Dexmedetomidine and Anaesthesia: Indications and Review of Literature

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Abstract
The use of alpha-2 agonists in anaesthesia practice is not new and had been started in the late twentieth century. Clonidine, the prototype of alpha-2 agonist, is widely used as an adjunct in anaesthesia and pain medicine. Dexmedetomidine is the next generation alpha-2 agonist with high selectivity for alpha-2 receptors (1600:1). This agent is 10 times more potent than clonidine and associated with fewer hemodynamic and systemic side effects. In addition, it has a reversible drug for its sedative property. More than 1000 clinical trials and studies have been published regarding the use of dexmedetomidine in humans with reasonable results. This article aims to illustrate the various modes and utilities of dexmedetomidine with its appropriate dosage in the field of anaesthesiology, pain and perioperative medicine.

INTRODUCTION
Dexmedetomidine is a fairly recent alpha-adrenergic agonist, approved by the Food and Drug Association (FDA) in 1999 for sedation in mechanically ventilated patients of the intensive care unit. In 2008, its use was extended to specific procedures outside the operation room. Central drugs standard control organisation (CDSCO) of India approved its use as a sedative agent for intubated patients in intensive care units and for non-intubated in the perioperative period in the year 2009 [1]. In addition to the above indications, several off-label clinical and investigational use of dexmedetomidine has suggested a wide variety of applications in the field of anaesthesia. Central Drug Standard Control Organisation (CDSCO) approved product does not require the submission of Investigational new drug (IND) application if the study population are well informed about the product and its use with firm scientific evidence [2]. As a result, Dexmedetomidine was tested in various clinical studies according to the institutional ethics and found to be a wonder drug in the current balanced anaesthesia practice (Figure 1).

MECHANISM OF ACTION
Dexmedetomidine is more selective α2 agonist (1600:1) than clonidine (200:1). There are 3 subtypes of α2 receptors in our body. The subtype A, the predominant subtype in the CNS (central nervous system), is responsible for the sedative, analgesic and sympatholytic effect. The subtype B, found mainly in the peripheral vasculature, is responsible for the short-term hypertensive response, and the subtype C, found in the CNS, is responsible for the anxiolytic effect. It undergoes complete hydroxylation through direct glucuronidation and cytochrome P-450 metabolism in the liver. Metabolites are excreted in the urine (95%) and in the faeces (4%). The elimination t1/2 (half-life) is 2 hours. The average protein binding of dexmedetomidine is 94%.

At the higher centres
Presynaptic activation of the α2-A adrenoceptor in the locus ceruleus inhibits the release of norepinephrine (NE) and results in the sedative and hypnotic effects [3]. In addition, locus ceruleus is the site of origin for the descending medullar-spatial noradrenergic pathway and an important modulator of nociceptive neurotransmission. Stimulation of the α2

![Chemical Structure of Dexmedetomidine](image-url)
Dexmedetomidine is successfully used in the dose varying from 0.25-1mcg/kg for blunting the hemodynamic responses in the perioperative period. Optimal dose for attenuating intubation response seems to be 1 mcg/kg with lesser doses not being effective. All India Difficult airway association guidelines (2016) recommended the administration of 0.75mcg/kg dexmedetomidine 15 minutes before extubation for smooth recovery from anaesthesia [8]. Bolus doses in the range of 0.5 mcg/kg not only blunted the extubation response but also reduced the emergence reaction at the end of surgical procedures. It also provides the additional benefits of reducing the dose of inhalation agent and opioid analgesics, improving the quality of recovery, decreasing the postoperative nausea and vomiting and enhancing the postoperative gastrointestinal motility. Infusion continued into the postoperative period has been associated with reduced hemodynamic fluctuations and decrease in plasma catecholamines levels. There was no delay in recovery or prolonged sedation when boluses were given before induction or before extubation. Similar effects were observed during infusion of dexmedetomidine lasting for first 2 hours of surgery only. Bradycardia and hypotension are the major side effects reported in the literature and they are due to the central sympatholytic activity. Transient hypertension has also been observed with higher bolus doses (1-4 mcg/kg) and it is due to alpha-2B receptors present in vascular smooth muscle [9]. Talke et al., investigated the muscle relaxing effects of dexmedetomidine on the neuromuscular junctions and found no clinically relevant effects [10].

The research on dexmedetomidine for management of awake fibre-optic intubation has started only few years ago. After analysing the potential eligible randomized controlled trials, A Cochrane data base revealed that dexmedetomidine is an effective alternative for patient undergoing awake fibre-optic intubation and may provide better comfort and less airway obstruction. But, there is no significant difference in intubation time between dexmedetomidine and control groups [11].

Dexmedetomidine can be useful in middle ear surgeries to create oligemic operative field because of its hypotensive effects. In an Indian study, Gupta et al used the initial loading dose of 1 mcg/kg, followed by 0.5mcg/kg infusion and concluded that it may provide the better visualisation of surgical field under microscope [12]. Many other studies also quoted the use of dexmedetomidine infusion as a deliberative hypotensive agent instead of nitro-glycerine and propofol.

Dexmedetomidine in MAC (monitored anaesthesia care) is successfully useful in many situations where patients’ reusability is needed, such as in awake craniotomy, awake carotid endarterectomy and vitreoretinal surgeries. Dexmedetomidine is the best adjuvant to perform anaesthesia for awake craniotomy with high degree of safety and better hemodynamic stability. Dexmedetomidine does not have a role in increase in intracranial pressure (ICP). Dexmedetomidine in loading dose range 0.5 - 1 mcg/kg over 20-30 mins, followed by 0.2-0.4 mcg/kg/hr infusion provides better sedation in patients undergoing awake craniotomy without causing any airway compromise. But, the reduced heart rate seen in such kinds of increased ICP patients may interfere with the use of dexmedetomidine infusion [13]. In cardiac surgeries, the use of dexmedetomidine infusion is beneficial both in adult and paediatric patients. While dexmedetomidine improves the systolic blood pressure and lowers tachycardia and arrhythmias, this drug also increases the incidence of bradycardia, indicating that care must be taken while administering dexmedetomidine to the patients in shock and in those with a conduction block [14].

Dexmedetomidine can be used as a premedication in the range of 2 – 4 mcg/kg in various studies. Oral, Intranasal and Sublingual routes have been extensively used in paediatric age group. Intranasal route is the most preferred as there is extensive first pass metabolism with poor oral bioavailability of around 16%. Preoperative administration of intravenous (1mcg/kg) or intramuscular (2.5mcg/kg) dexmedetomidine in adult population was also tested and the authors found that there was a reduction in anaesthetic agent requirement, adequate sedation and decrease in oxygen consumption during and after the surgical procedure [7].

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mediates its synergistic analgesic action. Dexmedetomidine has been found to prolong analgesia when used as an adjuvant to local anaesthetics for spinal, epidural and caudal epidural blocks. However, there is no proper consensus regarding the dose of the drug to be used for the neuraxial blocks. Doses varying from 3 mcg to 15 mcg of dexmedetomidine has been used as adjuvant to 0.5% bupivacaine (heavy) for spinal anaesthesia [9]. Neuraxial dexmedetomidine has been associated with quicker onset of block and also the prolongation of both motor and sensory block. Intraoperative heart rate and mean blood pressure was significantly affected in many studies reported in literature. But, bradycardia was the only concern and there was no evidence of hypotenison, pruritus, or postoperative nausea and vomiting. Dose- dependent prolongation of analgesia is seen with mean duration of approximately 7 hours. Prolongation of motor block with neuraxial dexmedetomidine may interfere in early ambulation and discharge or may result in patient fall [15].

A meta-analysis on epidural use of dexmedetomidine showed that dexmedetomidine in the dose range of 0.5mcg/kg to 1 mcg/kg given along with bupivacaine, levobupivacaine and ropivacaine provides a longer duration of analgesia, as well as highly significant improvements in the time of onset of sensory blocks and the sedation score. But, the risk of bradycardia and fluctuations in blood pressure are the common problems interfering with the effective epidural use of dexmedetomidine [16].

Addition of 1-2 mcg/kg of dexmedetomidine to caudal local anaesthetics significantly prolonged the analgesia effect with better sedation score in children aged 6 months to 6 years. The incidence of bradycardia was more in children receiving 2 mcg/kg dexmedetomidine when compared with 1 mcg/kg. Hence, it is safer to use a dose less than 2 mcg/kg of dexmedetomidine as an adjuvant to caudal local anaesthetics [17]. Despite one study showing neurotoxic effects at the spinal level of high dose of dexmedetomidine, there is a growing evidences that dexmedetomidine has anti-apoptotic properties and might have future applications as a neuroprotective agent [18].

Safety of neuraxial dexmedetomidin in parturient has not been explored so far much. There are no proper randomized trials to support its use in labour anaesthesia. However, there is a single meta-analysis (including 6 randomized controlled trials or RCT), supporting its safe use in caesarean sections without causing any neonatal respiratory depression. This beneficial safe effect of dexmedetomidine for neonate can be explained by the virtue of its unique sedative property and its high placental retention characteristics [19]. Another recent article (Hariharan U, Revista Brasileira de Anestesiologia, 2017) explored its tocolytic property and its use in patients with PH (pregnancy induced hypertension). Further well-designed RCTs with large number of parturients are warranted to clarify the safety of dexmedetomidine before it can be recommended for routine clinical use.

**DEXMEDITOMIDINE IN PERIPHERAL NERVE BLOCKS**

There are several meta-analyses quoting the perineural use of dexmedetomidine as the best adjuvant to local anaesthetics for brachial plexus blocks to prolong the duration of motor and sensory blockade. Dexmedetomidine in the dose of 1 mcg/kg is generally sufficient to provide a high quality of peripheral nerve block with minimal risk of transient bradycardia and postoperative sedation. The onset of motor and sensory block is very quick and within 10 minutes. The duration of motor block will be around 7-8 hours and that of sensory block will be around 10-12 hours, when dexmedetomidine is used as an adjuvant. These time durations are higher than that of any other adjuants like clonidine, dexmethasone etc. Dexmedetomidine may mediate its peripheral neural block faciliatory effects via mechanisms that are probably independent of alpha-2 receptors. In fact, this effect may be due to hyperpolarization of neuronal cation currents resulting in the inhibition of substance P release in the nociceptive pathway at the dorsal root neurons. Dexmedetomidine has a clear advantage of producing differential sensory – motor blockade (more sensory) which is unlikely to be achieved with dexamethasone and liposomal bupivacaine. The precise mechanism of differential sensory motor effects with dexmedetomidine is yet to be confirmed and it may be due to more pronounced inhibitory effects on A-delta and C-fibre action potentials, rather than the motor neurons [20].

Many randomized trials support the perineural use of dexmedetomidine along with local anaesthetic agents in brachial plexus blockade alone. There are only a few trials favouring its use in transverse abdominal plane (TAP) blocks and fascia-iliaca compartment block (FICB). Many more studies are needed to support the generalized use of dexmedetomidine in all other peripheral nerve blocks [21].

**DEXMEDITOMIDINE IN INTRAVENOUS REGIONAL ANAESTHESIA (IVRA)**

Intravenous regional anaesthesia is a simple and reliable method for providing anaesthesia for hand surgery but it is limited by tourniquet pain. Addition of 1mg/kg dexmedetomidine to lignocaine for IVRA improves the quality of anaesthesia and postoperative analgesia without causing any side effects. Alpha-2 receptors located at the nerve endings may play a role in the analgesic effect of the drug by preventing norepinephrine release. In the postoperative period, it is essential to monitor the possible excess sedation and fall in haemoglobin saturation. This might be due to the central effects of dexmedetomidine occurring after the tourniquet release [22].

**DEXMEDITOMIDINE AS AN INFILTRATION AGENT**

Lignocaine with adrenaline skin infiltration is a standard practice in many surgeries and it reduces the blood loss via vasoconstriction caused by adrenaline. Postoperative bupivacaine/ropivacaine skin infiltration is being practised at several centres. Addition of 1mcg/kg dexmedetomidine with lignocaine and adrenaline infiltration has been found to cause less surgical-site bleeding, better visualisation of surgical field, improved postoperative analgesia, stable haemodynamics and early discharge from post-anesthesia care unit. Bradycardia and sedation are the common problems encountered after subcutaneous use and when used in infiltration [23]. Intra articular infiltration of dexmedetomidine in the dose of 1 mcg/kg...
kg provides a more comfortable postoperative period for the patients undergoing arthroscopic knee surgeries. Wound infiltration of dexmedetomidine 1mcg/kg with local anaesthetics provides superior pain relief in abdominal hysterectomy and inguinal herniorrhaphy, as compared to infiltration with local anaesthetics alone. It can be used as an alternative to other pain relief methods [24].

**DEXMEDETOMIDINE IN ICU**

The highly selective effect of dexmedetomidine promotes its use for sedation in intensive care unit (ICU). Reduced ICU stay, decreased mechanical ventilation duration, haemodynamic stability and reduced agitation are its purported advantages. The risk of bradycardia was increased when both loading dose and maintenance dose greater than 0.7mcg/kg/hr are used. In addition, doses greater than 0.7mcg/kg/hr did not enhance the sedation. Patients are able to communicate pain when on sedation with dexmedetomidine. Greater side effects are seen with dexmedetomidine sedation when compared to midazolam and propofol [25]. Recent guidelines of society of critical care medicine (SCCM) recommends dexmedetomidine as a first line sedative agent in patients at risk of delirium that is not related to alcohol and benzodiazepine use. It is an ideal sedative agent in compensated liver failure patients. Its side effects, bradycardia and hypotension, limit the use of dexmedetomidine in patients who are dependent on their cardiac output, such as in the acute phase of shock. Altered blood sugar values are another problem associated with dexmedetomidine sedation in intensive care unit [26].

In ICUs, dexmedetomidine was successfully used in unusual clinical situations, such as recovery from deep sedation of patients undergoing extracorporeal membrane oxygenation (ECMO) therapy [27]. The simultaneous administration of midazolam and dexmedetomidine for sedation provides the spectacular improvement. A dose of 0.7 mcg/kg dexmedetomidine was also found to be useful in the treatment of supraventricular tachy-arrhythmias and is superior to adenosine treatment [28]. Dexmedetomidine can be good alternative to control sympathetic over activity in tetanus patients as well. Its central sympatholytic action helps in control of tachycardia and high blood pressure [29].

Thus, dexmedetomidine can be suitable agent for mild to light sedation for a short-term period in the intensive care unit. An All-India Difficult Airway Association (AIDAA-2016) guideline also recommends its use for the management of difficult intubation attempts in the ICU setup [30].

**DEXMEDETOMIDINE IN CHILDREN**

Although Dexmedetomidine is not yet fully approved for its use in paediatric population, it is used extensively and increasingly in various settings. The slower onset of action of intranasal/oral dexmedetomidine (30 - 60 mins) premedication makes it less appropriate than oral midazolam premedication in children. Its role as adjuvant for total intravenous and neuraxial anaesthesia holds very realistic and practical promise. The risk of apoptosis in young children remains a problem to paediatric anaesthesiologists [31]. Among the other anaesthetic agents implicated in causing apoptosis, dexmedetomidine has been found to be safe in infant rodents. Human studies in future may alleviate such unclear doubts and may establish its pivotal role in the field of anaesthesiology. If there is no specific indication for its use in paediatric population, it is always better to limit the role of dexmedetomidine in paediatric anaesthesia [32]. There are also case reports of clerical errors in the usage of high dose of dexmedetomidine in paediatric population, resulting in stressful resuscitative efforts and unwanted ICU admissions in ambulatory surgery [33].

Atipamezole, a non-selective alpha-2 antagonist is found to be effective in reverting the sedative/analgesic effects of dexmedetomidine. However, there are no reports of using it in dexmedetomidine over-dose/toxicity. Moreover, atipamezole itself at higher doses produces restlessness and increase in blood pressure [34].

A recent Cochrane review suggested the role of dexmedetomidine in preventing emergence delirium in children [35].

**CONCLUSION**

Dexmedetomidine is slowly finding its way into every segment of perioperative care through its off label/investigational use and it is becoming a “wonder drug” in the field of anaesthesiology and intensive care. It is high time for well-powered randomized, controlled trials and subsequent clear meta-analysis to demonstrate the precise uses of dexmedetomidine. Till the formal regulatory board approval, the investigator, the institute and the ethical board are at risk of medical malpractice litigations, if there are any drug related adverse effects on studies with dexmedetomidine.

**REFERENCES**


