INTRODUCTION: Procedural sedation and analgesia (PSA) is a method of administering sedatives or dissociative agents to patients undergoing unpleasant procedures. It has become the international standard of care for managing acute anxiety and pain, practiced by multiple specialists in varying settings outside the operating room. The aim of procedural sedation is to enable painful procedures to be performed safely and effectively with minimal discomfort to the patient. It is important that the depth of sedation is controlled to achieve these aims without compromising the patient’s airway or causing haemodynamic instability. PSA for children is the use of sedative, analgesic, and/or dissociative agents to relieve anxiety and pain associated with diagnostic and therapeutic procedures.

Various drugs are being used for the procedural sedation e.g. Propofol, midazolam, ketamine and fentanyl. The respiratory depressant effects of opioids, benzodiazines, Propofol and ketamine create the need for a drug without adverse respiratory profile that can be safely used in both healthy and high risk patients undergoing PSA. An ideal drug required for PSA should be able to provide patient comfort, blunting of airway reflexes, patient cooperation, haemodynamic stability, amnesia and the maintenance of a patent airway with spontaneous ventilation and analgesia. Of late dexmedetomidine is emerging as one of the popular drugs for PSA as it meets many of the requirements of PSA.

Dexmedetomidine is an alpha 2-adrenoreceptor agonist, which provides sedation, analgesia, and anxiolysis in clinical practice. It is an imidazole compound, is the active d-isomer of medetomidine. Activation of central alpha 2-adrenoreceptors in the locus ceruleus is responsible for both analgesic and sedative effects. It has a very high alpha-2 to alpha-1 selectivity, 1620 to 1, or approximately 8 times that of clonidine.

Pharmacodynamic Properties of Dexmedetomidine - Sedative Effects: Induces dose-related sedation. Induces a form of sedation resembling natural sleep from which the patient is easily and quickly aroused. The participation of non-rapid eye movement sleep pathways seems to explain why patients who appear to be “deeply asleep” from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep.

This type of sedation is branded “cooperative” or “Arousable”, to distinguish it from the sedation induced by drugs acting on the gamma amino benzoic acid (GABA) system, such as midazolam or propofol, which produce a clouding of consciousness. This sort of arousable sedation produced by dexmedetomidine is crucial in some of the procedures where patient’s cooperation is mandatory, for example in awake nasotracheal intubation.

Opioid-sparing/analgesic Effects: Induces dose-related analgesia in healthy volunteers. Reduces, but does not replace, requirements for opioids and other analgesics. Prolongs sensory and/or motor
blocks induced by bupivacaine spinal or epidural, analgesia. Prolongs the duration of the brachial plexus blocks and the spinal anaesthetic action of prilocaine.³

**Haemodynamic Effects:** Demonstrates a biphasic effect on blood pressure (BP). Transient elevations observed with high doses (e.g. during the loading dose) as a result of peripheral vasoconstriction, followed by reductions in BP owing to central and peripheral sympatholytic effects. At lower doses, reductions in BP are observed.³ If an initial loading dose of dexmedetomidine is not administered or if the loading dose is infused slowly (i.e., over 10 minutes), the severity of the hypotension after dexmedetomidine is attenuated. In such cases, systolic blood pressure decreases up to 30% from baseline, although hypertension has occurred.⁴ Dexmedetomidine has the potential for pronounced hypotension in patients with pre-existing hypovolaemia. Reduces heart rate, even at low doses. Associated with clinically significant bradycardia and sinus arrest in young, healthy volunteers with high vagal tone or with different routes of administration, including bolus or rapid intravenous administration. Reduces cerebral blood flow in a dose-related manner.³

**Respiratory Effects:** Dexmedetomidine has a minimal effect on respiratory function, with the respiratory rate and oxygen saturation remaining within normal limits and no evidence of respiratory depression.³ Respiratory rate and hemoglobin oxygen saturation are unchanged after 1micro g/kg dexmedetomidine infused over 10 minutes Upper airway patency is maintained during dexmedetomidine sedation in children.⁴ In a magnetic resonance imaging (MRI) study of healthy children who breathed spontaneously during dexmedetomidine (1 or 3 micro g/kg/h), the cross sectional areas of the nasopharynx and retroglossal space were only modestly reduced in comparison with baseline, and respiratory indices were maintained.⁵ However, doses of 2 micro g/kg given as a bolus resulted in short episodes of apnoea. Also, co-administration of dexmedetomidine with other sedatives, hypnotics or opioids is likely to cause additive effects.³

**Metabolic Effects:** Dexmedetomidine reduces cerebral metabolic rate in a dose-related manner. It is associated with reduced shivering.³

**Endocrine Effects:** It does not appear to inhibit adrenal steroidogenesis. Has no apparent effect on blood glucose concentrations.³

**Gastrointestinal effects:** Inhibits gastric emptying and gastrointestinal transit times.³

**Ocular effects:** Reduces intraocular pressure.³

**Pharmacokinetics of Dexmedetomidine:** Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life (t ½ α) of 6 min, a terminal elimination half-life (t ½ β) of 2 hours, and a steady-state volume of distribution (Vss) of 118 liters. Dexmedetomidine exhibits linear kinetics when infused in the dose range of 0.2-0.7 μg/kg/h for no more than 24 hours.⁶ Dexmedetomidine undergoes almost complete biotransformation through direct glucuronidation and cytochrome P450 metabolism. Metabolites of biotransformation are excreted in the urine (95%) and feces. It is unknown if they possess intrinsic activity. The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl,
digoxin, theophylline, lidocaine and ketorolac.\textsuperscript{6} A very small fraction of dexmedetomidine is excreted unchanged in urine and feces. When delivered by non-IV routes, the bioavailability of dexmedetomidine follows the order orogastric 16%, intranasal (IN) 65%, buccal 82%, and IM 100%. There have been no sex or age-based differences in the pharmacokinetics of dexmedetomidine; however, it has not been studied in paediatric patients.\textsuperscript{7,8} The dose of dexmedetomidine should be decreased in patients with hepatic or renal impairment. Dexmedetomidine do cross the placenta and should be only used during pregnancy if the potential benefits justify the potential risk to fetus.\textsuperscript{6}

**Dose and Administration:** Dexmedetomidine is a white powder that is freely soluble in water and has a pka of 7.1. It is supplied as 100 μg/ml 2 ml vial which must be diluted with 48 ml of 0.9% sodium chloride prior to administration. For adult patients, dexmedetomidine is administered by a loading infusion of 0.5-1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 μg/kg/h. The effect appears in 5-10 min, and is reduced in 30-60 min. The maintenance infusion is adjusted to achieve the desired level of sedation (Table 1).\textsuperscript{6}

| INDICATION LOADING DOSE MAINTENANCE |
|-------------------------------------|
| **Adult patients**                  |
| 1.0 micro g/kg (0.5 micro g/kg for less invasive procedures [e.g. ophthalmic surgery]) infused over 10min |
| Commence at 0.6 micro g/kg/h and titrate from 0.2 to 1.0 micro g/kg/h to achieve the desired level of sedation |
| **Awake fibreoptic intubation**     |
| 1.0 micro g/kg infused over 10min |
| 0.7 micro g/kg/h is recommended until the endotracheal tube is secured |
| **Pts. aged >65 y**                 |
| 0.5 micro g/kg infused over 10min |
| Consider a dosage reduction         |
| **Pts. with impaired hepatic function** |
| Consider a dose reduction           |
| Consider a dosage reduction         |

Table 1: Recommended dosage regimens of intravenous dexmedetomidine in adult patients for procedural sedation

**Use of dexmedetomidine in adult patients for PSA:** Dexmedetomidine, outside the operation theatre is commonly used in ICU for sedation of mechanically ventilated patients. The most important advantage of it in these patients is in its production of arousable sedation, natural sleep like state and opioid sparing analgesic effect without respiratory depression. These beneficial pharmacodynamic effects have been successfully used for procedural sedation also, especially for percutaneous dilatational tracheostomies, and central venous cannulations in the ICU.\textsuperscript{6}

Dexmedetomidine in monitored anaesthesia care (MAC) was used successfully in many situations: when patient arousability needed to be preserved, as for awake craniotomy, for awake carotid endarterectomy and for vitreoretinal surgery. In addition, dexmedetomidine was used for sedation in difficult airway patients; during fibreoptic intubation, and for sedation of a patient with difficult airway undergoing lumbar laminectomy surgery in the prone chest position under spinal anesthesia.\textsuperscript{6}
Use of dexmedetomidine in paediatric procedural sedation: Paediatric procedural sedation and sedation for noninvasive imaging and testing has been a continually evolving and expanding field for the past several decades. Many agents are currently used outside the operating room by nonanesthesiologists for procedures and diagnostic evaluations. When selecting an agent for sedation, the individual patient characteristics as well as the setting the sedation is taking place, at times, will dictate which agent is used. As dexmedetomidine can also be administered orally and nasally and many of the children will not have an intravenous access, its popularity as an agent for PSA in paediatrics is increasing.

Noninvasive procedural sedation in paediatric Patients: The largest experience with dexmedetomidine as a sedative for children outside the operating room has been in MRI. Although initial reports suggested that dexmedetomidine at 1 micro g/kg IV initial loading dose over 10 minutes followed by 0.5 micro g/kg/h provided effective sedation for MRI scans, these data could not be corroborated. The current evidence suggests that to provide sedation in 90% of children with dexmedetomidine, either supplemental sedative must be co administered with the dexmedetomidine (e.g., IV midazolam) or the bolus or infusion rate of dexmedetomidine must be more rapid than that reported initially.

For its use outside the intensive care unit, dexmedetomidine was first described in the paediatric population in a case series of 48 children in 2005. These children required sedation for magnetic resonance imaging (MRI), electroencephalography (EEG), a nuclear medicine study, or a combination of these. Thirty-three of the 48 children received dexmedetomidine as their primary sedation. Dexmedetomidine was given as a loading dose of 1 micro g/kg for 10 minutes, followed by an infusion of 0.7 micro g/kg per hour. The remaining patients were treated with dexmedetomidine after failing midazolam and/or chloral hydrate. There were decreases from baseline in blood pressure and heart rate, but all remained within reference limits for age. All studies were performed successfully.

Koroglu et al. also performed a randomized trial comparing dexmedetomidine and midazolam for 80 paediatric patients undergoing MRI. They received a loading dose of either 1 micro g/kg dexmedetomidine or 0.2 mg/kg midazolam for 10 minutes, followed by an infusion of 0.5 micro g/kg per hour of dexmedetomidine or 6 micro g/kg per minute of midazolam. Adequate sedation was obtained in 80% of the dexmedetomidine group and in only 20% of the midazolam group. There were no episodes of respiratory depression in the children receiving dexmedetomidine.

Dexmedetomidine for invasive procedural sedation in Children: Six spontaneously breathing children, five infants and one toddler, age 3 days–29 months, all with congenital heart disease, received dexmedetomidine as the primary sedative agent while undergoing an invasive procedure. Five of the patients were <6 months of age. Each patient underwent an invasive procedure including...
central venous line placement, chest tube insertion, fiberoptic bronchoscopy, and femoral cut-down for Broviac placement. All patients were breathing spontaneously throughout their procedure. Dexmedetomidine was used as the primary sedative agent during the procedure with additional sedation provided with low dose ketamine for patient movement in three of the six patients. The average dexmedetomidine dose used was 1.5 micro g/kg (1–3 micro g/kg).

An additional low dose of ketamine, 0.7 mg/kg (0.3–1.5 mg/kg), was used in 50% of the patients. All patients breathed spontaneously without significant desaturation throughout the procedure, and although there was a trend toward lower blood pressure and heart rate, all patients remained warm and well perfused. Each of the six procedures was successfully completed without any associated complications. The authors concluded that invasive procedures can be successfully performed in spontaneously breathing infants and toddlers with congenital heart disease using dexmedetomidine alone or in combination with low dose ketamine.13

**Dexmedetomidine administration through oral route for PSA:** Zub et al.14 published a retrospective review in 2005, of children who received oral dexmedetomidine as a premedication for general anesthesia induction or for procedural sedation. They observed 13 patients aged 4 to 14 years who received oral dexmedetomidine in the range of 1 to 4.2 micro g/kg. They found that effective sedation was achieved in 11 of the 13 patients, with 1 child having mild resistance to IV placement and 1 child receiving 1 micro g/kg dexmedetomidine and not achieving anxiolysis. After this review, these authors recommended a dose of 3 to 4 micro g/kg oral dexmedetomidine for anxiolysis.

**Dexmedetomidine administration through nasal route for PSA:** Yuen et al.15 found that a dose of 1 to 1.5 micro g/kg intranasal dexmedetomidine was effective as a premedication that was equivalent to an oral dose of 0.5 mg/kg midazolam. Dexmedetomidine has a neutral pH and is virtually painless when administered intranasally. The use of dexmedetomidine intranasally at a dosage of 4 micro g/kg has also been shown to be successful for short scans and for measurement of auditory brainstem responses.16

When intranasal dexmedetomidine of 1 micro g/kg was used for premedication in children, the median onset time of sedation was 25 min with a median duration of 85 min. In a study conducted in healthy volunteers, intranasal administration of dexmedetomidine 1 micro g/kg produced significant sedation within 45 min, with a clinical sedative effect lasting 180 min. Bioavailability of intranasal dexmedetomidine has recently been evaluated in a small number of healthy volunteers. After intranasal administration of 84 micro g of dexmedetomidine, it was found that the median time to reach peak plasma concentration and the elimination half-life were 38 and 114 min, respectively, with the median absolute bioavailability of 65%. Pharmacological effects were demonstrated to be similar between intranasal and IV routes of administration except that onset was more rapid for IV administration. Because the onset of clinical sedation was at 30–45 min after intranasal administration, it was suggested to be given 45–60 min before a surgical procedure.17

**Disadvantages of propofol for PSA:** Propofol is another very popular drug for PSA. But it has many disadvantages.

**Egg and soy Allergies:** Patients allergic to eggs or soy should not receive propofol, as it is formulated for IV administration as an emulsion containing soybean oil and purified egg phosphatide.18
Decrease in blood pressure (BP) and heart rate (HR): Decreases in BP and HR are common with propofol, although the majorities, especially in children, are not clinically significant. Mean arterial pressure decreases by a mean of 10–25% and heart rate decreases by a mean of 20%.\textsuperscript{19-21}

Respiratory Depression and Apnea: Respiratory depression, including apnoea, occurs in patients receiving propofol, with evidence of decreased minute ventilation and CO2 retention, but low incidence of hypoxia in adequately preoxygenated patients.\textsuperscript{22,23}

Painful Injection: Propofol causes pain on injection related to the lipid content of the formulation. This can be reduced by pretreatment of the vein with 1 mg/kg of 1–2% lidocaine left in the vein for 1 min with a proximal tourniquet in place, by giving the infusion slowly, or by using a larger vein (e.g., antecubital veins).\textsuperscript{24}

Propofol infusion Syndrome: has not yet been reported in procedural sedation. It occurs in prolonged, higher-dose infusions of propofol in young or head-injured patients and is characterized by refractory bradycardia, metabolic acidosis, hyperlipidemia, rhabdomyolysis, and hepatomegaly.\textsuperscript{25}

Rapid attainment of greater depth of sedation than Intended: Because of the individual variation, sedative doses of propofol can produce anaesthesia in certain patients and the subsequent complications.\textsuperscript{25}

Studies comparing propofol and dexmedetomidine for PSA: Kaygusuz K et al compared propofol and dexmedetomidine for extra corporeal shock wave lithotripsy (ESWL) as agents for procedural sedation in adult patients and found that Visual analog scale values with dexmedetomidine were significantly lower than those with propofol and also during sedation, the respiratory rate with dexmedetomidine was significantly slower but SpO2 was significantly higher than with propofol. The authors concluded that a combination of dexmedetomidine with fentanyl can be used safely and effectively for sedation and analgesia during ESWL.\textsuperscript{26} Techanivate et al compared dexmedetomidine and propofol for sedation during colonoscopy in adult patients. They found that the incidence of hypotension in propofol group (Group P) was significantly greater than dexmedetomidine group (Group D) (50% vs. 20%). There were no statistically significant differences in the induction time, intraoperative bradycardia, postoperative complications and patient satisfaction between the two groups. The patients in Group P recovered from sedation more slowly than Group D and there were fewer patients in Group P who think that they can resume normal activities on the day of colonoscopy.\textsuperscript{27}

There have been studies comparing propofol and dexmedetomidine regarding pediatric sedation and have found no difference in the success of procedures between the 2 agents.\textsuperscript{10} Hasanin et al compared dexmedetomidine versus propofol for sedation during gastrointestinal endoscopy (GIE) in paediatric patients and concluded that dexmedetomidine sedation during GIE provides more respiratory safety & HR stability presenting itself as a suitable alternative agent especially for the relatively longer procedures.\textsuperscript{28} In paediatric PSA dexmedetomidine had the unique advantage of noninterference with EEG results compared with other medications used as sedation options and also has analgesic properties, which propofol lacks. Another advantage of dexmedetomidine in some
institutions is that it is commonly available for use by multiple levels of practitioners, whereas in other institutions, propofol is reserved for usage by anesthesiologists alone.

CONCLUSION: Dexmedetomidine is fast emerging as one of the most popular drugs for PSA. It scores over propofol for PSA in many ways because of its unique properties of - a) producing arousable sleep like sedation, b) no respiratory depression, c) minimal cardiovascular effects, d) Opioid sparing analgesic effect. e) Routes of administration can also be either oral or nasal – which is very important in paediatric PSA as children do not cooperate for IV cannulation, and f) can also be used by non anaesthesiologist practitioners.

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# REVIEW ARTICLE

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