

Dexmedetomidine: New avenues

Alpha (α)-2-Adrenergic receptor (AR) agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing properties.^[1] Dexmedetomidine, a highly selective α 2-AR agonist with a relatively high ratio of α 2/ α 1-activity (1620:1 as compared to 220:1 for clonidine), possesses all these properties but lacks respiratory depression,^[2,3] making it a useful and safe adjunct in diverse clinical applications.^[4] Numerous investigations into its uses have featured in various issues of this journal. This editorial aims to provide an overview of its current clinical status and new therapeutic avenues under investigation.

Mechanism of action

The hypnotic and supraspinal analgesic effects of dexmedetomidine are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway, secondary to activation of central α 2-ARs.^[2,5,6] This suppression of inhibitory control triggers neurotransmitters that decrease histamine secretion producing hypnosis similar to normal sleep, without ventilatory depression, making dexmedetomidine a near ideal sedative.^[1,2,7] Suppression of activity in the descending noradrenergic pathway, which modulates nociceptive neurotransmission, terminates propagation of pain signals leading to analgesia.^[6]

In the spinal cord, activation of both α 2-C and α 2-ARs, situated in the neurons of superficial dorsal horn especially lamina II,^[5,8,9] directly reduces pain transmission by reducing the release of pro-nociceptive transmitter, substance P and glutamate from primary afferent terminals and by hyperpolarizing spinal interneurons via G-protein-mediated activation of potassium channels.^[5] Postsynaptic activation of central α 2-ARs results in sympatholytic effect leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery.^[10,11]

Other useful effects of activation of α 2-ARs include decreased

salivation, increased glomerular filtration, decreased intraocular pressure, and decreased shivering threshold.^[12] Majority of the above effects of dexmedetomidine can be utilized beneficially in the intensive care and in the conduct of anesthesia.

Intensive Care Sedation

In 1999, Food and Drug Administration (FDA) approved dexmedetomidine as a sedative and supplement to sedation in the intensive care units (ICU) for patients undergoing mechanical ventilation of less than 24 hours duration. It has a short elimination half life of 2 h and a linear pharmacokinetic behavior, in continuous infusion for 24 h, with a short α - half-life of 6 min.^[12,13] These pharmacokinetic properties and the availability of an antagonistic agent Atipamezole,^[12,14] make it an ideal drug for intravenous titration both as a sole agent and for continuous infusion in the ICU, operating room, and other areas. Its unique sedative action mimics normal sleep, which translates into an advantage during weaning from mechanical ventilation. Dexmedetomidine need not be discontinued and the ongoing sedation can be maintained following tracheal extubation, preventing emergence delirium and agitation.^[2,15]

With a large body of recent research supporting its favorable profile in improving outcome and long-term brain function in the critically ill, studies are now focusing on the safety and efficacy of dexmedetomidine beyond 24 h.^[2,16-18] In a Phase IV study, dexmedetomidine was safe in dosages up to 1.4 mcg/kg/hour for greater than 24 h and did not produce rebound tachycardia or hypertension when abruptly discontinued.^[18,19] The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) randomized trial^[20] reported an earlier return to a delirium-free cognitive state and more ventilator-free days with dexmedetomidine when used for 24 to 120 h.^[2,20] The above studies indicate that it can be used long-term (>24 h) in critically ill patients.

Recent work has shown that omitting or halving the loading dose eliminates adverse cardiovascular effects like hypotension and bradycardia but preserves dexmedetomidine's sedative action.^[2-4,21,22] Caution should be exercised in patients who are volume depleted, vasoconstricted, or have severe heart block.^[2,4,21] Publication of few cases of asystole after its use warrants intense vigilance with its use and the need for a large-scale study on its safety.^[23,24]

Sole agent for Procedural Sedation

A new role as a sole agent for procedural sedation is fast

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emerging mainly due to its faster onset of action, faster recovery and discharge times. The Federal Drug Administration (FDA) has approved the use of dexmedetomidine as a sedative–analgesic and/or total anesthetic in adults and pediatric patients undergoing small minimally invasive procedures, with or without the need for tracheal intubation.^[4] It is a safe sedative alternative to benzodiazepine / opioid combinations in patients undergoing monitored anesthesia care for a multitude of procedures because of its analgesic, “cooperative sedation,” and lack of respiratory depression properties.^[4,11,25-28] For the same reason, it has been used in the pediatric population and its use has even been reported in a 24-week gestation neonate treated for refractory agitation while on mechanical ventilation.^[29,30]

An novel therapeutic role of dexmedetomidine is its use for opioid/benzodiazepine withdrawal in sedated pediatric patients during mechanical ventilation in critical care areas.^[31] It counters the physiologic effects of withdrawal secondary to decrease in sympathetic outflow and noradrenergic activity, mediated mainly through postsynaptic α_2 -AR subtype in the locus ceruleus.^[32,33] It has potential for treatment of agitation and alcohol withdrawal in alcoholic patients after brain trauma, who require reliable, serial neurological testing to monitor the course of their traumatic brain injury.^[34] This neuroprotective property is attributed to its preservation of sleep architecture and ventilatory drive with decreased sympathetic tone and inflammatory responses.^[35,36] Dexmedetomidine has shown neuroprotective effects in animal models of perinatal excitotoxic injury and hypoxic-ischemic injury,^[37] making it a therapeutic option for prevention and treatment of post-anesthesia emergence, shivering, or delirium.^[35,38,39]

Perioperative use

Perioperative applications of dexmedetomidine include premedication, as part of multimodal anesthetic regimen, prevention of emergence delirium, and pain in the postoperative period.^[2,12]

Premedication with dexmedetomidine not only offers anxiolysis, sedation and analgesia, but also helps in attenuating the stress responses to tracheal intubation/extubation and emergence from anesthesia. Dexmedetomidine has high bioavailability when administered by the relatively noninvasive buccal or nasal route.^[40] The buccal route ensures more compliance and better absorption (up to 82%) in younger children than intravenous administration.^[2,40] Studies evaluating the efficacy, safety, optimal dosage of buccal dexmedetomidine in children have found a dose of 3–4 mcg/kg, one hour before surgery to be safe and effective.^[41]

Preliminary studies^[40,42] report better sedation at parental separation and induction of anesthesia with 1 mcg/kg intranasal

dexmedetomidine when given 30-45 minutes prior to surgical procedure as compared to oral midazolam.^[43,44] The technique causes no discomfort during administration,^[42] is relatively quick, simple, and may have benefits over transmucosal routes and rectal administration. The nasal route is effective and well tolerated for sedation and postoperative analgesia in adults in the dose of 1 μ g/kg given 45 min before surgery.^[45] More studies are needed to evaluate the effect of premedication routes on various outcome measures like preoperative anxiety levels, induction time, emergence excitation, postoperative analgesic requirements, and postoperative behavior disturbances.^[44, 45]

As an adjunct to general anesthesia it has minimum alveolar concentration (MAC) and opiate sparing properties, which helps in decreasing the inhalational anesthetic and opioid requirements by up to 90%,^[2,46,47] which can be used to advantage in situations where high anesthetic concentration is either undesirable or not tolerated.

Certain neurosurgical procedures require a hemodynamically stable, comfortable, sedated patient who is awake and cooperative enough to perform neuromotor and neurocognitive tests on demand. Dexmedetomidine achieves this desired neurophysiologic profile, in dose of 0.2 to 0.5 mcg/kg/h, for procedures like awake craniotomies, deep brain stimulation, surgery near speech areas, minimally invasive endoscopic procedures, stereotactic interventions, interoperative imaging etc.^[2,37,48-50]

Dexmedetomidine reduces rocuronium requirements during sevoflurane anesthesia, by altering the pharmacokinetic profile of rocuronium.^[51] This effect may decrease muscle relaxant requirements during surgery, thereby potentially reducing the risk of residual muscle weakness during emergence. Dexmedetomidine significantly attenuates postoperative pain and reduces opioid and volatile anesthetic requirements in morbidly obese patients, without causing any cardio-respiratory depression and ensuring faster, neuromuscular recovery and smooth emergence.^[52] 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.^[2,4,53]

An emerging application, is its role in facilitating awake fiber-optic intubation (AFOI) in difficult airway situations.^[54,55] Successful AFOI in patients with a difficult airway necessitates maintenance of a clear dry airway, with spontaneous ventilation, such that the airway is secured without any discomfort to the patient and complications like upper airway obstruction, respiratory depression, and aspiration are avoided. Dexmedetomidine provides an

ideal solution to this problem especially in critical airways compromised due to anatomical distortions and infections.^[56] Series of case reports document efficacy of dexmedetomidine as a sole sedative for awake intubations in managing a critical airway, as a bolus ranging from 0.5 to 1 mcg/kg followed by infusion of 0.2 to 0.7 mcg/kg/hr, with no evidence of respiratory depression.^[57,58] An unique attempt in this field has been the use of dexmedetomidine without any topicalization for AFOI in a patient with a critical airway who had a true documented allergy to local anesthetics.^[59]

For acute/chronic pain - The greater α_2 -AR selectivity of dexmedetomidine enhances the therapeutic window of dexmedetomidine in the treatment of pain.^[60] Its opiate sparing effects has important implications for the management of acute postoperative pain and chronic pain states, including disorders involving spasticity or myofascial pain, neuropathic pain, sympathetically maintained pain such as complex regional pain syndrome (CRPS) and chronic daily headaches. It is evolving as an adjuvant analgesic, both as intravenous and intrathecal infusion, in cancer pain refractory to multiple treatment modalities.^[61,62]

Pre- and intra-operative intravenous dexmedetomidine prolongs the duration of sensory block of local anesthetics during spinal anesthesia^[63] and peripheral nerve block.^[64] Postoperatively, intravenous dexmedetomidine infusion is associated with a reduction in nausea and vomiting, reducing postoperative morbidity.^[60] Its use in obstetric analgesia is being explored in view of the high lipophilicity. It is retained in the placental tissue, thereby resulting in less fetal transfer and a decreased incidence of fetal bradycardia. Continuous intravenous dexmedetomidine infusion has been successfully used as an adjunct to systemic opioids in laboring parturients who could not benefit from epidural analgesia.^[65,66]

As a neuraxial adjuvant - α_2 -AR agonists can activate a number of antinociceptive mechanisms depending on the dose and the route of administration; however, the main site for their antinociceptive effect in physiological pain conditions seems to be the spinal dorsal horn.^[67] Evidence indicates that neuraxial administration of dexmedetomidine produces spinal analgesia as efficiently as clonidine.^[5,68,69]

Epidural dexmedetomidine exhibits synergism with local anesthetics prolonging the sensory/motor block duration time, postoperative analgesia, and results in intense motor block,^[70] without any additional morbidity. Clinical studies exhibit potentiation of neuraxial local anesthetics, decrease in intraoperative anesthetic requirements with prevention of intraoperative awareness, improved intraoperative oxygenation, and improved postoperative analgesia when

epidural dexmedetomidine was used in conjunction with general anesthesia.^[71] Experimental animal and human studies of intrathecal dexmedetomidine as an additive to local anesthetics, have observed a dose dependent prolongation of sensory block, increase in motor block, along with prolongation of the postoperative analgesia, thus allowing for a decrease in the local anesthetic dose in high risk group of patients.^[5, 68,69,72,73]

In a few dose finding studies, investigators have used 3, 5, and 10 mcg of intrathecal dexmedetomidine in human subjects with favorable results,^[72-74] along with preserved hemodynamic stability and lack of sedation. A drawback of dexmedetomidine supplemented spinal block characteristics may be an increase in the duration of motor block, which may not suit ambulatory procedures.^[74] More clinical studies are needed to validate the efficacy and safety of the optimum intrathecal dose of dexmedetomidine for supplementation with spinal local anesthetics.

No neurological deficits have been reported till date in studies on both humans and animals during intrathecal/epidural use.^[5,68,72,75] However, there is some evidence of demyelination of the oligodendrocytes in the white matter, suggesting harmful effects on the myelin sheath when administered via the epidural route in animal studies.^[76] Advanced pathologic investigations are required to establish its safety.

As an adjuvant in peripheral nerve block and intravenous regional anesthesia - Few clinical studies have evaluated the effect of adding dexmedetomidine to local anesthetics in peripheral nerve blocks. In a randomized double blind trial, dexmedetomidine shortened the onset time and prolonged the duration of the block and postoperative analgesia, when added to levobupivacaine for axillary brachial plexus block.^[77] Animal studies have not shown any evidence of neurotoxicity even at higher doses, when applied directly to sciatic nerve models.^[78] Furthermore, addition of dexmedetomidine in clinically relevant doses to ropivacaine results in a dose dependent increase in the duration of sensory and motor block.^[79,80] Dexmedetomidine has also been reported to improve block quality, prolong post-deflation analgesia, and decrease tourniquet pain when used as an additive to lignocaine in intravenous regional anesthesia.^[81]

The peripheral analgesic effects of dexmedetomidine that potentiate local anesthetics are mediated by α_2 A-AR binding^[60,82] and have been utilized to enhance postoperative analgesia after intra-articular administration and direct infiltration of dexmedetomidine in a dose of 1 mcg/kg as an adjunct to local anesthetics.^[82-84]

Dexmedetomidine has evolved as a panacea for various applications/procedures with multiple promising delivery routes. Its clinical applications in adults and children include premedication, as part of multimodal anesthetic regimen, regional anesthesia, sedation, monitored anesthesia care, procedural sedation, prevention / treatment of emergence delirium, alcohol withdrawal & shivering, and the list continues to grow. Dexmedetomidine appears to have promising future applications in the field of neuroprotection, cardioprotection, and renoprotection, especially in children.^[44,45] The novel therapeutic uses of this α_2 -AR agonist can be put safely into practice after thorough evaluation by Randomized Controlled Trials .

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