in a more relaxed state after completion of a clinical step. This effect could not be attributed to midazolam sedation alone, as the trend was similar in the two groups for the two most fear evoking stimuli, that is, LA and RDA. The decrease in final anxiety could therefore, be a result of BMT employed during the steps, which was similar in the two groups. The effect of midazolam sedation, however, becomes apparent when we compare the increase in final anxiety levels at "on entry" in the control group to a decreased value in the experimental group [Table 3]. It shows that midazolam in conjunction with behavior management is more helpful in relaxing the child initially than behavior management alone, thus increasing the chances of successful and easy accomplishment of further treatment steps. The effect of midazolam sedation in decreasing the anxiety levels in children becomes even more apparent when the baseline and final anxiety levels were compared for each step between the two groups. It was observed that the anxiety levels remained lower in Group I as compared to Group II, throughout the treatment. This difference was statistically significant for steps "on entry" and "LA" and not significant for the steps "RDA" and "OP." The effect could be totally attributed to the sedative effect of midazolam, which significantly reduced the child's anxiety right at the first step, that is, OE and lasted until the last step thereby maintaining a lower anxiety state throughout the procedure. Though the anxiety levels in Group I increased with an introduction of each new stimulus, they still remained much lower than that in Group II. Therefore, the anxiety levels in the two groups showed a somewhat similar trend, but at different levels [Graph 1]. When the anxiety levels at the end of one step (final anxiety level) were compared with the anxiety level at the start of the succeeding step (baseline anxiety level), it was observed that after the child was brought inside the



Graph 1: Mean anxiety scores during treatment

operatory, introduction of the LA needle and syringe and rubber dam caused a significant increase in anxiety levels in both groups. Therefore, even though midazolam produced a lesser anxiety state in Group I, introduction of a new fear evoking stimuli produced a significant increase in anxiety levels even in this group, similar to that of Group II, where no sedation was present. However, it is appreciable that even after an increase in anxiety levels, children remained in a much more manageable state in the experimental group, leading to significantly greater number of completed procedures. A total number of case that could not be completed even under the effect of midazolam (Group I) were 2 out of 20 (90% successful) and 13 out of 20 could not be completed using only routine BMTs (Group II), bringing their success rate to 35% only. Moreover, the successfully accomplished procedures in Group I required physical restraint as a means of behavior management only in 10% of cases compared with 59% of times in Group II.

Midazolam, via the oral route in a dose of 0.5 mg/kg body weight has been shown to have very few side effects in the literature. The adverse experiences reported are hiccups, coughing, nausea and vomiting.[24] Paradoxical reactions of midazolam have also been recorded in children, which include hallucinations, agitation, inconsolable crying, restlessness and disorientation.[26] In our study, no such undesirable effects were seen except for two cases of mild hiccups. The vital parameters of the sedated children remained stable and within normal limits. For any sedation procedure, however, individual variations are always present and the change in depth of sedation can never be predicted. Appropriate monitoring of the patient by a trained anesthetist is therefore, always recommended.

Conclusion

From the above discussion of this study, it can be concluded that midazolam via the oral-transmucosal route in a dose of 0.5 mg/kg is an effective anxiolytic drug or sedative agent for successful accomplishment of a moderate time duration procedure like a Class II restoration (approximately 30 min). It significantly reduces a child's anxiety right at the beginning of the procedure, which causes the children to remain within normal limits of behavior management, even in cases of heightened anxiety during invasive procedures like LA and fear evoking ones like RDA. Midazolam was seen to relax the child and improve his disposition, showing a synergistic effect with BMTs, as it becomes easier to manipulate and coax children under sedative effect into accepting more difficult procedural steps and thus increasing the chances of a successful treatment.

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