Breif Review Article

Sleep and anesthesia: can we use a physiologic model to decrease risks of a medical intervention

Samira Rajaei[1], Ali Dabbagh[2*]

Abstract

Anesthesiology is one of the most important creations of the modern science, basically based on the anesthetic drugs; however, there are a few concerns regarding the effects of the anesthetic drugs. Would there be any progress in the current trend of anesthesiology, both clinically and basically. There would be a possibility to use the physiologic mechanisms of sleep to be incorporated into clinical practice instead of pharmacologic agents in order to decrease their unwanted effects.

Keywords: Sleep, Anesthesia, Analgesia, Mechanism, Pain

Please cite this article as: Rajaei S, Dabbagh A. Sleep and anesthesia: can we use a physiologic model to decrease risks of a medical intervention. J Cell Mol Anesth. 2017;2(2):77-81.

1. Immunology Department, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Cardiac Anesthesiology Department, Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Ali Dabbagh, MD. Professor, Anesthesiology Research Center, Cardiac Anesthesiology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: (+98) 912 197 2368; Fax: (+98) 21 2207 4101.
E-mail: alidabbagh@yahoo.com

Introduction

Anesthesiology is a relatively new convention of medicine. Many surgeries are nowadays performed just because we can anesthetize patients; otherwise, there was no progress in the many fields of surgery. In the United States, nearly 60,000 patients are anesthetized each day, mainly for surgical operation.

The first time that anesthesia was "created", one of the greatest fears of mankind was overcome (1): since the first patient was anesthetized in October 16, 1846 by Dr William T. G. Morton at Massachusetts General Hospital, Boston, the science and practice of anesthesiology has made many great developments, increasing its efficacy and safety and at the same time, decreasing the anesthesia-related morbidity and mortality (2, 3).

In the current era of modern anesthesiology, the practice and science of anesthesia is composed of 4 basic elements; each being one of its permanent counterparts; without each of them, anesthesia is not complete. These 4 basic elements are (4, 5):

1) hypnosis (an iatrogenic pharmacologic-based coma)
2) amnesia (forgetting the unpleasant events during operation)
3) analgesia (painlessness)
4) akinesia (lack of movements in response to noxious stimuli, including the surgical incisions and manipulations).

Very interesting issue is that all of these basic elements of anesthesia are created after interaction of anesthetic drugs with different parts of the nervous system (including central, peripheral, and autonomic nervous systems). However, CNS remains the primary site of action for "anesthesia". In other words, anesthesia is an iatrogenic, reversible, pharmacologic-based coma; affecting CNS neuronal circuits at many levels including the molecular level; for example, the mechanism of anesthesia in some volatile agents (i.e. Isoflurane and Sevoflurane) is through inhibition of

orexinergic neurons; also, ketamine acts through "pyramidal cells and also, seven different types of CA1 interneurons" (6-13) or amnesia is induced primarily through effects of anesthetics on hippocampus neurons (14-16). Also, the majority of CNS anesthetics act through N-methyl-D-aspartate (NMDA) receptor or gamma-amino butyric acid (GABA) receptor subunits (17-30).

Globally, some believe that anesthesia induction is due to "drug-induced global modulation of neuronal function"; meanwhile, termination of anesthesia is spontaneous and passive, occurring after termination of pharmacologic effects of anesthetics from "their sites in the central nervous system"; though this mechanism might be somewhat oversimplification and the neural inertia could have a role (31-36).

But are we doing anesthesia in a right way? Are the modern anesthetic drugs as safe and physiology-compatible as we want? To answer this questions, one could consider the many animal and human studies proving the very safe anesthetic agents and the very diminutive incidence of unwanted effects of anesthetic drugs. Despite the many available proofs for modern anesthesia safety, there are some considerations regarding the effects of anesthetics on organ functions described in the following paragraphs.

If we want to discuss more specifically, anesthesia is not so much physiologic. It is demonstrated in cerebral cortex and hippocampus neurons of rats that neuronal spikes from these sites are "very stable across physiologic states i.e. waking, slow-wave sleep and rapid-eye-movement sleep"; however, these neuronal spikes and avalanches "would collapse during anesthesia". Also, waiting time distributions obey a single scaling function during all natural behavioral states, but not during anesthesia (34, 36-38).

From another viewpoint, anesthesia is an iatrogenic pharmacologic based coma; of course with a reversible nature. In fact, electroencephalographic studies performed in patients undergoing general anesthesia has demonstrated an EEG pattern similar to patients with coma; in other words, the EEG waves in "comatose patients" and "patients undergoing general anesthesia" both demonstrate high amplitude, low-frequency waves (4, 39, 40).

Now let's discuss the issue from a different viewpoint; i.e. the neurophysiologic point of view. During normal sleep, the arousal status is depressed and we would go unconscious. During the rapid eye movement (REM) phase of sleep, EEG waves have an active high-frequency, low-amplitude pattern; while in the non- rapid eye movement (Non-REM) phase of sleep the EEG waves are high amplitude, low frequency (33, 39-44). In contrast to this dual stage pattern of EEG in sleep, the EEG pattern in "general anesthesia" or "coma" has high amplitude, low-frequency waves. Although coma and general anesthesia have some similarities with the Non-REM phase of sleep, "coma and general anesthesia" are not the same as Non-REM (4, 32, 41, 45, 46). As we see, EEG assessments also suggest us that possibly; the current anesthetic pharmacologic agents are not as physiologic as we need.

Concerning the clinical point of view may be all above comments are not as worrying as the following lines of this paragraph; which addresses a sample of the many studies published mainly in the last decade. There are an increasing number of evidence demonstrating the unwanted effects of anesthetic agents on the synaptogenesis processes in the animal neonates receiving modern anesthetic agents; these animal and lab studies have demonstrated the clues to apoptotic effects of anesthetics; some even well demonstrating these effects on animal CNS; though human CNS studies are not so much available due to technical problems (12, 46-74); also, there are a number of studies raising the questions regarding the effects of some of the current anesthetic agents on the behavioral and learning aspects of the human neonates, though none of them still have not presented definite proof for this effect (75).

There are some new windows which could help us use the sleep mechanism as a "physiologic mechanism" instead of the current "pharmacologic mechanism" for anesthesia. In one direction, there is a concordance between interventions which disturb sleep and/or cause some types of somatic pain; in other words, these interventions have the "same direction effects" for pain and sleep; i.e. there is a concordance between them (76-79); so, possibly we

could use the physiologic mechanisms maintaining normal sleep for suppressing those surgical stimuli which create pain. On the other hand, we could use some newer molecules like urethane which could induce anesthesia with mechanisms different from current anesthetics; it means that urethane induces anesthesia with a mechanism "closely mimicking natural sleep" (8, 80-83).

Conclusion

The above paragraphs are brief concerns regarding the importance of a new look at our current approach for a very common medical practice. In other words, in the current era of clinical and basic studies, the effects of anesthetic agents in creating the "pharmacological coma" is a very important concern with high priority, in medicine, in pharmaceutical studies and more importantly, in neuroscience. We anticipate a very important turning point, which would add another improvement to the safety of anesthesia and add another revolution to the previous "jump up's" of this field of medicine, as a number of relatively safe anesthetic agents have emerged and shown to be neuroprotective (5, 84-90); however, this time, the turning point would be at the cellular and subcellular levels.

Acknowledgment

The authors would like to acknowledge the kind help of Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their invaluable support.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Robinson DH, Toledo AH. Historical development of modern anesthesia. J Invest Surg. 2012;25(3):141-9.
2. LeVasseur R, Desai SP. Ebenezer Hopkins Frost (1824-1866): William T.G. Morton's first identified patient and why he was invited to the Ether demonstration of October 16, 1846. Anesthesiology. 2012;117(2):238-42.
3. Bause GS, Sim PP. C.T. Jackson's 15 October 1846 letter to J.-B.A.L. Elie de Beaumont: Jackson's thoughts on Ether Day's Eve? Bull Anesth Hist. 2011;29(1):12-4.
4. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med. 2010;363(27):2638-50.
5. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness not equal unconsciousness. Anesthesiology. 2012;116(4):946-59.
6. Kelz MB, Sun Y, Chen J, Cheng Meng Q, Moore JT, Veasey SC, et al. An essential role for orexins in emergence from general anesthesia. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(4):1309-14.
7. Laorden ML, Ferenczi S, Pinter-Kubler B, Gonzalez-Martin LL, Lasheras MC, Kovacs KJ, et al. Hypothalamic orexin–a neurons are involved in the response of the brain stress system to morphine withdrawal. PLoS One. 2012;7(5):e36871.
8. Clement EA, Richard A, Thwaites M, Ailon J, Peters S, Dickson CT. Cyclic and sleep-like spontaneous alternations of brain state under urethane anaesthesia. PLoS One. 2008;3(4):e2004.
9. Seamari Y, Narvaez JA, Vico FJ, Lobo D, Sanchez-Vives MV. Robust off- and online separation of intracellularly recorded up and down cortical states. PLoS One. 2007;2(9):e888.
10. Reig R, Sanchez-Vives MV. Synaptic transmission and plasticity in an active cortical network. PLoS One. 2007;2(7):e670.
11. Kuang H, Lin L, Tsien JZ. Temporal dynamics of distinct CA1 cell populations during unconscious state induced by ketamine. PLoS One. 2010;5(12):e15209.
12. Chen G, Gong M, Yan M, Zhang X. Sevoflurane induces endoplasmic reticulum stress mediated apoptosis in hippocampal neurons of aging rats. PLoS One. 2013;8(2):e57870.
13. Forgacs PB, Frey HP, Velazquez A, Thompson S, Brodie D, Moitra V, et al. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest. Annals of clinical and translational neurology. 2017;4(2):119-29.
14. Perouansky M, Pearce RA. How we recall (or don't): the hippocampal memory machine and anesthetic amnesia. Can J Anaesth. 2011;58(2):157-66.
15. Wang DS, Orser BA. Inhibition of learning and memory by general anesthetics. Can J Anaesth. 2011;58(2):167-77.
16. Changeux JP. Conscious processing: implications for general anesthesia. Curr Opin Anaesthesiol. 2012;25(4):397-404.
17. Dong Y, Wu X, Zhang G, Xu Z, Zhang Y, Gautam V, et al. Isoflurane facilitates synaptic NMDA receptor endocytosis in mice primary neurons. Curr Mol Med. 2012.
18. Esencan E, Yuksel S, Tosun YB, Robinot A, Solaroglu I, Zhang JH. XENON in medical area: emphasis on neuroprotection in hypoxia and anesthesia. Med Gas Res. 2013;3(1):4.
19. Jin J, Gong K, Zou X, Wang R, Lin Q, Chen J. The blockade of NMDA receptor ion channels by ketamine is enhanced in developing rat cortical neurons. Neuroscience letters. 2013;539:11-5.
20. Kuhlmann L, Foster BL, Liley DT. Modulation of Functional EEG Networks by the NMDA Antagonist Nitrous Oxide. PLoS One. 2013;8(2):e56434.
21. Liu CL, Gao M, Jin GZ, Zhen X. GABA neurons in the ventral tegmental area responding to peripheral sensory input. PLoS One. 2012;7(12):e51507.
22. Liu F, Patterson TA, Sadovova N, Zhang X, Liu S, Zou X, et al. Ketamine-induced neuronal damage and altered N-methyl-D-aspartate receptor function in rat primary forebrain culture. Toxicol

Sci. 2013;131(2):548-57.
23. Wang S, Tian Y, Song L, Lim G, Tan Y, You Z, et al. Exacerbated mechanical hyperalgesia in rats with genetically predisposed depressive behavior: role of melatonin and NMDA receptors. Pain. 2012;153(12):2448-57.
24. Trudell JR, Bertaccini E, Maciver MB. Teaching an old GABA receptor new tricks. Anesth Analg. 2012;115(2):270-3.
25. Akk G, Steinbach JH. Structural studies of the actions of anesthetic drugs on the gamma-aminobutyric acid type A receptor. Anesthesiology. 2011;115(6):1338-48.
26. Forman SA. Clinical and molecular pharmacology of etomidate. Anesthesiology. 2011;114(3):695-707.
27. Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT. Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. Pharmacological reviews. 2011;63(1):243-67.
28. Olsen RW, Li GD. GABA(A) receptors as molecular targets of general anesthetics: identification of binding sites provides clues to allosteric modulation. Can J Anaesth. 2011;58(2):206-15.
29. Drexler B, Antkowiak B, Engin E, Rudolph U. Identification and characterization of anesthetic targets by mouse molecular genetics approaches. Can J Anaesth. 2011;58(2):178-90.
30. Kafashan M, Ching S, Palanca BJ. Sevoflurane Alters Spatiotemporal Functional Connectivity Motifs That Link Resting-State Networks during Wakefulness. Frontiers in neural circuits. 2016;10:107.
31. Friedman EB, Sun Y, Moore JT, Hung HT, Meng QC, Perera P, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. PLoS One. 2010;5(7):e11903.
32. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. Physiol Rev. 2012;92(3):1087-187.
33. Cannon J, McCarthy MM, Lee S, Lee J, Borgers C, Whittington MA, et al. Neurosystems: brain rhythms and cognitive processing. The European journal of neuroscience. 2014;39(5):705-19.
34. Kepecs A, Tan AY. Spatial diversity of spontaneous activity in the cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015;9:48.
35. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016;42(6):962-71.
36. Mitra A, Raichle ME. How networks communicate: propagation patterns in spontaneous brain activity. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2016;371(1705).
37. Ribeiro TL, Copelli M, Caixeta F, Belchior H, Chialvo DR, Nicolelis MA, et al. Spike avalanches exhibit universal dynamics across the sleep-wake cycle. PLoS One. 2010;5(11):e14129.
38. Lin SC, Brown RE. Optogenetic Dissection of the Basal Forebrain Neuromodulatory Control of Cortical Activation, Plasticity, and Cognition. 2015;35(41):13896-903.
39. Stamatakis EA, Adapa RM, Absalom AR, Menon DK. Changes in resting neural connectivity during propofol sedation. PLoS One. 2010;5(12):e14224.
40. Mitra A, Snyder AZ, Tagliazucchi E, Laufs H, Raichle ME. Propagated infra-slow intrinsic brain activity reorganizes across wake and slow wave sleep. eLife. 2015;4.
41. Lydic R, Baghdoyan HA. Sleep, anesthesiology, and the neurobiology of arousal state control. Anesthesiology. 2005;103(6):1268-95.
42. McCarthy MM, Ching S, Whittington MA, Kopell N. Dynamical changes in neurological diseases and anesthesia. Current opinion in neurobiology. 2012;22(4):693-703.
43. Picchioni D, Duyn JH, Horovitz SG. Sleep and the functional connectome. NeuroImage. 2013;80:387-96.
44. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. Anesthesiology. 2015;123(4):937-60.
45. Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci. 2011;34:601-28.
46. Sivadas N, Radhakrishnan A, Aswathy BS, Kumar VM, Gulia KK. Dynamic changes in sleep pattern during post-partum in normal pregnancy in rat model. Behavioural brain research. 2017;320:264-74.
47. Creeley CE, Olney JW. The young: neuroapoptosis induced by anesthetics and what to do about it. Anesth Analg. 2010;110(2):442-8.
48. Jevtovic-Todorovic V. Developmental synaptogenesis and general anesthesia: a kiss of death? Curr Pharm Des. 2012;18(38):6225-31.
49. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2003;23(3):876-82.
50. Jevtovic-Todorovic V, Olney JW. PRO: Anesthesia-induced developmental neuroapoptosis: status of the evidence. Anesth Analg. 2008;106(6):1659-63.
51. McCann ME, Soriano SG. General anesthetics in pediatric anesthesia: influences on the developing brain. Current drug targets. 2012;13(7):944-51.
52. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agents in neonates and young children. Anesth Analg. 2007;104(3):509-20.
53. Persson J. Wherefore ketamine? Curr Opin Anaesthesiol. 2010;23(4):455-60.
54. Vutskits L. Anesthetic-related neurotoxicity and the developing brain: shall we change practice? Paediatr Drugs. 2012;14(1):13-21.
55. Allegaert K. The clinical pharmacology of short acting analgo-sedatives in neonates. Curr Clin Pharmacol. 2011;6(4):222-6.
56. Allegaert K, Tibboel D, van den Anker J. Pharmacological treatment of neonatal pain: In search of a new equipoise. Semin Fetal Neonatal Med. 2013;18(1):42-7.
57. Brambrink AM, Back SA, Riddle A, Gong X, Moravec MD, Dissen GA, et al. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Annals of neurology. 2012;72(4):525-35.
58. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Martin LD, et al. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. Anesthesiology. 2012;116(2):372-

84.
59. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology. 2010;112(4):834-41.
60. Brambrink AM, Orfanakis A, Kirsch JR. Anesthetic neurotoxicity. Anesthesiol Clin. 2012;30(2):207-28.
61. Koerner IP, Brambrink AM. Brain protection by anesthetic agents. Curr Opin Anaesthesiol. 2006;19(5):481-6.
62. McCann ME, Soriano SG. Is anesthesia bad for the newborn brain? Anesthesiol Clin. 2009;27(2):269-84.
63. Reddy SV. Effect of general anesthetics on the developing brain. Journal of anaesthesiology, clinical pharmacology. 2012;28(1):6-10.
64. Schubert H, Eiselt M, Walter B, Fritz H, Brodhun M, Bauer R. Isoflurane/nitrous oxide anesthesia and stress-induced procedures enhance neuroapoptosis in intrauterine growth-restricted piglets. Intensive Care Med. 2012;38(7):1205-14.
65. Zhou ZW, Shu Y, Li M, Guo X, Pac-Soo C, Maze M, et al. The glutaminergic, GABAergic, dopaminergic but not cholinergic neurons are susceptible to anaesthesia-induced cell death in the rat developing brain. Neuroscience. 2011;174:64-70.
66. Bai X, Yan Y, Canfield S, Muravyeva MY, Kikuchi C, Zaja I, et al. Ketamine Enhances Human Neural Stem Cell Proliferation and Induces Neuronal Apoptosis via Reactive Oxygen Species-Mediated Mitochondrial Pathway. Anesth Analg. 2013;116(4):869-80.
67. Bajic D, Commons KG, Soriano SG. Morphine-enhanced apoptosis in selective brain regions of neonatal rats. Int J Dev Neurosci. 2013;31(4):258-66.
68. Boscolo A, Milanovic D, Starr JA, Sanchez V, Oklopcic A, Moy L, et al. Early Exposure to General Anesthesia Disturbs Mitochondrial Fission and Fusion in the Developing Rat Brain. Anesthesiology. 2013.
69. Jevtovic-Todorovic V, Boscolo A, Sanchez V, Lunardi N. Anesthesia-induced developmental neurodegeneration: the role of neuronal organelles. Frontiers in neurology. 2012;3:141.
70. Lei X, Guo Q, Zhang J. Mechanistic insights into neurotoxicity induced by anesthetics in the developing brain. International journal of molecular sciences. 2012;13(6):6772-99.
71. Liu JR, Liu Q, Li J, Baek C, Han XH, Athiraman U, et al. Noxious stimulation attenuates ketamine-induced neuroapoptosis in the developing rat brain. Anesthesiology. 2012;117(1):64-71.
72. Yu D, Jiang Y, Gao J, Liu B, Chen P. Repeated exposure to propofol potentiates neuroapoptosis and long-term behavioral deficits in neonatal rats. Neuroscience letters. 2013;534:41-6.
73. Mintz CD, Smith SC, Barrett KM, Benson DL. Anesthetics interfere with the polarization of developing cortical neurons. J Neurosurg Anesthesiol. 2012;24(4):368-75.
74. Lewis LD, Weiner VS, Mukamel EA, Donoghue JA, Eskandar EN, Madsen JR, et al. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(49):E3377-86.
75. Davidson AJ. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. Paediatr Anaesth. 2011;21(7):716-21.
76. Doufas AG, Panagiotou OA, Ioannidis JP. Concordance of sleep and pain outcomes of diverse interventions: an umbrella review. PLoS One. 2012;7(7):e40891.
77. Cascella M. Mechanisms underlying brain monitoring during anesthesia: limitations, possible improvements, and perspectives. Korean J Anesthesiol. 2016;69(2):113-20.
78. Ching S, Brown EN. Modeling the dynamical effects of anesthesia on brain circuits. Current opinion in neurobiology. 2014;25:116-22.
79. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. Journal of applied physiology (Bethesda, Md : 1985). 2014;116(3):325-36.
80. Pagliardini S, Greer JJ, Funk GD, Dickson CT. State-dependent modulation of breathing in urethane-anesthetized rats. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2012;32(33):11259-70.
81. Whitten TA, Martz LJ, Guico A, Gervais N, Dickson CT. Heat synch: inter- and independence of body-temperature fluctuations and brain-state alternations in urethane-anesthetized rats. J Neurophysiol. 2009;102(3):1647-56.
82. Wolansky T, Clement EA, Peters SR, Palczak MA, Dickson CT. Hippocampal slow oscillation: a novel EEG state and its coordination with ongoing neocortical activity. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2006;26(23):6213-29.
83. Sharma AV, Wolansky T, Dickson CT. A comparison of sleeplike slow oscillations in the hippocampus under ketamine and urethane anesthesia. J Neurophysiol. 2010;104(2):932-9.
84. Dabbagh A, Rajaei S. Xenon: a solution for anesthesia in liver disease? Hepat Mon. 2012;12(11):e8437.
85. Benggon M, Chen H, Applegate R, Martin R, Zhang JH. Effect of dexmedetomidine on brain edema and neurological outcomes in surgical brain injury in rats. Anesth Analg. 2012;115(1):154-9.
86. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology. 2012;116(6):1312-22.
87. Hong JY, Kim WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia in elderly patients. Acta Anaesthesiol Scand. 2012;56(3):382-7.
88. Lin Y, He B, Chen J, Wang Z. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients: a meta-analysis? Crit Care. 2012;16(5):R169.
89. Bantel C, Maze M, Trapp S. Neuronal preconditioning by inhalational anesthetics: evidence for the role of plasmalemmal adenosine triphosphate-sensitive potassium channels. Anesthesiology. 2009;110(5):986-95.
90. Bantel C, Maze M, Trapp S. Noble gas xenon is a novel adenosine triphosphate-sensitive potassium channel opener. Anesthesiology. 2010;112(3):623-30.