Dexmedetomidine Use in General Anaesthesia

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Abstract: Dexmedetomidine is a potent and highly selective α2-adrenoreceptor agonist currently utilized for continuous infusion for sedation/analgesia in the intensive care unit (ICU). Dexmedetomidine offers remarkable pharmacological properties including sedation, anxiolysis, and analgesia with the unique characteristic to cause no respiratory depression. In addition it posses sympatholytic and antinociceptive effects that allow hemodynamic stability during surgical stimulation. Different from most of clinically used anesthetics, dexmedetomidine brings about not only a sedative-hypnotic effect via an action on a single type of receptors, but also an analgesic effect and an autonomic blockade that is beneficial in cardiac risk situations. Several studies have demonstrated its safety, although bradycardia and hypotension are the most predictable and frequent side effects.

Dexmedetomidine has shown to consistently reduce opioids, propofol, and benzodiazepines requirements. In the last years it has emerged as an affective therapeutic drug in a wide range of anesthetic management, promising large benefits in the perioperative use. In particular this review focuses on dexmedetomidine utilization in premedication, general surgery, neurosurgery, cardiac surgery, bariatric surgery, and for procedural sedation and awake fiberoptic intubation. In all these fields dexmedetomidine has demonstrated to be an efficacious and safe adjuvant to other sedative and anesthetic medications.

Keywords: α2-Adrenoreceptor agonists, dexmedetomidine, sedation, anesthesia, perioperative use.

INTRODUCTION

Dexmedetomidine is a potent, highly selective and specific α2-adrenoreceptor agonist that has both sedative and analgesic effects. The prototype of α2-adrenoreceptor agonist clonidine was initially developed in 1960s as a nasal decongestant for its locally acting α1-adrenergic vasoconstrictor action, but later in 1966 it was introduced into the market as a potent antihypertensive drug [1]. Nowadays the therapeutic use of this class of drugs has shifted to various other clinical indications including anxiolysis, analgesia, sedation that render them suitable as adjuncts in anesthesia. Dexmedetomidine was approved in the USA in 1999 for sedation and analgesia in the intensive care unit. Compared with clonidine, dexmedetomidine is about eight times more specific for α2-adrenoreceptors with an α2: α1 selectivity ratio of 1600 : 1 Fig. (1). These unique properties of dexmedetomidine make it an α2-adrenoreceptor full agonist agent with sedative and anxiolytic effects. The elimination half-life of dexmedetomidine is approximately 2 hours with a rapid distribution half-life being approximately 6 min [2, 3]. It has a rapid onset of action. It undergoes biotransformation in the liver, and the kidney excretes 95% of its metabolites.

The short half-life of dexmedetomidine makes it particularly suitable for intravenous infusion. Although dexmedetomidine is approved for sedation/analgesia in an intensive care setting, in the last years it has emerged as an affective therapeutic drug in a wide range of anesthetic management.

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Fig. (1). The chemical structure of α2-adrenoreceptor agonists clonidine and dexmedetomidine.

PHARMACOLOGY

α2-adrenoreceptor agonists act at pre- and postsynaptic adrenoceptors and their pharmacology is complex. The human α2-adrenoreceptors can be classified into α2A, α2B and α2C adrenoceptors subtypes. These receptor subtypes are distributed ubiquitously and each may be responsible for a specific action of α2 -agonists [4, 5]. The predominant α2-adrenoreceptor agonist subtype mediating sedative and antinociceptive actions is the α2A-adrenoceptor. Whereas stimulation of α2B-adrenoceptor mediates the vasoconstrictive cardiovascular effect, which causes the initial hypertension observed after the administration of α2-adrenoceptor agonists [6,7]. The α2C - adrenoceptors subtype has
been shown to modulate dopaminergic neurotransmission, hypothermia and a variety of behavioral responses.

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons located in the locus ceruleus [8]. Dexmedetomidine acts through a G-coupled protein receptor that produces an inhibition of adenyl cyclase and this results in decreased formation of cyclic AMP (cAMP), that is an important regulator of many cellular functions acting in various intracellular subsystems like the control of phosphorilation state of regulatory proteins. Other effects of α₂-adrenoreceptor agonists include activation of potassium ion channels causing efflux of potassium and an inhibition of calcium entry into calcium channels in neuronal cell [9]. These effects lead to change in membrane ion conductance and produce α₂-adrenoreceptor agonist hyperpolarization of the membrane which suppresses neuronal activity. The main effect is an inhibition of noradrenalin release causing a reduction in excitation, especially in locus coeruleus. The locus coeruleus is α₂-adrenoreceptor agonist small neuronal nucleus located bilaterally in the upper brainstem and is the α₂-adrenoreceptor agonist major site of noradrenergic innervations in the brain [10]. The locus coeruleus has also been implicated as α₂-adrenoreceptor agonist key modulator for α₂-adrenoreceptor agonist variety of important brain functions, including arousal, sleep, anxiety and drug withdrawal associated with CNS depressant, like opioids.

Cardiovascular Effects

The hemodynamic effects of dexmedetomidine result from peripheral and central mechanism. Alpha₂-adrenoreceptor agonists show a biphasic, dose-dependent, blood pressure effect. At low doses the dominant action of α₂-adrenoreceptor agonist activation is a reduction in sympathetic tone, mediated by a reduction of norepinephrine release at the neurotransmitter junction, and a inhibition of neurotransmission in sympathetic nerves [11]. The net effect of dexmedetomidine action is a significant reduction in circulating catecholamines with a slight decrease in blood pressure and a modest reduction in heart rate [12]. When dexmedetomidine is administered as a continuous infusion, is associated with an expected and stable hemodynamic response. Significant hypotension is usually only observed in patients with preexisting hypovolemia or vasoconstriction. The bradycardia frequently seen after the administration of dexmedetomidine may be due to the central sympatholytic action and partly by baroreceptor reflex and enhanced vagal activity. This effect is frequently observed in younger patients with high levels of vagal tone.

At higher doses of dexmedetomidine produce an hypertensive action caused by the activation of α₂β adrenoceptors located on vascular smooth muscle cells. This effect proscribes the rapid intravenous injection of dexmedetomidine.

Respiratory System Effects

The α₂-adrenoreceptor agonists have minimal effects on ventilation. Although dexmedetomidine produces sedative, analgesic and anxiolytic effects, unlike other sedatives, it provides respiratory stability and does not cause ventilator depression. This was shown in healthy volunteers in whom even very high doses of dexmedetomidine did not compromise respiratory function [13]. Absence of respiratory depression was also observed in patients sedated with dexmedetomidine, which was administered at infusion rates 10 to 15 times higher than maximally recommended [14]. It was also demonstrated that combination of α₂-adrenoreceptor agonist with opioids does not lead to further ventilator depression.

Central Nervous System Effects

Dexmedetomidine, like other α₂-adrenoreceptor agonists, provides sedation, anxiolysis and analgesia. The sedation produced by α₂-adrenoreceptor agonists does not depend primarily on activation of the γ-aminobutyric acid (GABA) receptors like that produced by traditional sedatives, such as propofol or benzodiazepines. The primary site of action of α₂-adrenoreceptor agonist is the locus ceruleus and not the cerebral cortex, as would be the case with GABA-mimetic drugs [15]. This should be the reason why this class of drugs produces a different type of sedation compared with benzodiazepines and propofol.

Sedation induced by dexmedetomidine has unique properties, it produces an unusually cooperative form of sedation in which the patient is calmly and easily roused from sleep to wakefulness to allow task performance and excellent communication and cooperation while intubated and ventilated and then quickly back to sleep when not stimulated [16]. The unusual subcortical form of dexmedetomidine induced sedation is characterized by an easy and quick arousal, resembling natural sleep. With increasing doses of dexmedetomidine, profound anesthetic actions have been demonstrated, and this advocates that dexmedetomidine could be used as total intravenous agent. The neuroprotective properties of dexmedetomidine have been demonstrated in various animal models of cerebral ischemia [17]. There are recent experimental data suggesting that in addition to α₂-adrenoreceptor agonists, the neuroprotective effect of dexmedetomidine may include other pathways in the brain, independent of α₂-adrenoreceptor agonists and most probably involve I1-imidazoline receptors in the brainstem and hippocampus [18].

Analgesia

Dexmedetomidine has been demonstrated to have significant analgesic effects and consistently reduce opioid requirements [19]. It is believed that the spinal cord is probably the major site of analgesic action, where the activation of α₂-adrenoreceptor agonist subtype seems to increase the analgesic action of opioids in lowering the transmission of nociceptive signals to brain centers [20]. Dexmedetomidine also inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects.

Renal System Effects

Stimulation of α₂-adrenoreceptors in the kidneys results in diuresis and natriuresis possibly through an ability to reduce efferent sympathetic outflow of the renal nerve. In addition dexmedetomidine has shown to decrease the secretion of vasopressin and to antagonize its effect on renal
tubules. $\alpha_2$-adrenoreceptor agonists are also thought to increase the release of atrial natriuretic peptide resulting in natriuresis [21].

**Endocrine System Effects**

Action of $\alpha_2$-adrenoreceptor agonists on endocrine system are mainly related to their action on sympathetic outflow and the decrease of catecholamines, this can attenuate the responses to stress by inhibiting the secretion of adrenocorticotrophic hormone (ACTH) and cortisol [21]. In addition stimulation of $\alpha_2$-adrenoreceptor agonists located on cells of the islet of Langerhans can temporally cause direct inhibition of insulin release with concomitant detectable clinical hyperglycemia [22].

**CLINICAL APPLICATIONS IN ANESTHESIA**

**Premedication**

The sedative and anxiolytic properties of dexmedetomidine as well as sympatholytic characteristics make this drug of particular interest for premedication. Most of the studies focusing at dexmedetomidine as premedicant have found interesting benefits. Dexmedetomidine lower the tachycardic response to endotracheal intubation and assures a greater hemodynamic stability during the intraoperative period. It has the ability to potentiate the anesthetic requirements for opioids as well as volatile and regional agents. Several studies have demonstrated the beneficial effects of dexmedetomidine premedication in patients with coronary artery disease because it allows a stable perioperative hemodynamic. Jaakola [23] evaluates the efficacy and safety of intravenous dexmedetomidine as a premedication before regional anesthesia showing that dexmedetomidine attenuated the increase in HR and BP during extubation. Patients received either dexmedetomidine i.v. or saline placebo i.v. 10 minutes before exsanguination and inflation of a tourniquet. Regional blockade was induced with 0.5% lidocaine 3 mg/kg. Dexmedetomidine preoperatively induced 16% to 20% decreases in blood pressure and heart rate. The subjective intensity of pain during tourniquet inflation was similar in both groups, but fewer intraoperative opioids analgesics were needed in the dexmedetomidine group. General effectiveness was graded superior in the dexmedetomidine group. The author at the end accomplished that dexmedetomidine is an effective premedication before i.v. regional anesthesia because it reduces patient anxiety, sympahtoadrenal responses, and opioids analgesic requirements.

Unlugenc et al. [24] gave 1 $\mu$g/kg dose of dexmedetomidine within 10 minutes of induction and they found a marked decrease in HR within 10 minutes, whereas heart rate an mean arterial pressure were similar to values seen in the other group during surgery. In a recent study Basar et al. [25] utilized dexmedetomidine as a single preanesthetic drug to investigate the hemodynamic, cardiovascular and recovery effects in patients undergoing elective cholecystectomy. 40 adult patients were randomly assigned to receive 0.5 $\mu$g/kg dexmedetomidine or saline solution. Main cardiovascular parameters, times for awakening, and postoperative Aldrete’s recovery score were recorded. The authors observed that a single dose of dexmedetomidine given before induction of anesthesia decreased thiopental requirements without serious hemodynamic effects or any effect on recovery time.

Dexmedetomidine premedication has been evaluated in children population too. Yuen et al. [26] evaluated whether intranasal dexmedetomidine was as effective as oral midazolam for premedication in children. 96 children scheduled for elective minor surgery were randomly assigned to receive oral midazolam 0.5 mg/kg, and intranasal dexmedetomidine at 0.5 or 1 $\mu$g/kg respectively. Patient’s sedation status and cardiovascular parameters were recorded until induction of anesthesia together with recovery characteristics. They concluded that intranasal dexmedetomidine produces more sedation than oral midazolam, but with similar and acceptable cooperation. Schmidt et al. [27] assessed the effects of preanesthetic administration of midazolam, clonidine or dexmedetomidine on postoperative pain and anxiety in children. They found that children receiving clonidine or dexmedetomidine have similar levels of anxiety and sedation postoperatively as those receiving midazolam. However children given $\alpha_2$-adrenoreceptor agonists had less perioperative sympathetic stimulation and less postoperative pain.

**Perioperative Use**

Dexmedetomidine may be a useful adjuvant during general anesthesia to employ its sedative, hypnotic, analgesic and sympatholytic properties for the benefit of surgical patients by promoting hemodynamic stability and decreasing the doses of anesthetics and analgesics. Aho et al. [28] reported that the administration of an infusion of dexmedetomidine in patients undergoing abdominal hysterectomy was able to reduce isoflurane requirements by 90%. The heart rate response to endotracheal intubation was significantly blunted. Khan et al. [29] have investigated the pharmacokinetic and pharmacodynamic interactions of dexmedetomidine and isoflurane in human volunteers. Nine male subjects were allocated randomly to receive isoflurane anesthesia preceded by infusion of dexmedetomidine. They observed that dexmedetomidine decreased isoflurane requirements in a dose-dependent manner and reduced heart rate and arterial pressure. Sedation and slight impairment of cognitive function persisted for several hours after anesthesia. Isoflurane did not appear to influence the pharmacokinetics of dexmedetomidine. Since dexmedetomidine sedative properties could possibly prolong recovery from anesthesia Ohtani et al. [30] examined the effect of co-administration of dexmedetomidine on the recovery profiles from sevoflurane and propofol based anesthesia. Sixty patients were divided into four groups according to the anesthetic to be administered: sevoflurane, propofol, sevoflurane and dexmedetomidine and propofol and dexmedetomidine as maintenance general anesthetics. The main findings of this study are that dexmedetomidine delays recovery from propofol but not from sevoflurane and that postoperative cognitive function is not affecting by co-administration of dexmedetomidine in both groups. Dexmedetomidine was also utilized as a total intravenous anesthetic; Ramsay et al. [31] reported the administration of dexmedetomidine in this fashion in three patients with potential airway management
patients were included. Overall, and cardiac surgery. Twenty-three trials comprising 3.395 complications and mortality in adults undergoing vascular clonidine, and mivazerol, on perioperative cardiovascular increase of blood pressure, but increased slightly the need for norepinephrine concentrations by 90%, attenuated the artery bypass grafting receiving intravenous infusion of evaluated eighty patients scheduled for elective coronary pathogenesis of cardiovascular complications. The surgical stress response is important in the normal preoperative renal function and undergoing fluid restriction. They conclude that “ although the possible monotherapeutic application of α2-adrenoreceptor agonists to provide an anesthetic state suitable for general anesthesia has been described, it is much more likely that this class of compound will be used in combination with other anesthetic adjuvants in the perioperative period “.

**Thoracic Surgery**

In thoracic surgery the use of dexmedetomidine may offer numerous physiologic benefits. It lowers the perioperative oxygen consumption and the sympathetic response to surgical stimulus that may assure cardioprotective benefit. Wahlander et al. [33] have observed that the use of dexmedetomidine in post-thoracotomy patients as a supplementation to a low-dose thoracic epidural bupivacaine (0.125%) reduce the requirement for opioids and the potential for respiratory depression. In the same study a post hoc analysis was conducted to test the hypothesis that dexmedetomidine enhances urine flow rate and perioperative renal function and it was found that dexmedetomidine infusion induced diuresis in patients with normal preoperative renal function and undergoing fluid restriction.

**Cardiac Surgery**

The surgical stress response is important in the pathogenesis of cardiovascular complications. The α2-adrenoreceptor agonists attenuate the stress response and therefore potentially reduce cardiovascular complications. There are a large number of studies that evaluated dexmedetomidine as an adjunct to cardiac surgery. Wiyeysundera et al. [34] investigated the effects of α2-adrenoreceptor agonists, including dexmedetomidine, clonidine, and mivazerol, on perioperative cardiovascular complications and mortality in adults undergoing vascular and cardiac surgery. Twenty-three trials comprising 3.395 patients were included. Overall, α2-adrenoreceptor agonists reduced the incidence of myocardial infarction and mortality significantly during vascular surgery. During cardiac surgery, α2-adrenoreceptor agonists reduced the number of ischemic episodes and were associated with a reduced risk of myocardial infarction and trend toward decreased mortality. The risk of hypotension during cardiac surgery was highlighted in this analysis, but the authors did not find statistically significant increases in the occurrence of hypotension, bradycardia, or heart failure. Jalonen et al. [35] evaluated eighty patients scheduled for elective coronary artery bypass grafting receiving intravenous infusion of dexmedetomidine. Dexmedetomidine decreased plasma norepinephrine concentrations by 90%, attenuated the increase of blood pressure, but increased slightly the need for intravenous fluid challenge and induced more hypotension during cardiopulmonary bypass. In addition it decreased the incidence of intraoperative and postoperative tachycardia. In another study But et al. [36] investigated the effects of preoperative dexmedetomidine infusion on hemodynamic in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Patients received dexmedetomidine infusion until the surgical incision. They found that dexmedetomidine decreases the fontanel requirement and attenuates the increase in systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) at the post-sternotomy period relative to the baseline levels, and decreases effectively mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP) and pulmonary artery wedge pressure (PCWP) in comparison with the values in the placebo group.

Few studies of the use of dexmedetomidine have been performed during pediatric cardiac surgery. Muktar et al. [37] evaluated the effects of dexmedetomidine on circulatory dynamics and serum cortisol, glucose, epinephrine, and norepinephrine concentrations in 30 children undergoing cardiopulmonary bypass. Relative to baseline, arterial blood pressure and heart rate decreased significantly after the administration of dexmedetomidine through skin incision. In the control group, heart rate and arterial blood pressure increased after skin incision until the end of bypass. In both groups, plasma cortisol, epinephrine, norepinephrine, and blood glucose increased significantly relative to baseline, after sternotomy, and after bypass. However, the values were significantly higher in the control group compared with the DEX group. They concluded that intraoperative dexmedetomidine infusion can be a useful adjuvant in pediatric cardiac anesthesia because it attenuates the hemodynamic and neuroendocrinal response of surgical trauma.

Dexmedetomidine has also been utilized as an antiarrhythmic drug; Crystostomou et al. [38] examined the possible effect of dexmedetomidine on atrial and junctional tachyarrhythmia. Fourteen patients admitted to the cardiac intensive care received dexmedetomidine for both sedation/analgesia and for junctional ectopic tachycardia, atrial ectopic tachycardia, reentry type supraventricular tachycardia, atrial flutter and functional accelerated rhythm. Dexmedetomidine was used as a primary drug or as a rescue drug if other antiarrhythmics had been used. Ten patients (71%) received an initial loading dose of 1.1 ± 0.5 μg/kg. A continuous infusion, 0.9 ± 0.3 μg/kg/hr was administered in 12 patients. Adverse effect was seen in four patients (28%).Three had hypotension and one had a possible brief atrioventricular block. The primary outcome with rhythm and/or heart rate control was achieved in 13 patients (93%). The authors concluded that dexmedetomidine may have a potential therapeutic role in the acute phase of perioperative atrial and functional tachyarrhythmias for either control of heart rate or conversion to normal sinus rhythm.

**Neurosurgery**

During intracranial surgical procedures the neurosurgeon must often performs neurophysiological testing to evaluate that the surgical target has been localized or to assess the responses following deep brain stimulation for electrode
implantation, surgical management of epilepsy and other procedures. In this context an intraoperative active patient participation is required. Drugs utilized in these procedures should permit to modify rapidly the level of anesthesia from a deep level during periods of intense stimulation to consciousness during functional testing. In these circumstances dexmedetomidine may be a useful adjunct to the currently utilized anesthetic techniques. Low doses of this drug, in fact, provide sedation that can be easily reversed with verbal stimulation. Bekker et al. [39] reported the first successful application of dexmedetomidine combined with BIS monitoring in an awake craniotomy setting necessitating an awake, cooperative patient. The pharmacology of dexmedetomidine allowed achieving a level of sedation and analgesia sufficient to complete the neuropsychiatric testing required for the mapping of the cortical language area, as well as to perform an awake tumor resection. The patients remained hemodynamically stable and cooperative during the “awake” portion of the procedure. In this case series dexmedetomidine was selected also for its lack of respiratory depression as well as its sedative and analgesic properties. They concluded that dexmedetomidine appears to be a useful sedative for awake craniotomy when sophisticated neurologic testing is required. Souter et al. [40] utilized dexmedetomidine in patients with refractory seizures that underwent awake craniotomy for cortical resection of the seizure area using intraoperative functional mapping and electrocorticography (ECoG). In this situation the authors found that dexmedetomidine does not suppress epileptiform activity and then can be used in patients with seizures disorders requiring brain mapping. Dexmedetomidine has been also used during stereotactic implantation of deep brain stimulators and has shown an improvement in patient satisfaction without compromising target localization. Rozet et al. [41] performed a retrospective chart review of anesthesia records of patients who underwent deep brain stimulator implantation. Demographic data, use of antihypertensive medication, and duration of mapping were compared between patients who received dexmedetomidine and patients who did not receive any sedation. Dexmedetomidine provided patient comfort and surgical satisfaction with mapping in all cases, and significantly reduced the use of antihypertensive medication. In deep brain stimulator implantation, sedation with dexmedetomidine did not interfere with electrophysiologic mapping, and provided hemodynamic stability and patient comfort. Bekker et al. [42] have also been used Dexmedetomidine as a primary sedative agent for sedating patients performing awake carotid endarterectomy to allow intraoperative neurological examination. Sixty-six patients were randomly assigned to receive either dexmedetomidine (total dose of 97.5 +/- 54.7 µg) or normal saline (control). Supplemental doses of midazolam, fentanyl, and/or propofol were administered as deemed necessary by the anesthesiologist. The use of dexmedetomidine in these patients resulted in fewer fluctuations from the desired sedation level. In addition patients receiving dexmedetomidine required less antihypertensive therapy compared with the midazolam/fentanyl/propofol combination. Dexmedetomidine has found useful also in patients undergoing craniotomy under general anesthesia to obtain hemodynamic stability and modulation of intraoperative sympathetic responses to attenuate cerebrovascular and myocardial risks and avoid intracranial hemorrhage, in addition it allows immediate neurological evaluation upon emergence. Tanskanen et al. [43] have used dexmedetomidine as an anesthetic adjuvant to neurosurgical anesthesia in patients scheduled for elective surgery of supratentorial brain tumor. They were randomized to receive a continuous dexmedetomidine infusion or placebo, beginning 20 min before anesthesia and continuing until the start of skin closure. Anesthesia was maintained with nitrous oxide in oxygen and isoflurane. They found that dexmedetomidine significantly attenuated the hemodynamic responses to intubation and the emergence from anesthesia. In addition, it increased intraoperative cardiovascular stability. Most of the effects were concentration dependent, and the higher dose was more effective than the lower dose. Patients receiving dexmedetomidine had their tracheal tubes removed faster than those in the placebo group, indicating preserved respiratory function. In a recent study Bekker et al. [44], considering that the perioperative course of patients undergoing intracranial surgery is frequently complicated by hypertensive episodes, designed the study to assess the efficacy of dexmedetomidine in controlling hypertensive responses during the surgery. Patients were randomly divided to receive either sevoflurane-opioids or sevoflurane-opioids-dexmedetomidine. The dexmedetomidine group required fewer opioids in the intraoperative period, but there were no differences in the use of sevoflurane. In the intensive care unit, patients in dexmedetomidine group had fewer hypertensive episodes and were discharged earlier. There were no differences in the requirement for postoperative opioids or antiemetics. They concluded that dexmedetomidine improved hemodynamic stability and was effective for blunting the increase of systolic blood pressure perioperatively. In addition the drug did not increase the incidence of hypotension and bradycardia, common side effect of this drug.

Procedural Sedation

There is a growing interest in utilization of this agent in the pediatric population who require sedation for radiographic procedures, in particular with radiologic imaging (computed tomography and magnetic resonance imaging - MRI). Koroglu et al. [45] randomized 80 children (1-7 yrs of age) to dexmedetomidine or midazolam during MRI. Dexmedetomidine was administered as a loading dose of 1 µg/kg over 10 min followed by an infusion of 0.5 µg/kg/hr, whereas midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 µg/kg/hr. The quality of sedation was better in the dexmedetomidine group than in the midazolam group, as they achieve an adequate lack of movement and sedation. In addition the need for rescue sedation was less with dexmedetomidine compared with midazolam. A second study by Koroglu et al. [46] randomized 60 children to dexmedetomidine or propofol during MRI. Although equally effective in providing sedation, a faster onset of action, faster recovery and discharge were noted in propofol group. Adverse effects including hypotension and oxygen desaturation were more common with propofol. Oxygen desaturation requiring intervention (chin lift, discontinuation of the infusion, and supplemental oxygen) occurred in four children receiving propofol vs. none of those receiving dexmedetomidine. In
another study Heard et al. [47] compared the pharmacodynamic responses to dexmedetomidine–midazolam and propofol in children anesthetized with sevoflurane undergoing magnetic resonance imaging (MRI). Forty children were randomized to receive either dexmedetomidine-midazolam or propofol for maintenance of anesthesia for MRI after a sevoflurane induction. Dexmedetomidine was administered at an initial loading dose of 1 μg/kg followed by a continuous infusion of 0.5 μg/kg/hr. Midazolam (0.1 mg/Kg) was administered when the infusion started. Propofol was administered as a continuous infusion (250-300 μg/kg/hr). The authors found that dexmedetomidine-midazolam provides adequate anesthesia for MRI but the times to fully recover and to discharge after dexmedetomidine administration were significantly greater than those after propofol. Heart rate and systolic blood pressure was greater with dexmedetomidine compared with propofol. Respiratory indices were similar for the two treatments.

Dexmedetomidine was also used in pediatric population for invasive procedures like gastrointestinal endoscopy, fiber optic intubation and cardiac catheterization. Tosun et al. [48] compared a dexmedetomidine-ketamine combination with a propofol-ketamine combination in 44 children (4 months to 16 yrs) with acyanotic congenital heart disease undergoing cardiac catheterization. Although sedation was managed effectively with both regimens, patients sedated with ketamine-dexmedetomidine required more ketamine and more supplemental doses of ketamine and had longer recovery times than patients sedated with a propofol-ketamine combination. The authors concluded that the dexmedetomidine-ketamine combination was not superior to a propofol-ketamine combination because of insufficient sedation and analgesia and a longer recovery. For the same purpose dexmedetomidine has also been used in adult population, in fact in MRI setting where stereotactic frame placement and accurate imaging in tremulous Parkinson’s patients makes anesthetic management particularly complex. In these circumstances dexmedetomidine utilization represents a safe alternative with the classic deep propofol sedation, assuring a sedation that reduces movement and causes no respiratory depression [49].

Dexmedetomidine may also represents a good option during sedation of adult patients requiring endoscopy, Demiraran et al. investigate [50] and compare the safety and efficacy of dexmedetomidine versus midazolam in providing sedation for gastroscopy in 50 adult patients. After the procedure, full recovery time, mean arterial pressure, heart rate, respiratory rate and hemoglobin oxygen saturation levels were similar in both groups. Dexmedetomidine performed as effectively and safely as midazolam but it was superior to it with regard to vomiting, rate of side effects and endoscopist satisfaction. It was concluded that dexmedetomidine may be a good alternative to midazolam to sedate patients for upper endoscopy. In another study dexmedetomidine showed negative effects, Jalowiecki et al. [51] performed a study to evaluate the ability of dexmedetomidine to provide analgesia and sedation for outpatient colonoscopy. Sixty-four patients were randomly assigned to one of three treatment regimens. In group D, patients received 1/g/kg dexmedetomidine over 15 min followed by an infusion of 0.2 μg/kg/h. Group P received meperidine (1 mg/kg) with midazolam (0.05 mg/kg), and group F received fentanyl (0.1- 0.2 mg intravenous) on demand. The study was terminated before the planned 90 patients had been recruited because of adverse events in group D. In all groups, negligible hemoglobin oxygen saturation and respiratory rate variations were observed. In group D, there was a significantly larger decrease in heart rate (to approximately 40 beats/min in 2 out of 19 cases) and blood pressure (to less than 50% of the initial value in 4 of 19 patients). Supplemental fentanyl was required in 47% of patients receiving dexmedetomidine to achieve a satisfactory level of analgesia (vs. 42.8% of patients in group P and 79.2% of patients in group F). Vertigo (5 patients), nausea/vomiting (5 patients), and ventricular bigemism (1 patient) were observed only in group D. Time to home readiness was longest in group D. The authors of this work concluded that in patients undergoing colonoscopy, dexmedetomidine provides a relatively satisfactory level of analgesia and sedation without clinically notable adverse respiratory effects. However, compared with commonly used sedation regimens, dexmedetomidine was associated with the frequent requirement for supplemental fentanyl, sometimes profound hypotension and bradycardia, and prolonged recovery time. At the end they affirmed that these side effects may limit dexmedetomidine usefulness for this indication.

Awake Intubation

Awake intubation in the patient with a potentially difficult airway is a problematic procedure which may be associated with wide hemodynamic changes. To attenuate this response, blunting of airway reflexes is required without losing the patient’s cooperation. Conventional agents such as opioids, benzodiazepines, and propofol carry the risk of respiratory depression, with possible inability to ventilate the patient. Dexmedetomidine offers an ideal solution to this problem because patients are maintained in spontaneous breathing while attempts are made to secure their airway. In addition thanks to its antialagogue effect it maintains a dry field for the anesthesiologist thus facilitating the procedure. Bergese et al. [52] in a recent investigation reported on 4 patients with particularly difficult airways who underwent successful awake fiberoptic intubation with dexmedetomidine. Dexmedetomidine was used to provide a moderate level of conscious sedation without causing respiratory distress or hemodynamic instability during fiberoptic intubation. Abdelmalak et al. [53] reported a series of successful awake fiberoptic intubations in patients with critical (unstable and difficult) airways using dexmedetomidine. The authors affirmed that dexmedetomidine appears to be a useful agent for sedation during awake fiberoptic intubation in difficult airway patients. Recently [54] dexmedetomidine has been utilized for laryngeal mask insertion comparing with fentanyl combined with propofol. The authors in their conclusion stated that dexmedetomidine, when used before propofol induction provides successful laryngeal mask insertion comparable to fentanyl, while preserving respiratory functions more than fentanyl.

Bariatric Surgery

Obesity is increasingly common, particularly in developed countries, and represents a serious hazard to
largely due to increasing obesity and the higher rate of bariatric surgery, the anesthetic management of patients undergoing these procedures has become more complex. Bariatric surgery represents a great advance in the treatment of obese patients. Applied when all other measures have failed, this therapeutic option is achieving very favorable outcomes and is therefore being carried out with increasing frequency. Obese patients are at a disadvantage during anesthesia, given that techniques are more difficult to perform and risk increases. Obesity is often associated with marked respiratory co-morbidities such as obstructive sleep apnea and/or pulmonary hypertension that may have a profound impact on anesthetic management of these patients and may increase the risk of morbidity and mortality due to inadequate postoperative ventilation. Because of opioid ventilatory depressing effect, dexmedetomidine has been used to diminish this threat and thereby decrease the incidence of respiratory depression. Feld et al. [55] evaluated whether dexmedetomidine infusion could replace fentanyl for facilitation of open gastric bypass surgery. In this context, they observed that dexmedetomidine treatment during bariatric surgery decreased blood pressure, heart rate, and desflurane anesthetic requirement and attenuated pain level and morphine use in the PACU compared with fentanyl. The decrease in morphine use in dexmedetomidine-treated patients may be important for attenuating the risk of narcotic-induced postoperative respiratory depression and hypoxemia in patients after this type of surgery. In one case report, Hofer et al. [56] describe the anesthetic management of a patient with extreme obesity undergoing bariatric surgery whose intraoperative narcotic management was entirely substituted with dexmedetomidine, because of the concern that the use of narcotics might cause postoperative respiratory depression. They substituted the intraoperative use of narcotics with dexmedetomidine; isoflurane was administered at an initial end-tidal concentration of 0.9% and then reduced to an averaged 0.6%. After completion of the operation and after tracheal extubation, the dexmedetomidine infusion was continued uninterrupted throughout the end of the first postoperative day. A significant reduction in the morphine dose requirements was observed on the first postoperative day when compared with the second postoperative day.

Dexmedetomidine has been also evaluated during laparoscopic bariatric surgery to assess the effect on both early and late recovery [57]. Dexmedetomidine infusion at 0.2, 0.4, and 0.8 µg/kg/h rates reduced the average end tidal desflurane concentration by 19, 20, and 22%, respectively. However, it failed to facilitate a significantly faster emergence from anesthesia. In addition it decreased fentanyl use, antiemetic therapy, and the length of stay in the PACU. However, it failed to facilitate late recovery (e.g., bowel function) or improve the patients’ overall quality of recovery. When used during bariatric surgery, the authors recommend a dexmedetomidine infusion rate of 0.2 µg/kg/h to minimize the risk of adverse cardiovascular side effects. From these studies it can be concluded that dexmedetomidine may be a useful adjuvant in this type of surgery for the minimal respiratory depression that it causes while offering adequate pain relief.

Lithotripsy

The new generation lithotriptors are less painful, thus the anesthetic techniques have shifted from general anesthesia to analgesia. At present propofol is the most frequently used sedative hypnotic agent for this purpose but it may have some respiratory depression effect, especially when used in conjunction with opioids. Dexmedetomidine in this context may be a safe and attractive option for its analgesic and sedative properties with little effect on ventilation. Kaygusuz et al. [58] have thus evaluated the utility of dexmedetomidine compared with propofol during extracorporeal shockwave lithotripsy (ESWL) procedure. Forty-six patients were randomly allocated into two groups to receive either dexmedetomidine or propofol for elective ESWL. Dexmedetomidine was started at 6 µg/kg/h infusion rate for 10 min, followed by a 0.2 µg/kg/h rate. Propofol was infused at 6 mg/kg/h for 10 min, followed by an infusion of 2.4 mg/kg/h. Fentanyl, 1 µg/kg, was given i.v. to all patients 10 min before ESWL. Pain intensity was evaluated with a visual analog scale at 5-min intervals during ESWL. Sedation scores and hemodynamic and respiratory variables were recorded regularly during ESWL (35 min) and up to 85 min after. The authors observed that analgesic and respiratory variables were better with dexmedetomidine than propofol. Therefore, they concluded that dexmedetomidine in combination with a small dose of fentanyl can be useful during ESWL and it may be a valuable alternative to propofol. In another study Alhashemi et al. [59] compared the analgesic effects of dexmedetomidine/morphine with those of tramadol/midazolam in patients undergoing extracorporeal shockwave lithotripsy (ESWL). Sixty patients were randomized to receive either dexmedetomidine 1 g/kg iv followed by 0.5 g/kg/h infusion together with morphine patient-controlled analgesia, or tramadol 1.5 mg/kg pre-mixed with midazolam 30 g/kg iv followed by tramadol patient-controlled analgesia. Pain was assessed at baseline and every 15 min thereafter. Patients’ and urologist’s satisfaction with analgesia and sedation were determined on a seven-point scale ranging from 1 (extremely dissatisfied) to 7 (extremely satisfied). Patient’s discharge time was also documented. Results showed that visual analogue scale scores over time were consistently lower in the group treated with dexmedetomidine compared with the group treated with tramadol. Patients’ satisfaction with analgesia and with sedation and urologist’s satisfaction were all higher amongst treated with dexmedetomidine. They concluded that dexmedetomidine in combination with morphine PCA provided better analgesia for ESWL and was associated with higher patients’ and urologist’s satisfaction when compared with tramadol/midazolam PCA combination.

Ambulatory Anesthesia

In ambulatory anesthesia the choice of a safe and effective anesthetic is of paramount importance due to the need to have quick recovery and minimal complication and to assure an excellent level of safety in patients that have to come back home. Dexmedetomidine appears to be a good option because of its analgesic and short-lived sedation properties that improves safety and efficacy by maintaining hemodynamic stability. Thaghinia et al. [60] conducted a retrospective study to evaluate the safety and efficacy of dexmedetomidine in rhytidectomy surgery. Records were reviewed for 155 consecutive face lifts performed under sedation by the same surgeon over 3.5 years. Intraoperative and postoperative parameters and outcomes were compared...
for 78 patients sedated with dexmedetomidine (dexmedetomidine group) and 77 sedated without dexmedetomidine (propofol, ketamine, fentanyl, and midazolam). Intraoperatively, the dexmedetomidine group had significantly lower mean systolic and diastolic blood pressures and heart rate. Fewer dexmedetomidine group patients had oxygen desaturation below 92% and fewer required antihypertensives, although more required vasopressors. The dexmedetomidine patients needed less midazolam and fentanyl. Postoperatively, the dexmedetomidine group again had lower mean systolic and diastolic blood pressures and heart rate. In addition, fewer patients in this group needed postoperative antiemetics. The results of this study suggest that when compared with conventional sedation, dexmedetomidine appears to improve anesthetic safety and efficacy for rhytidectomy patients. Ustün et al. [61] performed a study in dental surgery setting comparing the use of dexmedetomidine with the use of midazolam during intravenous conscious sedation in third molar surgery. Twenty healthy patients with symmetrically impacted mandibular third molars were included in this double-blind, crossover, randomized study. Either dexmedetomidine (group D) (4 mg/kg/h) or midazolam (group M) (0.4 mg/kg/h) was administered intravenously for 15 minutes before the first operation. At the second operation, the other agent was applied. The intraoperative sedation level, patient cooperation, and postoperative performance were scored and any pain reaction during the local anesthetic injection was recorded. Visual analog scales were additionally used for the subjective assessment of pain and patient satisfaction. Amnesia was evaluated by the patients’ ability to recall the objects shown during the operations and the local anesthetic injection. Patients’ preferences were recorded during the interview at the end of the second operations. The results showed that the mean heart rate and blood pressure measurements were significantly lower in group D. There was no significant difference in the respiratory findings. A significantly higher number of patients showed pain reactions in group M. Sedation level, postoperative performance, and VAS pain scores were not statistically significant, whereas the differences in cooperation score and VAS for patient satisfaction were significant. Adequate amnesia was obtained in group M, however, no amnesia was demonstrated in group D. Sixty-five percent of the patients indicated a preference for dexmedetomidine sedation. The authors concluded that dexmedetomidine may be a remarkable alternative to midazolam for intravenous sedation because it seems to be a reliable and safe method, with additional analgesic effect providing a satisfactory sedation level without any serious side effects during impacted third molar surgery.

CONCLUSIONS

In last years dexmedetomidine has been increasingly utilized especially in ICU settings for sedation of intubated patients. It offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability associated with the great advantage to avoid respiratory depression. In particular dexmedetomidine can provide dose dependent “cooperative sedation” that allows ready interaction with the patient. All these aspects of its pharmacological profile render it suitable not only for sedation in the ICU but also for anesthetic management. Data regarding the perioperative utilization “off label” are promising but are limited in number. Further studies are required to establish a definitive role of this drug in the anesthetic field.

REFERENCES

Dexmedetomidine Use in General Anaesthesia

