Dexmedetomidine for Neurosurgical Procedures

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Abstract While earlier clinical investigations focused on characterizing the physiologic effects of dexmedetomidine and its role as a sedative drug in critically-ill patients, newer studies suggest that the α_2 adrenergic receptor agonist may have a role as an adjunct in intraoperative neuroanesthesia. Dexmedetomidine has been shown to have multiple favorable clinical effects such as lack of respiratory depression, neuroprotection, hemodynamic stability, and no apparent interference with intraoperative neurophysiologic monitoring. This suggests that dexmedetomidine can be useful in the management of neurosurgical patients.

Keywords Dexmedetomidine · Alpha receptor agonist · Sedation and analgesia · Cardiovascular effects · Neuroprotection · Neurophysiologic monitoring · Awake craniotomy · Cerebral blood flow · Pediatric patients

Introduction

The expanding role of dexmedetomidine beyond sedation in the intensive care unit (ICU) and the rapidly approaching

patent expiration in July of 2013 has led to a growing interest in the use of dexmedetomidine as an adjunct during general anesthesia and for sedation in the perioperative setting. The unique properties of dexmedetomidine, such as minimal respiratory depression and little interference with neurophysiologic monitoring, make it a useful adjunct in the perioperative care of neurosurgical patients. Clinical neuroanesthesiologists are challenged by many dynamic factors such as restricted access to the airway, constraints of intraoperative neurophysiologic monitoring, and deriving an anesthetic plan that provides optimal neuro protection and hemodynamic stability with rapid emergence to facilitate a neurological exam. Recent data suggests that dexmedetomidine may help facilitate these demanding requirements.

Similar to clonidine, a well-established medication used of the treatment of hypertension, the primary site of action of dexmedetomidine is the α_2 adrenoreceptor. Dexmedetomidine has a 1,600 times greater affinity for α_2 adrenoreceptor and over eight times greater affinity for the α_1 receptor when compared to clonidine [1]. Original approval by the Food and Drug Administration in 1999 limited its use to sedation in the critically ill patient, but now dexmedetomidine has expanding roles in anesthesia and neuroanesthesia.

Dexmedetomidine is rapidly becoming a favored drug in anesthesia care because of its sedative and analgesic properties. The principal hypnotic effects are mediated by hyperpolarization of noradrenergic neurons in the locus coeruleus [1]. Sedation can be profound and has been reported to decrease anesthetic maintenance requirements by 35–50 % with isoflurane anesthesia [2]. Analgesic effects are produced by action of α_2 adrenoreceptors in the spinal cord, as well as at supraspinal and peripheral sites [3]. Analgesic properties are not negligible as

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dexmedetomidine has been reported as the solo analgesic agent after minor surgeries and has been shown to significantly reduce perioperative opioid requirements [2].

Original interest in dexmedetomidine was tempered by reports of deleterious hemodynamic sequelae, which includes bradycardia, hypotension, and hypertension with rapid infusion. Bradycardia is induced via a vagomimetic action and blocked cardioaccelerator nerves, making it relatively contraindicated in patients with atrioventricular conduction abnormalities. Transient hypertension with bolus injection or during a loading dose is the result of smooth muscle contraction due to peripherally located α_2 adrenoreceptor on blood vessels, and can be attenuated with slower bolus loading [3]. Dexmedetomidine has a well described biphasic effect on blood pressure, with hypotension following the transient hypertension. Hypotension is mainly the result of decreased central sympathetic outflow [2]. Caution must be taken with administering this medication to patients that cannot tolerate the sequelae of sympatholysis such as hypovolemic patients or patients dependent of catecholamines for hemodynamic stability. Despite the concerns of the side effect profile in patients with preexisting cardiac conduction abnormalities, over 1 million patients have safely received dexmedetomidine since 1999, and healthy volunteers tolerated doses 15–20 times the intended clinical concentrations without complications [4].

Dexmedetomidine and Cerebral Blood Flow

Early pharmacologic studies in canines suggested a worrisome effect of dexmedetomidine on cerebral blood flow compared to the cerebral metabolic rate of oxygen consumption. These studies showed pharmacologic vasoconstriction of the cerebral vasculature with an increase in cerebral metabolic rate of oxygen consumption when dexmedetomidine was infused in halothane anesthetized dogs [5•, 6]. The cerebral vasoconstriction described is likely a direct effect of dexmedetomidine on arterioles as well as an indirect effect by way of the drug's actions at the locus coeruleus [5•]. In a rat model, the vasoconstrictive effects of topical dexmedetomidine on arterioles could be attenuated with application of atipamezole, a synthetic α_2 -adrenergic antagonist, however, effects on the locus coeruleus continued to produce indirect cerebral vasoconstriction [5•, 7]. Recent human studies are consistent with early animal models as Zornow and colleagues showed a strongly correlated linear relationship with middle cerebral artery velocity and dexmedetomidine infusion. Serial transcranial Doppler exams showed a significant reduction in middle cerebral artery velocity with increasing intermittent dosing [8]. While both dog and human models

show infusion rates of 10 $\mu\text{g}/\text{kg}$ produce reduction in cerebral blood flow, the reduction does not appear to correspond with a proportional decrease in cerebral metabolic rate [6, 9]. A study performed by Drummond and colleagues in six healthy volunteers contradicted prior scientific evidence, by showing a reduction in cerebral metabolic rate and cerebral blood flow [10•]. Until this data is confirmed, neuroanesthesiologists must be vigilant in avoiding hypotension during dexmedetomidine administration because of its reduction in cerebral blood flow and dampening of physiologic autoregulation [11].

Neuroprotection

There is a growing body of work demonstrating the neuroprotective role of dexmedetomidine. It has been hypothesized that global and focal cerebral ischemic events can be attenuated by the use of α_2 adrenoreceptor agonists. Catecholamine release is likely a factor contributing to injury [12]. Catecholamines can potentially exacerbate neuronal injury by multiple mechanisms, such as: (1) catecholamine-mediated increases in sensitivity to neurotransmitters such as glutamate; (2) increased neuronal activity leading to expression of catabolic enzymes and possibly cell death due to excessive excitation; (3) a direct toxic effect of catecholamines on neurons; and (4) free radical formation [5•]. As such, dexmedetomidine can potentially attenuate neuronal injury by reducing catecholamine production. Alternative hypotheses are being examined that suggest that the neuroprotective effects of dexmedetomidine may also be due to enhanced production of epidermal growth factor and brain-derived neurotrophic factors [13].

Numerous in vitro and in vivo investigations have demonstrated that dexmedetomidine possesses neuroprotective properties during ischemic conditions; however, recent novel research in canines suggests that traumatic brain injury induced cell necrosis and apoptosis can be attenuated by dexmedetomidine. The traumatic brain injury model utilized was a standard focal trauma applied to hippocampal culture followed by application of varying concentrations of dexmedetomidine. A neuroprotective effect was demonstrated even after a delay in application by 2–3 h. Interestingly the authors found dexmedetomidine to have a significantly greater protective effect than hypothermia [14•].

Hemodynamic Stabilization

It is well established that dexmedetomidine decreases adrenergic outflow which is accompanied by a decrease in blood

pressure and heart rate. With widespread use intraoperatively, there are growing concerns over its hemodynamic consequences. A recent retrospective review of 15,656 non-cardiac surgeries demonstrated an 8 % increase in the use of vasoconstrictors and atropine with dexmedetomidine. However, dexmedetomidine was not associated with more hypotension or bradycardia [15•]. This hemodynamic profile makes it an attractive adjunct to general anesthesia to improve hemodynamic stability during neuroanesthesia because it is of the utmost importance to avoid hypertension which can lead to bleeding, edema, increased intracranial pressure, and worsen surgical field visualization [16]. A recent prospective, randomized, double-blinded study examined the role of an adjunctive dexmedetomidine infusion on the perioperative management of patients undergoing craniotomy. Patients receiving a continuous intraoperative infusion of dexmedetomidine required fewer pharmacological interventions with antihypertensive medications such as labetalol, metoprolol and hydralazine to control blood pressure—43 versus 86 % in the placebo cohort. Investigators also found reduced use of phenylephrine and ephedrine in the dexmedetomidine infusion cohort. Of note, not only were hypertensive episodes less common in those who received dexmedetomidine, but mean duration of stay in the post-anesthesia recovery unit was also significantly shorter in the dexmedetomidine group [17]. Dexmedetomidine was recently shown to attenuate hemodynamic and neuroendocrine responses to insertion of skull pins when administered as a single bolus (1 µg/kg over 10 min) prior to induction of anesthesia [18].

Dexmedetomidine, when administered as an infusion during cardiopulmonary resuscitation in animals, reduced phenylephrine requirements to maintain a target blood pressure and also reduced the number of ventricular ectopic beats observed after cardiopulmonary resuscitation. These findings were attributed to hemodynamic stabilization and suggest that dexmedetomidine might improve outcomes after cardiopulmonary resuscitation [5•, 19].

Intraoperative Neurophysiologic Monitoring

Neurophysiologic monitoring has become an integral component of neuroanesthesia because spinal surgery with instrumentation can result in iatrogenic injuries to the spinal cord but can also be used to warn of injury during intracranial procedures. Monitoring allows for early detection of injury, however volatile anesthetics beyond one minimum alveolar concentration (MAC) greatly interfere with monitoring. While dexmedetomidine will likely not replace other anesthetics, when used as an adjunctive agent, it can serve to decrease the dose requirement of inhaled anesthetics, propofol and fentanyl [20]. This is potentially useful to clinicians to help reduce the doses of drugs with known

suppressive effects on evoked potential monitoring. In a rat model, investigators found adequate conditions for somatosensory-evoked potential (SEP) monitoring at all clinically relevant doses of dexmedetomidine and even at supra therapeutic blood concentrations [20]. A small study in humans validated the finding that dexmedetomidine had no clinically relevant suppressive effect on SEP monitoring, however an ambiguous effect was found involving motor evoked potentials. Specifically, motor evoked potential monitoring was possible at varying infusion doses; however, it was underpowered to statistically state that dexmedetomidine had no effect on motor evoked potentials [21]. A recent case report described two pediatric patients in whom loss of motor evoked potentials was attributable to a dexmedetomidine infusion, however, the unusually large doses that were used were most likely the etiology of this finding [5•, 22].

Awake Craniotomy

Patients requiring surgery involving eloquent areas of brain may benefit from intraoperative neurocognitive testing. The awake craniotomy is a complex technique because it poses unique and challenging intraoperative complications, such as agitation, pain, seizures, and respiratory depression. Respiratory depression in this patient population can also pose a difficult airway management scenario because the patients may be in a stereotactic frame or prone hiding the airway from the anesthesiologist [23].

Two emerging methods of anesthesia that allow for intraoperative neurocognitive testing are described in the literature. The asleep-awake-asleep technique typically entails general anesthesia with a laryngeal mask airway (LMA) during exposure. The patient then is awakened and the LMA is withdrawn for neurocognitive testing, and low doses of propofol or dexmedetomidine are used during the ‘awake’ portion [24]. In this scenario, dexmedetomidine is especially useful because of its ability to achieve sedation while the patient remains cooperative and able to communicate with the surgeon. At the end of testing, the patient is again anesthetized and the LMA is replaced during closure.

The alternate method entails monitored anesthesia care for the duration of the procedure with a reduction in dosing around the time of neurocognitive and motor testing [24]. Dexmedetomidine was shown to be an ideal sedative agent with patients sleeping comfortably but easily arousable by voice stimulation and experiencing no difficulty in performing complex neurocognitive testing during awake craniotomy with a continuous dexmedetomidine infusion [24]. The other notable benefit of dexmedetomidine over opioid sedation is minimal respiratory depression, which can result in hypercapnia induced brain swelling and increased intracranial pressure [5•]. Interestingly, dexmedetomidine

inhibits hypercapnic cerebral vasodilation, which could prove to be an added benefit during awake craniotomy [5•]. Different infusion protocols are described but generally dexmedetomidine is loaded at 0.5–1 µg/kg/h over 20 min, then infused at 0.1–0.7 µg/kg/h until 20 min prior to testing. The infusion rate is decreased to 0.1–0.2 µg/kg/h during neurocognitive testing [25]. Often, additional drugs, such as propofol—administered as intermittent boluses or as a low-dose infusion, may be required.

The pediatric population can present additional challenges for an awake technique which requires cooperation, full understanding, and managing concomitant anxiety. However, two case reports describing successful craniotomy utilizing dexmedetomidine as the primary sedative agent suggest that this is a feasible option in select pediatric patients [26].

Conclusion

Caring for the neurosurgical patient presents the anesthesiologist with interesting and challenging problems; dexmedetomidine may be a solution. Utilization of this agent offers hemodynamic stability and neuroprotective properties in this at risk patient population. Dexmedetomidine allows for the possibility of improved patient outcomes, and appears to accommodate the growing trend of intraoperative neurophysiologic monitoring. Few drugs are available to meet these demanding requirements, and for this reason dexmedetomidine is proving to be an invaluable tool for the neuroanesthesiologist.

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