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"Dexmedetomidine:" Role in Pediatric Dentistry

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Abstract

A number of sedative agents have been in use in pediatric dentistry to gain a child's cooperation with dental treatment. Dexmedetomidine is one such agent that was introduced as a sedative in the dental practice in 2005 due to a more stable respiratory drive and higher success rates in allowing pediatric dentists to carry out non-painful dental examinations and procedures compared to other sedatives such as chloral hydrate and midazolam. The most distinguishing feature of this sedative is its ability to produce a form of sedation that mimics natural sleep. The high safety margin of dexmedetomidine and its satisfactory sedative action makes it important for us to review its potential applications in pediatric dentistry.

Keywords: Dexmedetomidine, Sedation, Paediatric

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Introduction

A child's cooperation with a dental procedure usually requires various behavioral management strategies conveyed by the entire dental team.[1] Children who are extremely uncooperative are seen to be best managed pharmacologically by general anesthesia, deep sedation, and conscious sedation. General anesthesia, however, requires more time, special training, a high level of hospital setup, and a high cost. Therefore, conscious sedation is accepted as an alternative because it is more economical and convenient for both the patient and the operator.

Dexmedetomidine is a newer sedative agent which was approved by Food and Drug Administration in 1999 for provision of short-term sedation (<24 h) in adult patients in the intensive care unit setting.[2,3] It was introduced to dentistry after 2005,[4] and since then, a multitude of reports describing its use as a safe and efficient agent as a sedative agent for dental procedures in adult and pediatric populations have been published, especially in the recent years, and the results have been encouraging.[5]

The most distinctive characteristic of dexmedetomidine is the high quality of its hypnotic action. Specifically, unlike existing sedatives, it has been described as inducing a state that is close to physiologic sleep, but allowing full awakening with stimulation.[6]

Therefore, dexmedetomidine is a very useful addition to the family of drugs used in dentistry and is regarded as a potentially successful sedative for pediatric dental procedures because of its stable respiratory profile, analgesia, and anti-salivary properties.[7] Hence, it becomes important for us to review its role in present dentistry, especially in the behavior management of pediatric patients and also compare its effects to other sedative agents used in moderate sedation.

Insight

A number of sedative agents have been in use in pediatric dental settings, that is, midazolam, ketamine, propofol, chloral hydrate, promethazine, hydroxyzine, nitrous oxide, and sevoflurane. Each of these has its own sets of limitations.[8] Oral chloral hydrate has been frequently used in pediatric sedation, its mechanism being supported by the activation of gamma-aminobutyrate (GABA) receptors.[9] The main reasons for its use were long time experience, easy application method, and decreased rejection of children and their parents.[10] However, chloral hydrate has a long half-life and impairs respiration and upper airway mechanics associated with desaturation.[11,12] This increased the necessity for the development of more comfortable and safer drugs for sedation in pediatric dentistry.

Dexmedetomidine was introduced as a sedative agent in the dental practice in 2005 due to a more stable respiratory drive and higher success rates in allowing pediatric dentists to carry out non-painful dental examinations and procedures compared to chloral hydrate and midazolam.

Dexmedetomidine is an imidazole compound and is the pharmacologically active dextroisomer of medetomidine that displays specific and selective alpha-2 adrenoceptor agonism.[12,13] Dexmedetomidine is an alpha-2 adrenoceptor agonist that, although similar in site of action to clonidine, is a pure agonist rather than a partial agonist at the receptor level.[14] Its affinity for binding to the alpha-2/alpha-1 receptor is 1300:1 compared with 39:1 for clonidine.[15] Dexmedetomidine is a selective α2-adrenergic agonist and induces sedative effect by affecting α2-adrenergic receptor of central nervous system and cerebrospinal system.[16,17]

Mangano and the MSPI European Research Group have shown that perioperative therapy with alpha-2 agonists or beta-blockers decrease the incidence of myocardial ischemia, perhaps due to a direct effect of reducing heart rate (HR) as opposed to beta-adrenergic receptor blockade.[7,18,19]

Sedation with dexmedetomidine may be optimal for dental procedures because it possesses many of the properties of an ideal sedative agent, such as minimal influence on respiration and

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circulation, easy and rapid control of sedative and conscious levels, amnesia, and rapid recovery after sedation.[7]

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. It is a highly selective and potent α2-adrenoceptor agonist [α2: α1 magnitude relation = 1620: 1]. Its empirical formula is $C_{13}H_{16}HCl$ [Figure 1].[1]

Mechanism of Action

Dexmedetomidine is an agonist of α-2 adrenergic receptors. It is also an imidazole compound and s-enantiomer of medetomidine that displays specific and selective α-2 adrenoceptor agonism.[20] It is a unique esthetic agent that activates the α-2 adrenergic receptor which leads to reduction in noradrenergic neurotransmitter release and depression of adrenergic pathways.[21]

Locus ceruleus that is located at the brain stem is the area that is believed to provide the sedative effects of dexmedetomidine. It is shown to involve in the circadian wake and sleep cycles as well as the center for the management of stress responses. Locus ceruleus has a high adrenergic output which decreases during deeper levels of sleep. Therefore, dexmedetomidine is unique in a manner that it produces sedation in a manner similar to natural sleep.[4]

There are four mechanisms by which dexmedetomidine produces analgesia.

- Direct action on the peripheral nerve
- Centrally mediated analgesia
- α-2-mediated vasoconstrictive effect
- Attenuation of inflammatory response.[22]

Centrally, they act by either direct activation of the descending inhibitory pain pathway or by inhibiting the release of substance P. The suppression activity in the descending noradrenergic pathway, which modulates nociceptive neurotransmission, terminates propagation of pain signals that lead to analgesic effect.[23]

Routes of Administration

Dexmedetomidine can be administered orally, buccally, intravenously, intranasally, and intramuscularly.

Oral Route

One of the simplest and popular routes for drug administration is the oral route [Figure 2]. Its advantages include simplicity and ease of administration, affordability, risk free, and worldwide acceptance. The rate of drug absorption through the oral mucosa is influenced by multiple factors, including the duration of its contact with the mucosa, its lipophilicity, quantity of saliva, and physiochemical characteristics at the site of action.[1] At physiological pH, dexmedetomidine is present in a non-ionized form and has a pKa value of 7.1. Being a highly lipophilic drug, it is easily transported into tissues.[24]

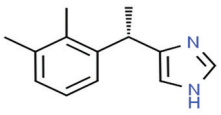

Figure 1: Chemical formula of dexmedetomidine[1]

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.[25]

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.[1] 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.[26]

Time of onset

Oral dexmedetomidine needs to be administrated 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.[1]

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 μg/kg/h dexmedetomidine over a 24 h period leads to the linear expression of its pharmacokinetic effects.[1]

Dexmedetomidine exerts a biphasic effect on blood pressure; as its concentration decreases, vasodilatation increases, due to its central effect. Doses of 0.25–1 μg/kg in adults and 0.5–6 μg/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.[1]

Intranasal Route

Intranasal route is popular in pediatric sedation due 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 [Figure 3] is easy, safe, effective, and non-invasive. In children, the acquiescence to sedation through intranasal administration is higher than that of oral administration.[27]

Intranasal drug delivery is favorable in children when time is limited. At most, 0.15–0.2 ml should be administered in each nostril, as volumes greater than this will be partly be absorbed orally.[28,29] Dexmedetomidine is best absorbed after sublingual and intranasal administration, with a bioavailability of about 82% post-intranasal administration.[1]

Yuen *et al*.[22] conducted a clinical trial to assess the efficacy of intranasal dexmedetomidine and oral midazolam in pediatric premedication.

Figure 2: Dexmedetomidine oromucosal gel

They reported that premedication by intranasal administration of 1 μg/kg dexmedetomidine produced moderate sedation compared to oral administration of midazolam.

A randomized double-blind controlled trial on 2–12-year-old children showed that intranasal administration of 0.5–l μg/kg dexmedetomidine produces a stronger sedative effect than oral administration of 0.5 μg/kg midazolam.[30]

In addition, intranasal dexmedetomidine administration in children results is inadequate hemodynamic effects; however, these actions are clinically irrelevant and no interference is needed.[29] Maximum reduction of systolic blood pressure (SBP) (14.1%) and HR (16.4%) was observed after the intranasal administration of 0.5 and 1 μg/kg dexmedetomidine, respectively.[1]

Moreover, the nasal mucosa has an abundant blood supply, leading to quick drug absorption and onset of action. All these make intranasal dexmedetomidine administration more tolerable and favorable in children than oral administration.[2]

Intramuscular Route

The intramuscular administration of up to 2.5 μg/kg dexmedetomidine as premedication has previously been reported. Furthermore, intramuscular route permits a rapid onset of action and offers better predictability because its plasma concentration peaks within 15 min of administration.[1]

Dosage and Availability of Dexmedetomidine

Dexmedetomidine is commercially available as a water-soluble HCl salt.[31] Dexmedetomidine is available in the US by the trade name Precedex.[2] Vials of Dexdor and Precedex contain a concentrate of dexmedetomidine hydrochloride, equivalent to 100 μg/mL dexmedetomidine. Before infusion, this is diluted to 4 or 8 micro g/mL. Precedex is also available in pre-diluted solutions containing the required concentrations of 4 μg/mL in sodium chloride 0.9%.[31]

In India, it is available under the trade names Alphadex, Dexdine, Dextomid, Dexon, and Xamdex. Availability is in the form of injecting solution in 100 mcg/05 ml, 1 ml, and 200 mcg/2 ml vials. The dosage is mainly based on the weight of the patient. Infusion is frequently initiated with 1 μg/kg loading dose and is administered around 10 min followed by a maintenance dose of 0.2–1.0 μg/kg/h.[2]

Bioavailability of oral dexmedetomidine is only 16% due to extensive first-pass metabolism but that by buccal mucosa is 82% and that of intramuscular route is 104%.[32] The plasma concentration of dexmedetomidine that confers sedation in children is 0.4–0.8 μg/L. This would mean that a dose of 6–8 μg/kg of oral dexmedetomidine would be required to produce effective concentration in children for sedation.[33]

Zub *et al*. were the first to recommend the dose of 3–4 μg/kg of oral dexmedetomidine for premedication to reduce anxiety in children undergoing surgical procedures.[34] They suggested that intravenous preparation of dexmedetomidine could be used orally with acceptable palatability. Mountain *et al*.[35] used oral dexmedetomidine in dose of 4 μg/kg and found it comparable to 0.5 mg/kg midazolam in reducing anxiety in children during mask acceptance and separation from parents without any adverse effects such as hypotension and bradycardia. Because of the individual variability, drug should be carefully calculated and administered to achieve desired sedative effects.

Figure 4 shows the various routes of administration of dexmedetomidine along with their preferred dosages and routes of administration.[1]

Figure 3: Mucosal atomizer device connected to a 2.5 ml syringe for intranasal administration of dexmedetomidine

Pharmacokinetics

Absorption

After oral administration, an extensive first-pass effect is observed, with a bioavailability of 16%.[25] Dexmedetomidine is well absorbed through the intranasal and buccal mucosae, a feature that could be of benefit when using dexmedetomidine in uncooperative children or geriatric patients.[31]

Distribution

Dexmedetomidine is a highly protein-bound drug. In plasma, 94% of dexmedetomidine is bound to albumin and a1-glycoprotein. Using non-compartmental analysis, a distribution half-life of about 6 min was found in healthy volunteers.[31] The apparent volume of distribution was found to be related to body weight, with a volume of distribution at steady state in healthy volunteers of approximately 1.31–2.46 L/kg (90–194 L).

Metabolism and Elimination

Dexmedetomidine is eliminated mainly through biotransformation by the liver. A hepatic extraction ratio of 0.7 was found.[36] Less than 1% is excreted unchanged with metabolites being excreted renally (95%) and fecally (4%).[37,38] Direct N-glucuronidation by uridine 5-diphos-pho-glucuronosyltransferase accounts for about 34% of dexmedetomidine metabolism. In addition, hydroxylation mediated by cytochrome P450 (CYP) enzymes (mainly CYP2A6) was demonstrated in human liver microsomes.[31] An elimination half-life of 2.1–3.1 h is reported in healthy volunteers.

Pharmacodynamics

Dexmedetomidine is 8–10 times more selective toward α2-AR than clonidine.[5] Higher affinity to α2 receptor selectively leads to vagomimetic action on heart (bradycardia) and vasodilatation.[17]

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

Figure 4: Routes of administration of dexmedetomidine[1]

Pharmacodynamic Effects

Cardiovascular and hemodynamic effects

In healthy adult patients following dexmedetomidine administration, an initial increase in SBP and a reflex decrease in HR followed by a stabilization of SBP and HR at values below the baseline, that is, a biphasic effect is seen.[25] Bradycardia and sinus arrest have been reported with dexmedetomidine.[31,39]

Respiratory effects

Few studies on adult human volunteers have reported an increase in paCO2 without affecting respiratory rate.[5] Conflicting findings have been published elsewhere, where an increase in respiratory rate, a decrease in the hypopnea/apnea index, and no change in the end-tidal CO2 when compared with baseline values were reported.

Inhibition of histamine-induced bronchoconstriction has also been reported. Despite these findings, monitoring of respiratory function during the administration of dexmedetomidine in high-risk patients or those receiving other agents that may depress respiratory function is recommended.[30]

Central nervous system effects

A number of clinical trials have reported a dose dependent sedative response with dexmedetomidine. An interesting finding regarding this drug's sedative effect is its resemblance with natural sleep.[40] A decrease in cerebral perfusion pressure with no effect on intracranial pressure has been reported.[5] Reports regarding effect on seizure threshold have given conflicting results with some studies reporting anticonvulsant[41] and some reporting pro-convulsant (lowering of seizure threshold) effect.[42]

Gastrointestinal motility

Dexmedetomidine has been known to inhibit gastrointestinal motility to a greater extent than that reported with clonidine but lesser than opioids, that is, morphine.[5]

Adrenocortical function

Although concerns regarding potential suppression of adrenocortical function were raised, in clinical doses when used for short-term sedation, no such effects on steroidogenesis were reported.[5]

White blood cell function and inflammatory response

Reports regarding dexmedetomidine effect on white blood cell function and inflammatory response have given mixed results with some reporting no effect and some studies reporting a decrease in inflammatory response.[5]

Clinical Applications of Dexmedetomidine in Pediatric Dentistry are as Follows

Premedication

Some studies have recommended the use of dexmedetomidine as a premedication for children, to decrease anxiety and the occurrence of delirium. It is recommended that 0.33–0.67 mg/kg (i.v) or 2.5 μg/kg (i.m) should be administered 15 min before operations.[1]

A meta-analysis of dexmedetomidine as a premedication reported that, compared to midazolam, it results in greater preoperative sedation and decreased postoperative pain.

Another meta-analysis reported the observation of a similar effect on post-operative pain, significant reduction in the doses of rescue analgesic drugs, decreased anxiety with parental separation, and decreased post-operative agitation with dexmedetomidine compare with midazolam.[43]

Sedation

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. Dexmedetomidine was used for sedation in uncooperative children.[1] After an initial dose of 1 μg/kg over 10 min, intravenously, the sedation levels were maintained by continuous infusion. Children were successfully treated with no post-treatment complications. This was possible only because dexmedetomidine has very little influence on respiratory system even at high doses.[4]

Analgesia

The analgesic effect of dexmedetomidine results from its stimulation of central nervous system α2-adrenergic receptors. A recent systematic review of various randomized control trails on α2-adrenergic receptor agonists stated that the post-operative clinical use of dexmedetomidine was sparsely similar to that of morphine as they both decrease the intensity of pain in the 24 h post-operative period.[1]

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[4]

Oral Surgical Procedures

The greater palatine nerve blocks given using bupivacaine and dexmedetomidine during cleft palate surgery in children showed delayed request of analgesics postoperatively compared to the children given blocks with bupivacaine alone. This study concluded that dexmedetomidine had increased the local anesthetic action by prolonging analgesia. Pain scores were lower during the first 24 h and there was no difference in sedation scores or hemodynamic variables in both the groups.[4]

Dexmedetomidine in Combination With Other Drugs

Dexmedetomidine Ketamine Combination

The opposing hemodynamic profiles of two, that is, negative hemodynamic effects of dexmedetomidine and positive cardiostimulatory effects of ketamine may provide balanced hemodynamic parameters in sedated patients. Ketamine has an adverse effect of increased salivation which is undesirable, especially during dental procedures due to implications of

increased salivary secretions in adverse airway events, while dexmedetomidine has antisialagogue properties on account of its sympatholytic potential. Dexmedetomidine has limited analgesia while ketamine has an effective analgesic action.[44]

Both of the agents act on different parts of central nervous system to produce sedation. Hence, a combination of two may provide synergistic sedation with decreased dose. Furthermore, faster onset of action on induction as well as faster recovery can be expected with combination when compared to dexmedetomidine alone.

Dexmedetomidine Fentanyl Combination

Dexmedetomidine has an analgesic-sparing effect, significantly reducing opioid requirements both during and after surgery.[45] Reduction in dose requirement of opioid could further reduce the postoperative complications of nausea, vomiting, and physical dependence which are specifically associated with opioids.[46]

Dexmedetomidine-Midazolam Combination

Compared with propofol or midazolam, dexmedetomidine has a smaller inhibitory effect on respiration, and its use in pediatric patients has recently increased.[47] Midazolam, on the other hand, exhibits dose-dependent anterograde amnesia and also less cardiac inhibition than the other two drugs. Therefore, combination of dexmedetomidine and low-dose midazolam may provide an effective sedative combination for dental treatment.[48]

It is frequently difficult to maintain a sufficient depth of sedation using either dexmedetomidine or midazolam alone.[49] In another study, it was reported that respiratory depression, leading to severe hypoxia, was induced by midazolam in a dose-dependent manner.[50]

Dexmedetomidine in Combination with Local Anesthesia

Singh *et al*.[51] conducted a study in 2018 to compare the effect of dexmedetomidine added to lidocaine against epinephrine added to lidocaine on potency of local anesthesia and to look for future prospects of dexmedetomidine as an additive to local anesthesia in dentistry.

The study included 25 healthy volunteers in whom extraction of all first premolars was scheduled as part of their orthodontic treatment plan. In this split-mouth, double-blind, crossover, randomized controlled trial, Group 1 received injection lidocaine plus dexmedetomidine, and Group 2 was administered lidocaine plus epinephrine. The results showed that the duration of anesthesia was longer in Group 1 in which the requirement for the first analgesic on request was seen after a longer time interval, when compared with Group 2 (lidocaine plus epinephrine). Pain perception elicited statistically significant results with less perception of pain in Group 1 (lidocaine plus dexmedetomidine). The vital parameters remained stable, and the results were not statistically significant.

It was, therefore, concluded that the addition of dexmedetomidine to lidocaine for maxillary and mandibular nerve blocks significantly prolonged the block duration and shortened the onset of action, as well as improved post-operative analgesia in terms of the need for fewer analgesics in the post-operative period. Furthermore, the vital parameters remained stable and no complications were encountered.

Comparison of Dexmedetomidine With Other Drugs

Dexmedetomidine versus Midazolam

Effect of dexmedetomidine versus midazolam on separation from parents

In a systematic review and meta-analysis conducted by Ke *et al*. in 2014,[52] seven trials including 650 patients compared dexmedetomidine versus midazolam premedication for satisfactory separation from parents. The meta-analysis revealed that more children experienced satisfactory separation following treatment with dexmedetomidine.

Effect of dexmedetomidine versus midazolam on mask induction

Six trials including 475 patients compared satisfactory mask induction in children treated with dexmedetomidine versus midazolam The meta-analysis showed that there was no significant difference between the groups.[52]

Effects of dexmedetomidine versus midazolam on HR, SBP, and oxygen saturation (SpO2) before induction

Two trials including 162 patients compared HR before induction in children treated with dexmedetomidine versus midazolam.[12,53] The meta-analysis revealed that the HR before induction was significantly lower in the children treated with dexmedetomidine.

Two trials including 184 patients compared SBP before induction in children treated with dexmedetomidine versus midazolam.[12,54] There was no significant difference between the groups.

Two trials including 184 patients compared SpO2 before induction in children treated with dexmedetomidine versus midazolam.[12,54] The meta-analysis showed that there was no significant difference between the groups.

Effects of dexmedetomidine versus midazolam on recovery time

Three trials including 204 patients compared the recovery times of children treated with dexmedetomidine versus midazolam.[12,55,56] There was no significant difference between the groups.

Effects of dexmedetomidine versus midazolam on post-operative nausea and vomiting (PONV)

Three trials including 226 patients compared dexmedetomidine with midazolam premedication for PONV treatment.[54-56] The meta-analysis showed that there was no significant difference between the groups.

Dexmedetomidine versus Ketamine

- Dexmedetomidine and ketamine have opposing hemodynamic profiles. Dexmedetomidine has negative hemodynamic effects[5,57] while ketamine has positive cardiostimulatory effects.[58]
- Ketamine has an adverse effect of increased salivation[59,60] which is undesirable especially during dental procedures due

to implications of increased salivary secretions in adverse airway events,[61] while dexmedetomidine has anti-sialagogue properties on account of its sympatholytic potential.[5]

- Dexmedetomidine has limited analgesia[62] while ketamine has an effective analgesic action.[5]

Dexmedetomidine versus Propofol

Previously concerns have been raised about cardio-depressant properties of dexmedetomidine and bradycardia has been the most feared adverse effect associated with this agent. In contrast to cardio-depressant properties of dexmedetomidine, effects of this agent on respiration are minimal while propofol has been reported to have respiratory depressant effects. However, propofol has been reported to be a faster acting induction agent when compared to dexmedetomidine.[12]

Dexmedetomidine versus Chloral Hydrate

Dexmedetomidine provides higher success rates in completing non-painful examinations in clinics with fewer adverse respiratory events than chloral hydrate.[63] Chloral hydrate has been commonly used for pediatric sedation, its mechanism is supported by activating as a GABA receptor;[9] however, chloral hydrate has a long half-life during which to impair respiration and upper airway mechanics associated with desaturation. The other issues for chloral hydrate include the cardiac toxicity and narrow therapeutic window which has limited the chloral hydrate to be widely used in pediatric sedation.

Effect of Dexmedetomidine Premedication on the Behavior of Patients in the Pediatric Dental Clinic

The premedication efficacy of dexmedetomidine can be assessed using Houpt scale [Figure 5].

Mahdavi *et al*.[63] conducted a study to assess the intranasal premedication effect of dexmedetomidine versus midazolam on the behavior of 2–6-year-old uncooperative children in dental clinic. The subjects were randomly given 1 μg/kg of dexmedetomidine and 0.5 mg/kg of midazolam through the intranasal route.

For the sedation protocol in the two groups, 0.25 mg/kg of atropine in combination with 0.5 mg/kg of midazolam added to 1–2 mg/kg of ketamine were used 30 min after premedication and transferring the patient to the operating room. The results reported that the comparison of sleep (S), movement (M), crying (C), and overall behavior (O) parameters showed no significant differences between the two groups ($P > 0.05$).

The conclusion of this study was that dexmedetomidine and midazolam showed comparable premedication efficacies. Both premedication regimens were efficient according to the Houpt scale. Both intranasal midazolam and dexmedetomidine regimens could provide certain levels of calmness for the child and dentist during dental procedures. Dexmedetomidine causes smaller degrees of postoperative agitation in children between the ages of 1 and 6 years old.

Dexmedetomidine group received lower amounts of sedative agents compared to the midazolam group. This difference in dosage suggests the higher sedative effect of dexmedetomidine. All the vital signs remained within the normal range during the procedure, and no interventions were needed. The most common side effects during the first 24 h were vomiting and dizziness for both premedication regimens.

Rating scale	Definition	Score
Rating scale for sleep	Fully awake, alert	1
	Drowsy, disoriented	2
	Asleep	3
Rating scale for movement	Violent movement that interrupts treatment	1
	Continuous movement that makes treatment difficult	2
	Controllable movement that does not interfere with treatment	3
	No movement	4
Rating scale for crying	Hysterical crying that interrupts treatment	1
	Continuous, persistent crying that makes treatment difficult	2
	Intermittent, mild crying that does not interfere with treatment	3
	No crying	4
Rating scale for overall behavior	Aborted: No treatment	1
	Poor: Treatment interrupted, only partial treatment completed	2
	Fair: Treatment interrupted but eventually all completed	3
	Good: Difficult, but all treatment performed	4
	Very good: Some limited crying or movement, e.g. during anesthesia or mouth prop	5
	Excellent: No crying or movement	6

Figure 5: Houpt scale[63]

Surendar *et al*.[55] conducted a study in 2014 to evaluate and compare the efficacy and safety of intranasal (IN) dexmedetomidine, midazolam, and ketamine in producing moderate sedation among uncooperative pediatric dental patients. All the children were randomized to receive one of the four drug groups dexmedetomidine 1 μg/kg (D1), 1.5 μg/kg (D2), midazolam 0.2 mg/kg (M1), and ketamine 5 mg/kg (K1) through IN route.

In all four groups, the success rate was highest in D2 (85.7%) and M1 the least (61.9%). In all four groups, the sedation was highest in D2 (95.2%) and least in M1 (71.4%). In all four groups, the satisfactory behavior was highest in D2 (90.5%) and least in M1 (71.4%). Hence, it was concluded that dexmedetomidine can be used safely, effectively, and with the same efficacy as midazolam and ketamine, through IN route in uncooperative pediatric dental patients for producing moderate sedation.

Advantages of Dexmedetomidine

In 2002, Tobias *et al*.[60] stated that dexmedetomidine was a safe sedative for children and infants.

1. Dexmedetomidine exerts sedative, anxiolytic, and analgesic effects, with insignificant respiratory system distress and inhibits tachycardia.[1]
2. 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.
3. During its sedative action, it prevents hypoxia by maintaining the airway and enabling spontaneous respiration. It also preserves CO2 reactivity and increases.

4. 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.
5. Dexmedetomidine can be administered by various routes including oral, buccal, intravenous, intranasal, and intramuscular.
6. Its effects can be reversibly reversed by its specific antagonist atipamezole.[1]

Adverse Effects of Dexmedetomidine

Jannu *et al*.[64] after orally administering dexmedetomidine as premedication to children reported its 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 HR.[64] Mountain *et al*.[63] suggested that oral administration of up to 4 μg/kg dexmedetomidine results in no adverse events other than hypotension and bradycardia.

Other adverse effects include nausea, sinus arrest, atrial fibrillation, and hypoxia. Furthermore, an overdose may cause atrioventricular block. Most of the adverse effects occur briefly after loading the drug, which can be prevented by reducing the loading dose. The drug does not cross the placenta and should be used during pregnancy with caution.

Contraindications of Dexmedetomidine[29]

Dexmedetomidine is Contraindicated in

1. Patients at risk for bradycardia or atrioventricular nodal block.
2. Patients with a compromised cardiovascular state,
3. Patients with hypovolemia,
4. Patients with atrioventricular nodal block,
5. Patients taking concurrent medications that increase vagal tone or delay atrial-ventricular conduction.
6. Patients using beta-adrenergic antagonists.

When pronounced hypotension or bradycardia occurs, treatment includes cessation of drug administration, volume expansion, vasopressor infusions, and/or administration of anticholinergic agents.[29]

Conclusion

Dexmedetomidine is a newer sedative drug with wide safety margin, excellent sedative capacity, and moderate analgesic properties and with clinical applications. The very properties of dexmedetomidine make it a better choice than other sedatives available. It is also used as an adjunctive agent along with other drugs. Even though the use of dexmedetomidine in dentistry started recently, many clinical studies till now have proven that dexmedetomidine is effective in dental procedures and also in pediatric patients. With minimal adverse effects and better properties, at present, it is ideally a better choice of sedative.

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