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NARRATIVE REVIEW **APPLIED PHARMACOLOGY**

Use of dexmedetomidine for anesthesia and pain management: an updated review of literature

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Abstract

Background & objective: Since 1999, dexmedetomidine has been used in several patient populations after its approval as a sedative by the FDA. Subsequently, a large number of clinical trials on its benefits have been published widely in the literature. This review aims to update readers regarding recent evidence for approved as well as novel uses of dexmedetomidine and identify future areas of clinical research involving this relatively new drug.

Sources: Randomized controlled trials conducted between January 2000 and August 2021, which compared dexmedetomidine with other sedative agents used in adult and pediatric patients undergoing mechanical ventilation in ICU, bronchoscopy and endoscopic procedures, general and locoregional anesthesia and chronic pain management were included in this review of the literature. PubMed, Science Direct, the Cochrane library and Google Scholar were used as databases.

Implications: Dexmedetomidine is a multipurpose drug that has found unparalleled utility in intensive care medicine and anesthesiology. Its various advantages over traditional sedative agents have been documented, including decreased duration of mechanical ventilation, decreased incidence of delirium, perioperative analgesia and organ protective properties. Recently there has been mounting interest in dexmedetomidine as an analgesic adjunct in chronic and cancer pain management. However, there is still a paucity of well controlled studies evaluating the use of dexmedetomidine outside of a traditional sedative/analgesic role. The future direction of the research may focus on long term clinical benefits of dexmedetomidine in certain perioperative populations and its non-conventional use in palliative care and pain medicine.

Key words: Dexmedetomidine; Anesthesiology; Intensive Care Medicine; Pain Medicine

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1. Introduction

Seldom has a drug found such widespread applicability and use in the field of medicine as dexmedetomidine has in anesthesiology. This review of literature will focus on the early history of research that lead to the development of dexmedetomidine, the mechanism of action of dexmedetomidine, it's systemic effects on the human physiology and the various established and novel uses of dexmedetomidine that hold relevance to the anesthetists practicing in our current, ever-evolving, healthcare system.

2. Early History

The ability of humankind to manipulate naturally occurring substances for human use sets humanity apart from the 8.7 million species that share this blue rock with us. The resourcefulness that allowed our ancestors to tame fire was also responsible for rapid advances in

medicine, whereby humankind started using nature's gifts as the first arsenal in the fight against mortality and suffering. Our remarkable journey as a species is accompanied by our equally enviable capacity to discover, investigate, synthesize and utilize newer chemicals and substances to our benefit as our understanding of the complex bio-chemical processes central to our existence deepen and clarify. The field of anesthesiology is no stranger to man's ingenuity. The earliest written records dating back thousands of years document the use of alcohol as the first sedative during the birth of civilization in early Mesopotamia. It is an indisputable fact that anesthesiology, as a field, has advanced exponentially since then and flourished within a century, evolving from an investigative field open for non-specialized personnel to experiment with untested, unregulated and novel agents and techniques into an increasingly specialized, safe and effective field of medicine. This rapid growth as a specialty has placed anesthetists at the frontline of various medical disciplines, including intensive care medicine, pain medicine and rehabilitation. A study into the discovery and the use of dexmedetomidine in the field of anesthesiology serves as a perfect homage to the vision of anesthetists responsible for such an explosion of knowledge and skill in a field which, until so recently, had been deemed by many to be shrouded in shadows of obscurity and intrigue.

The journey towards the discovery of dexmedetomidine will be incomplete without recognizing the accomplishments of early physicians who were responsible for unmasking the physiology of the central nervous system; the antagonistic role of the parasympathetic and the sympathetic nervous systems, and the mechanisms through which these biological actions would be explained.

It may be fitting to mention that one of the first steps towards the use of dexmedetomidine in the field of anesthesiology may have been when Dale demonstrated the duality of action of epinephrine on the adrenergic system.[1] At that time, this strange phenomenon went unexplained until it was hypothesized to be in response to certain receptors present in the human body by Cannon and Rosenbluth.[2] These preliminary, crude ideas of receptors proposed that the adrenergic receptors were no more than a tissue component that combined with epinephrine and formed a receptor-drug complex to bring about antagonizing responses in the human body. This receptor-drug complex was thought to exist in two forms, sympathin E and I, bringing about excitatory and inhibitory effects in the human body respectively.

Ahlquist is credited with the discovery of two different receptor systems responsible for the opposing cardiovascular responses under the same sympathetic nervous system.[3] This discovery of the alpha receptor, a G protein coupled receptor, subsequent identification of two subsets of the alpha receptors using drugs such as prazosin and yohimbine, the discovery of clonidine and its initial use as a nasal decongestant, remains central to the development of dexmedetomidine, a synthetic agent.

3. Search Strategy

Randomized controlled trials conducted between January 2000 and August 2021, that compared dexmedetomidine with other sedative agents used in adult and pediatric patients undergoing mechanical ventilation in ICU, bronchoscopy and endoscopic procedures, general and locoregional anesthesia and chronic pain management ,were included in this literature review. Multiple bio-medical databases were used to conduct the literature search. These included PubMed, Science Direct, the Cochrane library and the Google Scholar. There was no imposition of language restrictions. Databases were searched using different combinations of keywords "dexmedetomidine," "Anesthesia," "sedation", "Randomized controlled trial," "Intensive Care Unit," and "Comparison". Boolean operators AND/OR were used, and relevant reference lists were screened for further studies which were missed from the initial search. Data was collected by two independent authors and analyzed, and compiled for review.

4. Mechanism of Action

Dexmedetomidine is a highly selective alpha 2 adrenergic receptor agonist.[4] Being an imidazole derivative it is an enantiomer of levomedetomidine with the chemical name 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole corresponding to the molecular formula C13H16N2. The analgesic effects of dexmedetomidine are mediated through the negative feedback control mechanisms existing within the autonomic nervous system and, to some extent, in sensory neurons. Dexmedetomidine inhibits the transduction process by acting on pre-ganglionic alpha 2 receptors leading to decreased neurotransmitter release at the synaptic junction. The alpha 2 receptor is a G protein coupled receptor, where G protein, a heterotrimer consisting of 3 subunits, is coupled with various effector proteins responsible for control of the cellular activity. Stimulation of alpha 2 receptors leads to decreased activity of adenyl cyclase and hence decreased production of cyclic AMP, an important intracellular messenger responsible for various cellular functions.[5] The sedative and analgesic effects of dexmedetomidine have been postulated to be brought about by the agonism of these alpha 2 receptors which are found on pre- and post-synaptic membranes within the locus ceruleus.[6] This modulation of non-adrenergic arousal circuitry

disrupts the functional connectivity between the locus ceruleus and higher order brain centers, including the reticular system and the thalamus. The locus ceruleus serves as the origin point for the descending medullary noradrenergic pathways which have a prominent role in modulation of nociceptive signals. [6] Furthermore, evidence exists for the association between dexmedetomidine, and various alternative actions mediated via the activation of the alpha 2 receptors which bring about the same effects of sedation and analgesia. Possible targets include ion-gated channels within the neurons, including sodium gated channels and inward rectifying potassium channels.[6] Dexmedetomidine alters ion exchange through these channels leading to hyperpolarization, making it increasingly difficult to reach the threshold potential for depolarization. It effectively reduces the transmission of nerve impulses and blocks the pain pathway at the level of transmission. Alternatively, sedative, and analgesic effects of dexmedetomidine are in part also dependent on the blockade of voltage gated calcium channels found in the neuronal circuitry through pathways other than the G-protein coupled mechanisms already described above. The result of hyperpolarization leads to decreased neuronal impulse conductance.

5. Physiological effects

Dexmedetomidine has a biphasic response with a tendency to initially elevate the blood pressure by increasing the peripheral vascular resistance,[7] a possible mechanism for this phenomenon is the activation of a subset of alpha 2 receptors present peripherally (the alpha 2B receptors). This in turn leads to increased parasympathetic tone leading to bradycardia. Subsequent hypotension and bradycardia ensue due to dexmedetomidine agonistic effect on centrally present alpha 2A receptors leading to a decreased sympathetic tone. The dose dependent occurrence of bradycardia can therefore be explained in part by the activity of the baroreceptor reflex and the sympatholysis due to centrally acting dexmedetomidine.

The peculiar characteristic of dexmedetomidine, when compared to other agents used for sedation and analgesia such as propofol and benzodiazepines is that even when high doses of the drug are used, there is minimal respiratory depression.[7]

The renal effects of dexmedetomidine[8] have generated further interest in its role as a nephroprotective agent when used in major cardiac surgery. These effects are due to the preservation of cortical blood flow by inhibition of norepinephrine release by the renal cortex, inhibition of the effects of vasopressin at the level of the collecting duct leading to diuresis, shifting the balance in favor of anti-oxidants to combat oxidative stress and anti-coagulation properties that might prevent microthrombi formation in renal circulation.

Dexmedetomidine attenuates inflammatory responses. In addition to that, it may activate protective signal pathways, such as ERK and phosphoinositide 3-kinase (PI3K) /Akt pathway, to provide neuroprotection for patients suffering from either ischemic or possible septic insult.[9]

6. Role as a sedative for adult patients

The FDA approved the use of dexmedetomidine in 1999 via the intravenous (IV) route to provide sedation for mechanically ventilated patients for up to 24 h in the intensive care unit (ICU) setting.[10] Since then, there has been a growing body of evidence advocating the safety and efficacy of its use compared to standard drugs used in the ICUs to provide sedation for critically ill adults.

Jean-Michel Constantin et al. reported that, dexmedetomidine as a sedative for critically ill, non-cardiac patients requiring mechanical ventilation, was both efficacious and safe. This meta-analysis of 1994 patients from 16 randomized controlled trials concluded that the use of dexmedetomidine was associated with a reduction in the ICU length of stay by 48 h, decreased duration of mechanical ventilation and decreased incidence of delirium. Dexmedetomidine use, however, was associated with an increased incidence of bradycardia and hypotension.[11]

Similar findings were reported in a recent meta-analysis published this year. Midazolam and dexmedetomidine were compared as sedative agents in 1379 mechanically ventilated, critically ill adult patients. Compared to midazolam, the use of dexmedetomidine led to shorter duration of mechanical ventilation, decreased incidence of delirium and shorter ICU stay. There was no difference in the incidence of hypotension between the usage of these two agents however, incidence of bradycardia was greater in the dexmedetomidine group.[12]

Dexmedetomidine has also been highlighted as an agent to mitigate agitation to reduce the failure of non-invasive ventilation in critically ill patients. Dexmedetomidine is not associated with ventilatory impairment, an unwanted side-effect of other sedative agents currently in use. Therefore, it can be the agent of preference to prevent agitation induced failure of non-invasive ventilation in critically ill patients. This was reported in a meta-analysis of 6 randomized controlled trials with over 500 patients. The use of dexmedetomidine infusion significantly reduced intubation rates and escalation of therapy from NIV to intubation (20.1%) compared to controls (39.8%). A decrease in length of ICU stay was

also seen; however there was no mortality benefit observed.[13]

The emergence of the new COVID-19 pandemic has expanded the prospective role of dexmedetomidine in the ICU setting. The immunomodulatory, cytoprotective, anti-inflammatory and organ protective properties of dexmedetomidine make it an ideal candidate for clinical research as an agent to provide sedation for critically ill COVID-19 patients who require either non-invasive or invasive ventilation.[14] A recent retrospective study concluded that in a cohort of patients suffering from severe/critical COVID-19, dexmedetomidine was effective for sedation and may lead to improved oxygenation by possibly facilitating ventilator/patient synchrony. In addition, the higher incidence of bradycardia in these patients was associated with lower levels of inflammatory markers and troponin levels as well.[15] Further research needs to be conducted to ascertain the role of dexmedetomidine as another agent in the management of critical COVID-19 cases.

7. Role as a sedative in pediatric ICU

Although dexmedetomidine has been used off label to provide sedation in pediatric ICUs since 1999 in the United States, it was approved for marketing and use in Europe more than a decade later in September 2011. Therefore, there is a lack of high quality data regarding the use of dexmedetomidine as a sedative agent for prolonged sedation in critically ill pediatric patients as physicians familiarize themselves with the use of this relatively new drug.

Evidence of its use exists mainly as retrospective studies without controls. In a retrospective cohort of 219 critically ill children with a median age of 25 months, dexmedetomidine was used as a first-line sedative in almost half of the patients. It was also used commonly among children requiring non-invasive ventilation (20%). A majority of patients were successfully weaned off dexmedetomidine; however, 42% of patients experienced adverse events related to dexmedetomidine use.[16] This incidence may be higher than that observed in the adult population.

Another retrospective analysis on 40 pediatric patients with a median age of 16 months advocated the use of dexmedetomidine to facilitate the provision of non-invasive ventilation. They concluded that dexmedetomidine provided safe light levels of sedation leading to decreased failure rates of non-invasive ventilation.[17]

Suffice to say that the evaluation of the safety and efficacy of dexmedetomidine as a sedative in pediatric ICUs may become the next arena for high quality clinical trials due to a lack of data currently.

8. Dexmedetomidine for procedural sedation

One of the off-label use of dexmedetomidine in Anesthesiology has been its use as an agent for procedural sedation in the pediatric population. When used via the intranasal route in a dose of 2-3 µg/kg,[18] it has been demonstrated to be similarly efficacious and safe when compared to other drugs used including chloral hydrate and midazolam.

A meta-analysis of 7 randomized controlled trials consisting of 730 patients found this drug to be safe and effective at providing sedation for minor pediatric procedures 80% of the time. This success rate was similar in comparison to chloral hydrate. Use of dexmedetomidine was also associated with decreased incidences of nausea and vomiting in the said population when compared to control agents.[18]

Literature exists for the use of dexmedetomidine as a single sedative agent for outpatient procedures in the adult population. In a meta-analysis of 5 randomized controlled trials comparing the use of dexmedetomidine versus propofol in 570 patients receiving sedation for endoscopies, dexmedetomidine exhibited fewer adverse effects on respiratory function. It provided a higher level of satisfaction among endoscopic performers when compared to propofol, but there was an associated increased risk of failed sedation.[19]

Recently, dexmedetomidine has been used as an adjunct to sedation with midazolam in a cohort of very elderly (80 y and above) patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP) and was found to decrease the total dose of other sedative agents used and the incidence of respiratory complications in this cohort of patients.[20]

Low dose dexmedetomidine has been safely used to provide conscious sedation for patients undergoing flexible bronchoscopy as well. Patients sedated with dexmedetomidine had fewer procedural interruptions and greater performer satisfaction when compared to conventional sedatives.[21] It is also being used as a sedative when given through a continuous infusion during endobronchial ultrasound (EBUS) examinations. Its use in nebulized form as a topical agent, when mixed with lignocaine before conducting flexible bronchoscopies, is a novel use.[22]

9. Role in difficult airway

Many surgical procedures necessitate intubating the trachea with a nasal or oral endotracheal tube. The

difficult airway is the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation and or difficulty in tracheal intubation.[23] The incidence of difficult airways in the literature ranges from as low as 0.3% to more than 10% of the patients.[24] There is a chance of airway related morbidity and mortality, whenever approaching a patient with a difficult airway.[25] Therefore, use of a drug that can provide adequate level of sedation without compromising respiratory drive and ventilation in such situations may offer unparalleled advantages over other conventional sedatives.

Dexmedetomidine has been used as a sedative and topical anesthesia for safe awake fiber-optic intubation. Its benefits in improving intubating conditions, providing amnesia, improving patient satisfaction and mitigating hemodynamic stress responses are acknowledged in the literature.[26]

When used as a sole agent for sedation and compared to the short acting opioid remifentanil for facilitating awake fiberoptic intubations in 412 patients, dexmedetomidine was found to be both effective and well-tolerated. It was more effective in reducing the incidence of hypoxemia and memory recall compared to remifentanil.[27]

A randomized controlled trial compared thirty patients undergoing awake fiberoptic intubation and sedated with intravenous dexmedetomidine with thirty patients sedated by a combination of intravenous fentanyl and ketamine. It concluded that dexmedetomidine provided better intubating conditions and hemodynamic stability.[28]

Similar success with dexmedetomidine is seen in the pediatric population presenting with difficult airways.[29]

10. Perioperative role

The use of intraoperative intravenous dexmedetomidine as an analgesic adjunct as part of multimodal analgesia shows decreased postoperative pain and reduced consumption of opioids in the postoperative period after major surgical procedures.[30] However, evidence for the analgesic and opioid sparing benefits of using dexmedetomidine are conflicting, especially in surgical procedures where higher levels of post-surgical pain are anticipated.[31]

Dexmedetomidine is also being used effectively in non-cardiac surgery to reduce the incidence of postoperative delirium.[32]

Perhaps most interestingly, evidence is coming to light supporting the long term benefits of perioperative use of intravenous dexmedetomidine in cardiac surgery. In a retrospective cohort of 2068 adult patients undergoing cardiac surgery, dexmedetomidine was associated with a statistically significant lower 5-year mortality rate (13%) compared to the controls (20%).[33]

As a neuroprotective agent, dexmedetomidine already has an established role in the perioperative period for neurosurgical procedures,[34] patients with traumatic brain injuries[35] and the conduct of more complex procedures including awake craniotomies.[36] With further advances in surgical and anesthetic techniques there is an increasing interest in the development of enhanced recovery protocols for neurosurgical patients as well, where dexmedetomidine has been used effectively in conjunction with other sedatives and regional anesthesia techniques to enable faster postoperative recovery in patients undergoing neurosurgery.[37]

In a multi-cohort of 3395 patients who received intraoperative dexmedetomidine, there was a decreased incidence of acute kidney injury, decreased duration of postoperative ICU stay and decreased inpatient mortality.[38] This further highlights the systemic benefits associated with its use during the perioperative period.

11. Dexmedetomidine & locoregional anesthesia

In a prospective, randomized, double-blind placebo controlled study on patients undergoing endourological procedures, addition of 5 µg of dexmedetomidine to local anesthetic given via intrathecal route lead to significant prolongation of effective analgesia when compared to midazolam or a saline placebo.[39]

A meta-analysis of 639 patients supported the findings that dexmedetomidine, when given as an adjunct via the intrathecal route, significantly prolonged the duration of the effective analgesia after spinal anesthesia.[40]

Evidence for the role of dexmedetomidine as an adjunct agent to prolong the duration of analgesia of peripheral nerve blocks exists. It points towards a per neural mechanism of action. In a cohort of patients undergoing breast surgery, the addition of dexmedetomidine with dexamethasone prolonged the analgesia of pectoral plane blocks for postoperative pain.[41] Recently dexmedetomidine has been used as an additive to local anesthetic solution to decrease postoperative pain. A review of 330 patients revealed that dexmedetomidine use as an adjunct for would infiltration successfully decreased postoperative pain intensity, and increased the duration of analgesia after lumbar surgery. Moreover, there was a decrease in the postoperative nausea and vomiting observed in the dexmedetomidine group.[42]

Dexmedetomidine offers similar benefits to patients undergoing surgical procedures in intravenous regional anesthesia (IVRA). The addition of 1 µg/kg of dexmedetomidine to local anesthetic solution resulted in faster onset and a prolonged duration of sensory block in

patients undergoing upper limb orthopedic surgeries in IVRA. Moreover, there was better hemodynamic safety and no increased risk of side effects.[43]

A similar study involving patients undergoing below elbow surgical procedures under IVRA concluded that the addition of dexmedetomidine intraoperatively significantly improved the quality of the produced regional anesthesia compared to midazolam.[44]

The role of dexmedetomidine as an adjunct to locoregional anesthesia is expected to expand with the development of newer techniques and a shift from traditional approaches in anesthesia towards more patient centered care tailored to individual patient needs.

12. Role in cancer and chronic pain

One of the more novel uses of dexmedetomidine is at the end-of-life intractable cancer pain management for pediatric and adult patients. A recent pilot study involving adult patients with metastatic cancer pain suggested that addition of dexmedetomidine to analgesics (morphine) decreased the requirement for rescue analgesia and improved the quality of communication between patients and their families.[45] Similarly, there are instances when dexmedetomidine is used for palliative sedation to relieve suffering and provide comfort to terminally sick cancer patients.[46] Benefits of the addition of dexmedetomidine to locoregional techniques for the management of refractory cancer pain have also been reported.[47]

A recent case report suggests the use of intrathecal dexmedetomidine can help ease symptoms for patients suffering from opioid induced hyperalgesia.[48] Strong evidence, however, is lacking.

There is also evidence that dexmedetomidine given in combination with local anesthetic in lumbar transforaminal block achieved better pain control and decreased disability of patients suffering from chronic low backaches compared to steroid injections alone.[49]

13. Conclusion

Two decades into clinical use, dexmedetomidine has achieved unprecedented success as a multi-purpose drug used in various clinical settings and for an more and more indications. Dexmedetomidine has proven to be comparable to conventional sedatives. It may have the edge over other sedatives as evidenced in literature by decreasing the length of ICU stay, and offering neuroprotection, and hence decreasing the incidence of delirium. It has already been established as an efficacious and safe agent to provide procedural sedation for minor procedures. Its use as an adjunct in anesthesia during the perioperative period is well documented. It is recognized as a meaningful adjunct to locoregional anesthesia. Data from long term studies is still emerging where the long-lasting benefits of dexmedetomidine use are highlighted. Continued research into the mechanism of action by dexmedetomidine at the molecular level, is making it easier for clinicians to find new uses for it. The ever-expanding collection of evidence advocating for its use to achieve different clinical goals demands frequent reviews of literature to expand our current understanding of this drug's true potential.

14. Data availability

The numerical data generated during this research is available with the authors.

15. Conflict of interest

The study did not require any grant, and no external or industry funding was involved.

16. Authors' contribution

Both authors took equal part in the concept, search and collection of dat and manuscript writing.

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