PERIOPERATIVE USES OF DEXMEDETOMIDINE

Vanda G. Yazbek-Karam[*]
and Marie M. Aouad[**]

Dexmedetomidine is a new alpha2-agonist that received FDA approval in 1999 for use as a short-term (less than 24 h) sedative-analgesic in the intensive care unit. The use of alpha2-agonists as anesthetics is not new since many alpha2-agonists are used in veterinary medecine to induce anesthesia[1]. Clonidine, the prototype of alpha2-agonists, has been synthesized in early 1970's for its use as nasal decongestant and antihypertensive drug. Clonidine is widely used as an adjunct to anesthesia and pain medicine[2]; however, it has been little used as sedative[3].

With dexmedetomidine, there are a number of reasons for the growing and renewed interest in the use of alpha2-adrenoceptors agonists as sedatives: Dexmedetomidine compared to Clonidine is a much more selective alpha2-adrenoceptor agonist, which might permit its application in relatively high doses for sedation and analgesia without the unwanted vascular effects from activation of alpha1-receptors. In addition, Dexmedetomidine is shorter-acting drug than clonidine and has a reversal drug for its sedative effect, Atipamezole. These properties render Dexmedetomidine suitable for sedation and analgesia during the whole perioperative period: as premedication, as an anesthetic adjunct for general and regional anesthesia, and as postoperative sedative and analgesic[4].

* Department of Anesthesiology, Clinique Dr. Rizk, Beirut-Lebanon.
** Department of Anesthesiology, American University of Beirut-Lebanon.

Physiology of alpha2-adrenoceptors

Alpha2-receptors are found in many sites throughout the body. Alpha2-adrenoceptors are found in peripheral and central nervous systems, in effector organs such as the liver, kidney, pancreas, eye vascular smooth muscles and platelets[5]. Physiologic responses mediated by alpha2-adrenoceptors vary with location and can account for the diversity of their effects.

The classification of alpha2-receptors based on anatomical location is complicated since these receptors are found in presynaptic, postsynaptic and extrasynaptic locations[6]. Alpha2-adrenoceptors are divided into three subthypes; each subtype is responsible uniquely for some of the actions of alpha2-receptors. The subtype A, the predominant subtype in CNS, is responsible for the sedative, analgesic and sympatholytic effect; the subtype B, found mainly in the peripheral vasculature, is responsible for the short-term hypertensive response, and the subtype C, found in the CNS, is responsible for the anxiolytic effect[7].

There is no alpha2-subtype agonist and therefore the goal of producing a desirable alpha2-agonist effect such as sedation without the unwanted effect such as hypotension is elusive. All the subthypes produce cellular action by signaling through a G-protein which couples to effector mechanisms. This coupling appears to differ depending on the receptor subtype and location. The alpha2 A-adrenoceptor subtype seems to couple in an inhibitory fashion to the calcium channel in the Locus Ceruleus of the brainstem, whereas, in the vasculature, the alpha2 B-adrenoceptor subtype couple in an excitatory manner to the same effector mechanism[8].

Mechanism of action of Dexmedetomidine

The mechanism of action of dexmedetomidine is unique and differs from the currently used sedative drugs. Alpha2-adrenoceptors are found in many sites through the CNS, however, the highest densities of alpha2-receptors are found in the Locus Ceruleus, the predominant noradrenergic nuclei of the brainstem and an important modulator of vigilance. Presynaptic activation of the alpha2-A adrenoceptor in the Locus

Ceruleus inhibits the release of norepinephrine (NE) and results in the sedative and hypnotic effects[9]. In addition, the Locus Ceruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of the alpha2-adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha2-adrenoceptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradychardia. Also, activation of the alpha2-adrenoceptors in the CNS results in an augmentation of cardiac-vagal activity. Combined, these effects can produce analgesia, sedation and anxiolysis.

At the spinal cord, stimulation of alpha2-receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of the release of substance P[10]. Also, the alpha2-adrenoceptors located at the nerve endings have a possible role in the analgesic mechanisms of alpha2-agonists by preventing NE release. The spinal mechanism is the principal mechanism for the analgesic action of Dexmedetomidine even though there is a clear evidence for both a supraspinal and peripheral sites of action[11].

Alpha2-recepots are located on blood vessels where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit NE release. The responses of activation of alpha2-adrenoceptors in other areas include contraction of vascular and other smooth muscles; decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract, inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased insulin release from the pancreas, decreased intraocular pressure, decreased platelet aggregation and decreased shivering threshold by $2°C$[4].

Pharmacodynamics of Dexmedetomidine

Alpha-adrenoceptors agonists have different alpha2/alpha1 selectivity. Clonidine, the first developed and the most known alpha2-

agonist is considered as a partial alpha2-agonist since its alpha2/alpha1 selectivity = 200, while the alpha2/alpha1 selectivity of dexmedetomidine is 1620 and hence is 8 times more powerful alpha2-adrenoceptor than clonidine and is considered as a full alpha2 adrenoceptor agonist[5]. The alpha2-adrenoceptor selectivity of dexmedetomidine is dose-dependent; at low to medium doses or at slow rates of infusion, high levels of alpha2-adrenoceptor selectivity are observed, while high doses or rapid infusions of low doses are associated with both alpha1 and alpha2 activities[12].

Dexmedetomidine-induced sedation qualitatively resembles normal sleep. The participation of nonrapid eye movement sleep pathways seems to explain why patients who appear to be "deeply asleep" from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep[9]. This type of sedation is branded "cooperative" or "arousable", to distinguish it from the sedation induced by drugs acting on the GABA system, such as midazolam or propofol, which produce a clouding of consciousness[13]. Sedation induced by dexmedetomidine is dose-dependent; however, even low doses might be sufficient to produce sedation. Hall[11] evaluated sedation, analgesia and cognition after infusion of small and moderate doses of dexmedetomidine (0.2 and 0.6 μg/kg/h) in seven healthy volunteers. He found that both doses produced significant sedation, analgesia and reduced performance on psychomotor tests. However, dexmedetomidine may lack amnestic properties: more patients who received dexmedetomidine for postoperative sedation were able to recall their ICU stay when compared to those receiving propofol for sedation[15].

Studies conducted on human volunteers to explore the analgesic properties of intravenous dexmedetomidine showed conflicting results. Ebert[16] found that increasing concentrations of dexmedetomidine resulted in a dose-dependent sedation and analgesia based on VAS pain score in response to the cold pressor test. Jaakola[17] found that a single IV dose used for human tourniquet pain resulted in analgesia with a ceiling effect at the dose of 0.5 μg/kg. Another study comparing the analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and alfentanil concluded that systemic dexmedetomidine lacks analgesic

efficacy for heat and electrical pain at doses causing mild to severe sedation[18]. However, clinical studies showed that systemic administration of the alpha2-adrenoceptor agonists dexmedetomidine and clonidine produce sedative and opioid-sparing effects in the perioperative setting, providing indirect evidence for some analgesic efficacy[19,20,21], although it is difficult in this special setting to distinguish between sedation and analgesia as a cause for this opioid-sparing effect. While the analgesic effect of systemic dexmedetomidine is still debatable, administration of an alpha2-agonist (clonidine) via the intrathecal or epidural route provides analgesic effects in postoperative pain and in neuropathic pain state without severe sedation[3]. This effect is due to sparing of the supraspinal CNS sites from excessive drug exposure resulting in robust analgesia without heavy sedation.

Alpha2-adrenoceptors do not have an active role in the respiratory center, therefore, dexmedetomidine throughout a broad range of plasma concentration, has minimal effects on the respiratory system[14]. However, doses of 2 µg/kg given as a bolus resulted in short episodes of apnea. Also, coadministration of dexmedetomidine with other sedatives, hypnotics or opioids is likely to cause additive effects[22].

Dexmedetomidine does not appear to have direct effects on the heart. In the coronary circulation, dexmedetomidine causes a dose-dependent increase in coronary vascular resistance and oxygen extraction, but the supply/demand ratio is unaltered[23]. A biphasic cardiovascular response has been described after the administration of dexmedetomidine. A bolus of 1 µg/kg results in a transient increase in blood pressure (BP) and a reflex decrease in heart rate (HR), especially in the young healthy patients. This initial response is attributed to the direct effects of alpha2 B-adrenoceptor stimulation of vascular smooth muscle. This response can be attenuated by a slow infusion over 10 min, but even at slower infusion rates, the transient increase in mean BP and the decrease in HR over the first 10 min is shown. This initial response lasts for 5 to 10 min and is followed by a decrease in BP of 10-20% below baseline and by stabilization of the HR below baseline values. Both these effects are presumably caused by an inhibition of

central sympathetic outflow that overrides the direct effects of dexmedetomidine on the vasculature. Hypotension and bradycardia induced by dexmedetomidine are reversed by ephedrine and atropine respectively, but large doses are required[24].

Ebert[16] studied the autonomic, cardiovascular, and sedative responses to increasing plasma concentrations of dexmedetomidine; he found that low plasma concentrations resulted in sedation, mild analgesia with preservation of recall and recognition. In addition, it resulted in a decrease in HR and BP, without changes in central venous pressure or pulmonary artery pressure and without respiratory changes. Subsequent higher doses resulted in increased sedation, analgesia and memory impairment, as well as an increase in BP, systemic and pulmonary vascular resistance. A significant decrease in HR and progressive decreases in cardiac output, and stroke volume is also noted. Even at higher doses, there was no respiratory compromise.

Pharmacokinetics of Dexmedetomidine

Dexmedetomidine, an imidazole compound, is the active d-isomer of medetomidine. Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{\frac{1}{2}\alpha}$) of 6 min, a terminal elimination half-life ($t_{\frac{1}{2}\beta}$) of 2 hours, and a steady-state volume of distribution (Vss) of 118 liters. Dexmedetomidine exhibits linear kinetics when infused in the dose range of 0.2-0.7 μg/kg/h for no more than 24 hours. Dexmedetomidine undergoes almost complete biotransformation through direct glucuronidation and cytochrome P450 metabolism. Metabolites of biotransformation are excreted in the urine (95%) and feces. It is unknown if they posses intrinsic activity.

The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl, digoxin, theophilline, lidocaine and ketorolac. There have been no sex or age-based differences in the pharmacokinetics of dexmedetomidine; however, it has not been studied in pediatric patients. The dose of dexmedetomidine should be decreased in

patients with hepatic or renal impairment. Dexmedetomidine do cross the placenta and should be only used during pregnancy if the potential benefits justify the potential risk to fetus.

Dexmedetomidine is a white powder that is freely soluble in water and has a pka of 7.1. It is supplied as 100 μg/ml 2 ml vial which must be diluted with 48 ml of 0.9% sodium chloride prior to administration. For adult patient, dexmedetomidine is administered by a loading infusion of 0.5-1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 μg/kg/h. The effect appears in 5-10 min, and is reduced in 30-60 min. The maintenance infusion is adjusted to achieve the desired level of sedation[25].

The most frequently observed adverse events in patients receiving dexmedetomidine for ICU sedation include hypotension, hypertension, nausea, bradycardia, atrial fibrillation and hypoxia[15]. Most of these events occur after or during the loading dose, therefore, reducing or omitting the loading dose could result in decreasing the incidence and severity of these adverse events[13].

Appropriate patient selection for dexmedetomidine administration is crucial; because it decreases sympathetic nervous activity, its effects may be most pronounced in patients with decreased autonomic nervous system control such as the elderly, diabetic patients, patients with chronic hypertension or severe cardiac disease such as valve stenosis or regurgitation, advanced heart block, sever coronary artery disease, or in patients who are already hypotensive and/or hypovolemic[4].

The tolerability of dexmedetomidine was noted in three cases of overdosage[26]; In 2 cases, the dose administered was 0.5 mg/kg/h instead of 0.5 μg/kg/h, and in one case, the dose 4 μg/kg/h instead of 0.4 μg/kg/h. In the three cases, the overdosage resulted in oversedation only. However, first and second-degree heart block or even cardiac arrest following administration of dexmedetomidine were reported[27].

Dexmedetomidine do not affect the synthesis, storage or metabolism of neurotransmitters and do not block the receptors, thus providing the possibility of reversing the hemodynamic effects with vasoactive drugs or the specific alpha2-antagonist: Atipamezol (Antisedan)[28]. Atipamezol acts

by increasing the central turnover of norepinephrine. Its duration of action is 2 hours[29].

Perioperative uses of dexmedetomidine

I – Premedication

Dexmedetomidine possesses anxiolytic, sedative, analgesic, antisialogogue and sympatholytic properties, which render it suitable as a premedication agent. Dexmedetomidine potentiates the anesthetic effects of all intraoperative anesthetics[30,31,32] (intravenous, volatile or regional block). Bohrer[33] showed that preoperative administration of intravenous or intramuscular dexmedetomidine resulted in a decrease in induction dose of thiopentone by up to 30%. The administration of intramuscular dexmedetomidine at a dose of 1 μg/kg for premedication in outpatient cataract surgery resulted in sedation, and decrease in intraocular pressure without significant hypotension or bradycardia[34,35]. Also, the administration of dexmedetomidine for premedication decreases oxygen consumption intraoperatively by 8% and postoperatively by 17%[36]. Indications to the use of dexmedetomidine as premedication include patients susceptible to preoperative and perioperative stress, drug addicts and alcoholics, chronic opioid users and hyertensive patients.

II – Intraoperative uses of dexmedetomidine

Intraoperative uses of dexmedetomidine include its use as adjunct to general anesthesia, as adjunct to regional anesthesia, in monitored anesthesia care (MAC), or as a sole agent for total intravenous anesthesia (TIVA).

1 – Use of dexmedetomidine as adjunct to general anesthesia

The use intraoperative dexmedetomidine may increase hemodynamic stability because of attenuation of the stress-induced sympathoadrenal responses to intubation, during surgery and during emergence from anesthesia[37]. Talke[38] evaluated the effects of varying plasma concentrations

of dexmedetomidine on HR, BP and catecholamines concentrations during emergence from anesthesia in the setting of vascular surgery. This study demonstrated that dexmedetomidine attenuates the increases in heart rate and plasma norepinephrine levels observed during the emergence from anesthesia.

Administration of intravenous dexmedetomidine produces an anesthetic-sparing effect[39]. Aho[40] showed 25% reduction of maintenance concentrations of isoflurane in patients undergoing hysterectomy. Khan found 35%-50% reduction in isoflurane concentrations with either low or high doses of dexmedetomidine. Fragen[41] noted 17% reduction in sevoflurane requirements for maintenance of anesthesia in elderly patients. In addition, the use of dexmedetomidine produces intraoperative and postoperative opioid-sparing effect. Aho[20] administered dexmedetomidine at dose of 0.4 μg/kg in patients undergoing laparoscopic tubal ligation and found a 33% decrease in morphine use postoperatively.

Talke[42] investigated the muscle relaxant effects of dexmedetomidine on the neuromuscular junction and found no clinically relevant effects. Dexmedetomidine reduces the vasoconstriction threshold and the shivering threshold and is associated with a lower incidence of shivering[4].

2 – Use of dexmedetomidine for regional anesthesia

The use of dexmedetomidine as adjuvant in regional anesthesia is still not validated. Maarouf[43] explored the effect of epidural dexmedetomidine on the incidence of postoperative shivering in 60 patients undergoing orthopedic surgery. He found that patients who received dexmedetomidine at a dose of 100 μg added to 20 ml 0.5% bupivacaine showed lower incidence in postoperative shivering when compared to patients who received epidural bupivacaine alone (10% vs. 36%). Memis[44] noted that the addition of 0.5 μg/kg dexmedetomidine to lidocaine for intravenous regional anesthesia improves the quality of anesthesia and perioperative analgesia without causing side effects. Kanazi et al[45] investigated the effect of adding a small dose of 3 μg of

intrathecal dexmedetomidine to 12 mg bupivacaine. They found a significant prolongation of sensory and motor block as compared to bupivacaine alone. In this study, the effect of 3 μg intrathecal dexmedetomidine was similar to that produced by the addition of 30 μg of intrathecal clonidine.

3 – Use of dexmedetomidine in monitored anesthesia care

Dexmedetomidine confers arousable sedation with ease of orientation, anxiolysis, mild analgesia, lack of respiratory depression and hemodynamic stability at moderate doses. These properties allow dexmedetomidine to be an almost ideal agent for MAC despite its lack of amnesia and poor controllability because of its slow onset and offset. The efficacy, side effects, and recovery characteristics of dexmedetomidine were compared to propofol when used for MAC[19]. This study showed that dexmedetomidine achieved similar levels of sedation to propofol, albeit with a slower onset and offset of sedation. Neither dexmedetomidine nor propofol influenced respiratory rate, but propofol resulted in lower mean arterial pressure during the intraoperative period. In the recovery room, dexmedetomidine was associated with an analgesia-sparing effect, slightly increased sedation, but no compromise of respiratory function or psychomotor responses. Dexmedetomidine in MAC was used successfully in many situations: when patient arousability needed to be preserved, as for awake craniotomy[46-47], for awake carotid endarterectomy[48] and for vitreoretinal surgey[49]. In addition, dexmedetomidine was used for sedation in difficult airway patients; during fiberoptic intubation[50-51], and for sedation of a patient with difficult airway undergoing lumbar laminectomy surgery in the prone-chest position under spinal anesthesia[52].

4 – Use of dexmedetomidine as a sole anesthetic agent

Ramsay[53] has used dexmedetomidine as a sole anesthetic agent. The report describes three patients who presented for surgery with potential

airway management challenges. Dexmedetomidine was infused in increasing doses (up to 10 μg/kg/h) until general anesthesia was attained. No respiratory depression was noted, only one patient required chin lift. Also no hypotension or severe bradycardia were noted. The rationale for this new, off-label use of dexmedetomidine is based on its known properties to provide sedation, analgesia while avoiding respiratory depression at low doses. These effects were maintained at higher doses without hemodynamic instability.

III – Use of dexmedetomidine in the postoperative period

Dexmedetomidine special properties favor its use in recovery room. In addition to its sympatholytic effects, analgesic effects and decreased rate of shivering, the preservation of respiratory function allows the continuation of the dexmedetomidine infusion in the extubated, spontaneously breathing patient. The possibility of ongoing sedation and sympathetic block could be beneficial in reducing high rates of early postoperative ischemic events in high-risk patients undergoing non-cardiac surgery[54]. In a study conducted by Talke[38], high-risk patients who received dexmedetomidine from 1 h before until 48 h after vascular surgery experienced significantly fewer ischemic episodes than did patients in the placebo grou (8% vs 29%). During emergence from anesthesia, NE levels in the placebo group were 2 to 3 times higher than those in the dexmedetomidine group. However, patients who received intraoperative dexmedetomidine needed more fluids to avoid hypotension, a side effect that may be unfavorable in volume-sensitive patients with reduced left ventricular function. In addition, care should be taken in patients who depend on a high level of sympathetic tone or in patients with reduced myocardial function who cannot tolerate the decrease in sympathetic tone[4]. Perioperative administration of dexmedetomidine could be beneficial in chronic opioid users and alcoholics, in high-risk patients as well as in cardiac patients with good to moderately decreased left ventricular function.

IV – Use of Dexmedetomidine in the pediatric-age group

Only few cases about the use of dexmedetomidine in the pediatric-age group are found in the literature[55,56]. Tobias used dexmedetomidine for ICU sedation in a 10-week old infant requiring mechanical ventilation and in a 14-y old patient after posterior spinal fusion for scoliosis. The use of dexmedetomidine at a dose of 0.25 μg/kg/h for 24 h in these two cases resulted in acceptable sedation without significant hemodynamic changes. Dexmedetomidine was also used for sedation and anesthesia in an 11-y old patient undergoing gastroscopy; however, it resulted in insufficient sedation. Another study conducted in pediatric-age group explored the use of intraoperative dexmedetomidine at different doses with the goal of reducing the post sevoflurane agitation in children aged 1-10 y. The optimal dose of dexmedetomidine was 0.3 μg/kg and its use did not result in adverse effects[57].

Conclusions

In summary, dexmedetomidine is a short-acting alpha2-adrenoceptor agonist with many desirable clinical benefits that encourage its use in the perioperative period.

Dexmedetomidine provides a sedated patient in the preoperative period. Intraoperatively, in addition to its anesthesia-sparing effects, it provides a stable hemodynamic profile by attenuating the stress response during tracheal intubation, during surgery and emergence from anesthesia. Dexmedetomidine offers the possibility of continuing sedation throughout the extubation process and in the recovery room without significant respiratory impairment, and with lower analgesic requirements. In addition, it may offer protection from ischemia due to attenuated neuroendocrine response in the perioperative period. Dexmedetomidine offers a special type of sedation in which patients are readily arousable with preservation of respiratory function; therefore, it could be useful for surgery perfomed under MAC, especially in patients with compromised airway, and whenever patients' arousability is needed to be present as during awake craniotomy,

carotid endarterectomy and vitreoretinal surgery.

Because of its sympatholytic and vagomimetic actions, dexmedetomidine is approved with a warning about hypotension, bradycardia, and sinus arrest, and therefore, appropriate patient selection is crucial. In addition, we should be mindful that many of the perioperative applications of dexmedetomidine remain "off-label"[58].

Fundamentally, whether of not dexmedetomidine turns out to be just another sedative agent depends on how we benefit from the new opportunities it provide.

References

1. CLARKE KW, HALL LW: "Xylazin"-a new sedative for horses and cattle. *Vet Rec*; 85:512-517, 1969.

2. KAMIBAYASHI T, MAZE M: Clinical uses of alpha2-adrenergic agonists. *Anesthesiology;* 93:1345-9, 2000.

3. TAMSEN A, GORDH T: Epidural clonidine produces analgesia. *Lancet;* 2:231-232, 1984.

4. GERTLE R, BROWN C, MITCHELL D ET AL: Dexmedetomidine: a novel secative-analgesic agent. *BUMC Proceeding;* 14:13-21, 2001.

5. MAZE M, TRANQUILI W: Alpha2-adrenoceptor agonists: Defining the role in clinical anaesthesia. *Anesthesiology;* 74:581-605, 1991.

6. DREW GM, WHITING SB: Evidence for two distinct types of postsynaptic alpha-adrenoceptor in vascular smooth muscle in vivo. *Br J Pharmacol;* 67:207-215, 1919.

7. HUNTER, JC, FONTANA DJ, HEDLEY LR ET AL: Assessment of the role of alpha2-adrenoceptor subtypes in the anticociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. *Br J Pharmacol;* 122:1339-1344, 1997.

8. BIRNBAUMER L, ABRAMOWITZ J, BROWN AM: Receptor-effector coupling by G proteins. *Biochim Biophys Acta;* 1031:163-224, 1990.

9. JONES MEP, MAZE M: Can we characterize the central nervous system actions of alpha2-adrenergic agonists? *British Journal of Anaesthesia;* 86(1):1-3, 2001.

10. KURAISHI Y, HIROTA N, SATO Y ET AL: Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. *Brain Res;* 359:177-182, 1985.

11. JAAKOLA ML, SALONEN M, LEHTINENR, SCHEININ H: The analgesic action of dexmedetomidine-a novel alpha2-adrenoceptor agonist-in healthy volunteers. *Pain;* 46:281-285, 1991.

12. VIRTANEN R, SAVOLA JM, SAANO V, NYMAN L: Characterization of the selectivity, specificity and potency of medetomidine as an alpha2-adrenoceptor agonist. *Eur J Pharmacol;* 150:19-14, 1998.

13. AHO M, ERKOLA O, KALLIO A, SCHEININ H, KORTTILA K: Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. *J Clin Anesth;* 5:194-203, 1993.

14. HALL JE, UHRICH TD, BARNEY JA, ARIAN SR, EBERT TJ: Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg;* 90:699-705, 2000.

15. VENN RM, GROUND RM: Comparison between dexmedetomidine and propofol for sedation in the intensive care unit. Patient and clinician perceptions. *Br J Anaesth;* 87:684-90, 2001.

16. EBERT TJ, HALL JE, BARNEY JA, UHRICH TD, COLINCO MD: The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology;* 93:382-394, 2000.

17. JAAKOLA ML: Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. *J Clin Anesth;* 6(3):204-11, May-Jun, 1994.

18. ANGST M, RAMASWAMY B, DAVIES F, MAZE M: Comparative analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and fentanyl in humans. *Anesthesiology;* 101:744-52, 2004.

19. ARAIN SR, EBERT TJ: The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg;* 95(2):461-6, Agu 2002.

20. AHO MS, ERKOLA OA, SCHEININ H, LEHTINEN AM, KORTTILA KT: Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg;* 73:112-118, 1991.

21. ARAIN SR, RUEHLOW RM, UHRICH TD, EBERT TJ: The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg;* 98(1):153-8, Jan 2004.

22. BELLEVILE JP, WARD DS, BLOOR BC, MAZE M: Effects of intravenous dexmedetomidine in humans. I. Sedation, Ventilation, and metabolic rate. *Anesthesioloty;* 77:1134-1142, 1992.

23. BLOOR BC, WARD DS, BELLEVILLE JP, MAZE M: Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology;* 77:1134-1142, 1992.

24. HOGUE CW JR, TALKE P, STEIN PK, RICHARDSON C, DOMITROVICH PP, SESSLER DI: Autonomic nervous system responses during sedative infusions of dexmedetomidine. *Anesthesiology;* 97(3):592-8, 2002.

25. Abbott Labaratories. Precedex. Dexmedetomidine hydrochloride injection prescribing information. Abbott Labaratories, USA, 2000.

26. JORDEN VS, POUSMAN RM, SANFORD MM, THORBORG PA, HUTCHENS MP: Dexmedetomidine overdose in the perioperative setting. *Ann Pharmacother;* 38(5):803-7, May 2004.

27. INGERSOLL-WENG E, MANECKE G, THISTLETHWAITE P: Dexmedetomidine and cardiac arrest. *Anesthesiology;* 100:738-9, 2004.

28. TALKE P: Receptor-specific reversible sedation: beginning of new era of anesthesia? *Anesthesiology;* 89:560-561, 1998.

29. SCHEININ H, AANTAA R, ANTTILA M, HAKOLA P, HELMINEN A, KARHUVAARA S: Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha2-adrenoceptor antagonist atipamezole: a pharmacodynamic and kinetic study in healthy volunteers. *Anesthesiology;* 89:574-584, 1998.

30. LAWRENCE CJ, DELANGE S: Effect of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. *Anaesthesia;* 52:736-44, 1997.

31. AANTAA R, KANTO J, SCHEININ M: Intramuscular dexmedetomidine, a novel alpha2-adrenoceptor agonist, as premedication for minor gynaecological surgery. *Acta Anaesthesiol Scand;* 35:283-288, 1991.

32. AANTAA RE, KANTO JH, SCHEININ M, KALLIO AM, SCHEININ HL: Dexmedetomidine premedication for minor gynecologic surgery. *Anesth Analg;* 70:407-413, 1990.

33. BOHRER M, MAPPES A, LAUBER R, STANSKI DR, MAITRE PO: Dexmedetomidine decreases thiopental dose requirement and alters distribution pharmacokinetics. *Anesthesiology;* 80:1216-1227, 1994.

34. VIRKILLA M, ALI-MELKKILA T, KANTO J, TURUNEN J, SCHEININ H: Dexmedetomidine as intramuscular premedication in outpatient cataract surgery. A placebo-controlled dose-ranging study. *Anaesthesia;* (6):482-7, Jun 1993.

35. VIRKILLA M, ALI-MELKKILA T, KANTO J, TURUNEN J, SCHEININ H: Dexmedetomidine as intramuscular premedication for day-case cataract surgery. A comparative study of dexmedetomidine, midazolam and placebo. *Anaesthesia;* 49(10):853-8, Oct 1994.

36. TAITTONEN MT, KIRVELA OA, AANTAA R, KANTO JH: Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth;* 78:400-406, 1997.

37. SCHEININ B, LINDGREN L, RANDELL T, SCHEININ H, SCHEININ M: Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and perioperative fentanyl. *Br J Anaesth;* 68:126-131, 1992.

38. TALKE P, CHEN R, THOMAS B ET AL: The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg;* 90:834-9, 2000.

39. AANTAA R, KANTO J, SCHEININ M, KALLIO A, SCHEININ H: Dexmedetomidine, an alpha2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology;* 73:230-235, 1990.

40. AHO M, LEHTINEN AM, ERKOLA O, ET AL: The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology;* 74:997-1002, 1991.

41. FRAGEN RJ, FITZGERALD PC: Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. *J Clin Anesth;* 11:466-470, 1999.

42. TALKE PO, CALDWELL JE, RICHARDSON CA, KIRKEGAARD-NIELSEN H, STAFFORD M: The effects of dexmedetomidine on neuromuscular blockade in human volunteers. *Anesth Analg;* 88:633-639, 1999.

43. MAROOF M: Evaluation of effect of dexmedetomidine in reducing shivering following epidural anesthesia. *ASA annual meeting.* Abstract A-49.

44. MEMIS D, TURAN A, KARAMANLIOGLU B, PAMUKCU Z, KURT I: Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. *Aneth Analg;* 98(3):835-40, 2004.

45. KANAZI GE, AOUAD MT, JABBOUR-KHOURY SI, AJ JAZZAR MD, ALAMEDDINE MM, AL-YAMAN R, BULBUL M, BARAKA AS: Effect of Small Dose Dexmedetomidine or Clonidine on the Characteristics of Bupivacaine-Spinal Block. *Acta Anaesthesiol Scand 2005;* 50:222-7, 2006.

46. MACK PF, PERRINE K, KOBYLARZ E, SCHWARTZ TH, LIEN CA: Dexmedetomidine and neurocognitive testing in awake craniotomy. *J Neurosurg Anesthesiol;* 16(1):20-5, Jan 2004.

47. BEKKER AY, KAUMAN B, SAMIR H, DOYLE W: The use of dexmedetomidine infusion for awake craniotomy. *Anesth Analg;* 92(5):1251-3, May 2001.

48. BEKKER A, BASILE J, GOLD M ET AL: Dexmedetomidine for Awake Carotid Endarterectomy: Efficacy, Hemodynamic Profile, and Side Effects. *Journal of Neurosurgical Ansthesiology;* 16(2):126-135, 2004.

49. YAZBEK-KARAM V, AOUAD MT: Dexmedetomidine vs propofol for vitreoretinal surgery under local anesthesia. *World Congress Ophthalmic Anaesthesia;* April 2003, Abstract.

50. GRANT SA, BRESLIN DS, MACLEOD DB, GLEASON D, MARTIN G: Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. *J Clin Anesth;* 16(2):124-6, 2004.

51. SCHER CS, GITLIN MC: Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fibreoptic intubation. *Can J Anaesth*; 50(6):607-10, Jun-Jul 2004.

52. GUNAYDIN B ET AL: Intravenous dexmedetomidine sedation for spinal anesthesia in the prone-chest position for lumbar laminectomy surgery. *Turk J Med Sci;* 34:353-355, 2004.

53. RAMSAY M, KUTERMAN D: Dexmedetomidine as a total intravenous anesthetic agent. *Anesthesiology;* 101:787-90, 2004.

54. TALKE P, LI J, JAIN U, LEUNG J, DRASNER K, HOLLENBERG M, MANGANO DT: Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology;* 82:620-633, 1995.

55. TOBIAS JD, BERKENBOSCH JW: Initial experience with dexmedetomidine in paediatric-aged patients. *Peadiatr Anaesth;* 12(2):171-5, 2002.

56. NICHOLS D, BERKENOSCH J, TOBIA J: Rescue sedation with dexmedetomidine for diagnostic imaging: a preliminary report. *Pediatric Anesthesia;* 15(3):199, 2005.

57. IBACACHE M, MUÑOZ H, BRANDES V ET AL: Single-Dose Dexmedetomidine Reduces Agitation After Sevoflurane Anesthesia. *Anesth Analg;* 98:60-63, 2004.

58. EBERT T, MAZE M: Dexmedetomidine: Another arrow for the clinician's quiver. *Anesthesiology;* 101:568-70, 2004.