Review Article

Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice

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Abstract

The introduction of newer more selective α^{-2} adrenergic agonist, dexmedetomidine has made a revolution in the field of anesthesia owing to its varied application. The aim of the current review is to highlight the various clinical and pharmacological aspects of dexmedetomidine in daily routine practice of anesthesiology and intensive care besides its potential role in other clinical specialties. This review of dexmedetomidine was carried out after searching the medical literature in Pubmed, Science direct, Scopus, Google scholar and various text books and journal articles using keywords anesthesia, dexmedetomidine, neurosurgery, pediatric surgery, regional dexmedetomidine, anesthesia, regional, neurosurgery, and pediatric surgery. Dexmedetomidine has made its application from a novel sedating agent in the intensive care unit to its use as an adjuvant in various regional anesthetic techniques because of its "cooperative sedation" without any respiratory depression. It has a favorable pharmacokinetic profile suitable to be used in the perioperative period to reduce the requirements of opioids and anesthetic drugs. There are few side-effects of dexmedetomidine, which should always be kept in mind before choosing the patients for its use. The various side-effects associated with dexmedetomidine include, but are not limited to hypotension, bradycardia, worsening of heart block, dry mouth, and nausea. However, large scale randomized controlled trials are still needed to establish various effects of dexmedetomidine and to clearly define its safety profile.

Keywords: α^{-2} adrenergic agonist, Dexmedetomidine, General anesthesia, Regional anesthesia

Introduction

The continued quest for a novel sedating agent for intensive care and need for drugs to blunt the stress response to the surgical stimulus has led to the increasing use of α^{-2} adrenergic agonists in these clinical settings. These drugs have a favorable pharmacological profile owing to their sympatholytic, sedative, analgesic, anxiolytic, and anesthetic drugs sparing effects.[1] Clonidine, which was introduced earlier as an anti-hypertensive was commonly used α^{-2} adrenergic agonist in various clinical scenarios including regional and general anesthesia.[2-4] However, with the introduction of newer more selective α^{-2} agonist dexmedetomidine, which has 8 times more affinity than clonidine for α^{-2} receptors is bringing newer concepts in anesthesia and intensive care practice. It was approved by the Food and Drug Administration (FDA) in 1999 for use in humans for short term sedation in intensive care unit. Initially used for sedation and analgesia in intensive care, its use has been extended to other various clinical situations as well as in regional anesthesia as a useful adjunct.[5]

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Method of Literature Search

The review was performed after searching the full text and abstracts from the literature in PubMed, HINARI, Scopus, Science Direct, Ovid MEDLINE, and Google scholar and the following keywords combinations were used: Dexmedetomidine, α^{-2} adrenergic agonist, pharmacokinetics of dexmedetomidine, cardiac surgery, neurosurgery, pediatric surgery and regional anesthesia. Various text books of clinical pharmacology and anesthesiology as well as national and international anesthesia journals were also searched for full text articles related to dexmedetomidine.

Pharmacodynamics

Dexmedetomidine, an α^{-2} adrenergic agonist, acts by binding to G-protein coupled α^{-2} adrenergic receptors, which are found in central, peripheral, and autonomic nervous systems and also in various vital organs and blood vessels throughout the body.[6] There are three subtypes of these receptors namely α^{-2}A, α^{-2}B and α^{-2}C each having different functions and activities. Dexmedetomidine is considered to have more affinity for α^{-2}A and α^{-2}C receptors as compared to clonidine.[7]

The site of action for sedative effects of dexmedetomidine is locus ceruleus and is mediated by hyperpolarization of noradrenergic neurons thus inhibiting noradrenaline release and inhibiting activity in descending medullospinal noradrenergic pathways.[8,9]

Analgesic effects are mainly mediated by α^{-2}C and α^{-2}A receptors present on the neurons of superficial dorsal horn in lamina II, by inhibiting the release of pro-nociceptive transmitters namely substance P and glutamate and by hyperpolarization of spinal interneurons.[10]

Activation of post-synaptic α^{-2} receptors lead to sympatholysis and results in hypotension and bradycardia; thus, helps in attenuating the stress response. Other useful actions of dexmedetomidine include decreased salivation, increased glomerular filtration, decreased intraocular pressure, decreased shivering threshold, decreased bowel motility, and decreased insulin release from pancreas.[11]

Pharmacokinetics

Dexmedetomidine has poor bioavailability due to extensive first pass metabolism; however, sublingual route has high bioavailability of about 84%.[12] It exhibits linear pharmacokinetics over a dose range of 0.2-0.7 μg/kg/h intravenous infusion. It is rapidly distributed with a volume of distribution being 118 l and has an elimination half-life of 2 h. It is 94% protein bound and does not displaces most of the protein bound drugs used commonly in anesthesia and intensive care. The context-sensitive half-life varies from 4 min for a 10 min infusion to 250 min for an 8 h infusion.

Dexmedetomidine undergoes complete biotransformation by glucoronidation and by cytochrome P-450 mediated aliphatic hydroxylation to inactive metabolites. These metabolites are excreted in the urine (95%) and in feces (4%). The dose needs to be adjusted in patients with hepatic failure towing to lower rates of metabolism.

Clinical Effects

Cardiovascular system

The effects of dexmedetomidine on blood pressure are biphasic with an initial transient rise with a reflex fall in heart rate brought about by stimulation of α^{-2}B subtypes of receptors present in vascular smooth muscles. This is followed by fall in blood pressure and heart rate due to inhibition of central sympathetic outflow and stimulation of pre-synaptic α^{-2} receptors cause decreased release of nor-adrenaline leading to further fall in the blood pressure.[13,14] These hemodynamic effects; however, may be deleterious in patients with fixed stroke volume, on rate reducing drugs such as beta blockers, digitalis etc., and in hypovolemic patients.

Central nervous system

Dexmedetomidine causes a reduction in cerebral blood flow and cerebral metabolic demand of oxygen with a slight reduction in intracranial pressure. It has found to have neuroprotective effects by reducing the circulating and cerebral catecholamines; thus, reducing the excitotoxicity and improving the blood supply to the ischemic cerebral tissues. It also reduces the levels of glutamate, which is found to enhance the cellular brain injury especially in subarachnoid hemorrhage.[15]

Respiratory system

Dexmedetomidine does not have any depressant effects on respiratory function even at higher doses with no impairment of ventilation or gas exchange; however, may produce mild hypercapnia.[16,17] It is considered to be a good sedating agent with good cardiovascular stability; thus, facilitating weaning in patients on prolonged ventilatory support with failed previous attempts.

Endocrine and renal system

Dexmedetomidine causes suppression of stress response to surgery by activation of peripheral α^{-2} receptors and reducing the release of catecholamines. It is found to have no inhibitory effects on steroidogenesis when used for short term sedation by intravenous infusion.[18,19]

Adverse effects

The common side-effects include hypotension, bradycardia, dry mouth, nausea, desaturation, pulmonary edema, atelectasis etc., Long-term infusions of dexmedetomidine may result in up-regulation of receptors leading to the development of withdrawal syndrome on abrupt discontinuation manifesting as nervousness, agitation, headaches, and hypertensive crisis.[20]

Its use is not recommended in patients with advanced heart block and with ventricular dysfunction and it is classified as category C risk in pregnant patients.[6]

Clinical Utility of Dexmedetomidine

Dexmedetomidine is increasingly being used in various clinical situations. The clinical utility of this wonder drug is getting expanded with availability of more and more literature from various studies carried out throughout the globe. The major clinical role of dexmedetomidine in anesthesiology

and intensive care practice, which has been established can be summarized as:

Sedation in Critically Ill Patients

Dexmedetomidine was initially approved by FDA for use as sedative agent in intensive care unit owing to its favorable properties of linear pharmacokinetic profile, short elimination half-life and no respiratory depression. It mimics the normal sleep pattern and thus keeps the patients calm, quiet but arousable and cooperative. It was initially approved for use for less than 24 h as an intravenous infusion, but recently studies have demonstrated its efficacy for use beyond 24 h.[21-23] In the maximizing efficacy of targeted sedation and reducing neurological dysfunction trial, it is reported that the use of dexmedetomidine intravenous infusion for 24-120 h results in earlier return of a delirium-free cognitive state with an increase in ventilator-free days. Compared to propofol, it has been found to be equally effective for sedation in intensive care with added advantage of minimal respiratory depression and maintenance of stable hemodynamics with easy arosability.[24]

Caution should be exercised in patients with hypovolemia, reduced ventricular functions, high degree of conduction blocks and in patients who are vasoconstricted, in whom its adverse-effects can be partially attenuated by lowering the initial bolus dose.[25]

Procedural Sedation

The role of dexmedetomidine as a sole agent for sedation in various minimally invasive procedures is fast emerging owing to its faster onset of action and fast recovery times.[26] It has been found to be a safe alternative to a benzodiazepine/opioid combination for a variety of procedures requiring monitored anesthesia care for its "cooperative sedation" and no respiratory depression.[27-31]

The effects of dexmedetomidine can also be reversed by an antagonist of α^{-2} receptors named "atipamezole" so its sedation can easily be titrated and can be reversed.[32]

Perioperative Use

Dexmedetomidine because of its anxiolytic, analgesic, sympatholytic, and sedative effects, has found its application in premedication, prevention of stress response to laryngoscopy, and prevention of emergence delirium.

Use as Premedicant

Dexmedetomidine have been found to be very effective as a premedicant before the institution of general anesthesia owing to its sedative, anxiolytic and sympatholytic effects and has been found to reduce oxygen consumption in intraoperative (8%) as well as post-operative (17%) periods.[33] It has been found to have good bioavailability when given through relatively non-invasive routes such as nasal or buccal. The buccal route in particular, have found to have better compliance and good absorption when given in a dose of 3-4 μg/kg about 1 h prior to surgery.[34,35]

Intranasal administration of dexmedetomidine have also been found to provide better sedation and facilitates better parental separation when compared to oral midazolam given in a dose of 1 μg/kg intranasally 1 h prior to surgery. It may provide good and safe sedative effects and may have benefits over transmucosal or rectal routes of administration.[36,37]

During intraoperative period

Dexmedetomidine, due to its sympatholytic effects, blunts the hyperdynamic response to laryngoscopy and surgery and maintains a stable hemodynamic profile.[38,39] [Table 1]. It also has been found to potentiate the effects of all the anesthetic agents namely intravenous and inhalational and have opioid sparing effects thereby reducing the doses required.[40-43] It can also help in reducing the oxygen requirements of the body and helps in prevention of intraoperative myocardial ischemia.[44,45]

Dexmedetomidine have been reported to decrease the requirements of rocuronium in sevoflurane anesthesia and this effect may be attributed to the alteration of pharmacokinetics of rocuronium by dexmedetomidine.[46]

Dexmedetomidine has recently been utilized for facilitation of awake fiberoptic intubation in patients with compromised airway due to anatomical distortions and infections of upper airway. It provides a good sedation with analgesia with little or no respiratory depression as well as no effect on airway reflexes so that the patient remains calm and chances of aspiration are minimized.[47-49] Recently, it has been used in awake fiberoptic intubation without topical anesthesia of the upper airway as a sole sedative agent in a patient with documented allergy to local anesthetics.[50]

Dexmedetomidine have both sympatholytic effects and sparing of anesthetic effects, which make it an ideal for induction and maintenance of controlled hypotension in various surgeries minimizing the blood loss as well as providing optimal conditions for surgery such as spinal fusion surgery, endoscopic nasal, and sinus surgery and maxillofacial surgery.[51-53]

As postoperative adjunct and analgesic

Dexmedetomidine intravenous infusion can be continued during extubation as it has no respiratory depressant effects and it helps in blunting the stress response of extubation and the emergence delirium in some patients by keeping them calm and sedated. It also provides good post-operative analgesia and reduction in opioid requirements owing to its selective blockade of α^{-2}A receptors.[54] It has also been shown to reduce the incidence of postoperative nausea and vomiting and helps

Table 1: The effect of IV dexmedetomidine on haemodynamics and other vitals during peri-op and recovery period

Study group	Dose and route of dexmedetomidine administration	Clinical effects observed	Pharmacological effects observed	Recovery characteristics	Side effects observed
Bajwa *et al.* 2012	1 μg/kg IV	Attenuation of stress response to laryngoscopy, intubation and surgery	Dose reduction of anesthetics and opioids	Rapid and smooth recovery and desirable sedation	Non-significant incidence of nausea, vomiting and dry mouth
He *et al.* 2012	0.5 μg/kg and 1 μg/kg IV	Stable hemodynamic variables	Suppression of fentanyl induced cough	Recovery smooth	No significant side effects
Bajwa *et al.* 2011	1 μg/kg IV	Stable cardio-respiratory parameters	Sedative action	Reduction in shivering	Headache, nausea, vomiting, dry mouth
Menda *et al.* 2010	1 μg/kg IV	Effectively blunts the hemodynamic response to endotracheal intubation	Analgesic and sedative action	Smooth recovery	Non-significant bradycardia and hypotension
Lee *et al.* 2007	2.5 μg/kg/h IV	Decrease the excitatory response during extubation	Decrease in dose of inhalational anesthetics	No significant reduction in IOP with dexmedetomidine	Non-significant
Guler *et al.* 2005	0.5 μg/kg IV	Attenuation of airway-circulatory reflexes during extubation	Lower median coughing scores	Lesser increase in hemodynamic parameters after extubation	Non-significant
Sturaits *et al.* 2002	1 μg/kg IV and 0.5 μg/kg/h	Stable hemodynamic variables	Dose reduction of opioids	Shorter PACU stay and fewer hypertensive episodes	Non-significant

IV: Intravenous, PACU: Post-anaesthesia care unit, IOP: Intra-ocular pressure

in attenuating post-operative shivering; thus, reducing the post-operative oxygen metabolic demand, which can be very helpful in cardiac patients.[55]

Beneficial Role in Regional Anesthesia

Neuraxial anesthesia

Dexmedetomidine is highly lipophilic and thus is rapidly distributed in neural tissues and produces its antinociceptive effects by binding to α^{-2} receptors in spinal dorsal horn when used neuraxially.[56]

Epidural dexmedetomidine as adjuvant with local anesthetics prolongs the duration of sensory as well as motor blockade with more intense motor blockade and good postoperative analgesia.[57] The use of epidural dexmedetomidine as an adjuvant to local anesthetics when used in conjunction with general anesthesia have shown to lower intraoperative anesthetic requirements, improved oxygenation and prolonged post-operative analgesia [Table 2].[58-63] Few concerns have been raised from time to time with failure of breastfeeding after epidural anesthesia, but with epidural dexmedetomidine such concerns are out of question as studies are not available where dexmedetomidine is used as an adjunct in labor analgesia.[64] Dexmedetomidine has shown to be better when used as an adjuvant with ropivacaine in epidural anesthesia as compared to clonidine and fentanyl.[62,63]

Intrathecal dexmedetomidine added to local anesthetic augments the sensory block, produces more intense motor blockade and prolongs the post-operative analgesia thus can decrease the dose of local anesthetics used.[60,65] Various doses have been tried intrathecally (3, 5, 10 μg) with favorable outcomes of prolongation of sensory/motor block with preserved hemodynamics; however, the prolonged motor block may not be ideal for ambulatory surgeries.[66] All the studies evaluating intrathecal dexmedetomidine are devoid of any neurological deficits, but some evidence of demyelination of oligodendrocytes in white matter have been seen in animal studies suggesting probable harmful effects of epidural dexmedetomidine on myelin sheath.[67] However, further clinical and pathological studies are required to safely establish the efficacy of intrathecal dexmedetomidine [Table 2].

Regional nerve blocks

In peripheral nerve blocks also dexmedetomidine has shown its efficacy in prolonging the duration of sensory block as well as prolongation of post-operative analgesia when used along with local anesthetic. Animal studies have validated the absence of neurotoxicity when directly applied to nerve models.[68,69] Dexmedetomidine have been successfully combined with various local anesthetics such as levobupivacaine, ropivacaine etc., with favorable results.[70] Furthermore, dexmedetomidine has been compared to clonidine as an adjuvant to the local anesthetic in peripheral nerve blocks like supraclavicular brachial plexus block and has been found to enhance the duration of sensory and motor blockade with prolongation of requirement of rescue analgesic.[70]

Intravenous regional anesthesia

Dexmedetomidine added to lignocaine in the intravenous regional blocks have shown to improve the block quality, decrease the tourniquet pain and prolongs the post-operative analgesia with minimal side-effects.[71,72]

Table 2: The effect of dexmedetomidine on nerve blockade parameters and other vitals during peri-op and recovery period when administered as adjuvant

Study group	Dose and route of dexmede-tomidine	Clinical effects observed	Pharmacological effects observed	Recovery characteristics
Oriol-lopez *et al.* 2008	Epidural (1 μg/kg)	Early onset and prolonged sensory and motor blockade	Significant sedation level	Increase time to two segmental regression and decreased local anesthetic dose requirement as top ups
Al-Mustafa *et al.* 2009	Intrathecal (5 μg and 10 μg)	Dose dependent early onset of sensory and motor blockade	Prolonged analgesia	Delayed regression with 10 μg dexmedetomidine
El-Hennawy *et al.* 2009	Caudal (2 μg/kg)	Significantly promoted analgesia time	Stable hemodynamic parameters	Mean PACU stay and time to first oral clear liquid intake was same as with clonidine
Bajwa *et al.* 2011	Epidural (1.5 μg/kg)	Early onset of sensory and motor blockade as compared to clonidine	Better sedation scores with dexmedetomidine as compared to clonidine	Prolonged post-op sensory analgesia and decreased local anesthetic requirement for pain relief
Bajwa *et al.* 2011	Epidural (1 μg/kg)	Early onset of sensory and motor blockade as compared to fentanyl	Better sedation scores with dexmedetomidine as compared to fentanyl	Prolonged post-op sensory analgesia and decreased local anesthetic requirement for pain relief

PACU: Post-anaesthesia care unit

Intra-articular infiltration

The peripheral analgesic effects of dexmedetomidine mediated through α^{-2}A receptors have been utilized in direct intrarticular infiltration in arthroscopic knee surgeries with a prolongation of post-operative analgesia.[73]

Neuro-protective Role in Neurosurgical Procedures

Dexmedetomidine has an important role in neurosurgery by providing stable cerebral hemodynamics, blunting any rise in intracranial pressures during laryngoscopy and head pin insertion. It also helps in making the patients calm, comfortable and sedated, but easily arousable to perform neurocognitive and neuromotor examination as required in procedures like awake craniotomies, deep brain stimulation, minimally invasive endoscopic procedures, intraoperative imaging, stereotactic interventions etc.[74-76]

Studies have shown that when used for labor analgesia, dexmedetomidine is retained in the placental tissue owing to its high lipophilicity resulting in decreased transfer to the fetus leading to less chances of fetal bradycardia. Its use has been studied in parturients with failed epidural analgesia along with systemic opioids with a resultant good maternal anxiolysis, hemodynamic stability, and stimulation of uterine contractions.[77,78]

Role in Cardiac Surgery

Dexmedetomidine has been studied in vascular and cardiac surgery for its sedation and sympatholytic effects and has been found to be effective in maintenance of myocardial oxygen supply/demand ratio with consequent less chances of perioperative ischemia.[79] Studies have shown it to be helpful in managing patients undergoing mitral valve replacement surgery with co-existing pulmonary hypertension by reduction in pulmonary vascular resistance, pulmonary artery pressure, and pulmonary capillary wedge pressure.[6]

Use in Pediatric Population

As stated earlier, dexmedetomidine has been studied extensively as a premedicant in the pediatric population especially by nasal and buccal route with acceptable absorption and good compliance and better parental separation.[35,36] Few studies have been done on its role as an adjuvant in sedation of pediatric patients in critical care unit and during non-invasive procedures in radiology such as computed tomography and magnetic resonance imaging.[80]

Therapeutic Role in Opioid and Alcohol Withdrawal

Recently, dexmedetomidine have been shown to be an effective drug in opioid or benzodiazepine withdrawal by reducing the sympathetic outflow and noradrenergic stimulation caused by the withdrawal. This is mainly attributed to their blocking of α^{-2}A receptors situated in the locus ceruleus.[81,82] It has been found to be helpful controlling the agitation in alcoholics after traumatic brain injury and thus helps in monitoring and allows serial neurotesting in these patients.[83]

Role in Cancer Pain

Dexmedetomidine has been studied as an adjuvant in intractable cancer pain and has been found to benefit in reduction of pain refractory to multiple treatment modalities.[84]

Newer Potential Uses

Few studies in animals have found a diuretic effect of dexmedetomidine by inhibition of antidiuretic action of

vasopressin at the collecting duct and have also been found to attenuate radio contrast nephropathy by preserving cortical blood flow.[85] Recently, it has been found to be effective in controlling supraventricular and junctional tachyarrhythmias.[86]

Evidence Based Comparison with Other Drugs

Dexmedetomidine has been compared with propofol for sedation in intensive care patients and has been found to be equally efficacious with less incidence of respiratory depression, easy arousabilty and stable hemodynamic parameters.[24] Compared to a benzodiazepine and opioid combination, dexmedetomidine has been found to be more effective in providing sedation in procedures involving monitored anesthesia.[30,31]

Dexmedetomidine has been compared to oral midazolam through intranasal route as a premedicant in a dose of 1ug/kg in the pediatric population and has been found to be more effective in providing sedation as well as good parental separation.[36] it has been compared to remifentanyl and esmolol for providing controlled hypotension in tympanoplasty surgery, which suggests it to be equally effective in reducing mucosal bleeding with less adverse effects and favorable recovery profile.[87]

Recently, dexmedetomidine has been compared to ketamine and placebo on emergence agitation after strabismus surgery in pediatric patients under sevoflurane anesthesia and was found to inhibit the postoperative emergence agitation, which was similar to the ketamine, but had a greater effect in reducing the post-operative nausea and vomiting when compared to ketamine.[88]

Dexmedetomidine used as an adjuvant to epidural local anesthetics has been compared to clonidine and fentanyl and has shown to shorten the onset of sensory and motor block as well as prolongs the post-operative sensory analgesia with reduced requirements of local anesthetics.[62,63] it has been shown to prolong post-operative sensory analgesia when used as an adjuvant to local anesthetic intrathecally as well as in peripheral nerve blocks when compared to fentanyl and clonidine.[66,70]

Recently, a comparison has been carried out between different infusion doses of dexmedetomidine (0.2 ug/kg/h and 0.4 ug/kg/h) on sedation profile and was found have similar results; however, increasing the infusion dose delayed some recovery parameters.[89] A comparison of two different doses of dexmedetomidine (0.5 ug/kg and 1 ug/kg) to suppress hemodynamic changes to tracheal intubations showed that the higher dose was more effective when used as bolus.[90]

Conclusion

In conclusion, from the above discussion, it is clear that the newer α^{-2} adrenergic receptor blocker dexmedetomidine is a promising drug having numerous useful applications. It can be a very helpful drug in the armamentarium of an anesthesiologist having its use in perioperative care as well as in the treatment of chronic pain. Since, its introduction in the clinical practice, dexmedetomidine has come a long way with a new use being discovered every day, but still a lot of research has to be carried out with randomized controlled trials for its various effects.

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