Midazolam-Fentanyl Analgo-Sedation in Pediatric Dental Patients – A Pilot Study

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Objective: *The objective of this study was to comparatively evaluate the effectiveness of submucosal fentanyl when administered in conjunction with oral midazolam during pediatric procedural sedations.* ***Study design:*** *Twenty three uncooperative ASA type I children who met the selection criteria were randomly assigned to receive either submucosal fentanyl (3µg/kg) or placebo, along with oral midazolam (0.5mg/kg). A triple blind, 2-stage cross-over design was adopted so that each child received both the regimens.* ***Results:*** *Transient oxygen desaturation was observed in 4 children who were sedated with the combination of oral midazolam and submucosal fentanyl. The overall success was 73.91% with oral midazolam and submucosal fentanyl regimen and 47.83% for oral midazolam and submucosal placebo regimen. The chances of 'satisfactorily' completing a 45 minute dental procedure in an uncooperative pediatric patient was 2.8 times more, when submucosal fentanyl was used along with oral midazolam.* ***Conclusion:*** *Submucosal fentanyl appears to improve the short working time associated with oral midazolam. But the oxygen desaturation associated with this regimen necessitates further studies to evaluate the efficacy of this combination at relatively lower doses before being used routinely for pediatric procedural sedation and analgesia.*
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INTRODUCTION

Oral midazolam is commonly used to sedate children undergoing dental out-patient procedures. The reported efficacy of oral midazolam when used alone for procedural sedation during pediatric dental treatment varies from 40% to 75%.[1,2] In spite of its wide usage, the shorter duration of sedation offered by midazolam can be a major limiting factor in pediatric dental patients. In order to address this issue, numerous workers have combined midazolam with a wide variety of drugs which possess different degrees of sedative and/or analgesic properties.[3]

Opioids are the most commonly used systemic analgesics during procedural sedation and analgesia (PSA).[4] A major drawback associated with oral administration of opioids is their extensive first pass degradation resulting in their lesser bioavailability.[5] Parenteral delivery of opioids along with oral sedatives was adopted as a viable option to administer analgo-sedation, in order to minimize the metabolic degradation of opioids.[6] For medical and surgical procedures lasting less than 1 hour, the short-acting opioids such as fentanyl and sufentanil are now preferred over the longer-acting agents, such as morphine, meperidine, and hydromorphone.[4] Fentanyl is a potent opioid analgesic with rapid onset, intermediate duration (30–45 minutes), and reversibility.[7] Because fentanyl is lipophilic, it is readily absorbed across any biological membrane.[8] It is a mild sedative and hence is usually combined with other sedatives during PSA.

The combination of midazolam and fentanyl has been used intravenously for PSA during many pediatric outpatient procedures.[9,10] Many attempts have been made to administer this combination non-invasively. Due to the poor oral absorption of fentanyl, oral transmucosal route of fentanyl citrate (OTFC) administration was considered as a viable option to deliver fentanyl non-invasively in children.[11, 12] In a recent prospective study, Klein et al compared the safety and effectiveness of the combination of oral transmucosal fentanyl plus oral midazolam and oral midazolam alone for sedation in pediatric patients undergoing laceration repair.[13] These workers found that the children sedated with OTFC had significantly greater side effects, with no additional improvement in pain or activity scores.

Administration of OTFC requires greater cooperation from the children. Even though the appearance of OTFC may be appealing to children, its application during PSA in uncooperative children is questionable. Moreover, it may be

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difficult to administer a standardized regimen for children, due to individual differences in rate of sucking and subsequent absorption of the ingested drug, thereby minimizing its applicability in multi-drug sedation regimens.

Submucosal route of fentanyl administration may be a viable option to deliver fentanyl in uncooperative children who may not accept OTFC. This route has been observed to provide rapid onset and plasma levels comparable to that of intravenous sedation, which can be attributed to the rich blood supply of the oral mucosa and bypass of the first pass metabolism achieved with this technique.[14] Moreover, submucosal drug injection is not technique sensitive unlike intravenous route of drug administration. Even though, submucosal injections are traumatic; this may be a better option when compared to other techniques (intravenous or intramuscular sedation) which can be adopted in uncooperative children, who do not cooperate for inhalational or transmucosal drug delivery.

We hypothesized that a combination of oral midazolam and submucosal fentanyl would provide superior and longer duration of sedation than oral midazolam alone. Hence this investigation was performed to analyze the safety and effectiveness of oral midazolam with submucosally administered fentanyl as compared to oral midazolam with submucosally administered placebo.

METHODS

This study was conducted with the approval of Institutional Ethics Committee, Research Cell, CSM Medical University, Lucknow, India. A randomized, triple-blind, 2-stage crossover design was adopted in this study, to compare the safety and efficacy between the following two regimens-

Regimen A- 0.5mg/kg midazolam administered orally with 3µg/kg fentanyl (Inj. Trofentyl 50µg/ml, Troikaa Pharmaceuticals Ltd, India) injected submucosally (MSF).

Regimen B- 0.5mg/kg midazolam administered orally with saline (placebo) injected submucosally (MSP).

The overall success rate of MSF and MSP was the primary outcome measured through this study. The success of each sedation session was determined based on the depth of sedation, ease of treatment completion, period required for complete recovery, side effects, and changes in vital signs and oxygen saturation during treatment and recovery. As very less work was performed previously related to the use of these analgo-sedative combinations, estimation of sample size was not possible and so, it was decided to perform a pilot study involving 20 patients.

Children between 2–6 years of age for whom basic behavior guidance techniques were not successful in rendering dental treatment (response to treatment rating scale score – 1 or 2, Table 1a) were recruited for this study. It was ensured that the participants required similar dental treat-

Table 1. Scales Used To Rate Behavior/Response To Treatment And Quality Of Sedation

SCORE	CLASSIFICATION	SIGN
Table 1a - Response to treatment (ease of treatment completion) rating scale		
5	**EXCELLENT**	Quiet and cooperative, treatment completed without difficulty
4	**GOOD**	Mild objections or whimpering but treatment not interrupted. Treatment completed without difficulty
3	**FAIR**	Crying with minimal disruption to treatment. Treatment completed with minimal difficulty
2	**POOR**	Struggling that interfered with operative procedures. Treatment completed with difficulty
1	**PROHIBITIVE**	Active resistance and crying ,treatment cannot be rendered
***Satisfactory'* session -** response to treatment rating score of '4' or '5' was obtained through the first 45 minutes of the session ***'Unsatisfactory'* session-** score lesser than '4' or '5' was obtained even in one reading during the first 45 minutes of the session.		
Table 1b - Sedation rating scale		
1	**NO SEDATION**	Typical response /cooperation for this patient
2	**MINIMAL**	Anxiolysis
3	**MODERATE**	Purposeful response to verbal commands
4	**DEEP**	Purposeful response after repeated verbal command or painful stimulation.
5	**GENERAL ANESTHESIA**	Not arousable
***Adequate'* sedation -** constant score of '2' or '3' was obtained through the first 45 minutes of the session ***'Inadequate'* sedation -** score other than '2' or '3' was obtained even in one reading through the first 45 minutes of the session		

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ment on both sides of an arch, which would involve local anesthetic infiltration adjacent to the maxillary primary molar. The inclusion criteria also required that these children were free of any physical, mental or systemic disabilities (ASA type I) and had no known contraindications to the use of benzodiazepines or opioids. Airway assessment was done to ensure that these children had no abnormalities related to the mobility of neck; mouth opening; size of jaws, tongue and tonsils and had no obstructions in the airway. No child with a previous history of dental treatment under sedation or anesthesia was selected. Twenty three pediatric outpatients, who met the inclusion criteria, were selected for the study after their parents/legal guardian gave informed consent. The parents were also explained about the necessity for applying restraints when the child became uncooperative during the sedation procedure. Pre-sedation instructions were given before scheduling the appointments. Nothing per oris (NPO) status was maintained for duration of at least 4 hours for solid and milk based foods, and 2 hours for clear liquids.

Procedure

On the day of sedation, the patient's medical history and the fasting status was reviewed with the care-takers. The vital signs and oxygen saturation levels (using a pulse oximeter) of the patient were evaluated and recorded by the primary investigator. A computer-generated random number list was used to determine the order in which the patients would receive the regimens. Accordingly, fentanyl or placebo was mixed along with 0.5ml of 2% lidocaine (with 1: 200,000 epinephrine) in a disposable syringe by an anesthetist who was present throughout the procedure.

Each patient received the weight-appropriate dose of midazolam orally. When a patient was noncompliant, the drug was administered slowly into the buccal vestibule using a needle-less syringe. After 15 minutes the monitors were re-applied and the vital signs were recorded. Depending upon the regimen to be administered, the primary investigator infiltrated the contents of the syringe which was provided by the anesthetist [fentanyl or saline which was mixed with 0.5ml of 2% lignocaine (with 1: 200000 epinephrine)] in the mucobuccal fold adjacent to the primary molar, in which dental work was planned to be performed. If the child became uncooperative, restraints were applied only during injection.

The tissue response at the injection site was assessed by the primary investigator after 10 minutes using the method adopted by Schmitt *et al* [14] and Cathers *et al* [6] as (1) none; (2) mild (redness or mild edema); (3) moderate (marked redness or edema persisting even after 45 minutes); and (4) severe (sloughing or ulceration of tissues).

Dental treatment

Once the child was sedated, a co-investigator continuously recorded the vital signs and oxygen saturation levels (using a pulse oximeter) at regular intervals of 5 minutes. All dental procedures were performed by the primary investigator. Each child had 1 quadrant of dental treatment completed when possible during a session which lasted approximately for 45minutes. The primary investigator guided all the patients through the procedure using appropriate euphemisms, tell-show-do technique and distraction techniques. The standard treatment protocol which was adopted for all the patients include, topical application (20% Benzocaine, ICPA Health Products Ltd, Mumbai, India) and local infiltration of local anesthetics (2% lidocaine with 1:200000 adrenaline, Warren Pharmaceuticals, Mumbai, India) in those sites (apart from the submucosal injection site) where local anesthesia was deemed necessary. Additional local anesthetic was infiltrated locally, when the primary investigator felt that the child experienced discomfort due to insufficient anesthesia.

If the child remained uncooperative even after verbal reassurances, physical restraints in the form of mouth prop, manual hold or velcro straps were applied by a trained dental assistant, to restrain the extremities and the use of the same was documented. The treatment session was aborted when the patient became highly uncooperative, that dental care cannot be rendered even with the use of physical restraints. The level of sedation and the ease with which treatment could be completed were measured using separate 5 point scales[15] (Table 1) at regular intervals of 5 minutes by the co-investigator. Calibration exercise for the co-investigator involved rating of recorded, videographic segments of sedation sessions conducted in this centre, which were previously rated by a Professor, who was an expert in the field of sedation. Spearman rank correlation found high inter-rater reliability between the ratings of the co-investigator and professor ($r = 0.828$, $p<0.001$). During the study around 10 sedation sessions were randomly selected and the level of sedation and ease of treatment completion were rated by the professor along with the co-investigator during these sessions, in order to assess the reliability of co-investigator's ratings.

Once the treatment was completed or after the treatment session was aborted, the patient was transferred to a quite room free from disturbances for recovery. Once fully recovered, the vital signs were re-checked and the patient was discharged, when the AAPD sedation guidelines for discharge were met[16] and an Aldrette score of 9 or greater was achieved.[17] The time required for complete recovery was recorded. The care-taker, who was accompanying the child patient, was provided with postoperative instructions, emergency telephone number and an appointment for the next treatment with the alternate regimen after a gap of 1 week. The care-takers were contacted the next day and enquired for the occurrence of any adverse reactions or side effects.

The treatment session was considered 'successful' if- (1) physiological parameters remained within 20% of baseline values, (2) oxygen saturation remained at or above 95%, (3) response to treatment score of '4' or '5' ('satisfactory' treatment session) and sedation score of '2' or '3' ('adequate' sedation) was obtained during the first 45 minutes of treatment session, (4) physical restraints were not used during

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Table 2. Characteristics Of Msf And Msp Observed During The Study

PARAMETERS		MSF	MSP	P VALUE
EASE OF TREATMENT COMPLETION – 'SATISFACTORY' SESSIONS (PERCENTAGE) n = 23*		17 (73.91%)	11 (47.83%)	p = 0.031 (McNemar test)
RECOVERY TIME *(in min)*	MEAN (95% CI)	72.38 (67.63, 77.13)	55.79 (52.09, 59.49)	p < 0.0001 (Paired 't' test)
	MEDIAN (25^{TH} ,75^{TH} PERCENTILE)	75.00 (65.00, 80.00)	60.00 (50.00, 60.00)	
TREATMENT OUTCOME- 'SUCCESSFUL' SESSIONS (PERCENTAGE) n = 23*		17 (73.91%)	11 (47.83%)	p = 0.031 (McNemar test)
'UNSUCCESSFUL' SESSIONS n = 23*	TREATMENT SESSIONS COMPLETED WITH PHYSICAL RESTRAINTS	4 (17.39%)	8 (34.78%)	
	ABORTED SESSIONS	2 (8.70%)	4 (17.39%)	

*n = 23, implies the number of sessions in each group

dental treatment and (5) no major side effects were encountered during the intra- or post-operative period.

Statistical analyses

The differences in the depth of sedation, response to treatment and treatment outcome between the two groups were evaluated using McNemar test, as the response variables for all these parameters had only two possible outcomes (*adequate/inadequate; satisfactory/unsatisfactory and successful/ unsuccessful*). Wilcoxon signed rank test was used to detect the differences in behavioral ratings before and during the study, and paired samples't' test was used to detect differences between the changes in vital signs and duration required for recovery between the two groups.

RESULTS

All 23 children had completed treatment under both the regimens. The mean age of the participants was 57.6 months (SD - 12.6, range 35 – 77) and a mean weight of 12.6 kg (SD 1.88, range 8 – 16). There were 11 males and 12 females. By virtue of randomization, 12 children received regimen A first and 11 children received regimen B first. The results obtained have been summarized in Table II.

Spearman rank correlation found significant inter-rater reliability between the response to treatment ratings ($r = 0.88$, $p < 0.001$) and sedation scores ($r = 0.90$, $p < 0.001$) of professor and co-investigator. The mean depth of sedation (Fig I) and the number of children sedated '*adequately'* at different time intervals (Fig II) were both found to be greater with MSF regimen. McNemar test revealed no significant difference between the number of children who were sedated adequately during 15 minutes ($p = 0.50$) and 30 minutes ($p = 0.375$), with both the regimens. However, there was a significant difference observed in the number of adequately sedated children at 45 minutes ($p = 0.031$).

Both MSF and MSP were found to improve the behavior/response to treatment as evidenced by the statistically significant difference ($p<0.001$, Wilcoxon signed rank test) observed between the pre-study behavior ratings and the mean behavior ratings observed with each regimen. MSF offered relatively greater ease in completing procedures, in that 17 out of 23 treatment sessions (73.91%) could be '*satisfactorily'* completed, whereas only 11 sessions (47.83%) could be completed satisfactorily with MSP regimen. McNemar test revealed a statistically significant difference between the number of successful treatment sessions between the two groups ($p = 0.031$). Table III summarizes the treatment-specific success of the sedative regimens.

Transient oxygen desaturation (< 95% & < 2 minutes) was observed in 4 patients in MSF group. The oxygen saturation values remained above 95% during the remaining sedation sessions. The differences between the vital signs recorded at different time intervals with both the regimens were evaluated using paired samples't' test. Even though statistically significant differences were observed between the vital signs of MSF and MSP groups, these differences cannot be considered clinically significant as all readings were within 20% of baseline values.

One patient in both MSF and MSP group vomited after they reached home. No other adverse effects were observed or reported in children when sedated with either regimen. No abnormal tissue responses were observed at the site of injec-

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Table 3. Treatment Outcome Under Different Regimens"

S No:	TREATMENT	VISIT 1		VISIT 2	
		TREATMENTS PLANNED	UNSUCCESFUL/ ABORTED	TREATMENTS PLANNED	UNSUCCESFUL/ ABORTED
1	INDIRECT PULP CAPPING	5	1	5	3
2	INTRA CORONAL RESTORATIONS	7	2	7	2
3	PULPOTOMY	10	3	10	7

tion following submucosal administration of placebo or fentanyl.

Taking into consideration all the parameters mentioned previously for safe and successful sedation, 17 out of 23 (73.91%) MSF sessions were considered safe and successful as compared to 11 MSP sessions (47.83%).

Relative risk estimates revealed that there was 2.8 times greater chance of '***satisfactorily'*** completing a 45 minute dental procedure in an uncooperative pediatric patient, when submucosal fentanyl was used along with oral midazolam as compared to oral midazolam/submucosal placebo combination.

DISCUSSION

The results of this study indicate that the combination of oral midazolam and submucosal fentanyl is an effective analgo-sedative combination for pediatric PSA during dental treatment, which requires further evaluation. Although the changes in vital signs during MSF sedation were found to differ significantly from those observed with MSP, these changes were clinically insignificant as all the recorded values were within 20% of baseline values. Moreover, no abnormal changes where observed at the site of injection following submucosal administration of fentanyl as compared to other submucosally administered opioid analgesics like meperidine which has been reported to produce marked tissue changes commonly (Schmitt et al – 100%[14], Cathers *et al* - 26.3%[6]) at the site of injection. This can be possibly attributed to the minimal histamine releasing properties of fentanyl[18] and to the presence of epinephrine in the local anesthetic administered along with fentanyl. Even though OTFC was reported to be an effective pre-anesthetic medication prior to pediatric anesthesia,[11,12] its role as a sole agent during procedural sedation and analgesia is questionable. Klein *et al* found the combination of oral midazolam and OTFC to provide no additional benefit over oral midazolam when used alone for PSA in children.[13] However, in their study the median time range of the procedures (including lozenge administration – fentanyl or placebo) was around 35 minutes. In the present study too, no significant difference was observed between the two regimens in the number of adequately sedated children during the first 30 minutes of the sedation session. However, at 45 minutes, significantly greater numbers of children were found to remain moderately sedated when MSF regimen was used as compared to midazolam used alone.

The oxygen saturation levels of four patients who

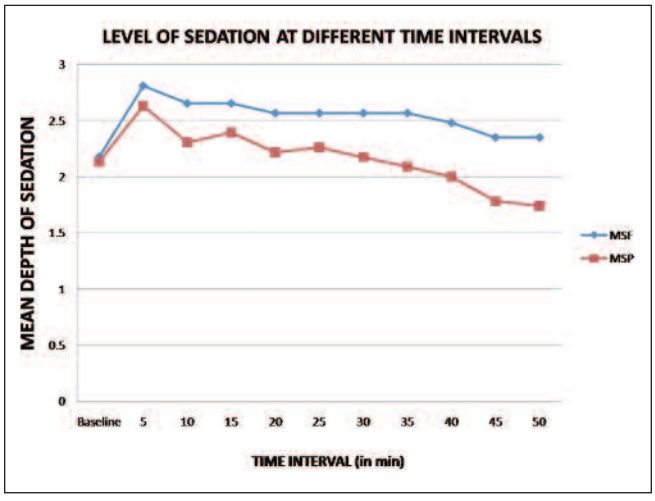

Figure 1. Number of adequately sedated patients at different time intervals with each sedation regimen.

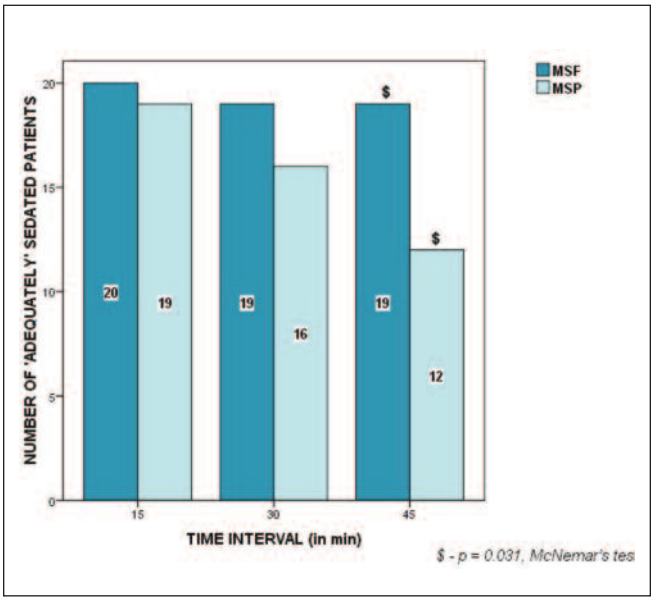

Figure 2. Level of sedation at different time intervals

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received submucosal fentanyl were found to be less than 95% for a transient period. These 4 children required only verbal or physical stimulation to increase their oxygen saturation. Similar reports of oxygen desaturation were also observed with the use of OTFC along with oral midazolam.[13]

The advantage of the crossover design adopted in this study is that it minimized the influence of confounding covariates, as the patient served as his own control, and the duration and type of dental procedures performed during each visit was standardized to reduce sample inequality. However, one major limitation of crossover studies is pertaining to the unknown effect of 'carryover'. The experiences of the children at each visit could have possibly influenced their behavior/response during the subsequent visits. But, no difference ($p = 1.000$, Fishers exact test) between the success rates of MSF was evidenced between the patients who were sedated with this regimen during the first (75%) and second (72.72%) appointments and hence it can be concluded that the influence of the 'carryover' effect was insignificant in influencing the outcome of sedation with MSF.

Only those patients who required local anesthesia adjacent to the primary molar region on both sides of the maxillary arch, and who require dental treatment which would at least last for 45 minutes during each session, were selected for the study. The combination of fentanyl and lidocaine is a commonly used regimen to provide regional anesthesia/analgesia.[19,20] In our study, apart from providing pulpal and periodontal anesthesia, the local anesthetic would have also served to minimize the pain/irritation which might have been perceived if fentanyl alone would have been injected.

In the recalcitrant child, sedation techniques that require patient co-operation (transmucosal, intravenous or inhalation) may prove difficult to be employed effectively. Although the intramuscular route may be used for administration of sedatives, submucosal route is preferable and relatively safer in uncooperative pediatric patients[21] for dental procedures which last less than an hour. In the present study, submucosal administration of fentanyl was found to significantly extend the period of sedation in children and improve the treatment outcome when compared to midazolam used per se, but the transient oxygen desaturation observed with this combination necessitates continuous monitoring of respiratory function and oxygen saturation levels.

CONCLUSION

The combination of oral midazolam and submucosal fentanyl may be considered as an effective alternative to provide extended period of analgo-sedation in uncooperative pediatric patients seeking dental treatment. However, the safety of this regimen needs to be established by further studies. Additional dose-response studies need to be conducted to evaluate the success and safety associated with relatively lower doses of submucosal fentanyl.

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