SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Review Article

A Randomized Trial of Intra-Nasal Dexmedetomidine and Sufentanil Compared with Oral Midazolam: A Pilot Study

Kelly Michienzi[1], Ramiro Mireles[2], Carrie Wanamaker[3], James Zemer[3]*, Paul Creighton[3], and Christopher Heard[2,3]

[1]*Department of Pharmacology, University at Buffalo, USA*
[2]*Department of Pediatric Anesthesiology, University at Buffalo, USA*
[3]*Department of Pediatric and Community Dentistry, University at Buffalo, USA*

***Corresponding author**
James Zemer, Department of Pediatric Anesthesiology, University at Buffalo, 1100 Main St. Buffalo, NY 14209, USA, Tel: 585-943-6551; Email: jzemer@updwny.com

Submitted: 18 June 2018
Accepted: 25 June 2018
Published: 28 June 2018
ISSN: 2333-7079

Keywords
- Dexmedetomidine; Sufentanil; Midazolam; Anesthesia; Pediatric

Abstract

Purpose: Intranasal medications have become increasingly used for moderate sedation. Intranasal sedation can facilitate procedures without intravenous line access or general anesthesia.

Methods: Pediatric patients age four to seven years old requiring moderate sedation for dental procedures were randomized to intranasal sufentanil and intranasal dexmedetomidine combination (DEX/SUF) or oral midazolam (MID). Treatment was blinded to the dentist and nurse evaluator. Efficacy outcomes included mean room noise level, Ohio State Behavior Rating Score (OSBRS) and University of Michigan Sedation Score (UMSS). Safety outcomes included pain assessment during treatment administration, oxygen desaturation, bradycardia, hypertension, nausea and olfactory function.

Results: Twenty-one patients were randomized. Baseline characteristics, median procedure times, discharge times, and pain on treatment administration did not vary. Mean room noise levels were significantly reduced in the DEX/SUF group as was median percent of time room noise level was over 80dB. DEX/SUF (n=10) behavior scores were significantly better than the MID group (n=11). UMSS values were greater in the DEX/SUF group during and post-procedure. Hemoglobin desaturation occurred more frequently with DEX/SUF. Hypertension or tachycardia occurred in five MID patients.

Conclusions: Intranasal dexmedetomidine / sufentanil combination provides greater sedation than oral midazolam, with potential over-sedation. Studies with greater patient enrollment are warranted.

ABBREVIATIONS

PO: Oral Administration; IN: Intranasal Administration; DEX: Dexmedetomidine

INTRODUCTION

Conscious or moderate sedation is routinely used to facilitate the dental care of the pre-operative or uncooperative child [1]. There are many drugs available for sedation as well as different routes of administration. At our dental clinic we provide dental sedations on a monthly basis using either oral (PO) or intranasal (IN) drugs. Oral midazolam is commonly used for these procedures. It has a good track record with respect to safety and is in expensive, however there is a significant rate of unsuccessful sedations using a fixed dose sedation regimen [2]. Intranasal midazolam can also be used, however it is no more effective than oral midazolam [2], and is painful on administration [3]. Other medications have been used for intranasal sedation such as ketamine [4], and fentanyl [5]. We have also used intranasal sufentanil as a dental sedation adjunct [2]. IN sufentanil has been used for procedures in the pediatric emergency room [6] and for anesthesia premedication [7]. Sufentanil, a potent synthetic opiate, is similar in action to fentanyl, however it is seven times more potent [8]. We have recently reported a case series using a combination of IN sufentanil with IN dexmedetomidine [9]. This case series suggested that the combination may be more effective than our routine oral midazolam regimen.

Dexmedetomidine is an alpha 2-agonist sedative agent used increasingly in children [10]. It is approved, by the FDA, for short-term ICU and procedural sedation in adults. It is usually administered by a loading dose (1 mcg/kg, given over 10 minutes) followed by an infusion at 0.3 to 0.7 mcg/kg/hour [11]. Dexmedetomidine causes less respiratory depression than most other sedative agents used [12], although it can cause severe bradycardia if given by bolus injection [13]. It has been used as a procedural sedative alone [14], or in combination with other agents [15], in children. Despite its higher cost, it is becoming more frequently used as an adjunct to anesthesia due to evidence that it has analgesic effects [16], as well as reports that it can reduce the incidence of post-operative delirium [17].

Previous published studies compared intranasal dexmedetomidine with PO midazolam for sedation of children prior to general anesthesia [18,19], but not as the sole sedative for actual treatment. One study by Talon et al., compared the

two drugs for preoperative sedation in pediatric burn patients undergoing general anesthesia. A significant difference was found in the preoperative stage, in that IN dexmedetomidine induced sleep more frequently than did PO midazolam. The drugs were found to provide a similar level of sedation [18]. A study by Yuen et al compared IN dexmedetomidine to PO midazolam as premedication for children ages 2-12 undergoing general anesthesia. This study found a significantly higher level of sedation in the patients who received IN dexmedetomidine at induction of anesthesia. No difference was found in the behavior of patients upon parental separation and induction of anesthesia [19]. Both studies support the use of IN dexmedetomidine as a safe and effective sedative agent in children.

Previously, we reported that for operative procedures that dexmedetomidine, as a solo agent, was unsatisfactory [20]. The patients appeared well sedated, however, when stimulated, they woke up and did not remain sedated during the procedure. This stimulus dependent nature of dexmedetomidine is well documented and dose dependent [21]. However, the use of higher doses can result in a significant delay in the recovery of patients [22]. The addition of an opiate improves the procedural sedation quality.

The aim of this study was to compare the effectiveness of sedation in our dental clinic of both our standard practice of PO midazolam and IN dexmedetomidine / sufentanil. We also compared the two regimens with respect cardio-respiratory stability, side effects, and safety concerns.

MATERIALS AND METHODS

After IRB approval was obtained, we aimed to recruit 50 patients that were randomized to receive either PO midazolam or IN dexmedetomidine / sufentanil for their sedation. The patients were assessed using our routine pre-sedation questionnaire, NPO status confirmed and the airway was assessed using the Mallampati score and the tonsil size using the Brodsky score. Informed consent was obtained from the parent and assent was obtained from the child if he/she was old enough (> 6 years) and not cognitively impaired. As intranasal administration of both sufentanil and dexmedetomidine are "off label", we obtained an IND from the FDA (IND#112699). The sedation regimen that the child received was randomized as well as blinded to the treating dentist and the research observer. Randomization was performed using Random Sequence Generator (www.random.org). The randomization was concealed in opaque envelopes and disclosed after consent/assent was obtained. Patients were excluded from the study if they were under 3 years of age or over 8 years of age, had a BMI of less than 5% or over 95%, were allergic to synthetic opioids, were taking an Alpha 2 agonist, 2 or more psychotropic medications, 2 or more seizure medications, or had autism or moderate to severe developmental delay. Data collection included age, weight, BMI, past procedural history, medications, drug allergies, cardio respiratory disease, and behavior disorders.

Group 1: DEX/SUF

Prior to IN drug application, olfactory function was assessed using a fruit flavored chap-stick applied to a cotton ball. After baseline vital signs were obtained, IN dexmedetomidine 2 mcg/kg (max dose 40 mcg/dose) was applied to the right nostril. After 30 minutes, 1 mcg/kg sufentanil (max dose 20 mcg) was applied to the left nostril. The child was assessed by a single anesthesiologist for any distress (1-10: no distress to max distress) during the IN drug administration. The child was asked to sniff in after each drug has been given to maximize drug absorption and reduce the risk for medication loss. The procedure started 15 minutes after the sufentanil dose was administered. All intranasal sedation medications were administered using the Mucosal Atomization Device (MAD®).

Group 2: MID

Prior to oral sedation, olfactory function was assessed using a fruit flavored chap-stick applied to a cotton ball. After baseline vital signs have been obtained, these children received PO midazolam 1 mg/kg (max dose 20 mg). After 30 minutes, the procedure started. The ease and completeness of oral drug administration was assessed by the dental resident administering the sedation and was appraised as: easy, coaxed, forced, or rejected.

Children in both groups were continuously monitored after receiving any sedative medication, including pulse oximetry until they were discharged home. All children were brought to the treatment chair and placed in a stabilization wrap (papoose board). Pulse oximetry and automatic blood pressure readings (every 5 minutes) were monitored.

The primary sedation assessment outcome was a non-subjective measurement, the noise level in the room, which was recorded every second using a Noisepro® noise logging device (3M, Oconomowoc, Wisconsin, USA). The microphone was placed 1m from the child's head. The device was calibrated at the start of each day. The data was transferred to a notebook using an infrared serial transfer system and imported into Microsoft Excel (Microsoft Inc., Redmond Washington, USA). The settings used for the noise logging are shown in Table 1.

Behavior during the procedure was assessed using the Ohio State Behavior Rating Score [5] (Table 2), by our research nurse observer. The depth of sedation was assessed using the University of Michigan Sedation Scale (Table 3), by our research nurse observer.

If either of the sedation regimens was inadequate and the dental care could not be completed, dental care was provided at a later date under general anesthesia. After the procedure was finished, the children were taken to the recovery room and observed until they had met discharge criteria, which includes stable vitals, minimum of 20 minutes in recovery room, no pain or nausea, and ability to walk unaided. We repeated the olfactory assessment after the child had woken up. A follow-up phone call within 24 hours was conducted which included a sedation satisfaction score rating from 1 to 10. In addition to our routine post sedation questions, we enquired as to whether there was any change in olfactory function.

A power analysis from our previous research and drug evaluation data [2,9], determined that using data from noise levels, with a noise level difference of 5dB, would require 40 patients. P value < 0.05 and B error < 0.2.

Table 1: NoisePro® Settings.

Setting	Description	Parameter
Recording Interval	1 second	Noise is averaged over this period
Response	Slow	Smooths out noise logging with sudden noise peaks
Exchange rate	3 dB	dB change equal to a doubling of the noise level
Threshold	40 dB	Below 40 dB all noise is ignored by the device
Range	LO	Expected range 40-110 dB noise exposure
Weighting RMS	A	Best fit of frequency response to the human ear
Weighting peak	Z	No weighting of frequency response to peak noise

Abbreviations: The NoisePRO® was setup using the same parameters for each session. The parameters used were selected as recommended for the level and type of noise exposure expected (loud, high pitched crying) as it would be heard by the human ear.

Table 2: Ohio State Behavior Rating Score (OSBRS).

Score	Behavior
1	Quiet behavior, no movement
2	Crying, no struggling
3	Struggling movement without crying
4	Struggling movement with crying

Table 3: University of Michigan Sedation Scale (UMSS).

Score	Behavior
0	Awake / Alert
1	Minimally Sedated: Tired / sleepy, appropriate response to verbal conversation and / or sounds
2	Moderately Sedated: Somnolent / sleeping, easily aroused with light tactile stimulation.
3	Deeply Sedated: Deep sleep, arousable only with significant physical stimulation.
4	Unarousable

Analysis of demographics was by Mann Whitney U and Chi Square. The OSBRS and UMSS were compared using Mann Whitney U tests and Wilcoxon signed-ranked tests. The raw noise data was compared using t-test and chi square analysis as well as one way repeated measure ANOVA. Post hoc analysis was performed using the Tukey method with a Bonferroni correction. The time / percent noise based assessments were assessed using Mann Whitney U as well as the Friedman test for repeated measures.

Children who did not receive the full dose of sedation medication (spitting out oral or sneezing/coughing out IN) were excluded from the final efficacy analysis.

RESULTS

We recruited 21 patients to this study. Patient demographics are shown in Table 4 (there were no significant differences between the groups). There were 10 children in the DEX/SUF group and 11 children in the MID group. There was also no difference between the groups for ASA classification, tonsil assessment, and airway assessment. The median doses for dexmedetomidine, sufentanil, and midazolam were 35.5 mcg, 18 mcg, and 19 mg respectively. The median procedure times for the DEX/SUF and MID were 36 and 38 minutes respectively (no significant difference). The median discharge times for the DEX/SUF and MID were 73 (range 31 to 84) and 76 minutes (range 22 to 185) respectively, there was also no significant difference.

Nine of the children took the PO midazolam easily; there were no instances of the drug being refused. The median assessment of pain with intranasal dexmedetomidine or sufentanil were both zero. The DEX/SUF group had a median of 3 procedures per patient compared to four in the MID group (no significant difference).

The noise levels from the procedure room are shown in Table 5. The mean noise level for the DEX/SUF group was significantly lower (6-10 dB) for both the local anesthesia and procedure. The mean percent of time the noise level in the room was over 80dB was also significantly less in the DEX/SUF group. Figure 1 shows the separation of the noise levels from when the child entered the operatory to going to the recovery area. The noise levels for the DEX/SUF group did not change from entry to leaving the operatory, For the MID group the noise levels were significantly different during the operatory time ($p < 0.01$). Post hoc analysis revealed that the procedure noise levels were significantly different from all other time periods except the local anesthesia placement. It appears that when a painful intervention was started the DEX/SUF group did much better. This is also borne out by the peak noise level data shown in Figure 2. The peak noise

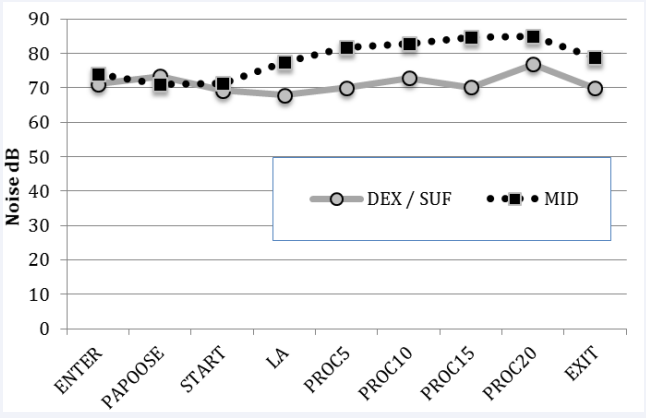

Figure 1 Mean Noise Level During Each One Second Recording Throughout the Procedure. Mean noise level during each one second recording throughout the procedure. The mean noise levels (recorded over a one second period) for each of the time periods, during the procedure for the two study groups is presented. There was no significant change in the noise levels in the DEX/SUF group over time (between the different periods of the procedure). The mean noise level in the MID group was significantly higher (*$p< 0.01$) during the operative period (PROC5 through PROC20) compared to baseline noise level on entry.
Papoose: child lightly restrained in Papoose
Start: start of the procedure; LA: placement of local anesthesia; PROC: operative procedure

Table 4: Patient Demographics.

	Age (years)	Weight (kg)	BMI Centile	Gender
	Median (Range)	Median (Range)	Median (Range)	Male / Female
DEX / SUF (N=10)	4.0 (3 to 8)	17.6 (11.8 to 25.2)	50.0 (5 to 80)	5 / 5
MID (N=11)	4.0 (3 to 8)	19.7 (12.4 to 40.0)	30.0 (18 to 95)	6 / 5

Table 5: Outcome Assessments for Both Groups during the Procedure.

	ENTER	LOCAL ANES	PROC	EXIT
Noise Levels During the Procedure (DEX / SUF)				
Mean	73.9	71.6*	73.7**	71.3*
SD	8.8	8.4	5.5	4.4
Noise Levels During the Procedure (MID)				
Mean	74.4	77.9	83.0	76.7
SD	6.6	6.3	5.9	6.2
Percentage of Time Noise level > 80dB During the Procedure (DEX / SUF)				
Median	0.8	4.0*	1.9**	1.4*
Minimum	0.0	0.0	0.0	0.0
Maximum	88.2	66.7	51.8	21.3
Percentage of Time Noise level > 80dB During the Procedure (MID)				
Median	6.2	15.5	47.0	21.3
Minimum	0.0	15.5	49.0	0.0
Maximum	41.0	44.7	79.7	87.7
University of Michigan Sedation Scores (UMSS) (DEX / SUF)				
Median	1.5	1.5	2.0*	1.5*
Minimum	0.0	0.0	1.0	1.0
Maximum	3.0	3.0	3.0	3.0
University of Michigan Sedation Scores (UMSS) (MID)				
Median	1.0	1.0	1.0	1.0
Minimum	1.0	1.0	0.0	0.0
Maximum	3.0	2.0	2.0	1.0
Ohio State Behavior Rating Scores (OSBRS) (DEX / SUF)				
Median	1.0	2.0	2.0*	2.0
Minimum	1.0	1.0	1.0	1.0
Maximum	3.0	4.0	3.0	3.0
Ohio State Behavior Rating Scores (OSBRS) (MID)				
Median	1.0	3.0	4.0	2.0
Minimum	1.0	1.0	2.0	1.0
Maximum	2.0	3.0	4.0	3.0

Abbreviations:* $p < 0.05$, ** $p < 0.002$ DEX/SUF compared to MID group.
ENTER: entering the operating room; LOCAL ANES: placement of local anesthesia; PROC: operative procedure; EXIT: exiting the operating room

recorded within any one second block if it was above 100 dB is recorded. Although the mean noise level in the DEX/SUF on entry to the room was not different than the MID group, the time spent over 80 dB (Table 5), and peak noise over 100 dB (Figure 2), were significantly greater in the MID group. These time based noise levels were also not significantly different during the operatory period for the DEX/SUF group but they were for the MID group, % time < 80 dB ($p < 0.01$) and % time peak < 100 dB ($p < 0.05$). Post hoc analysis also demonstrated these signficant differences were noted during the procedure segment.

The nurse observer sedation assessments are shown in Table 5. The DEX/SUF group was more sedated for the procedure and had better behavior scores during the procedure. For the painful local anesthesia placement, there appeared to be no benefit with the DEX/SUF group. Three children in the DEX/SUF group and one in the MID group had a UMSS of three, over-sedation by our definition of moderate sedation. All patients were rousable with stimulus, two of the children from the DEX/SUF group required supplemental oxygen.

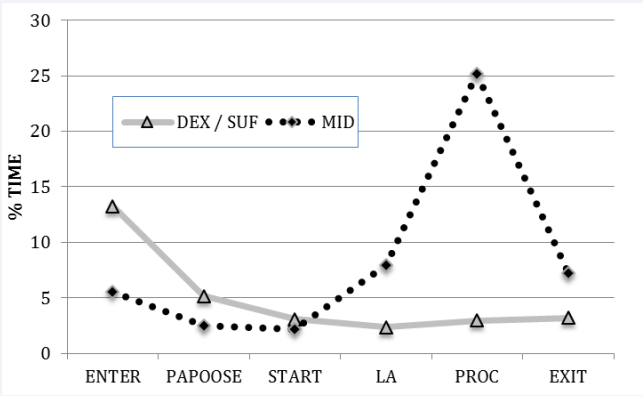

Figure 2 Median Percentage Time Peak Noise level > 100 dB During the Procedure. The percentage of time the peak noise level (noted during each one second of noise recording) that is greater than 100dB is presented for the different time periods in the two study groups. There was no significant difference over time (between the different periods of the procedure) for the DEX/SUF group. In the MID group the percentage of time with a peak noise level > 100dB was significantly higher (*p < 0.05) for the operative procedure (PROC) when compared to the papoose and start periods of the procedure.
Papoose: child lightly restrained in Papoose
Start: start of the procedure
LA: placement of local anesthesia; PROC: operative procedure

Minimal complications were present for both groups. The DEX/SUF (n=4) group had more (n=4) episodes of desaturation (< 96%) than the MID (n=1) group (p = 0.13). They were all successfully treated with the use of supplemental oxygen by nasal cannula, 2l/minute. Two patients needed a chin lift for a short period until the saturation returned to normal, after that no further interventions were required. There were no episodes of bradycardia in the DEX/SUF group. In the MID group, five patients had either tachycardia (> 180) indicative of inadequate sedation compared to none in the DEX/SUF group (p=0.038). One child receiving sufentanil had nausea, but no treatment was required. One patient in the MID group had some behavior issues on the first day at home and two patients in the MID group were sleepy and "took naps". The parents' median satisfaction scores for both sedation groups were 9.5.

The olfactory assessment using the chap-stick was not significantly different after the procedure in either group (n=15 patients), the other six children refused to participate in this assessment either pre or postoperatively.

DISCUSSION

This study was designed to compare our standard moderate sedation regimen of oral midazolam with a newer intranasal based sedation using intranasal sufentanil and dexmedetomidine. We have previously reported our experience with this intranasal combination, and the results of this case series were very promising leading us to this study.

The study, of pilot nature, was able to show some differences in these outcomes from these two techniques. The quality of the sedation from the DEX/SUF group appeared to be much better than the midazolam group. This was documented by both modes of assessment, the noise levels and the nurse observed sedation scores as well as the reduced incidence of tachycardia.

The intranasal dexmedetomidine has a slow onset, 45 minutes [23], to a good clinical effect. This is much slower than intranasal sufentanil's 10-15 minutes [24], onset. This is why we staggered the sedative administration in the DEX/SUF group. Interestingly, the children were often drowsy 30 minutes after dexmedetomidine dosing, However, when we gave the sufentanil, the stimulus of the IN administration (even though neither of these two medications causes discomfort intranasally) often woke the child up, indicating the stimulus dependent nature of dexmedetomidine and the need for an adjunct sedative. It has been shown that IN dexmedetomidine has an anesthesia potentiating effect [25], suggesting that it is a good choice as a sedation adjunct. In a busy sedation clinic, this 45 minute lead time must be taken into account.

Dexmedetomidine also has a longer duration of action. We previously reported a mean procedure time with the DEX/SUF combination of almost an hour [9]. This study did not report this; however, procedure time is dependent on how many teeth require care. Also, the discharge time was not significantly prolonged with dexmedetomidine. This can be an issue irrespective of the mode of administration.

The OSBRS and UMSS we used are validated scores that are easily taught, and we use them routinely for all of our sedation cases. However they are still subjective and non-continuous and it may be difficult to accurately score if the sedation level changes during the procedure. Another validated sedation assessment is the BIS monitor. This is objective and continuous [26], however it is best for patients who are deeply sedated and requires the purchase of an expensive machine as well as disposable probes. Movement or facial muscle activity can cause significant artifact and for moderate sedation, it may not be effective [27].

The room noise level has been reported as a method for assessing sedation [28]. It is objective and continuous. The NoisePro® is a small portable device that is simple to use. It logs the mean noise level over a specified time as well as peak noise levels during this time. It is approved for OSHA noise compliance practice and has been used in the health care setting both for the patient's perspective [29,30], as well as from dental staff [31]. The NoisePro® cannot differentiate the source of the sound in the operatory, however we have previously reported that the noise level in the operating room is less than 70dB for an anesthetized child undergoing dental restorative surgery. If the child is crying, then the room noise increases. Eighty dB has been used as a measure of poor sedation and has been shown to correlate with poor sedation scores [28]. The room noise levels in the MID group were significantly greater than the DEX/SUF. This outcome difference, between the groups, was also supported by both better sedation and behavior scores in the DEX/SUF group.

Rapid IV administration of dexmedetomidine can cause bradycardia [13], and this is why an intravenous load is given over 10 minutes. The onset from intranasal administration is similar to that from a 10 minute load and slower than IV bolus; mucosal absorption rate reduces the risk of both bradycardia and hypertension. The bioavailability of intranasal dexmedetomidine

is about 65% [32], and the dose of 2 mcg/kg (effective dose of 1.3 mcg/kg) is consistent with a 1 mcg/kg load and a 0.5 mcg/kg/hr. infusion for a 30 minute procedure (1.25 mcg/kg total).

Intranasal sufentanil has also been shown to be an effective premedication for children [33]. Doses up to 4.5 mcg/kg were used demonstrating a reduction in anxiety, however the highest doses were associated with increased nausea and vomiting, as well as reduced lung compliance. Sufentanil dosed at 2 mcg/kg intranasally did not cause discomfort [34], compared to midazolam, a well-known intranasal irritant [3]. The children given sufentanil were also more cooperative during anesthesia induction. Of note, respiratory depression has been reported after IN sufentanil 2 mcg/kg [35].

Due to its potency, sufentanil can be administered in a small volume. The high bioavailability (70%) of intranasal sufentanil also reduces the dose required [24]. Intranasal medications are best administered with a volume less than 0.5 ml to optimize the absorption of the whole dose. Larger volumes "spill over" and are usually swallowed and then subject to a slower onset and also the effects of first pass metabolism [24]. Our maximum dose of 20 mcg sufentanil is equal to 0.4 ml, and the dexmedetomidine maximum volume was also 0.4 ml (40 mcg).

We noted that desaturations occurred more commonly in the DEX/SUF group. This required the use of supplemental oxygen for 40% of the patients. This suggests that the respiratory depressant effect of the sufentanil occurs even with the presumed lower risk of this complication from dexmedetomidine. There is evidence that airway obstruction is less with dexmedetomidine sedation than with other sedative [36], or other anesthetic agents [37]. These studies, however, did not assess the effect of potent opiates on respiratory depression in combination with dexmedetomidine. The degree of hypoventilation was easily corrected with 2 l/minute of supplemental nasal cannula oxygen. As such, we recommend that whenever potent intranasal opiates are administered, supplemental oxygen as well as capnography are used. If over sedation does occur, then it is possible to reverse the sufentanil using intranasal naloxone. This route of naloxone administration is now commonly used by paramedics [38], and has been reported successfully for pediatric over-sedation [39].

The intranasal use of both medications is off label. Therefore we obtained an IND from the FDA. Approval was based upon the FDA requiring an assessment of olfactory function with respect to these unapproved medications being administered intranasally. This olfactory assessment did not note any change either, immediately nor on the follow-up phone call.

A problem with our study was the small number of patients we were able to recruit. We were able to recruit just over half of the predicted cases as suggested by our power analysis. There appeared to be a difference between these sedation groups both with respect to clinical efficacy as well as the incidence of side effects, however this result could be misleading due to the sample size. The results we obtained for the DEX/SUF group do, however, resemble those from our previously reported case series [9], leading some credence to its validity.

The small recruitment with respect to our power analysis may not be as detrimental as it appears. We actually found almost twice the expected noise level difference between the groups, with about a 10 dB difference for the procedure assessment. Also the % time noise based assessments showed even larger benefits with a 20- 40% reduction in the DEX/SUF group. As such we believe that this data has clinical utility due to the degree of response noted.

CONCLUSION

Although there was a small sample size in this study, there is evidence that intranasal dexmedetomidine and sufentanil is a superior moderate sedation regimen compared to oral midazolam. The onset of dexmedetomidine may be slower, but the duration and depth of sedation appear to longer and more adequate. The possibility of over-sedation must be acknowledged. The use of supplemental oxygen appears to correct the mild respiratory depression. In addition, nausea may be a concern with opiate use, however our study was not able to detect this. Further studies are required to fully determine the efficacy and safety profile for this intranasal sedation regimen combination.

REFERENCES

1. Heard CMB, Wanamaker C. Dental Sedation in Children. Curr Anesthesiol Rep. 2015; 5: 115-124.
2. Heard CMB, JoshiP, Michienzi K, Feldman D, CreightonP. A comparison of 4 different conscious sedation techniques for the pediatric dental patient. Pediatr Anesth. 2010; 20: 924-930.
3. Antonio C, Zurek J, Creighton P, Johnson K, Heard C. Reducing the Pain of Intranasal Drug Administration. Pediatr Dent. 2011; 33: 415-419.
4. Andolfatto G, Willman E, Joo D, Miller P, Wong WB, Koehn M, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series. Acad Emerg Med. 2013; 20.
5. Saunders M, Adelgais K, Nelson D. Use of intranasal fentanyl for the relief of pediatric orthopedic trauma pain. Acad Emerg Med. 2010; 17: 1155-1161.
6. Stephen R ,Lingenfelter E, Broadwater-Hollifield C, Madsen T. Intranasal sufentanil provides adequate analgesia for emergency department patients with extremity injuries. J Opioid Manag. 2012; 8: 237-241.
7. BayrakF ,Gunday I, Memis D, Turan A. A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. J Opioid Manag. 2007; 3: 74-78.
8. Lundeberg S, Roelofse JA. Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. Pediatr Anesth. 2011; 21: 274-279.
9. Hitt J, Coraconin T, Michienzi K, Creighton P, Heard C. An Evaluation of Intranasal Sufentanil and Dexmedetomidine for Pediatric Dental Sedation. Pharmaceut. 2014; 6: 175-184.
10. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice- a review. J Clin Diagn Res. 2014; 8: GE01-4.
11. Arnold HM, Hollands JM, Skrupky LP, Mice ST. Optimizing sustained use of sedation in mechanically ventilated patients: focus on safety. Curr Drug Saf. 2010; 5: 6-12.
12. Mason KP, Lerman J. Review article: Dexmedetomidine in children: current knowledge and future applications. Anesth Analg. 2011; 113: 1129-1142.
13. Wong J, Steil GM, Curtis M, Papas A, Zurakowski D, Mason KP. Cardiovascular effects of dexmedetomidine sedation in children.

Anesth Analg. 2012; 114: 193-199.

14. Siddappa R, Riggins J, Kariyanna S, Calkins P, Rotta AT. High-dose dexmedetomidine sedation for pediatric MRI. Paediatr Anaesth. 2011; 21: 153-158.

15. Heard CMB, Burrows F, Johnston K, Joshi P, Houck J, Lerman J. A comparison of propofol and dexmedetomidine for MRI sedation. Anesth Analgesia. 2008: 107: 1832-1839.

16. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth. 2011; 107: 430-437.

17. Sato M, Shirakami G, Tazuke-Nishimura M, Matsuura S, Tanimoto K, Fukuda K. Effect of single-dose dexmedetomidine on emergence agitation and recovery profiles after sevoflurane anesthesia in pediatric ambulatory surgery. J Anesth. 2010; 24: 675-682.

18. Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal Dexmedetomidine Premedication is Comparable with Midazolam in Burn Children Undergoing Reconstructive Surgery. J Burn Care Res. 2009; 30: 599-605.

19. 19. Yuen VM, Hui TW, Irwin MG, Yuen MK. A Comparison of Intranasal Dexmedetomidine and Oral Midazolam for Premedication in Pediatric Anesthesia: A Double-Blinded Randomized Controlled Trial. Anesth Analg. 2008; 106: 1715-1721.

20. Heard CMB. Internal data from Pharmacy & Therapeutics Committee, WCHOB: Evaluation of dexmedetomidine. 2008.

21. Heard CM, Joshi P, Johnson K. Dexmedetomidine for pediatric MRI sedation: a review of a series of cases. Paediatr Anaesth. 2007; 17: 888-892.

22. Makary L, Vornik V, Finn R, Lenkovsky F, McClelland AL, Thurmon J, et al. Prolonged Recovery Associated with Dexmedetomidine when used as a Sole Sedative agent in Office-Based Oral and Maxillo Surgery Procedures. JOMS. 2010; 68: 386-391.

23. Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesth. 2010; 65: 922-929.

24. Heshmati F, Noroozinia H, Abbasivash R, Mahoori A, Gharaee H. Intranasal Sufentanil for Postoperative Pain Control in Lower Abdominal Pediatric Surgery. Iran J Pharmacol Therapeut. 2006; 5: 131-133.

25. Yao Y, Qian B, Chen Y, Zhou L, Liu L. Intranasal dexmedetomidine premedication reduces the minimum alveolar concentration of sevoflurane for tracheal intubation in children: a randomized trial. J Clinical Anesth. 2014; 26; 4: 309-314.

26. Dag C, Bezgin T, Ozalp N, Golcuklu AG. Utility of Bispectral Index Monitoring during Deep Sedation in Pediatric Dental Patients. J Clin Pediatr Dent. 2014; 39: 291-296.

27. Religa ZC, Wilson S, Ganzberg SI, Casamassimo PS. Association between bispectral analysis and level of conscious sedation of pediatric dental patients. Pediatr Dent. 2002; 24: 221-226.

28. Sabouri AS, F Firoozabadi, Carlin D, Creighton P, Raczka M, Joshi P, et al. Noise Level Measurement, a new Method to Evaluate Effectiveness of Sedation in Pediatric Dentistry. Acta Anaesthesiol Taiwan. 2014; 52: 169-175.

29. Kramer B, Heard CMB. Noise Pollution levels in the PICU. Crit Care Med. 2010; 38: 157.

30. Kramer B, Heard CMB. Noise Pollution in the Pediatric Intensive Care Unit and Its Effect on Sedation Management. Crit Care Med. 2011; 39: 166.

31. Jadid K, Klein U, Meinke D. Assessment of noise exposures in a pediatric dentistry residency clinic. Pediatr Dent. 2011; 33: 343-348.

32. TimoIirola, Sanna Vilo, Tuula Manner, RikuAantaa, Maria Lahtinen, et al. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol. 2011; 8: 825-831.

33. Henderson JM, Brodsky DA, Fisher DM, Brett CM, Hertzka RE. Pre-induction of anesthesia in pediatric patients with nasally administered sufentanil. Anesthesiol. 1988; 68: 671-675.

34. Zedie N, Amory DW, Wagner BK, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clin Pharmacol Ther. 1996; 59: 341-348.

35. Bayrak F, Gunday I, Memis D, Turan A. A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. J Opioid Manag. 2007; 3: 74-78.

36. Mahmoud M, Jung D, Salisbury S, McAuliffe J, Gunter J, Patio M, et al. Effect of increasing depth of dexmedetomidine and propofol anesthesia on upper airway morphology in children and adolescents with obstructive sleep apnea. J Clin Anesth. 2013; 25: 529-541.

37. Heard C, Watt S, Hegazy R, Gupta P, Iqbal V, Sabouri S. Does Dexmedetomidine cause less Airway Collapse than Propofol when used for Deep Sedation. J Clin Anesth. 2016; 35: 259-267.

38. Robinson A, Wermeling DP. Intranasal naloxone administration for treatment of opioid overdose. Am J Health Syst Pharm. 2014; 71: 2129-2135.

39. Heard C, Creighton P, Lerman J. Intranasal Flumazenil and naloxone to reverse over-sedation in a child undergoing dental restorations. Pediatr Anesth. 2009; 19: 795-799.

Cite this article

Michienzi K, Mireles R, Wanamaker C, Zemer J, Creighton P, et al. (2018) A Randomized Trial of Intra- Nasal Dexmedetomidine and Sufentanil Compared with Oral Midazolam: A Pilot Study. J Pharmacol Clin Toxicol 6(4):1114.