Review Article

A Review of the Clinical Uses of Dexmedetomidine

Pierre S. Chue[1]* and James A. Chue[2]

[1]*Clinical Trials and Research Program, University of Alberta, Canada*
[2]*Department of Anesthesiology, State University of New York at Buffalo, USA*

Abstract

Dexmedetomidine is highly selective α$_{2A}$- adrenergic receptor agonist approved for short-term sedation in an intensive care unit (ICU) setting or in non-intubated patients prior to and/or during surgical and other procedures. Dexmedetomidine is the dextro isomer of medetomidine with eight times greater selectivity for α$_2$- adrenergic receptors than clonidine. This action in the central and peripheral nervous systems results in sedation and analgesia (sedoanalgesia). Dexmedetomidine is devoid of opioid and gabaergic activity and is not associated with respiratory depression resulting in cooperative and conscious (semi-arousable) sedation. The inhibition of sympathetic stress response mediated via α$_2$- adrenergic receptor reduces heart rate and blood pressure, which promotes cardiovascular stability and protection. When given by continuous intravenous infusion it has a rapid onset and a relatively short duration of action (offset is secondary to infusion duration). Dexmedetomidine has been associated with decreased ICU costs in adult patients due to reduced time on mechanical ventilation and length of stay. The lack of respiratory depression allows for rapid extubation despite sedative therapeutic plasma concentrations. Dexmedetomidine possesses some analgesic activity; other applications include as a premedication, in the prevention of emergence delirium or agitation, and for the control of shivering. Use of dexmedetomidine is associated with reduced requirements for analgesics, sedatives and general anesthetics. There are no significant drug-drug interactions due to protein binding or metabolism. Biotransformation is almost complete to inactive metabolites. Dexmedetomidine has been reported to cause higher rates of bradycardia and hypotension, but a lower incidence of neurocognitive dysfunction including delirium. Inhibition of inflammation and activation of protective signaling pathways suggest a possible neuro protective effect. Dexmedetomidine has a very low incidence of withdrawal effects, even after prolonged use. Intranasal, buccal and oral formulations have been developed. Dexmedetomidine is not known as a substance of abuse and it is not a controlled substance.

ABBREVIATIONS

ICU: Intensive Care Unit; MAC: Monitored Anesthesia Care; AFI: Awake Fiberoptic Intubation; RCT: Randomized Clinical Trial; MISS: Minimally Invasive Spine Surgery; C_{max}: Max Concentration; C_{ss}: Steady State Concentration; V_{ss}: Apparent Steady State Volume of Distribution

INTRODUCTION

The class of α$_2$- adrenergic receptor agonists includes clonidine, guanfacine, guanabenz, tizanidine, methyldopa, methylnorepinephrine (levonordefrin), medetomidine, and dexmedetomidine. The action of α$_2$- adrenergic receptor agonists in the central and peripheral nervous systems resulting in sedation and analgesia (sedoanalgesia) has led to the use of a number of these agents as sedatives in a wide variety of clinical settings including critical care and anesthesia as well as in dental and pediatric practice [1-4].

Dexmedetomidine is the dextro isomer of medetomidine and possesses at least an eight fold greater selectivity for α$_2$- adrenergic receptors than clonidine [5]. First approved in the USA in 1999; it is currently utilized for short-term sedation in an intensive care unit (ICU) setting or in non-intubated patients prior to and/or during surgical and other procedures [6]. It also possesses analgesic properties, but because it is devoid of opioid and gabaergic activity, it is not associated with respiratory depression allowing for cooperative and conscious (semi-arousable) sedation [7].

Use of dexmedetomidine has been associated with decreased ICU costs in adult patients, compared with traditional sedatives, principally due to reduced time on mechanical ventilation and length of stay [8]. It has been reported to cause higher rates of bradycardia and hypotension, but a lower incidence of neurocognitive dysfunction including delirium [9]. Dexmedetomidine is not known as a substance of abuse and it is not a controlled substance.

INDICATIONS AND USAGE

Dexmedetomidine is indicated for sedation of initially

intubated and mechanically ventilated patients in an ICU setting [10,11]. Treatment is by continuous intravenous (iv) infusion using a controlled infusion device; and not to exceed 24 hours. Dexmedetomidine can be used in mechanically ventilated patients prior to extubation, during extubation, and post-extubation (discontinuation prior to extubation is not required).

Dexmedetomidine is also indicated for conscious sedation of non-intubated patient's prior to and/or during surgical procedures such as Monitored Anesthesia Care (MAC) with an adequate nerve block and/or local infiltration; and Awake Fiberoptic Intubation (AFI) after adequate topical preparation of the upper airway with local anesthesia [10,11].

DOSAGE AND ADMINISTRATION

Dexmedetomidine is available in both concentrate (100 µg/mL) and ready to use (4 µg/mL) solutions for iv use [10,11]. Dosing should be individualized and titrated according to desired clinical effect [14]. For sedation of adults in the ICU initial dosing is 1µg /kg over 10 minutes, followed by a maintenance infusion of 0.2 - 0.7 µg/kg/hr. For adult procedural sedation initial dosing is 1 µg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 µg/kg/hr (range 0.2 - 1 µg/kg/hr). Dose adjustments are recommended for patients >65 years and for patients with impaired hepatic function. Caution is advised in patients with severe renal impairment especially if comorbidities.

Dexmedetomidine is not approved for use >24 hours [10,11]. Use of dexmedetomidine >24 hours has been associated with tolerance and tachyphylaxis and a dose-dependent increase in adverse events. Prolonged use of dexmedetomidine, ≤7 days, may result in some withdrawal symptoms. However the incidence is low (3-5%) and the most common withdrawal events are nausea, vomiting and agitation occurring up to 48 hours after discontinuation. No withdrawal events are described after short-term use (<6 hours).

PHARMACOKINETICS

Dexmedetomidine demonstrates linear pharmacokinetics for the dose range of 0.2 - 0.7 µg /kg/hr for up to 24 hours when administered by iv infusion [1,12]. Dexmedetomidine possesses a distribution half-life of approximately 6 minutes and a terminal elimination half-life of approximately 2 hours (2-compartment model). This allows for rapid onset and a relatively short duration of action; however, the offset is secondary to infusion duration. Thus, the context-sensitive half time may range from 4 to 250 minutes after infusions of 10 minutes and 8 hours duration, respectively. The lack of respiratory depression allows for rapid extubation despite plasma concentrations that remain at a sedative therapeutic level [15].

Total body weight has a significant effect on C_{max} and C_{ss}; the apparent volume of distribution is related to body weight and shows significant variability in ICU patients [14]. Early pharmacokinetic studies demonstrated that the apparent steady state volume of distribution (V_{ss}) is prolonged in postoperative patients compared with volunteers [15]. Dexmedetomidine is highly lipophilic and highly protein bound (94%); binding is significantly reduced in hepatic impairment, but hepatic blood flow appears to play the greater role in hepatic clearance [14]. Clearance decreases with increasing age; high plasma concentrations cause decreased cardiac output and vasoconstriction resulting in lower clearance [13].

From *in vitro* studies there was negligible protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine; similarly there was negligible protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by dexmedetomidine. The use of dexmedetomidine typically reduces anesthetic requirements, but studies in patients receiving certain concomitant central nervous system medications such as antidepressants and anticonvulsants have shown some variability in sedative effect, the latter due to enzyme-induced clearance changes [14].

Biotransformation of dexmedetomidine is almost complete via direct N-glucuronidation, aliphatic hydroxylation (principally by CYP2A6), and N-methylation. The metabolites are considered inactive and there is no chiral conversion to the levo isomer [14].

Other formulations have been evaluated including intramuscular, intranasal, buccal and oral [14,15]. There is an extensive first pass effect with oral administration with a reported bioavailability of 16%. Absorption is greater through intranasal and buccal routes, with a reported bioavailability of 82% for the intranasal route. Onset of sedation with intranasal formulations is approximately 45 minutes with a peak effect at 90-150 minutes for doses of 1-1.0 µg /kg.

PHARMACODYNAMICS

Dexmedetomidine is a highly selective and potent α_2-adrenoceptor agonist (α_2: α_1 ratio =1620:1) [7,14]. It also binds to imidazoline receptors that are postulated to play a role in lowering blood pressure and pain modulation [5]. Sedation is mediated through activation of α_2- adrenergic receptors in the locus coeruleus and is concentration-dependent; plasma concentrations of 0.2 - 0.3 ng/mL result in sedation, 0.7-2.0 ng/mL result in analgesia and conscious sedation, and 2.71 – 3.85 ng/mL result in deep sedation in adults [7,13]. Continuous infusion of 0.2-1 µg/kg/hr after a loading dose of 0.5-1 µg/kg results in sedation in infants. Duration of sedation is greater in severe renal impairment than in healthy subjects for the same dose, even though the elimination half-life is shorter.

Dexmedetomidine exerts a biphasic effect on blood pressure; decreasing blood pressure by central sympatholytic effects at lower concentrations mediated via α_2 - adrenergic receptors on peripheral presynaptic nerves, and increasing blood pressure at higher concentrations by peripheral vasoconstriction mediated via α_{2B} - adrenergic receptors on vascular smooth muscle [7,13]. Thus, a loading dose infused slowly over 10 minutes avoids any potential initial hypertension associated with rapid infusion. Doses of 0.25–1 µg/kg in adults and 0.5–6 µg/kg/hr in children decrease blood pressure by 13-16% and 20%, respectively. Another mechanism that influences cardiovascular parameters is via stimulation of presynaptic α_2-adrenoceptors resulting in decreased norepinephrine release. [7]. In adults heart rate is decreased by 16–30% at plasma concentrations >1–3 ng/mL; cardiac output is decreased by about 35%, but stroke volume stays stable at plasma concentrations <5 ng/mL. Elderly patients

may be more sensitive and require dose reduction [4]. In children heart rate is decreased by 13–20% at doses of 1–6 µg/kg/h. Other cardiovascular effects include increased pulmonary and systemic vascular resistance and increased central venous, pulmonary artery, pulmonary and capillary wedge pressures. Dexmedetomidine also reduces cerebral blood flow by 30% at 0.2–0.6 µg/kg/h in a dose-dependent manner.

CLINICAL USES

Sedation

A systematic review of α_2 – adrenergic receptor agonists for sedation of mechanically ventilated adults in the ICU reported that length of stay and time to extubation were significantly shorter for dexmedetomidine, compared with propofol or benzodiazepines (midazolam or lorazepam) [16]. There were no differences in time to target sedation between sedative interventions, but dexmedetomidine was associated with a higher risk of bradycardia. In a RCT of mechanically ventilated ICU patients on a dexmedetomidine infusion spent more time at the target level of sedation, and spent more days alive without delirium or coma than with a lorazepam infusion [17]. Two RCTs comparing dexmedetomidine with midazolam or propofol found that patients' interactions were improved with dexmedetomidine and median duration of mechanical ventilation was shorter compared with midazolam, but not compared with propofol [18]. A Cochrane review of α_2 – adrenergic receptor agonists compared to traditional sedatives (benzodiazepines) for long-term sedation of mechanically ventilated adults in the ICU found that dexmedetomidine reduced the mean duration of mechanical ventilation and length of stay, but had no effect on mortality or delirium [19]. The lack of respiratory depression with dexmedetomidine is of particular benefit for procedural sedation involving interventions in the prone position such as Minimally Invasive Spine Surgery (MISS), while the reusability aspect of dexmedetomidine-based sedation allows for use in procedures such as awake craniotomies [7,14]. However, because of the variability of hypercapnic ventilatory response in ICU patients (and also in the elderly) continuous cardiac and respiratory monitoring is recommended in these clinical settings.

Analgesia

Stimulation of central and spinal α_2 – adrenergic receptors plays a role in analgesic effect. A systematic review of RCTs of α_2 – adrenergic receptor agonists (clonidine or dexmedetomidine vs. placebo) found that the use of dexmedetomidine was associated with morphine – sparing postoperatively and decreased pain intensity, at 24 hours [20]. However, the direct effect on pain, for example, in monotherapy in healthy volunteers is less well demonstrated [14].

Anxiolysis

As a premedication, dexmedetomidine is associated with comparable anxiolysis to benzodiazepines and can reduce requirements of sedatives and general anesthetics as well as reducing agitation on recovery [2].

Delerium

Limited evidence suggests that dexmedetomidine may be associated with a lower incidence of delirium through avoidance of deep sedation and reduction in benzodiazepine use [21]. A RCT in elderly patients (> 65 years) after non-cardiac surgery found that the incidence of postoperative delirium was significantly lower with dexmedetomidine vs. placebo, with no difference in hypotension or bradycardia [22]. A meta-analysis reported significant reductions in the incidences of delirium, agitation and confusion with dexmedetomidine compared with controls [23].

PEDIATRIC POPULATION

There are very few RCTs in children and most of the information is derived from small observational studies or extrapolated from the adult data set. A systematic review of dexmedetomidine in the pediatric population reported on iv use for sedation in the ICU, and in intranasal, buccal and oral formulations as a premedication [24]. It is also used adjunctively for nerve blocks with local anesthetics, as a sedative for investigations such as magnetic resonance imaging, and for intraoperative analgesia for procedures such as extracorporeal shock wave lithotripsy. A review of α_2 - adrenergic receptor agonists for sedation in pediatric critical care found an opioid - sparing effect in two small RCTs with dexmedetomidine [25]. A systematic review and meta-analysis of dexmedetomidine as a premedication reported that there was greater preoperative sedation and decreased postoperative pain compared with midazolam, and superiority to placebo in providing satisfactory intravenous cannulation [26]. Another meta-analysis reported a similar effect on postoperative pain with significant reduction in the doses of rescue analgesic drugs as well as decreased anxiety with parental separation and decreased postoperative agitation vs. midazolam [27]. However, adverse events reported in another meta-analysis included reduced systolic and mean blood pressure and heart rate and prolongation of the onset of sedation when compared with midazolam [28].

THERMOREGULATION

The α_2 - adrenergic receptor agonists acting at the hypothalamic level and through the sympathetic nervous system are reported to be effective in the control of postoperative shivering and hyperthermia [2]. A Cochrane review reported that both clonidine and dexmedetomidine reduced postoperative shivering; there was more sedation and bradycardia with dexmedetomidine vs. placebo [29]. Three RCTs found dexmedetomidine to have a faster onset and lower recurrence rate than tramadol or clonidine [30-32]. There was greater sedation with dexmedetomidine, and one study reported more hypotension and bradycardia than clonidine.

TREATMENT OF WITHDRAWAL SYNDROMES

Given the role of the noradrenergic system in withdrawal syndromes it is postulated that the α_2- adrenergic receptor agonists are relevant in mitigating withdrawal-related symptoms. A review of case reports and series in alcohol withdrawal suggested that dexmedetomidine may be of benefit as an adjunctive agent [33]. However, no controlled trials have been conducted to date, thus there are no dosing recommendations either in terms of titration or maintenance schedules. Although, duration of treatment was typically > 24 hours adverse outcomes

appeared to be primarily related to the presence of medical comorbidities, concomitant sedatives and need for mechanical ventilation.

NEUROPROTECTION

Animal data report attenuation of propofol and isofluorane induced hippocampal neuro apoptosis with dexmedetomidine [34,35]. These models suggest a potential neuroprotective effect of dexmedetomidine postulated to act through decreased sympathetic activity, inhibition of inflammatory processes, and activation of protective signal pathways, for example, the extracellular signal-regulated kinase(ERK) and phosphoinositide 3-kinase (PI3K) /Protein Kinase B (Akt) pathway [36]. The U.S. Food and Drug Administration (FDA) issued new warnings about general anesthetic and sedative (benzodiazepine) drugs in April 2017 concerning the risks of negative effects on brain development in children < 3 years [37]. Dexmedetomidine was not included by this label change and while there are insufficient data to conclude a neuro protective effect nonetheless it would appear that there may be an overall decreased adverse risk with dexmedetomidine.

FUTURE DIRECTIONS

Dexmedetomidine is recommended as a first-line agent for sedation by the Society of Critical Care Medicine [38]. Pharmacogenomic studies may help elucidate interpatient variability [14,39]. In addition to the approved clinical applications dexmedetomidine's role in the treatment of emergence delirium and in the pediatric population would suggest future areas of research; the latter, particularly, when combined with alternate routes of administration such as intranasal or buccal [24,40]. Other populations that also warrant further study include the obese that are at risk of apnea and opioid-induced ventilator depression. As with other members of the class the potential for use in pain syndromes and in the treatment of alcohol and drug toxicity and withdrawal is also of interest. Translational studies would help demonstrate any specific benefit in terms of neuroprotection.

SUMMARY

Dexmedetomidine demonstrates clinical utility and overall safety in a wide variety of treatment environments. Dexmedetomidine's therapeutic actions in terms of sedoanalgesia are principally derived from its high selectivity for α_2 - adrenergic receptors, which also predicts its adverse effect profile. Currently it is the only agent in its class approved for short-term use in procedural sedation and for sedation in an ICU setting.

CONFLICT OF INTEREST

PSC has received research grants and honoraria from Janssen, Pfizer, Eli Lilly, Astra Zeneca, Glaxo Smith Kline, Lundbeck, Bristol Myers Squibb, Hoffmann la Roche, Sunovion, Mylan, Paladin, BoehringerIngelheim, Otsuka, HLS, Allergan and Novartis. JAC has no conflicts to report.

ACKNOWLEDGEMENTS

We are very grateful to Candace Necyk, BScPharm MSc, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta for her expert review of the manuscript and helpful comments.

REFERENCES

1. Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Anesth Prog. 2015; 62: 31-39.

2. Mavropoulos G, Minguet G, Brichant JF. Alpha-2 adrenoreceptor agonists in anaesthesia and intensive care medicine. Rev Med Liege. 2014; 69: 97-101.

3. Devasya A, Sarpangala M. Dexmedetomidine: A review of a newer sedative in dentistry. J Clin Pediatr Dent. 2015; 39: 401-409.

4. Jones CR. Perioperative uses of dexmedetomidine. Int Anesthiol Clin. 2013; 51: 81-96.

5. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice- a review. J Clin Diagn Res. 2014; 8: GE01-4.

6. Canadian Agency for Drugs and Technologies in Health. Dexmedetomidine for sedation of patients in the ICU or PICU: review of clinical effectiveness and safety. 2014.

7. Kim KH. Safe Sedation and hypnosis using dexmedetomidine for minimally invasive spine surgery in a prone position. Korean J Pain. 2014; 27: 313-320.

8. Canadian Agency for Drugs and Technologies in Health. Dexmedetomidine for ICU sedation: a cost-effectiveness analysis. 2016.

9. Keating GM. Dexmedetomidine: A review of it's use for sedation in the intensive care setting. Drugs. 2015; 75: 1119-30.

10. Precedex Product Monograph. Hospira Healthcare Corporation. Date of Revision: 2017.

11. Precedex Package Insert. Hospira Inc. Revised: June 2013

12. Ihmsen H, Saari TI. Dexmedetomidine. Pharmacokinetics and pharmacodynamics. Anaesthesist. 2012; 61: 1059-1066.

13. Li A, Yuen VM, Goulay-Dufay S, Kwok PC. Pharmacokinetics and pharmacodynamics of dexmedetomidine. Drug Dev Ind Pharm. 2016; 42: 1917-1927.

14. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017; 56: 893-913.

15. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive caret. Br J Anaesth. 2002; 88: 669-675.

16. Cruickshank M, Henderson L, MacLennan G, Fraser C, Campbell M, Blackwood B, et al. Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review. Health Technol Assess. 2016; 20: v-xx, 1-117.

17. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007; 298: 2644-2653.

18. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012; 307: 1151-1160.

19. Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients.

SciMedCentral

Cochrane Database Syst Rev. 2015; 1: CD010269.

20. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic a2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology. 2012; 116:1312-1322.

21. Nelson S, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. Defining the role of dexmedetomidine in the prevention of delirium in the intensive care unit. Biomed Res Int. 2015; 635737.

22. Plambech MZ, Afshari A. Dexmedetomidine in the pediatric population: A review. Minerva Anestesiol. 2015; 81: 320-332.

23. Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, et al. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2014; 28: 1459-1466.

24. Plambech MZ, Afshari A. Dexmedetomidine in the pediatric population: a review. Minerva Anestesiol. 2015; 81: 320-332.

25. Hayden JC, Breatnach C, Doherty DR, Healy M, Howlett MM, Gallagher PJ, et al. Efficacy of α2-agonists for sedation in pediatric critical care: A systematic review. Pediatr Crit Care Med. 2016; 17: 66-75.

26. Peng K, Wu SR, Ji FH, Li J. Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis. Clinics (Sao Paulo). 2014; 777-786.

27. Pasin L, Febres D, Testa V, Frati E, Borghi G, Landoni G, et al. Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials. Paediatr Anaesth. 2015; 25: 468-476.

28. Sun Y, Lu Y, Huang Y, Jiang H. Is dexmedetomidine superior to midazolam as a premedication in children? A meta-analysis of randomized controlled trials. Paediatr Anaesth. 2014; 24: 863-874.

29. Lewis SR, Nicholson A, Smith AF, Alderson P. Alpha-2 adrenergic agonists for the prevention of shivering following general anaesthesia. Cochrane Database Syst Rev. 2015; CD011107.

30. Venkatraman R, Karthik K, Pushparani A, Mahalakshmi A. A prospective, randomized, double-blinded control study on comparison of tramadol, clonidine and dexmedetomidine for post spinal anesthesia shiver. Rev Bras Anestesiol. 2017; S0034-7094: 30266-30269.

31. Kundra TS, Kuthiala G, Shrivastava A, Kaur P. A comparative study on the efficacy of dexmedetomidine and tramadol on post-spinal anesthesia shivering. Saudi J Anaesth. 2017; 11: 2-8.

32. Panneer M, Murugaiyan P, Rao SV. A comparative study of intravenous dexiemedetoimdine and intravenous clonidine for postspinal shivering in patients undergoing lower limb Orthopedic Surgery. Anesth Essays Res. 2017; 11: 151-154.

33. Muzyk AJ, Kerns S, Brudney S, Gagliardi JP. Dexmedetomidine for the treatment of alcohol withdrawal syndrome: rationale and current status of research. CNS Drugs. 2013; 27: 913-920.

34. Wang Y, Han R, Zuo Z. Dexmedetomidine-induced neuroprotection: is it translational? Translational perioperative and pain medicine. 2016; 1:15-19.

35. Wang Y, Wu C, Han B, Xu F, Mao M, et al. Dexmedetomidine attenuates repeated propofol exposure-induced hippocampal apoptosis, PI3K/Akt/Gsk-3β signaling disruption, and juvenile cognitive deficits in neonatal rats. Mol Med Rep. 2016; 14: 769-775.

36. Li Y, Zeng M, Chen W, Liu C, Wang F, Han X, et al. Dexmedetomidine reduces isoflurane-induced neuroapoptosis partly by preserving PI3K/Akt pathway in the hippocampus of neonatal rats. PLoS One. 2014; 9: 93639.

37. FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women issued on December 14, 2016. Safety Announcement [4-27-2017].

38. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013; 41: 263-306.

39. Holliday SF, Kane-Gill SL, Empey PE, Buckley MS, Smithburger PL. Interpatient variability in dexmedetomidine response: a survey of the literature. ScientificWorld Journal. 2014; 2014: 805013.

40. Sottas CE, Anderson BJ. Dexmedetomidine: the new all-in-one drug in paediatric anaesthesia? Curr Opin Anaesthesiol. 2017; 30: 441-451.