

# Has Time Come to Frame Clinical Practice Guidelines Recommending Dexmedetomidine as a Routine Adjuvant Agent in Balanced General Anesthesia Technique?

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## Abstract

In today's era of scientific research, recommendation through evidence based practice guidelines has got major impact on best clinical practice. Over the last decade or so Dexmedetomidine the selective alpha two agonist has contributed significantly to the practice of anaesthesia and Perioperative medicine. Though it has been used for various purposes the maximum uses and benefits have been related to general anaesthesia. In spite of plethora of Literature suggesting its positive role played during general anaesthesia, it is yet to be recommended as a routine adjunctive agent for balanced anaesthesia technique. Hence this review focuses on its different pharmacodynamic as well as pharmacokinetic properties attributing to its major advantages & few disadvantages during pre-operative, intra operative as well as postoperative period related to general anaesthesia. It also analyses the adequacy of scientific evidences raising the possibility of recommending Dexmedetomidine as a routine adjunct to balanced anaesthesia technique during framing of clinical practice guideline.

**Keywords:** Dexmedetomidine; Balanced General Anaesthesia; Clinical Practice Guideline

## Background

Best clinical practice evolves around the concept of maximum benefit- minimum adverse effect to the patient and guided by clinical practice guidelines based upon the best available research evidence and practice experience. The Institute of Medicine defines clinical practice guidelines as "...statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [1].

Over the years, the evolution and research over different uses of dexmedetomidine has not only brought a revolution, but also proved it to be a wonder drug in field of anaesthesia and perioperative medicine. Its anxiolytic, amnesic, analgesic, sympatholytic, sedative properties have been used for premedication, prevention of stress response to laryngoscopy, intubation, surgery & extubation, perioperative sedation & analgesia, cardiovascular stabilization, prevention of emergence delirium and post-operative shivering [2-4].

Over the last decade or so, a number of studies have demonstrated the safety as well as success of dexmedetomidine as an adjunct to general anaesthesia, which may play a promising as well as cost effective role during the conduct of balanced general anaesthesia. However some reservation may exist due to its potential adverse effects and higher price putting barriers to recommend it as a routine adjunct to balanced general anaesthesia technique

## Pharmacodynamics Favouring Its Role as a General Anaesthetic Adjunct

As an adjunct to general anaesthesia it has minimum alveolar concentration (MAC) and opiate sparing properties, which helps in decreasing the inhalational anaesthetic and opioid requirements by up to 90% [5-7]. Most importantly all these beneficial effects are not associated with respiratory depression [8].

It can significantly attenuate postoperative pain and reduce opioid requirements, while not appearing to cause cardio-respiratory depression and ensuring faster, neuromuscular recovery and smooth emergence even in morbidly obese patients [9, 10].

Dexmedetomidine has been proved to be a very useful drug for the anaesthesiologists due to its haemodynamic, sedative, anxiolytic, analgesic, and anaesthetic sparing effects along with other advantages like minimal respiratory depression with cardio protection, neuroprotection and Reno protection [11].

Successful use of dexmedetomidine for sedation during vascular and cardiac surgery has been reported due to its cardio-protective modulation of sympathetic tone and maintenance of myocardial oxygen supply/demand ratio with consequent less perioperative ischemia [12,13]. Several prospective, randomized, pediatric studies have documented the role of dexmedetomidine in preventing emergence delirium after general anaesthesia and two adult studies for delirium in the intensive care unit [14,15].

It is a safe alternative to a benzodiazepine/opioid combination for a wide range of procedures under monitored anaesthesia care for its "cooperative sedation" without any respiratory depression [16-19]. Though most commonly observed side effects are hypotension, bradycardia and nausea, Dexmedetomidine was well tolerated in phase 3 study [21]. Several studies have suggested that omitting or halving the loading dose avoids

adverse events like hypotension and bradycardia but preserves dexmedetomidine's sedative action [22].

Although it has been used very safely over years in a wide group of population, caution needs to be exercised in patients with advanced heart block, with ventricular dysfunction and in pregnant patients, where it is classified as category C risk [23]. Serious adverse effects like asystole documented in literature are probably because of other cofounders & hence should not deter a practitioner from using dexmedetomidine [24]. In pregnancy also hazards to the fetus is very unlikely, as it is retained in placental tissue because of high protein binding and thus does not pass onto the fetal circulation [25].

Because of all these above described attractive properties, it has not only made the task of the anaesthesiologists and perioperative physicians, easier but also safe. Even in paediatric population, dexmedetomidine is well tolerated when used at recommended doses, though has the potential to cause hypotension and bradycardia which resolves with dose reduction, but may require close monitoring [26].

The usual methods of administration of dexmedetomidine are intravenous, intranasal, sublingual and intramuscular. Being painless, odourless and tasteless, the intranasal mode may be preferable [27].

Let us further examine different research experiences & evidences regarding the suitability as well as advantages of dexmedetomidine and the possible reasons to recommend its use as a compulsory adjunct agent in balanced general anaesthetic technique.

Evidence shows that dexmedetomidine is being used as a very useful premedicant before the conduction of general anaesthesia for its favourable profile as sedative, anxiolytic and sympatholytic agent and has been found to reduce oxygen consumption in intraoperative (8%) as well as post-operative (17%) periods [28].

As explained in the following sections, it has a very favourable pharmacodynamics as well as pharmacokinetic properties with varied mechanisms of actions to rightly choose it as a dependable adjunct in balanced general anaesthesia technique. Being a  $\alpha$ -2 adrenergic agonist, Dexmedetomidine exerts its action through G-protein coupled  $\alpha$ -2 adrenergic receptors, distributed in central, peripheral, and autonomic nervous systems including various vital organs and blood vessels all over the body [23].

Out of three receptor subtypes, namely  $\alpha$ -2A,  $\alpha$ -2B and  $\alpha$ -2C, Dexmedetomidine is considered to have more affinity for  $\alpha$ -2A and  $\alpha$ -2C receptors as compared to clonidine [29].

The sedative, hypnotic & supraspinal analgesic effects of dexmedetomidine are mediated by hyperpolarization of noradrenergic neurons at locus ceruleus resulting in decrease in noradrenaline release and thus suppressing the activity in descending medullospinal noradrenergic pathways [5,30,31]. Spinal Analgesic effects are mostly mediated by  $\alpha$ -2C and  $\alpha$ -2A receptors at lamina II of superficial dorsal horn inhibiting the release of nociceptive transmitters namely substance P and glutamate and also by hyperpolarization of spinal interneurons [32].

Attenuation of the stress response by Dexmedetomidine during laryngoscopy, endotracheal intubation, surgery & extubation occurs due to its action on both pre & post-synaptic  $\alpha$ -2 adrenergic receptors resulting in sedation, anxiolysis, analgesia & sympatholysis leading to predictable, yet desirable hypotension and bradycardia, which is associated with decrease in plasma catecholamines [33].

While providing sedative & hypnotic effects, even at high doses Dexmedetomidine does not impair ventilation or gas exchange; although may produce mild hypercapnia [34,35].

Another advantage of dexmedetomidine is availability of an antagonist agent "atipamezole" (Antagonist of  $\alpha$ -2 receptors), allowing the effects of it to be reversed [36]. Other noted actions which would definitely prove useful for balanced general anaesthesia technique, when Dexmedetomidine is used as an adjunct are hypnosis mimicking natural sleep like state, perioperative haemodynamic stabilization, analgesic and anaesthetic sparing property, decreased salivation, increased glomerular filtration, decreased intraocular pressure, decrease seizure threshold, decreased shivering & decreased bowel motility, leading to not only smooth anaesthetic course as well as improved surgical field, and trouble free intraoperative and post anaesthetic period [37,38].

Animal studies have shown that, the diuretic effect of dexmedetomidine by inhibition of vasopressin action at the collecting duct and preservation of cortical blood flow [39], which according to the author, may play a role in preventing stress induced antidiuretic hormone related perioperative dilutional hyponatremia, where

hyponatremia being an independent risk factor for increased morbidity & mortality in hospitalised patients.

A recent rodent study establishes the similarity between the hypnotic state produced by dexmedetomidine and during non-rapid eye movement sleep [40]. In a crossover study in human volunteers, it has been shown that there is no difference in blood flow signal between dexmedetomidine infusion & natural sleep state, as evidenced from a functional magnetic resonance imaging [41]. The similarity between dexmedetomidine-induced hypnosis and natural sleep may maintain cognitive and immunologic function that deteriorates in sleep deprived states [42].

As it mimics the normal sleep pattern and thus keeps the patients calm & quiet but arousable and cooperative, the author assumes that, after recovery from anaesthesia, post-traumatic stress disorder is unlikely, when compared to alternative agents used for sedation, anxiolysis and analgesia during balanced anaesthesia technique. In fact a rat model data suggest that dexmedetomidine may exert preventive and protective effects against anxiety-like behaviours and cognitive impairments seen in posttraumatic disorder [43].

In vascular and cardiac surgery, Dexmedetomidine has been found to be associated with less perioperative ischemia & reduction in pulmonary vascular resistance, pulmonary artery pressure, and pulmonary capillary wedge pressure [23,44].

Postoperative nausea and vomiting, rigor and restlessness are common adverse effects of anaesthesia & surgery leading to unwanted consequences like decrease quality of life, prolonged convalescence resulting in increased length of hospital stay. Postoperative restlessness delays wound healing. Shivering will raise intracranial pressure, lead to adverse cardiovascular events and increase wound pain. All these adversities are reduced with the use of Dexmedetomidine [45]. The meta-analysis by Myriam Bellon et al. shows that intraoperative Dexmedetomidine administration in children also definitely reduces postoperative opioids consumption and postoperative pain in PACU. Their results indicated that optimal bolus dose of Dexmedetomidine to produce its postoperative analgesic and opioid-sparing effects must be more than 0.5  $\mu$ g/kg. According to other authors also the opioid sparing effect of dexmedetomidine allows a quick changeover from the intravenous administration of opioid analgesics (often administered via a patient or nurse-controlled analgesia)

to an oral administration of non-opioid analgesics [46, 47]. This accelerates the discharge from the hospital allowing domiciliary postoperative care, where due to decreased opioid consumption, opioid-related side effects like nausea, vomiting, and constipation are reduced leading to decrease in the time of first oral intake, even after abdominal surgery [48]. Dexmedetomidine has also been useful for prevention of emergence agitation following an anaesthetic course [49].

Besides all these actions literature shows that it has got potential benefits of organ protective effects, namely Reno protection, cardio protection & neuroprotection [50]. Experimental study also shows that dexmedetomidine has a significant hepato-protective effect in the obstructive jaundice model which might be due to its antioxidant and anti-inflammatory activities, though the exact mechanism of this hepato-protective effect is not known [51]. Its neuroprotective effects in perinatal excitotoxic injury and hypoxic-ischemic injury in animal models, have been documented [52], thus providing a therapeutic option for prevention and treatment of postanesthesia emergence, shivering, or delirium [53-55]. Another proposed mechanism for neuroprotective effect is by reduction in cerebral blood flow and cerebral metabolic demand for oxygen resulting in reduced intracranial pressure. Associated decrease in the circulating and cerebral catecholamine's, improves the blood supply to the ischemic cerebral tissues, hence reducing the seizure potential [37]. The cellular brain injury seen in subarachnoid haemorrhage is decreased by reduction of Glutamate level by Dexmedetomidine [56].

### **Favourable Pharmacokinetics Properties with Predictable Side Effect Profile Favouring an Adjunct Role during Balanced General Anaesthesia**

Besides most common intravenous route, alternate available, on-invasive routes like nasal & buccal/sublingual, having good bioavailability makes it an attractive adjuvant agent, especially in paediatric age group and anxiety prone adults, during balanced anaesthesia technique having a high bioavailability of around 84% [37]. The buccal/sublingual route in particular, has been found to have better compliance and good absorption when given in a dose of 3-4 µg/kg about 1 h prior to surgery [57,58]. It is the authors suggestion that this route must be utilised

For paediatric patients fearing intravenous cannula insertion, inhalation induction from an awake state or parental separation. Because Dexmedetomidine exhibits

linear pharmacokinetics over a dose range of 0.2-0.7 µg/kg/h intravenous infusion, it has got a dependable and predictable drug effect like hypotension & bradycardia, enabling the anaesthesiologist to titrate the dose response easily [37].

As it is rapidly distributed with a high volume of distribution (118 litres) and has an elimination half-life of 2 h, it is feasible to use it in a perioperative scenario without a significant residual sedation prolonging recovery room stay. It is the author's personal experience that, due to concomitant reduction in the doses of the anaesthetic, analgesic, sedative & muscle relaxants requirement, rather Dexmedetomidine hastens the process of anaesthetic recovery with a clear headed consciousness.

It is 94% protein bound and does not displace most of the protein bound drugs used commonly in anaesthesia and intensive care, enabling it to be considered as a routine adjunct to balanced anaesthesia technique involving other drugs .especially in an era of evidence based medicine with special emphasis on best clinical practice focussing on maximum benefit and minimum adverse effect to the patient.

With the known context-sensitive half-life, which varies from 4 min (for a 10 min infusion) to 250 min( for an 8 h infusion), it is possible to titrate the dose response, even during a long anaesthetic procedure without the risk of serious cumulations, and thus beneficial for short as well as long anaesthetic procedure [37].

As Dexmedetomidine undergoes complete biotransformation by glucuronidation and by cytochrome P-450 mediated aliphatic hydroxylation to inactive metabolites, the risk of cumulation does not arise with a good liver profile, though dose reduction should be considered in hepatic failure. Recently, Dexmedetomidine has also been found to be effective in controlling supraventricular and junctional tachyarrhythmias [59]. Dexmedetomidine has been proved to be a very useful drug for the anaesthesiologists due to its haemodynamic, sedative, anxiolytic, analgesic, and anaesthetic sparing effects along with other advantages like minimal respiratory depression with cardio protection, neuroprotection and Reno protection [60].

Following Precautions are needed before considering dexmedetomidine as a routine adjunct to balanced general anaesthesia technique. *In vitro* studies have shown that cytochrome P450 mediated drug interactions

are unlikely and not clinically significant with dexmedetomidine use. But, because of anaesthesia, analgesia & sedative sparing effect, co-administration of it during balanced general anaesthesia technique leads to an additive effect. Hence, a reduction in dosage of other anaesthetic, analgesic and sedative agents during balanced anaesthesia technique is necessary. Additionally, careful titration of dexmedetomidine is required during co-administration with other vasodilators or negative chronotropic agents because of a possible additive pharmacodynamic effect.

The initial rise of blood pressure with Dexmedetomidine infusion can be attenuated by slow infusion of bolus dose. The incidence of postoperative bradycardia has been 40% in healthy surgical patients, which can be managed by atropine, ephedrine & volume expansion [61,62]. In a nut cell by sparing the doses of all components of balanced anaesthesia technique namely anaesthesia, amnesia, analgesia & muscle relaxant, their dose related side effects will also be reduced [63].

## Conclusion

After examining all the evidences discussed till now, it is the author's perspective that dexmedetomidine when included as a component of balanced general anaesthesia technique, will definitely prove to be a positive step towards best clinical practice. It will also be prudent to recommend that, dexmedetomidine be included in the anaesthesia practice guideline as a routine, rather mandatory adjunct agent to balanced general anaesthesia technique barring a few special risk population discussed in earlier sections.

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