

Intranasal sedatives in pediatric dentistry

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ABSTRACT

الأهداف: تحديد المهدئات المستخدمة عبر الأنف (IN) لتحقيق التهدئ الواعي أثناء عمليات الأسنان بين الأطفال.

الطريقة: أجريت مراجعة أدبية من خلال تحديد الدراسات ذات الصلة بالبحث عبر ميدلاين Medline. وشمل البحث في dexmedetomidine و sufentanil و ketamine و midazolam و clonidine و haloperidol و lorazepam. أجريت الدراسات المشمولة بين الأفراد الأقل من 18 عام والتي نشرت باللغة الإنجليزية ولم تقيد بعد عام. وكانت معايير الاستبعاد للمقالات التي لم تركز على طب أسنان الأطفال.

النتائج: أُدرجت 20 دراسة وكانت المهدئات الأكثر شيوعاً هي midazolam يليها ketamine و sufentanil. كانت بداية مفعول مهدئ IN midazolam تتراوح بين 5-15 دقيقة، أما مفعول IN ketamine كان أسرع (متوسط 5.74 دقيقة) في حين المفعول في كلا من IN sufentanil (متوسط 20 دقيقة) و IN dexmedetomidine (متوسط 25 دقيقة) كان ابطأ. أما midazolam كان فعالاً في تعديل السلوك في الأطفال ذو القلق الخفيف إلى المتوسط، في العمليات الغزوية أو التي تتطلب فترات طويلة أوصي بمهدئات أقوى مثل IN ketamine و IN sufentanil وبالإضافة إلى ذلك، كان أداء ketamine أفضل في معدل النجاح الإجمالي (89%) مقارنة مع IN midazolam في 69%. واستخدم intranasal dexmedetomidine كعلاج تمهيدي بين الأطفال ولكن عند مقارنته تبين أن بداية مفعوله كانت أطول وقد ولدت تخديراً أعمق خلال وقت الانفصال عن الوالدين وفي وقت تحريض التخدير.

الخاتمة: تعد مهدئات intranasal midazolam و ketamine و sufentanil فعالة وآمنة للتهدئ الواعي في حين intranasal dexmedetomidine و sufentanil اثبتت فعاليتها كعلاج تمهيدي.

Objectives: To identify the intranasal (IN) sedatives used to achieve conscious sedation during dental procedures amongst children.

Methods: A literature review was conducted by identifying relevant studies through searches on Medline. Search included IN of midazolam, ketamine, sufentanil, dexmedetomidine, clonidine, haloperidol

and lorazepam. Studies included were conducted amongst individuals below 18 years, published in English, and were not restricted by year. Exclusion criteria were articles that did not focus on pediatric dentistry.

Results: Twenty studies were included. The most commonly used sedatives were midazolam, followed by ketamine and sufentanil. Onset of action for IN midazolam was 5-15 minutes (min), however, IN ketamine was faster (mean 5.74 min), while both IN sufentanil (mean 20 min) and IN dexmedetomidine (mean 25 min) were slow in comparison. Midazolam was effective for modifying behavior in mild to moderately anxious children, however, for more invasive or prolonged procedures, stronger sedatives, such as IN ketamine, IN sufentanil were recommended. In addition, ketamine fared better in overall success rate (89%) when compared with IN midazolam (69%). Intranasal dexmedetomidine was only used as pre-medication amongst children. While its' onset of action is longer when compared with IN midazolam, it produced deeper sedation at the time of separation from the parent and at the time of anesthesia induction.

Conclusion: Intranasal midazolam, ketamine and sufentanil are effective and safe for conscious sedation, while intranasal midazolam, dexmedetomidine and sufentanil have proven to be effective premedications.

*Saudi Med J 2016; Vol. 37 (9): 948-956
doi: 10.15537/smj.2016.9.15003*

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Received 9th March 2016. Accepted 22nd June 2016.

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Disclosure. Author has no conflict of interests, and the work was not supported or funded by any drug company.

Dental anxiety and phobia are common, especially amongst children. This anxiety can be exacerbated by parental anxiety, unfamiliar environments, and the anticipation of pain. Although local anesthetics can control pain, oral health professionals may need to use physical restraint to treat uncooperative children. This approach, however, causes further emotional trauma while reinforcing the fears associated with dental care. Alternative methods, such as hypnosis can be used, however, they are not universally effective. Hence, sedation, a vital component of pediatrics, should be used to help reduce and eliminate anxiety.^{1,2} Sedation facilitates dental treatment amongst uncooperative children, while avoiding the need for an operating room and general anesthesia. While intravenous therapy is the gold standard for sedation, its use can be limited in children. Hence, alternative methods specifically the intranasal (IN) approach can be of significant value while dealing with children.¹⁻⁶ The IN approach is a painless, needleless procedure that does not require intravenous catheters. The nasal mucosa offers a large absorptive surface with considerable blood flow allowing rapid drug absorption into the bloodstream and cerebral spinal fluid. Intranasal drug delivery results in direct medication absorption, while avoiding hepatic first-pass metabolism making more drug available more rapidly when compared with other routes.³ Intranasal sedation has 2 clinical utilizations - for sedation and as a premedication before the administration of general anesthesia usually to increase compliance of children or demanding patients by reducing the patient's anxiety related to painful or anxiety-provoking procedures. While IN sedatives do not relieve pain, they are a useful adjunct to analgesics, particularly in preparing patients for surgery, and are commonly given to patients before general anesthesia, known as premedication, or before invasive procedures. As a premedication, IN sedatives are effective in reducing anxiety associated with separation from parents and induction of anesthesia.⁴ Delivery of IN sedatives can be either via drops using a syringe/dropper or a sprayed/atomized medication delivery system that delivers a unit dose through a syringe, or a unit dose pump usually with a spray tip that fragments the IN sedative into fine particles as it is being sprayed into the nose. Pediatric sedation, a fast-growing area, is a vital option in treating anxious children. Research in this area is still fairly new; hence, this review aims to identify the IN sedatives used to achieve nasal conscious sedation during dental procedures amongst children. The predestined aim of this article was to review the evidence based studies for the purpose of identification of the IN sedatives that are used for nasal conscious

sedation among pediatrics during the dental procedures. Moreover, the prime focus area of this study was to assess the effectiveness and acceptability of different IN sedatives on the basis of the therapeutic index namely, safety and efficacy of these agents.

Methods. An initial pilot search using midazolam revealed that the IN route was used both as premedication and a sedative. Hence, it was decided that results will be presented as premedication and sedatives depending on the findings. Studies were identified from 2 sources: 1) a search on Medline, and 2) screening references from identified article. The inclusion criteria for studies were: studies conducted amongst individuals below 18 years; studies that focused on IN route of sedative administration; studies that were conducted to improve dental health; and studies published in English. While studies were not restricted by year, some of the exclusion criteria were articles that did not focus on pediatric dentistry, studies conducted in adults, and studies that used other modes of drug administration. Figure 1 details the search strategy.

Results. Criteria for assessment of effectiveness and acceptability. In most of the studies, the criteria used for the acceptability and effectiveness were the assessment of the adverse effects, affectivity, risk versus benefit ratios, the duration of action of the drugs, and the time taken by the sedatives to produce action. The risk and the benefits, and a comparison of both were the major features to determine the acceptability and effectiveness of sedatives.

Study characteristics. While the search was conducted for 7 IN sedatives (Figure 1), the articles included were based on 4 IN sedatives-midazolam, ketamine, sufentanil, and dexmedetomidine. Literature on IN clonidine, IN haloperidol, and IN lorazepam was not found, particularly its use amongst children in dentistry. The study characteristics are described in Table 1. This review included 20 studies spanning between 1988 to 2014. Of the studies included, 6 were non-randomized, while the others were randomized trials. The sample size of the studies ranged from 6-169. Two studies that included adults were included in this review as these individuals had underlying conditions, such as autism and Down's syndrome, and fell under the domain of pediatric dentistry.^{5,6} Based on the literature, results focused on different aspects of IN sedatives and are displayed in Table 2.

Intranasal midazolam. Intranasal midazolam is a hydrophilic, short-acting benzodiazepine, which produces sedation, anxiolysis, and amnesia.

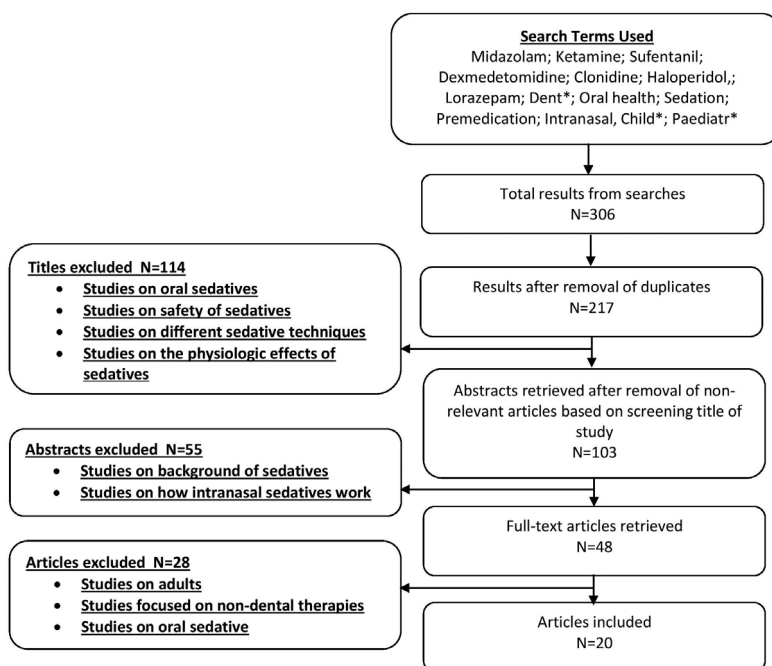


Figure 1 - Flow chart illustrating the study selection process for the study of intranasal sedative in the pediatric dentistry. N - number of studies

Table 1 - Study characteristics of intranasal sedatives in the pediatric dentistry.

Author, year of study	Study design	Sample size	Age, years	Interanasal sedatives under study
Wilton et al ⁶ 1988	Randomized	45	1.5-5	Midazolam
Rey et al ⁷ 1991	Randomized	12	1.5	Midazolam
Walbergh et al ¹¹ 1991	Non-randomized	18	1.2-5	Midazolam
Yearly et al ¹⁰ 1992	Retrospective cohort study	40	1-6	Midazolam
Abrams et al ¹⁸ 1993	Randomized	30	1.4-5.1	Midazolam, ketamine, sufentanil
Fukuta et al ⁹ 1993	Non-randomized	21	4-21	Midazolam
Connor & Terndrup ¹⁷ 1994	Randomized	58	1-10	Midazolam
Fuks et al ⁸ 1994	Randomized	30	2.6	Midazolam
Malinovsky et al ¹⁴ 1995	Randomized	30	2-5	Midazolam
Burstein et al ⁵ 1996	Non-randomized	6	20*	Midazolam
Zedie et al ²⁵ 1996	Randomized	60	0.5-6	Midazolam, sufentanil
Roelofse et al ²² 2004	Randomized	50	5-7	Midazolam/sufentanil combination Midazolam/ketamine combination
Heard et al ⁴ 2010	Non-randomized	102	1.8-30*	Midazolam, midazolam/oral transmucosal fentanyl citrate combination, midazolam/sufentanil combined
Johnson et al ¹³ 2010	Randomized	31	3.5-7	Midazolam
Wood ¹⁶ 2010	Non-randomized	100	3-13	Midazolam
Wood ¹² 2011	Non-randomized	114	2-15	Midazolam
Klein et al ¹⁹ 2011	Randomized	169	0.5-7	Midazolam
Pandey et al ²¹ 2011	Randomized	34	2-6	Ketamine
Bahetwar et al ²⁰ 2011	Randomized	45	2-6	Midazolam, ketamine, midazolam/ ketamine combination
Sheta et al ²⁸ 2013	Randomized	72	3-6	Midazolam, dexmedetomidine

* This study included 3 older individuals (aged 13, 21, and 30) with autism

Dose and time of onset. Intranasal midazolam was administered in a dose ranging from 0.1-0.5 mg/kg. An optimal dose of 0.2mg/kg produced rapid, non-invasive and safe preoperative sedation. Higher doses did not have clinical benefits and were associated to coughing, sneezing, and expulsion of the solution.⁷⁻¹⁰ Time of onset was dose dependent and ranged from 5-16 minutes (min).^{4,6,8,11-13} Although adequate sedation was achieved within 7-10 min,^{6,10} time taken to achieve maximum plasma level was between 10-35 min.^{6,8,11,14,15} A mean \pm standard deviation peak concentration of 72.2 \pm 27.3 ng/ml took 10.2 \pm 2 minutes, suggesting rapid attainment of significant plasma concentrations even after administration of 0.1 mg/kg IN midazolam.¹¹

Effectiveness. Intranasal midazolam achieved satisfactory sedation amongst 50-91% of children, however, was dose dependent.^{4,12,16} At doses of 0.2 to 0.29 mg/kg, satisfactory sedation occurred in 27% (credibility interval [CI]: 6-60%), while at 0.3 to 0.39 mg/kg and 0.4 to 0.5 mg/kg, satisfactory increased to 80% (CI: 52-95%) and 100% (CI: 79-100%). The highest dose associated with inadequate sedation was 0.35 mg/kg.⁴ Intranasal midazolam improved anxiety levels and behavior significantly ($p < 0.05$; maximum at

10 minutes 1.2 \pm 0.0 mm).¹⁷ Abrams et al,¹⁸ reported that IN midazolam had an acceptable sedation score (mean 4) in a system where 5 was ideal and 10 was obtunded, apneic, oximetry $< 80\%$, requires airway support. Overall, IN midazolam was effective for modifying behavior in mild to moderately anxious children. However, for more challenging patients, the addition of stronger sedatives was recommended.

Acceptability. The acceptability of IN sedatives was assessed on both patient reactions to the sedative as well as parents perspective. Intranasal midazolam was acceptable (50%)¹⁶ and successful (57%) according to patients' perspective, while parents rated midazolam higher making it 76-93% acceptable with 84% reporting to use the procedure again.^{12,16}

Recovery. Intranasal midazolam had a short duration of action (40-60 min),¹² and patients were ambulatory within 41 \pm 9 min (range: 30-65 min) and discharged within 54 \pm 15 min (range: 35-75 min).^{4,17}

Adverse effects and safety. All studies reported minor adverse reactions, such as burning of the nasal mucosa, stinging sensation, bitter taste, and the unpleasant IN squirting of IN midazolam.^{6,12,16,17}

Table 2 - List of intranasal sedative drugs used in pediatric dentistry.

Sedative drug	Optimal dose	Time of onset	Effectiveness	Acceptability	Recovery time	Adverse effects	Safety
Midazolam	0.2 mg/kg	5-16 minutes	Satisfactory	Acceptable	30-65 minutes	Burning of the nasal mucosa, Stinging sensation, Bitter taste, Lacrimation, Vomiting, Coughing, Sneezing, Deep sedation, Post discharge nightmares	Safe Small percent of individuals experienced clinically significant desaturated and managed with oxygen mask which corrected the complication
Ketamine	6 mg/kg	5.79 minutes	Satisfactory Better sedation when compared with midazolam	Acceptable More acceptable when compared with midazolam	39.98 \pm 3.18 minutes	Vomiting	Safe Only one case of brief desaturations of 88% reported which resolved spontaneously to 90%.
Sufentanil (Details for 1 ug/kg reported, higher dose associated with adverse effects)	1 ug/kg	4 \pm 1 minutes	Satisfactory Better sedation when compared with midazolam and ketamine	Acceptable More acceptable when compared with midazolam	7 \pm 13 minutes	Nausea Vomiting Itching	Safe No desaturation reported
Dexmedetomidine (as pre-medication)	1-2 μ g/kg	25 minutes	Satisfactory Better sedation when compared with midazolam	Acceptable Better postoperative analgesia and less agitation compared with midazolam	N/A	Nausea Vomiting Shivering Modest hemodynamic effects	Safe No bradycardia conduction abnormalities, hypotension, respiratory depression, apnea or desaturation reported

While 43% of children found the IN route unacceptable by exhibiting combative behavior, parents were of a contrary view. Other adverse effects were lacrimation, vomiting, coughing, sneezing, crying, deep sedation, and post-discharge nightmares.^{4,6,12,13,16,19}

When IN midazolam was administered as a spray, aversive behaviors reduced significantly ($p=0.025$) compared with drops administration, irrespective of the volume administered.⁹

There were no major adverse effects reported. Medication administration was reasonably well tolerated, with no reduction in heart rate and blood pressure.⁶ While the technique was safe with no desaturation below 90%, there was, however, one patient who had transiently desaturated well into recovery and was managed with an oxygen mask, which corrected the complication.^{12,18}

Intranasal ketamine. Intranasal ketamine, a phencyclidine derivative is a sedative, analgesic, and premedication agent.

Dose and time of onset. When IN ketamine was used in combination with IN midazolam, the dose administered varied from 3-5 mg/kg, however, when used alone was 6 mg/kg.^{18,20-22} IN ketamine had a faster onset of action compared with IN midazolam (5.79 ± 1.42),²⁰ and this increased further when administered through atomized spray (5.13 min) as oppose to drops (5.79 min).²¹

Effectiveness. 'Adequate' depth of sedation was achieved in 93% and 'satisfactory' completion of treatment was achieved in 89% of cases. Intranasal ketamine fared better in overall success rate (89%) compared with IN midazolam (69%) and IN midazolam-ketamine combination (84%).²⁰

Intranasal ketamine had a mean sedation score of 4 and was acceptable and ideal for short procedures, due to its ease of administration, effectiveness, and rapid onset of action.^{18,20-22} When administered through an atomizer, 'adequate' depth of sedation (97.1%) and a higher overall success rate (94.1%) was achieved when compared with drops (85.3%).²¹

Acceptability. When measured by the Ohio State Behavioral Rating Scale,²³ the acceptance of the atomized IN ketamine was significantly better than IN ketamine drops ($p<0.0001$) with minimal aversive behaviors increasing the acceptance of the drug.^{18,20-22}

Recovery. The mean recovery time was 39.98 ± 3.18 min, which was significantly longer than IN midazolam ($p<0.001$). When IN ketamine was administered via drops, the recovery time was significantly ($p<0.05$) longer than atomized IN ketamine.^{20,21}

Adverse effects and safety. A small percentage of children reported vomiting as an adverse effect.^{20,22}

Vomiting was twice as prevalent when IN ketamine was administered as drops when compared with an atomizer.²¹

The literature highlighted a case where brief desaturation of 88% occurred and resolved spontaneously to 90% oxygen saturation, whereas another case that reported with a history of biliary atresia, demonstrated several desaturations in the low 80% range but, again, quickly responded with mild stimulation and was not noted to be overly sedated.¹⁸

Intranasal sufentanil. Intranasal sufentanil is a powerful synthetic opioid analgesic, used extensively as a premedication and sedative.

Dose and time of onset. With the exception of one study,¹⁸ all studies used IN sufentanil in combination with IN midazolam. The dose ranged from 20 mcg to 1.5 ug/kg.^{5,24,25} The time of onset was 20 min (range -15-79 min).⁵ A high dose (1.5 ug/kg) of IN sufentanil achieved sedation in 7 ± 3 min while a dose of one ug/kg took 4 ± 1 min.¹⁸

Effectiveness. When IN sufentanil was used as a premedication, 30 min before general anesthetic administration, it enabled patients to be separated from their parents with minimum distress.²⁵ When intranasal sufentanil was used in combination with IN midazolam, patients experienced less pain than those administered a combination of IN ketamine/midazolam, with significantly more children responding to IN sufentanil (72%) than IN ketamine (52%).²² High dose IN sufentanil (1.5 ug/kg) had a mean sedation score of 7 (heavily sedated; arousable, oximetry 85-90%), while low dose (1.0 ug/kg) had a mean score of 4 (acceptable sedation; minor fussing, no struggle).¹⁸

Acceptability. The acceptability of IN sedatives was assessed on both patient reactions to the sedative, as well as parents perspective. Intranasal sufentanil was significantly more acceptable than IN midazolam (71% versus 20%, $p=0.0031$) at the time of drug administration, and produced more sedation and cooperation during induction of anesthesia.²⁵

When used in combination with IN midazolam, significantly more patients accepted the nasal premedication compared with a IN ketamine/midazolam combination (Chi-square test = 7.718, $p=0.021$).²²

Recovery. The mean recovery time was 58 ± 40 min for the high dose and 7 ± 13 min for the low dose.¹⁶ When used in combination with IN midazolam the recovery time ranged between 12-100 min.⁵

Adverse effects and safety. While some studies reported no adverse effects,²² others observed that IN sufentanil caused more postoperative nausea

and vomiting than IN midazolam (34% versus 6%, $p=0.02$).⁵

When used as premedication IN sufentanil was administered 30 minutes prior to surgery and general anesthetic administration. Although 2 patients had moderate reduction in ventilatory compliance after general anesthetic induction, vital signs and oxygen saturation did not change significantly with low doses before or after surgery.⁵ High dose (1.5 $\mu\text{g}/\text{kg}$), however, caused desaturation in 4 of the 5 patients. High doses produced more heavily sedated children (mean score 7; heavily sedated; arousable, oximetry 85-90%), with higher incidence of desaturation (80%) and prolonged recovery time (58 ± 40 min), while the low dose resulted in no desaturation, less sedation (mean score 4), and a brief recovery time (7 ± 13 min).¹⁸

Intranasal dexmedetomidine. Intranasal dexmedetomidine is a potent, highly selective, and specific α_2 adren-receptor agonist that has both sedative and analgesic effects.²⁶

Dose and time of onset. A dose of 1-2 $\mu\text{g}/\text{kg}$ of IN dexmedetomidine was effective for inducing sedation.^{27,28} The median onset of sedation was 25 (20-40) min and significantly longer than IN midazolam at 15 (10-25) min ($p=0.001$). When used as premedication, the time from administration to induction was also significantly shorter than IN midazolam ($p=0.002$).²⁸

Effectiveness. Children received the premedication 45-60 min before induction of general anesthesia. Patients who were premedicated were significantly more sedated when IN dexmedetomidine was administered compared with IN midazolam, at the time of separation from parents (77.8% versus 44.4%, CI 0.54-0.12) and at the time of anesthesia induction (66.7% versus 38.9%). In comparison with IN midazolam, there was better immediate postoperative analgesia. Compliance with mask application post-premedication was significantly better among children who were administered IN dexmedetomidine compared with IN midazolam (80.6% versus 58.3%),²⁸ remedication with 1 $\mu\text{g}/\text{kg}$ IN dexmedetomidine produced a sedation that was more effective than sedation induced by 0.2 mg/kg IN midazolam.²⁸

Satisfactory sedation was achieved in 59.4% of the children who received 0.5 $\mu\text{g}/\text{kg}$ IN dexmedetomidine, and 75% of the children who received 1 $\mu\text{g}/\text{kg}$ IN dexmedetomidine at separation from parents. At induction of anesthesia, 40.6% and 53.1% of the children who received 0.5 $\mu\text{g}/\text{kg}$ IN dexmedetomidine and 1 $\mu\text{g}/\text{kg}$ IN dexmedetomidine remained sedated.²⁷

Acceptability. The acceptability of IN premedication was assessed on both patient reactions to the sedative,

as well as parents perspective. In IN midazolam, there was better immediate postoperative analgesia and less agitation. In addition, IN dexmedetomidine was well tolerated, as it produced no unpleasant sensation during administration.^{27,28}

Recovery. The median duration of sedation was 85 min (95% CI: 55-100 min). As it can be difficult to accurately coordinate premedication with time of surgery, studies suggest 1 $\mu\text{g}/\text{kg}$ IN dexmedetomidine provides some flexibility, as long as it is administered at least 30-45 min prior.²⁷

Adverse effects and safety. While there was some nausea, vomiting, shivering,²⁸ and modest hemodynamic effects, these effects were clinically insignificant, and no intervention was required.²⁷ Maximum reduction of systolic blood pressure was 14.1% and heart rate was 16.4% after 1 $\mu\text{g}/\text{kg}$ IN dexmedetomidine.²⁷ Sheta et al,²⁸ reported no incidences of bradycardia (heart rate <60 b/min), conduction abnormalities, hypotension (systolic blood pressure <70 mm Hg), respiratory depression, apnea, or desaturation (<95%).

Intranasal sedation reversal agent. While IN sedatives are often safe, unplanned over-sedation may occur, irrespective of the drug or route of administration. Complications such as respiratory depression leading to hypoxic-cardio-respiratory arrest can occur if not recognized and treated in a timely and an appropriate manner. The studies included in this review have not reported such complications where IN flumazenil (a competitive benzodiazepine receptor antagonist, antagonizes benzodiazepine overdose) or IN naxolone (pure opioid antagonist, with no concomitant agonist properties) have been used as a sedative absorbed intranasally as it rarely achieves the same level as when administered intravenously.

Intranasal flumazenil. A case study⁵ reported use of IN flumazenil where combination sedation of 5 mcg sufentanil (1 mcg/kg) and 5 mg midazolam (0.3 mg/kg) were used in the first instance, followed by a second dose of 2.5 mg midazolam supplemented with 50% N_2O . There was desaturation (O_2 <80-85%) that continued, leading to laryngospasm, despite treatment with 100% O_2 , chin lift, and jaw thrust. To antagonize the sedation, 2 100 mcg doses of IN flumazenil were administered. Three minutes later, the patient was fully awake and monitored for 2 hours. During recovery, the patient was cooperative, oriented, and tranquil for the first 30 min, after which the patient remained fully awake, with no evidence of re-sedation.⁵

A dose of 40 mcg/kg flumazenil provides therapeutic plasma levels of 10-30 ng/ml, with a peak concentration

of 68 ng/ml. The time to maximum blood concentration was 2 min, while its elimination half-life was 2 hours. Hence, patients should not be discharged immediately but rather observed for 2 hours post-reversal to ensure re-sedation does not occur.²⁹

Intranasal Naxolone. Heard et al,³⁰ reported a case of over-sedation in a 3-year-old when sedation was achieved after a multi-drug combination was administered intranasally. Following an initial dose of 15 mcg IN sufentanil and 5 mg IN midazolam, which reached a Ramsay Score of one, sedation was supplemented with 2.5 mg IN midazolam followed by 50% N₂O. Twenty minutes post administration, the patient achieved a Ramsay Score of 6 (no response to painful stimulus), with airway obstruction and oxygen saturation decreasing to 80-85%.³⁰

A chin lift and jaw thrust was applied and 100% O₂ was administered along with a 70 mm oral airway inserted into the patient's mouth. Following this manoeuvre oxygen saturation, breathing rate, and pattern returned to normal, while heart rate remained unchanged between 140 and 150.³⁰

When the oral airway was removed, oxygen saturation decreased to 90-95%, despite applying jaw thrust and other maneuvers; oxygen saturation continued to decrease, suggesting respiratory depression and laryngospasm. This was treated with positive pressure ventilation through a full facemask and 100% O₂, which resolved the laryngospasm without further decreases in either the oxygen saturation or the heart rate.³⁰ This was followed by an IN dose of naloxone 0.4 mg using an atomizer, which resulted in an increase in the respiratory rate, however, with no change in the depth of sedation. To antagonize the sedation, 2,100 mcg doses of IN flumazenil was administered, which lead to the patient opening her eyes and becoming fully awake (Ramsay score = 1). The patient was monitored for the next 2 hours to ensure sedation did not recur.³⁰

Discussion. The most commonly used IN sedatives are midazolam, followed by ketamine and sufentanil. While IN midazolam takes 5-15 min to act, IN ketamine is faster in onset. Intranasal midazolam was effective for modifying behavior in mild to moderately anxious children, however, for prolonged procedures, stronger sedatives (for example, IN ketamine, IN sufentanil) are recommended. IN ketamine was considered to be more successful for conscious sedation when compared with IN midazolam and IN midazolam-ketamine combination. However, when IN sufentanil was used in combination with IN midazolam, patients experienced less pain when compared with a IN midazolam-ketamine combination.

Intranasal dexmedetomidine, a pre-medication, has a longer onset of action when compared with IN midazolam. It produces deeper sedation at time of separation from parents and at time of anesthesia induction.

Adverse effects of IN midazolam administration included stinging and bitter taste due to the low pH (approximately 3), benzoyl alcohol preservative, and the volume of solution administered. This can be eliminated by using a 4% lidocaine topical solution nasally prior to midazolam administration.⁶ Both IN ketamine and IN sufentanil produce nausea and vomiting, however, these adverse reactions have been attributed to failure to follow pre-procedural instruction regarding meals.

Although this review included a limited number of studies, there were numerous studies on sedatives in general, which were excluded as these studies did not focus on their application in pediatric dentistry.³¹⁻³³ This review highlights that there is currently a lack in this area of research and there is a need for further more comprehensive studies to be directed at the optimal dosage and timing of IN administration of sedative in children and its application in clinical settings, specifically in dentistry.

The IN sedative drugs included in this review were both safe and effective. Safety was measured based on parameters that included heart rates, systolic blood pressures, diastolic blood pressures, mean blood pressures, respiratory rates, and pulse oximetry readings. While dental practitioners with no training in sedation techniques can undertake these procedures, this should be attempted with a degree of caution.

Roelofse et al,²² reported that 2 children were unconscious following administration of an IN midazolam-ketamine combination for 15 and 20 min. While this is a common experience for anesthesiologists who are well experienced in handling such complications, these IN sedation techniques are not likely to be safe and effective in the hands of a dentist untrained in anesthesia.

Burstein et al,⁵ reported that a combination of sedatives resulted in over sedation leading to loss of consciousness and laryngospasm. It should be noted that dentists administering IN sedatives should not only be competent at basic life support, but they should also be prepared for other complications in general. While dentists can and do provide safe and effective IN conscious sedation without the need for general anesthesia training, it is vital that they abide by the American Dental Association's definition of conscious sedation.⁵

In conclusion, this review highlights the safety and effectiveness of IN midazolam, IN ketamine, IN sufentanil, and IN dexmedetomidine, while also adding a note of the antagonist agents of IN sedation. Midazolam was effective for modifying behavior in mild to moderately anxious children, however, for more invasive or prolonged procedures, stronger sedatives are recommended. Although this review is based on a small number of studies, results emphasize that the IN route of sedation administration to achieve conscious sedation is reliable, successful, and invaluable when treating anxious and un-cooperative children needing dental care. There is, however, a need for further well controlled prospective studies on pediatric dental IN sedation.

Acknowledgment. *The author would like to thank the University Library and staff of King Saud University, College of Dentistry, Riyadh, Kingdom of Saudi Arabia for providing the papers needed to complete this work.*

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