



Role of dexmedetomidine in pediatric dental sedation

Vedangi Mohite, Sudhindra Baliga, Nilima Thosar, Nilesh Rathi

Department of Pedodontics and Preventive Dentistry, Sharad Pawar Dental College, Sawangi (M), Wardha, Maharashtra, India

Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist with a vast array of properties, making it suitable for sedation in numerous clinical scenarios. Its use was previously restricted to the sedation of intensive care unit patients. However, its use in pediatric dental sedation has been gaining momentum, owing to its high suitability when compared with conventional pediatric sedatives. Its properties range from sedation to anxiolysis to analgesia, due to its sympatholytic properties and minimal respiratory depression ability. Because dexmedetomidine is an efficacious and safe drug, it is gaining importance in pediatric sedation. Thus, the aim of this review is to highlight the properties of dexmedetomidine, its administration routes, its advantages over the commonly used pediatric sedatives, and especially its role as an alternative pediatric sedative.

Keywords: alpha-2 Adrenergic Receptors Agonist; Dexmedetomidine; Midazolam.



This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.



INTRODUCTION

In pediatric dentistry, minimizing anxiety in children is an extremely challenging but is necessary. A child's cooperation with a dental procedure usually requires various behavioral management strategies conveyed by the entire dental team. If these strategies prove inadequate, the application of some form of pharmacological sedation or general anesthesia is indicated.

The benefits of administering general anesthesia must always be weighed against the risks. Its previously reported post-operative complications include arrhythmias, dislodged or obstructed endotracheal tube, IV infiltration or disconnection, edema of the tongue or lips, and nasal bleeding, which could range from negligible to severe (90%) [1]. However, nowadays, the rise of sedation, anxiety, and unwanted movement of children

during dental procedures has markedly reduced [2]. Sedation depresses the level of consciousness but allows the patient to respond appropriately to verbal commands and light tactile stimulation [3]. In dentistry, it has been used in the treatment of children or adults with high anxiety levels, thus optimizing the success of dental procedures.

Currently used sedatives include midazolam, chloral hydrate, ketamine, nitrous oxide, promethazine, propofol, hydroxyzine, sevoflurane, and opioids. In pediatric sedation, these drugs have been administered alone or in combination, for decades. Despite their efficiency, associated adverse effects limit their use in pediatric dental procedures. Thus, the quest for a sedative that can provide minimal to moderate sedation in children is ongoing.

Received: April 14, 2019 • Revised: April 23, 2019 • Accepted: April 24, 2019

Corresponding Author: Vedangi Mohite, Department of Pedodontics and Preventive Dentistry, Sharad Pawar Dental College, Sawangi (M), Wardha, Maharashtra, India

E-mail: drvedangi.mohite@gmail.com.

Copyright© 2019 Journal of Dental Anesthesia and Pain Medicine

Table 1. Selective and Non-selective α 2-adrenoceptor agonists

Non-selective α 2-adrenoceptor agonist	Selective α 2-adrenoceptor agonist
Noradrenaline	Dexmedetomidine
Adrenaline	Mivazerol
	Clonidine
	α -Methylidopa

α 2-ADRENORECEPTOR AGONISTS

1. Classification of α 2-adrenoreceptor agonists

There are several α 2-adrenergic receptor agonists, including clonidine, guanfacine, tizanidine, methylidopa, guanabenz, medetomidine, methyl norepinephrine, levonordefrin, and dexmedetomidine [4]. They can be classified as nonselective and selective α 2-adrenoceptor agonists, based on their affinity to α 2-adrenoceptors [5] (Table 1).

Dexmedetomidine is a short-acting central α 2-adrenoceptor agonist with a ratio of selectivity of 32 and 1300 for α -2a-to-imidazoline and α -2a-to- α -1, respectively. Like mivazerol and clonidine, it has a strong affinity for α 2-adrenoceptors. However, it also has a slight affinity for non-adrenergic imidazoline receptors [5] (Table 2). Eleven and twelve imidazoline receptor binding sites have been identified in the brain, and the pancreas and kidneys, respectively [5].

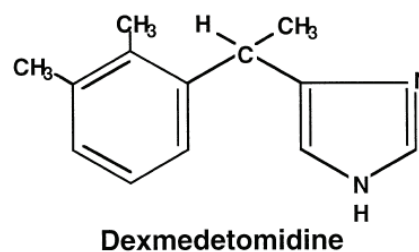
2. Dexmedetomidine

It has been reported that α 2-adrenoreceptor agonists cause sedation, anxiolysis, analgesia, an antisialogogue effect, sympatholytic, and postoperative reduction of nausea and vomiting better than benzodiazepines. Orally and intranasally administered clonidine has a slow onset of action, resulting in a half-life of 12.5 h [6,7]. In children, its plasma concentration peaks 60-90 min post oral administration. Hence, clonidine needs to be administered at least 1 h before the induction of anesthesia [8,9].

Dexmedetomidine was first approved by the Food and Drug Administration in 1999 for the sedation of intensive care unit patients and for premedication. In 2005, it was

Table 2. Imidazoline receptor agonists

Serial No.	Imidazoline receptor agonists
1	Moxonidine
2	Rilmenidine
3	Clonidine
4	Dexmedetomidine
5	Mivazerol

**Fig. 1.** Chemical formula structure of dexmedetomidine.

introduced to dentistry [3,10]. Dexmedetomidine is a more selective and specific α 2-adrenoreceptor agonist than clonidine [6]. Dexmedetomidine is 8 times more specific than clonidine and has a shorter half-life. Consequently, dexmedetomidine has more favorable pharmacokinetic properties than clonidine [3,7].

The properties dexmedetomidine include sedation, anxiolysis, and analgesia without significant respiratory depression [3]. These make it a preferable sedative in adult and pediatric dental procedures [11]. A few recent studies have investigated the various routes of administering dexmedetomidine, and its safety and efficiency, to develop a protocol that results in minimal to moderate sedation in pediatric dental patients [12].

1) Chemical formula of dexmedetomidine

Dexmedetomidine is the dextrorotatory S-enantiomer of medetomidine chemically described as $[+]$ -4-[2,3-dimethylphenyl]ethyl-1H-imidazole monohydrochloride, with a molecular weight of 236 [13]. It is a highly selective and potent α 2-adrenoceptor agonist [α 2 : α 1 magnitude relation = 1620 : 1]. Its empirical formula is $C_{13}H_{16}HCl$ [10,13] (Fig. 1).

2) Mechanism of action of dexmedetomidine

The central effect of dexmedetomidine is the inhibition

of noradrenaline release by acting on the α 2-adrenoceptors in the locus ceruleus. Thus, it produces a state similar to natural sleep, where the patient can be easily aroused by external stimulus [5]. Its primary mechanism of action is stimulation and cessation of parasympathetic and sympathetic outflows, respectively. Sedation is primarily induced by the activation of post-synaptic α 2-adrenergic receptors. Because dexmedetomidine attaches to the α 2 receptors of the locus ceruleus and spinal cord, it brings about effects such as sedation and analgesia [13]. Dexmedetomidine has a low affinity for beta muscarinic, adrenergic, serotonin, and dopaminergic receptors [13].

3) Pharmacodynamics and pharmacokinetics of dexmedetomidine

Dexmedetomidine is a potent drug; at plasma concentrations less than 1.0 μ g, it can produce profound physiological alterations [5]. There are 3 subtypes of α 2-adrenoreceptors: α 2A, α 2B, and α 2C, with different pharmacological properties and physiologic functions. They are found within the blood vessels, vital organs, and the autonomic, peripheral, and central nervous systems. Dexmedetomidine binds to this G-Protein-coupled α 2-adrenoreceptor. Its associated vagomimetic effects such as bradycardia and vasodilatation result from its high affinity to α 2-adrenoreceptors. Dexmedetomidine also displays a nonlinear concentration-dependent pharmacokinetic effect [5].

Dexmedetomidine has a distribution half-life of about 6 min and a terminal elimination half-life of about 2 h (2-compartment model). It has a quick onset and short duration of action. Dexmedetomidine is extremely lipophilic and about 94% protein bound. It is nearly completely biotransformed, and is excreted in feces (4%) and urine (95%) [13]. Biotransformation involves both direct glucuronidation (the major pathway) via direct N-glucuronidation, aliphatic hydroxylation (principally by CYP2A6), and N-methylation, as well as cytochrome P450 mediated metabolism [4,13]. Its metabolites are considered inactive and there is no chiral conversion to the levo-isomer.

4) Properties of dexmedetomidine

Dexmedetomidine exerts sedative, anxiolytic, and analgesic effects, with insignificant respiratory system distress [13]. It aids in the additional induction of anesthesia induced by other drugs and causes preoperative sympatholytic effects and hypotension, due to its stimulation of central α 2 and imidazoline receptors. Unlike midazolam, other benzodiazepines and opioids, dexmedetomidine does not have an affinity for GABA or opioid receptors and does not result in respiratory depression. Thus, it creates a compliant and semi-arousable kind of sedation [4]. Also, its effects can be reversibly reversed by its specific antagonist atipamezole [13].

5) Advantages of dexmedetomidine

In 2002, Tobias et al. [14] stated that dexmedetomidine was a safe sedative for children and infants. It induces minimal respiratory depression and inhibits tachycardia [13]. During its sedative action, it prevents hypoxia by maintaining the airway and enabling spontaneous respiration. It also preserves CO₂ reactivity and increase. Due to its low effect on respiratory function, dexmedetomidine could be a very valuable pediatric sedative [3,8].

6) Routes for administering dexmedetomidine for sedation

Dexmedetomidine can be administered orally, buccally, intravenously, intranasally, and intramuscularly (Table 3).

(1) Oral route

One of the simplest and popular routes for drug administration is the oral route. Its advantages include simplicity and ease of administration, affordability, risk free, and worldwide acceptance. In pediatric dental care, the ease of administration by this route makes it favorable. The rate of drug absorption via the oral mucosa is influenced by multiple factors, including the duration of its contact with the mucosa, its pKa, lipophilicity, quantity of saliva, and physiochemical characteristics at the site of action [15,16]. At physiological pH, dexme-

Table 3. Administration routes of dexmedetomidine for sedation

Route	Dose	Time of onset
Oral	0.5 mg/kg	40 min before the procedure
Buccal	1-2 μ g/kg	
Intravenous	Loading dose: 1 μ g/kg for 10-20 min. Maintenance dose: infusion dose of 0.2-0.7 μ g/kg/h	The rate of infusion can be increased in increments of 0.1 μ g/kg/h or higher
Intranasal	0.5-1.0 μ g/kg	45 min (peak onset: 1.5-2.5 h)
Intramuscular	2.5 μ g/kg	

detomidine is present in a nonionized form and has a pKa value of 7.1. Being a highly lipophilic drug, it is easily transported into tissues [17].

Multiple studies have reported that in approximately 90 min post administration, it permeated the oral mucous, achieved a buccal bioavailability of 82%, and achieved its highest concentration [18]. However, the most widely used oral pediatric sedative, midazolam, is more lipophilic. At a pH of 4.0-4.5, the closing of its imidazole ring occurs. This high pH leads to its high lipid solubility in and fast absorption via the oral mucosa [19]. When 0.5 mg/kg midazolam is orally administered as a premedication, its mucosal absorption is likely to be reliant on its pH [6]. Some of the adverse effects associated with its 70% oral bioavailability include restlessness and postoperative respiratory depression [6].

It has been reported that the high hepatic first pass metabolism associated with oral drug administration is responsible for the low (16%) bioavailability of dexmedetomidine post oral administration, compared with 82% post buccal administration [18,20]. As a result, the benefits of orally administered dexmedetomidine are low compared with those of midazolam [21]. Oral administration reportedly leads to few side effects such as gastric disturbances and change in taste, and shortcomings such as longer recovery time, high first pass metabolism, and slow onset of action [22].

Time of onset

Oral dexmedetomidine needs to be administered at most 40 min before the induction of anesthesia, to attain the most favorable sedative effect. Previously, it has been demonstrated that with midazolam, moderate sedation is

achieved about 20 min post administration [23].

(2) Intravenous route

Post intravenous administration, the half-life of dexmedetomidine and its terminal elimination half-life are about 6 min and 2 h, respectively. The administration of 0.2-0.7 μ g/kg/h dexmedetomidine over a 24 h period leads to the linear expression of its pharmacokinetic effects.

Dexmedetomidine exerts a biphasic effect on blood pressure; as its concentration decreases, vasodilatation increases, due to its central effect. Doses of 0.25-1 μ g/kg in adults and 0.5-6 μ g/kg/h in children decrease blood pressure by 13-16% and 20%, respectively. Therefore, dexmedetomidine should be administered slowly as it results in unwanted blood pressure changes [5,24].

(3) Intranasal route

Intranasal route is popular in pediatric sedation owing to its numerous advantages. It is void of the injections like in the intravenous and intramuscular routes, and the bitter taste associated with oral administration. Intranasal administration is easy, safe, effective, and non-invasive. In children the acquiescence to sedation via intranasal administration is higher than that of oral administration [20].

Intranasal drug delivery is also favorable in children when time is limited [25]. At most, 0.15-0.2 ml should be administered in each nostril, as volumes greater than this will be partly absorbed orally [25]. Dexmedetomidine is best absorbed after sublingual and intranasal administration, with a bioavailability of about 82% post intranasal administration.

However, midazolam has been the preferred intranasally administered premedication in children due to its ease of administration and efficiency [26]. Notwithstanding, its use is restricted by the resulting irritation and burning feeling in the nasal mucosa [20]. Yuen et al. [6] conducted a clinical trial to assess the efficacy of intranasal dexmedetomidine and oral midazolam in pediatric premedication. They reported that premedication by intranasal administration of 1 $\mu\text{g}/\text{kg}$ dexmedetomidine produced moderate sedation compared to oral administration of midazolam [6]. Reportedly, the time of onset of the sedative effect after the administration of 1-1.0 $\mu\text{g}/\text{kg}$ dexmedetomidine intranasally is about 45 min, with a peak onset at 1.5-2.5 h [4,27].

A randomized double-blind controlled trial on 2-12-year-old children showed that intranasal administration of 0.5-1 $\mu\text{g}/\text{kg}$ dexmedetomidine produces a stronger sedative effect than oral administration of 0.5 $\mu\text{g}/\text{kg}$ midazolam [27]. Additionally, intranasal dexmedetomidine administration in children results in inadequate hemodynamic effects; however, these actions are clinically irrelevant and no interference is needed [6]. Maximum reduction of systolic blood pressure (14.1%) and heart rate (16.4%) were observed after the intranasal administration of 0.5 and 1 $\mu\text{g}/\text{kg}$ dexmedetomidine, respectively.

The nasal mucosa has an abundant blood supply, leading to quick drug absorption and onset of action. Additionally, the proximity and access to the CSF via the subarachnoid space, and the olfactory nerve and its sheath leads to speedy attainment of desired CNS levels and quicker onset of action [6]. All these make intranasal dexmedetomidine administration more tolerable and favorable in children than oral administration.

(4) Intramuscular route

The intramuscular administration of up to 2.5 $\mu\text{g}/\text{kg}$ dexmedetomidine as premedication has previously been reported [13]. Also, it was suggested that the intramuscular route permits a rapid onset of action and offers better predictability because its plasma concentration

peaks within 15 min of administration [5].

7) Clinical uses

(1) Premedication

In children, an ideal premedication must: 1) be available in an acceptable form; 2) have a rapid onset of action; 3) provide mild sedation along with the desired anxiolytic effect; 4) exert its effects for a desired time; 5) have no adverse effects; and 6) facilitate post-operative recovery. Midazolam, commonly used as premedication in children, has been reported to significantly ameliorate preoperative anxiety and nervousness [6].

Some studies have recommended the use of dexmedetomidine as a premedication for children, to decrease anxiety and the occurrence of delirium [21]. It is recommended that 0.33-0.67 mg/kg (i.v) or 2.5 $\mu\text{g}/\text{kg}$ (i.m) should be administered 15 min before operations [13]. A meta-analysis of dexmedetomidine as a premedication reported that, compared to midazolam, it results in greater preoperative sedation and decreased postoperative pain [28]. Another meta-analysis reported the observation of a similar effect on postoperative pain, significant reduction in the doses of rescue analgesic drugs, decreased anxiety with parental separation and decreased postoperative agitation with dexmedetomidine compare with midazolam [4].

(2) Sedation

Dexmedetomidine is used for short sedation (≥ 24 h) of intensive care unit patients [3]. Its safety as a sedative is owed to its minimal induction of respiratory distress and high Carrico index: known as the ratio of the partial pressure of arterial oxygen and fraction of oxygen inspired [13].

(3) Analgesia

The analgesic effect of dexmedetomidine results from its stimulation of central nervous system α_2 -adrenergic receptors. A recent systematic review of various randomized control trails on α_2 -adrenergic receptor agonists stated that the post-operative clinical use of dexmedeto-

midine was sparsely similar to that of morphine as they both decrease the intensity of pain in the 24 h post-operative period [29].

(4) Anxiolysis

The anxiolytic effect of dexmedetomidine in premedication has been proven comparable to that of benzodiazepines. Overall, dexmedetomidine decreases the requirement of additional sedatives and post-operative delirium [3].

8) Adverse effects of dexmedetomidine

Jannu et al. [21] after orally administering midazolam and dexmedetomidine as premedication to children reported their two most common adverse effects to be decreased blood pressure and bradycardia. Dexmedetomidine can decrease sympathetic outflow by decreasing plasma epinephrine and norepinephrine levels, leading to hypotension and decreased heart rate [30]. Similarly, upon comparison of the hemodynamic parameters (before and during surgery) of midazolam, clonidine, and dexmedetomidine administered as premedication to children, it was found that both clonidine and dexmedetomidine resulted in decreased heart rate and blood pressure [13]. However, Mountain et al. [21] suggested that oral administration of up to 4 $\mu\text{g}/\text{kg}$ dexmedetomidine results in no adverse events other than hypotension and bradycardia.

9) α_2 -adrenoceptors antagonists of dexmedetomidine

α_2 -adrenoceptors antagonists are a group of drugs capable of crossing the blood-brain barrier and reversing the action of α_2 -adrenoceptors [5]. The main selective α_2 -adrenoceptor antagonists are atipamezole, idazoxan, and yohimbine [5]. Previous studies have demonstrated successful reversal of the sedative and hypotensive effects of dexmedetomidine by intravenously administered atipamezole [31,32,33].

Dexmedetomidine is a safe and widely used clinical sedative. Its therapeutic effects include sedation, analgesia, and anxiolysis, and primarily result from its

high-affinity binding to α_2 -adrenoceptors. Its properties therefore make it an efficacious and safe sedative for pediatric dental procedures.

AUTHOR ORCIDS

Vedangi Mohite: <https://orcid.org/0000-0002-9050-1006>

Sudhindra Baliga: <https://orcid.org/0000-0002-4799-8205>

Nilima Thosar: <https://orcid.org/0000-0003-3339-781X>

Nilesh Rathi: <https://orcid.org/0000-0003-0595-5191>

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

REFERENCES

1. Ramazani N. Different aspects of general anesthesia in pediatric dentistry: A review. *Iran J Pediatr* 2016; 26: e2613.
2. Patel V, Singh N, Saksena AK, Singh S, Sonkar SK, Jolly SM. A comparative assessment of intranasal and oral dexmedetomidine for procedural sedation in pediatric dental patients. *J Indian Soc Pedod Prev Dent* 2018; 36: 370-5.
3. Devasya A, Sarpangala M. Dexmedetomidine: A review of a newer sedative in dentistry. *J Clin Pediatr Dent* 2015; 39: 401-9.
4. Chue PS, Chue JA. A review of the clinical uses of dexmedetomidine. *Int J Clin Anesthesiol* 2017; 5: 1080.
5. Khan ZP, Ferguson CN, Jones RM. α_2 and imidazoline receptor agonists: Their pharmacology and therapeutic role. *Anaesthesia* 1999; 54: 146-65.
6. Yuen VM. Dexmedetomidine: perioperative applications in children. *Paediatr Anaesth* 2010; 20: 256-64.
7. Bergendahl H, Lonnqvist PA, Eksborg S. Clonidine: an alternative to benzodiazepines for premedication in children. *Curr Opin Anaesthesiol* 2005; 18: 608-13.
8. Nishina K, Mikawa K, Shiga M, et al. Clonidine in pediatric anesthesia. *Paediatr Anaesth* 1999; 9: 187-202.
9. Lonnqvist PA, Bergendahl HT, Eksborg S. Pharmacokinetics of clonidine after rectal administration in children.

- Anesthesiology 1994; 81: 1097-101.
10. Keles S, Kocaturk O. The effect of oral dexmedetomidine premedication on preoperative cooperation and emergence delirium in children undergoing dental procedures. *BioMed Res Int* 2017; 2017: 6742183.
 11. Mittal NP, Goyal M. Dexmedetomidine: a potential agent for use in procedural dental sedation. *Indian J Dent* 2014; 5: 21-7.
 12. Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. A comparative evaluation of intranasal dexmedetomidine, midazolam and ketamine for their sedative and analgesic properties: a triple blind randomized study. *J Clin Pediatr Dent* 2014; 38: 255-61.
 13. Naaz S, Ozair E. Dexmedetomidine in Current Anaesthesia Practice- A Review. *J Clin Diagn Res* 2014; 8: GE01-4.
 14. Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. *Paediatr Anaesth* 2002; 12: 171-5.
 15. Karl HW, Rosenberger JL, Larach MG, Ruffle JM. Transmucosal administration of midazolam for premedication of pediatric patients. Comparison of the nasal and sublingual routes. *Anesthesiology* 1993; 78: 885-91.
 16. Pimlott SJ, Addy M. Evaluation of a method to study the uptake of prednisolone sodium phosphate from different oral mucosal sites. *Oral Surg Oral Med Oral Pathol* 1985; 60: 35-7.
 17. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. *Pediatr Crit Care Med* 2003; 4: 203-5.
 18. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 2003; 56: 691-3.
 19. Lammers CR, Rosner JL, Crockett DE, et al. Oral midazolam with an antacid increases the speed of onset of sedation in children prior to general anesthesia. *Anesth Analg* 1999; 88: S300.
 20. Sheta SA, Al-Sarheed MA, Abdelhalim AA. Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double-blinded randomized controlled trial. *Paediatr Anaesth* 2014; 24: 181-9.
 21. Jannu V, Mane RS, Dhorigol MG, Sanikop CS. A comparison of oral midazolam and oral dexmedetomidine as premedication in pediatric anesthesia. *Saudi J Anaesth* 2016; 10: 390-4.
 22. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB. Parental presence during induction of anesthesia versus sedative premedication: which intervention is more effective? *Anesthesiology* 1998; 89: 1147-56.
 23. Schmidt AP, Valinetti EA, Bandeira D, Bertacchi MF, Simões CM, Auler JO Jr. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Paediatr Anaesth* 2007; 17: 667-74.
 24. Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. *Anesthesiology* 2006; 105: 1098-110.
 25. Shukry M, Clyde MC, Kalarickal PL, Ramadhyani U. Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? *Paediatr Anaesth* 2005; 15: 1098-104.
 26. Kim J, Kim S, Lee DW, Ryu DS. The alternative of oral sedation for pediatric dental Care. *J Dent Anesth Pain Med* 2015; 15: 1-4.
 27. 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: 1715-21.
 28. Peng K, Wu SR, Ji FH, Li J. Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis. *Clinics* 2014; 69: 777-86.
 29. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α_2 agonists on postoperative morphine consumption and pain intensity systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012; 116: 1312-22.
 30. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. *Paediatr Anaesth*

- 1998; 8: 117-21.
31. Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of α_2 -adrenoceptor agonist effects by atipamezole in human volunteers. *Br J Clin Pharmacol* 1991; 31: 160-5.
 32. McCormack L, Chen JW, Trapp L, Job A. A comparison of sedation-related events for two multiagent oral sedation regimens in pediatric dental patients. *Pediatr Dent* 2014; 36: 302-8.
 33. Levine MF, Spahr-Schopfer IA, Hartley E, Lerman J, MacPherson B. Oral midazolam premedication in children: the minimum time interval for separation from parents. *Can J Anaesth* 1993; 40: 726-9.
 34. Sheta SA, AlSarheed M. Oral midazolam premedication for children undergoing general anaesthesia for dental care. *Int J Pediatr* 2009; 2009: 274380.
 35. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth* 1992; 39: 545-50.