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Review Article

The Use of Dexmedetomidine on Pediatrics Undergoing Magnetic Resonance Imaging (MRI) Examination

Gembong Pandhu Suprobo[1], Karmini Yupono[2], Rudy Vitraludyono[3]
[1]Resident of Anesthesiology and Intensive Therapy Residency Program, Medical Faculty, Brawijaya University – Dr.Saiful Anwar General Hospital Malang Indonesia
[2]Pediatric Anesthesiologist Consultant of Anesthesiology and Intensive Therapy Residency Program, Medical Faculty, Brawijaya University – Dr.Saiful Anwar General Hospital Malang, Indonesia
[3]Teaching Staff of Anesthesiology and Intensive Therapy Residency Program, Medical Faculty, Brawijaya University – Dr.Saiful Anwar General Hospital Malang Indonesia

Correspondence:
Gembong Pandhu Suprobo, dr*
Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Brawijaya University/ RSUD Dr. Saiful Anwar, Malang, Indonesia
e-mail: Pandhu.suprobo@gmail.com

SUMMARY

Dexmedetomidine, an α2-adrenergic agonist, has been commonly used as an off-label anesthetic adjuvant in various procedures and age groups. Lately, dexmedetomidine is increasingly preferred as sedation for pediatric patients undergoing MRI, which requires the patient to remain still in deep sedation without disturbing airway patency. Dexmedetomidine administration via intranasal or buccal route is preferred for pediatric patients. Dexmedetomidine does not undergo significant pharmacokinetic changes when used in conjunction with other anesthetics and has a good safety profile. It is 8-10 times more selective against α2 receptors than clonidine and produces sedation, analgesia, vasodilation, and bradycardia without significant airway and respiratory depression risk. Compare to the other sedative agent, dexmedetomidine has a longer duration. Thus, dexmedetomidine can be used as the sole sedating agent in infants and children undergoing MRI procedures, with good sedation results and minimal side effects. However, it is very important to give the correct dose to avoid bradycardia and hypotension, which can be a side effect of its use.

Keywords: dexmedetomidine, pediatrics, MRI, anesthesia, ambulatory, sedation

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INTRODUCTION

Magnetic resonance imaging (MRI) is one of many diagnostic imaging tools that has been proven and established widely used for pediatrics now. It allows assessment of body structure, function, and morphology without giving any radiation harm.[1,2] Patients' cooperation is imperative in order to obtain good MRI images. MRI scanning process is very sensitive to motion artifacts. If any movement occurs during the imaging process for one sequence, the sequence must be repeated entirely.

Unfortunately, it is difficult to accomplish while dealing with the pediatrics population. Keeping pediatric patients immobilized in a dark, noisy MRI scanner gives some challenging problems. They may be frightened by being in the MRI tunnel and the loud noise generated during the imaging process. In some circumstances, the pediatric patient who undergoes MRI often requires moderate to deep sedation or general anesthesia (GA) to suppress patient motion, possibly compromising the image quality and diagnostic result and efficacy.[1,2] In this case, the use of a sedation agent seems to be important. The pediatric patient may need administration of sedative agents to ensure that they can be more calm and cooperative during the examination.[3] So, motion-artifact-free images can be successfully produced.

Some of the examples of currently preferred sedative agents available for children undergoing ambulatory MRI are dexmedetomidine, propofol, ketamine, and general anesthesia with sevoflurane.[4] Compare to the other sedative agent, dexmedetomidine has various beneficial physiological effects and now has been widely used as an off-label agent in various procedures and age groups, including as a sedative agent for pediatrics that are going to have magnetic resonance imaging (MRI) examination, which requires sufficient deep sedation without disturbing airway patency.[5,6] The use of dexmedetomidine as a sedative agent in infants undergoing MRI examinations will be the scope of this review.

DISCUSSION

Dexmedetomidine

Dexmedetomidine is a selective agonist of the α2-adrenergic receptor. Dexmedetomidine is an S-enantiomer of medetomidine (an imidazole-derived α2-adrenergic agonist).[7] Dexmedetomidine preparations are 50 μg/0.5 cm^3, 100 μg/cm^3, and 200 μg/2 cm^3, in the form of dexmedetomidine hydrochloride.[8]

Pharmacodynamics

Dexmedetomidine has various bioavailability based on the route. The lowest is 16% when given via oral route, followed by 65% via nasal route, 82% via buccal route, and the most are 84% when given via sublingual route with the potential to be used as sedation and premedication in pediatric patients.[8,9]

Linear pharmacokinetics were obtained in an intravenous infusion for a maximum of 24 hours within 0.2-0.7 μg/kg/hour dose range.[8] The distribution phase is fast with a distribution half-life of about six minutes, and the volume distribution is in a stable state, about 118 L. This figure increases in patients with hypoalbuminemia, thereby extending the elimination half-life and context-sensitive half-life.[9] The percentage of dexmedetomidine that bonds with proteins (albumin and α1-glycoprotein) are 94%. The unbound drug fraction can cross the blood-brain and placenta barrier freely.[6] It is said that The context-sensitive half-life of dexmedetomidine is within four minutes (after 10 minutes of infusion) to 250 minutes.[7]

Almost all doses of dexmedetomidine undergo biotransformation through N-glucuronidation, N-methylation, and aliphatic hydroxylation with the intermediate cytochrome P450 (CYP2A6) into inactive metabolites.[9] Those metabolites are excreted within the urine (95%) and fecal route (4%), and only <1% is excreted in the active form. The terminal elimination half-life of dexmedetomidine ranges from 2.1–3.1 hours in the healthy population and 2.2–3.7 hours in patients admitted to the ICU. Dexmedetomidine clearance in a healthy population is 0.6-0.7 L/minute, and postoperative clearance in ICU patients ranges from 0.53-0.80 L/minute.[6] Dosage adjustments are needed in patients with liver disorders because of a decreased metabolic rate.

Pharmacokinetics

The α2-adrenergic agonists produce a clinical responses after binding to G-protein coupled (GPCR) α2 receptor. It is known three types of α2 receptors, called α2A, α2B, and α2C. Each has a different function, and they are easily found in the central, peripheral, and autonomic nervous system, as in organs and blood vessels.[8] Dexmedetomidine is known as α2-adrenergic agonist which activity is 8-10 times more α2-selective than clonidine. Neither clonidine nor dexmedetomidine showed total selectivity to these three receptors. However, clonidine is thought to have a lower affinity than dexmedetomidine to receptors of α2A and α2C.[7] The selectivity of α2 is seen at doses of 10-300 μg/kg by slow infusion, but α1 activity can also be found when the infusion dose slowly exceeds 1000 μg/kg or when the infusion is given rapidly. A previous study revealed that dexmedetomidine has a low affinity to β-adrenergic, serotonin muscarinic, and dopaminergic receptors.[8] Studies display that dexmedetomidine has sedation properties that just similar to natural sleep, anxiolytic, analgesic, sympatholytic, and an anesthetic-sparing impact with minimum respiratory depression.[10] It has an elimination half-life (T1/2b) of 2 hours, but it is a highly lipophilic drug that is rapidly distributed and redistributed, with a distribution half-life (T1/2a) of only 6 minutes. This provides a rapid onset but a short duration of clinical effect. Its rapid redistribution and elimination make it an acceptable agent for infusion techniques. The context-sensitive half-time of dexmedetomidine ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion.

Clinical Effect of Dexmedetomidine

1. *Sedative and Hypnotic Effects*

   Dexmedetomidine inhibits the release of norepinephrine from the locus coeruleus in the pons area resulting in ventrolateral nucleus disinhibition, which in turn releases inhibitory neurotransmitters. Patients sedated with dexmedetomidine maintained their muscle tone and ventilation; their spontaneous and triggered movements are observed, and they can be awakened by external stimuli. On the electroencephalogram, the sedation effect of dexmedetomidine is similar to that of phase 2 non-REM sleep waves.[9] The unique sedation response generated by dexmedetomidine is called cooperative sedation, occurring at doses of 0.2 or 0.6 μg/kg/hr after an initial dose of 1 μg/kg. Higher doses can cause deep sedation up to general anesthesia.[11] It is estimated that deep sedation can be achieved with plasma concentrations above 1.9 ng/ml.[6] Dexmedetomidine can also cause a decrease in cerebral blood flow (CBF) without changing intracranial pressure (ICT) and cerebral metabolic rate of oxygen ($CMRO_2$).[12]

2. *Analgesic effect*

   Activation of α2-adrenergic receptors on substantia gelatinosa of the dorsal horn of the spinal cord is the principle mechanism.[9] Hyperpolarization of interneurons and reduced delivery of nociceptive neurotransmitters like glutamate and substance P bring about inhibition of pain transmission. The ability of dexmedetomidine to provide analgesia is unclear.[6] However, dexmedetomidine has a sparing effect on opioids and can be used alone to reduce pain in some procedures, such as laparoscopic tube ligation. Some previous randomized controlled trials study revealed that intraoperative dexmedetomidine administration on general anesthesia was superior to remifentanil, with a lower pain scale within 24 h postoperatively also the lower occurrence of hypotension and PONV. Another meta-analysis identified that dexmedetomidine could provide analgesics for somatic and visceral pain when given neuraxial, resulting in decreased postoperative pain intensity and longer analgesic duration, but with a higher risk of bradycardia.[11]

3. *Effects on the cardiovascular system*

   The administration of dexmedetomidine shows a biphasic response, whether low plasma drug concentrations result in hypotension and high plasma drug concentrations result in hypertension.[6] Administering a loading dose of dexmedetomidine results in a blood pressure increase and a pulse rate decrease, especially in young and healthy patients. This is thought to be in relation to stimulation α2B receptors in vascular smooth muscle. Furthermore, the effect of the α2A receptor on the central nervous system predominates and results in vasodilation and

hypotension.[11] Activation of α2A receptors produces sympatholytic as vagomimetic responses as well. This occurs simultaneously with activation of α2A receptors on vascular endothelial cells, resulting in vasodilation and hypotension.[6] There have been reports of cases of severe bradycardia leading to asystole on loading doses of dexmedetomidine with other anesthetic drugs. The cardiovascular drop that correlates to dexmedetomidine use is higher in hypovolemic conditions, diabetes mellitus, chronic hypertension, old age, and high vagus nerve activity.[9] The response to anticholinergics used to treat bradycardia is not influenced by dexmedetomidine.[12]

4. *Effects on the respiratory system*

Dexmedetomidine differs from other sedative or anesthetic agents because it provides a minimal respiratory depressive effect, even at high doses.[11] Change in ventilation is minimal even when given at doses ten times greater than the maximum recommended dose. MRI studies also show that the patient's airway condition remains patent under dexmedetomidine-induced sedation.[9] Therefore, dexmedetomidine can be given during extubation and can help protect the airway in certain situations, such as conscious craniotomy. Dexmedetomidine also helps fiber optic intubation because it reduces patient discomfort with spontaneous breathing while maintaining airway patency and provides a dry field of action because it inhibits salivary secretion.[11] The ventilatory response to carbon dioxide is not affected, and the phenomenon of awakening due to hypercapnia (hypercapnic arousal pneumonia), which commonly occurs during natural sleep, can be observed on sedation using dexmedetomidine.[6] Although dexmedetomidine's effect on respiration is less severe than other anesthetic agents, airway obstruction due to sedation is still possible. The effect of dexmedetomidine on the airway is also synergistic with other sedative and hypnotic drugs.[12]

5. *Effects on other organs*

Activation of α2 receptors in other organs produces various effects such as decreased salivary secretion, nasal decongestion, and decreased intestinal motility, but so far, there have been no reports of complications due to the effect of dexmedetomidine on intestinal motility. Dexmedetomidine also suppresses shivering response by activating the α2B receptor in the hypothalamus. Although dexmedetomidine has an imidazole structure, no adrenal suppression effect was found on dexmedetomidine administration.[9] One of the effects of dexmedetomidine on the kidneys is a diuretic effect.

Side Effects and Tolerance

Dexmedetomidine is well tolerated, with plasma concentrations ranging from 1.8 times to 13 times higher than the upper limit of the therapeutic dose. At the highest plasma concentrations, the most visible effect is AV block but resolves spontaneously within one minute. Common side effects include nausea and vomiting, hypotension, dry mouth, bradycardia, and cardiac rhythm disturbance such as atrial fibrillation, AV block, angina pectoris, fever and chills, pleural effusion, hyperkalemia, hyperglycemia, and lactic acidosis.[13]

Hypertension can occur with a quick bolus of dexmedetomidine (loading dose 1 μg/kg/hr in under 10 minutes) and is caused by the α2B receptors stimulation that leads to vasoconstriction. On the other hand, continued use of dexmedetomidine results in bradycardia due to sympatholytic effects on the central nervous system α2A receptors. Application of dexmedetomidine in the long-term increases upregulation and α2-adrenergic receptors sensitization, but abrupt discontinuation will result in a withdrawal syndrome consisting of anxiety, headache, agitation, and crisis hypertension (similar to clonidine). The effects of dexmedetomidine can be attenuated with atipamezole, an α2-specific antagonist.[8]

Indication

In the pediatric setting, dexmedetomidine has been increasingly used off-label for various indications such as agitation prevention, intranasal, oral and buccal premedication, adjunct for elective surgery, intraoperative analgesia, as a sedative for ambulatory such as MRI, Extracorporeal shock wave lithotripsy (ESWL) and also used as an adjuvant to local anesthesia for nerve blocks. Dexmedetomidine is also used in intensive care units for pediatrics sedation.[14]

Contraindication

Dexmedetomidine can worsen uncontrolled hypertension and grade 2 or 3 AV block without a pacemaker, so dexmedetomidine is not recommended. Acute cerebrovascular conditions are relatively contraindicated because animal studies have shown a decrease in CBF, whereas human studies have shown a decrease in brain metabolism comparable to CBF.[9] Dexmedetomidine belongs to category C in the FDA pregnancy category.[7]

Use of Dexmedetomidine in Infant MRI

MRI is classified as a non-invasive imaging method. The need for sedation in MRI procedures for pediatrics is a challenge for researchers to study various types of sedative agents in terms of effectiveness, dosage, indications, and side effects. The ideal sedation is described as a condition in which the patient becomes relaxed, sleepy, or falls asleep.[15] Furthermore, the ideal sedative agent should fulfill the criteria that are listed below:

1. Assuring patient safety
2. Maintaining cardiovascular, respiratory, and autonomic patient stability.
3. Eliminating or minimizing pain and anxiety
4. Controlling patient movement (behavior) to ensure the adequacy of the test and/or a successful result
5. Avoiding emotional trauma

The child's response to sedative administration can be assessed using a modified Children's Hospital of Wisconsin Sedation Scale to obtain a specific level of sedation. The ideal level of sedation for the MRI procedure is a score of 2 – 3 (Table 1).[15]

Dexmedetomidine Route

Dexmedetomidine is available as an intravenous (IV.) preparation and can be used via transmucosal (buccal, intranasal) and intramuscular (IM). Mason et al. Reported successful sedation to infants that undergo CT or MRI examination using intravenous dexmedetomidine. He also described the success of sedation using dexmedetomidine IM in

Table 1. Modified Children's Hospital of Wisconsin Sedation Scale[15]

Score	Level	Description
0	Inadequate	Anxious, agitated, or in pain
1	Minimal	Spontaneously awake without stimulus
2	Drowsy	Eyes open or closed, but easily arouses to consciousness with verbal stimulus
3	Moderate-deep	Arouses to consciousness with moderate tactile or loud verbal stimulus
4	Deep	Arouses slowly to consciousness with sustained painful stimulus
5	Deeper	Arouses, but not to consciousness, with painful stimulus
6	Anesthesia	Unresponsive to painful stimulus

infants during MRI procedures. In 2012, Ambi et al. published a journal reporting the use of sedation with dexmedetomidine intranasal (IN) in MRI procedures.[15] The advantage of using the IN and the buccal route over the IV route is that the procedure is easier to use and does not cause traumatic effects on children because it does not cause pain (nonpainful procedure).

A retrospective study by Olgun et al. described the use sedation effect of dexmedetomidine intranasal (IN), which has been used in MRI of infants (ages 1 to 12 months). This study found that the success rate of using dexmedetomidine IN at a starting dose of 4 µg/kg was 94.2%, and the overall success rate was 96.2% (1 patient receives an additional dose of dexmedetomidine IN 2 µg/kg).[5]

Administration of dexmedetomidine via buccal is one route that does not cause pain other than the intranasal route. Buccal dexmedetomidine can be administered via the sublingual mucosa, buccal mucosa on the inner cheek, or through the buccal bag between the inner cheek and gum using an undiluted IV preparation in a 1 ml syringe.[16,17]

Dexmedetomidine dosage

One study of the application of dexmedetomidine Intranasal by Olgun et al. stated a dose of 4 µg/kg was proven effective in providing a sedative effect in infants aged 1 to 12 months.[5] This study determined the dose based on several previous studies. In a study by Sulton et al., the use of dexmedetomidine IN 3 mg/kg was proven to be effective in children's MRI procedures, without side effects.[18] In another study by Tug et al., subjects receiving higher doses had more effective sedation results. In that study, the percentage of rescue drug use was 70% in the 3 µg/kg dose group and only 30% in the 4 µg/kg dose group.[19]

The buccal doses of dexmedetomidine at a dose of 2 to 3 µg/kg for children during the MRI sedation procedure successfully provide a sedative effect with a success rate of 65%. Boriosi et al. found that the use of buccal dexmedetomidine for MRI at a mean dose of 2.2 ± 0.38 µg/kg proved sufficient to provide an adequate sedative effect. However, the presence of a failure rate approaching 20% indicates that the effective dose of buccal dexmedetomidine may be more than 2.2 ± 0.38 µg/kg.[15] Based on a study conduct by Siddapa et al. 2011, satisfied deep sedation comes with an intravenous loading dose of 1 - 2 µg/kg body weight and continues with a maintenance dose of 0.2 - 0.7 µg/kg body weight of dexmedetomidine. The sedation duration from dexmedetomidine usage varies from 30-94 minutes. The sedative effect of dexmedetomidine may be increased in younger patients, especially in neonates and infants, because of the lower clearance compared to school-age children. Thus the duration of dexmedetomidine activity will be longer.[5]

Side Effects of Dexmedetomidine

The side effects associated with infant MRI are statistically minimal. From a retrospective study conducted by Olgun et al., dexmedetomidine i intranasal was used in 56 infant MRI subjects was very effective without causing any side effects. While the use of buccal dexmedetomidine on MRI of children only gave minor side effects in 3.8% (7 of 182 subjects), in the form of 2 events of oxygen desaturation, two events of vomiting, and three episodes of vasovagal with one patient requiring fluid bolus).[5]

The side effects on hemodynamic are very mild and usually do not need any intervention in the infant MRI procedural sedation. Bradycardia may occur in mild to severe degrees, with an average heart rate decrease of >25% normal rate according to age.[15] In addition, a decrease in mean arterial pressure (MAP) of>20% may occur after dexmedetomidine administration. However, as long as the patient feels warm and perfusion is still good, no pharmacological intervention is needed.[5]

Comparison of Dexmedetomidine to Other Agents for MRI

Dexmedetomidine has unique properties. This drug does not cause respiratory depression and also minimal hemodynamic effects compared to other sedative agents.[15] A few meta-analysis studies found that compared with dexmedetomidine, propofol has faster sedation onset and shorter recovery time. However, in terms of sedation time, MRI scan time, and quality of MRI results, there were no significant differences between dexmedetomidine and propofol. Propofol has a lower incidence of delirium but a higher incidence of airway and breathing problems reflected by desaturation than dexmedetomidine.[20–22] When compared to pentobarbital, one study showed that dexmedetomidine had a shorter recovery time and total sedation time.[23] Other studies showed that ketamine has a significantly shorter onset of sedation compared to dexmedetomidine, with no significant differences in sedation failure, recovery time, separation, and sedation score.[24]

The combination of analgesics and sedatives such as opioids can cause respiratory depression that might prolong ambulatory surgery. Synergistic mechanism of action between opioids and local anesthetics will lower the required dose of each drug, thereby lowering the possibility of their side effects. Sedation with dexmedetomidine also has consequences, possibly a more extended recovery time in the post-anesthesia care unit.[25]

SUMMARY

Sedation in the pediatric population undergoing MRI examination is often challenging. Dexmedetomidine is an α receptor adrenergic agonist with a greater affinity for the α2

receptor, which produces sedation, analgesia, vasodilation, and bradycardia. It could be used safely as a sole sedative agent to pediatrics undergoing MRI procedures. It has several beneficial effects such as a smooth sedated state similar to natural sleep, with moderate analgesia, but without significant airway and respiratory depression risk and a longer duration of action. Dexmedetomidine has good bioavailability on various routes such as buccal, intranasal (transmucosal), intramuscular, and mainly Intravenous. Intra nasal and buccal routes offer a non-pain delivery of the dexmedetomidine to children and avoid traumatic events. It also has a good safety profile, although dosage adjustments are required in patients with liver disorders. Correct dosing and the choice of proper drug route delivery are important to reduce the side effects of bradycardia and hypotension that can occur with its use and increase the efficacy of the drug.

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CONFLICT OF INTEREST

None

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