Original Research Article

Indian Journal of Anesthesia and Analgesia
2018; 5(12): 1994-2000
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.51218.5

Comparison of Bispectral Index (BIS) of Halothane, Isoflurane, Desflurane and Sevoflurane at Equi-MAC end Tidal Concentration: A Randomized Control Study

Neerja Banerjee[1], Shradendu Shekhar Gupta[2], Jyoti Sharma[3], Namita Arora[4]

[1]Professor, Dept. of Anaesthesiology and Intensive Care, Post Graduate Institute of Medical Education and Research & Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi 110001, India. [2]Attending Consultant, Dept. of Anesthesiology, JAYPEE Hospital, Noida, Uttar Pradesh 201304, India. [3]Assistant Professor, Dept. of Anaesthesiology and Intensive Care, Pt. Bhagwat Dayal Sharma Post Graduate Institute of Medical Science Rohtak, Haryana 124001, India. [4]Associate Professor, Dept. of Anaesthesiology and Intensive Care, Post Graduate Institute of Medical Education and Research & Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi 110001, India.

Abstract

Background: MAC is most common method of titration of volatile anesthetics and BIS is used to measure the hypnotic effect of anesthetics. This study was undertaken to evaluate and compare the BIS value produced by different inhalational agents at their 1 MAC end tidal concentration. *Method:* 200 patients of ASA I - II of either sex between 20-50 years , for laparoscopic cholecystectomy were divided into 4 groups of 50 each and received either halothane, isoflurane, sevoflurane or desflurane. General anesthesia was administered using fentanyl, propofol, inhalational agents and vecuronium and maintained with 67% nitrous in oxygen. After achieving and maintaining 1 MAC for 15 min, BIS value were recorded for next 15 min at an interval of 1 min .Collected data was analyzed using ANOVA test. *Results:* At 1 MAC end tidal concentration mean BIS value for halothane was 57.0±3.51, for isoflurane 51.57±3.84, for sevoflurane value was 49.621± 3.82, and for desflurane BIS value 42.11±4.68, and difference among groups were statistically significant. *Conclusion:* At 1MAC, BIS values are agent specific and BIS value of halothane > isoflurane > sevoflurane > desflurane.

Keywords: Bispectral Index; MAC; Halothane; Isoflurane; Sevoflurane; Desflurane.

How to cite this article:

Neerja Banerjee, Shradendu Shekhar Gupta, Jyoti Sharma et al. Comparison of Bispectral Index (BIS) of Halothane, Isoflurane, Desflurane and Sevoflurane at Equi-MAC end Tidal Concentration: A Randomized Control Study. Indian J Anesth Analg. 2018;5(12):1994-2000.

Introduction

Measuring and assessing depth of anaesthesia is fundamental to anaesthetic practice. BIS is the most reliable tool for assessment of depth of anaesthesia known to us. BIS uses proprietary algorithms to process signals from an electroencephalogram (EEG) and produces a single value (number) that normally reflects consciousness/unconsciousness. BIS is based on analysis of thousands of EEGs from the patients anesthetized with various anesthetics [1].

Bispectral index shows a value of 100 while awake, 65-85 under sedation, 45-65 under general anaesthesia, < 40 for burst suppression, and 0 if no electrical activity.

Minimum alveolar concentratin (MAC) is most common method of titration of volatile anesthetics. It provides best available method to monitor continuous brain concentration of volatile anesthetic agents once equilibrium is established between alveolus, blood and brain. Anesthetic agents vary in their relative hypnotic and immobilizing potentials , therefore equal MAC concentration of various volatile agents

Corresponding Author: Dr. Namita Arora, Associate Professor, Dept. of Anaesthesiology and Intensive Care, Post Graduate Institute of Medical Education and Research & Dr. Ram Manohar Lohia Hospital, New Delhi, Delhi 110001, India.
E-mail: namitaarora16@yahoo.com

Received on 11.09.2018, **Accepted on** 01.10.2018

may produce different BIS value. Because of paucity of knowledge regarding BIS value of various inhalational agents at equal MAC, we planned this study to find correlation between BIS and end tidal concentration of various inhalational agents at 1 MAC value.

Material and Methods

Study was conducted after the approval of institutional review board. All patients of age group 20-50 years of either sex with American society of anaesthesiologists physical status I and II scheduled for laparoscopic cholecystectomy were enrolled in the study after obtaining a written informed consent. A total of 200 patients were divided into four groups of 50 each. , i.e. group H, group I, group D, group S, receiving halothane, isoflurane, desflurane and sevoflurane respectively along with standard anaesthetic technique. Exclusion criteria were patient with morbid obesity, impaired renal and hepatic function, history of drug and alcohol abuse and patient with history of seizures disorder.

All patients were fasted overnight and received tablet alprazolam 0.25 mg and tablet ranitidine 150 mg orally at night before surgery. In operation theatre, ECG, oxygen saturation, non-invasive blood pressure, core temperature (nasopharyngeal probe) and BIS was monitored. Drager infinity kappa monitor was used with Infinity BISx Smart Pod (trademarks of Aspect Medical Systems), was used to record brain activity continuously with a soothing rate of 15 seconds. After alcohol cleaning, disposable BIS sensor electrodes (Quatro Sensor™, BIS, Aspect Medical Systems) were applied to the patient's forehead. The sensor consisted of 4 connected parts. Part 1 was applied at the centre of the forehead approximately 5 cm above the nasal bridge, part 4 was applied directly above the eyebrow, part 2 was applied between parts 1 and 4, and part 3 was applied on the temple area between the corner of the eye and the hairline. All electrodes were within the range deemed acceptable by the manufacturer with impedances 7.5 kU.

An 18 gauge cannula was secured on non dominant hand. All patient received i/v fentanyl 2mcg/kg, 5 minutes before induction followed by, inj. propofol 2 -3mg/kg till loss of verbal command. Tracheal intubation was facilitated by vecuronium 0.1mg/kg and mechanical ventilation was provided with Drager primus machine using oxygen and nitrous oxide in ratio of 33:67 with total flow of 3L/ min . The ventilation was adjusted to maintain end tidal carbon dioxide concentration 35-40 mmHg.

After induction, either of four inhalational agents (halothane / isoflurane / desflurane /sevoflurane.) was administered to achieve 1 MAC for 15 minutes duration to allow for equilibrium between alveoli, blood and brain.

After this following parameters were recorded i.e. heart rate, blood pressure, oxygen saturation, inspired and expired concentration of oxygen, nitrous oxide and inhalational agents and BIS values were measured at an interval of 1 minute for further 15 minutes duration. Vecuronium 0.02mg/kg and fentanyl 0.5 mcg/kg were administered after every 20 minutes. At the end of surgery, inj.neostigmine 0.05 mg/kg and inj.glycopyrolate 0.01 mg/kg were administered and anaesthesia was reversed as per standard practice. After extubation the patients were shifted to recovery room.

The result obtained in the study were analyzed using Microsoft excel and SPSS software version 17.0. Data were collected and presented as mean± SD. The statistical significance in mean difference was performed using analysis of variance (ANOVA). Chi square test, pearson correlation test as appropriate. p value < 0.05 was considered significant. A Bonferroni correction was used to account for multiple comparisons.

Results

Total study population of 200 patients of laparoscopic cholecystectomy was divided into four groups, each group receiving halothane, isoflurane, sevoflurane or desflurane. All four groups were comparable with respect to their demographic profile i.e., age, weight, height, sex, ASA status. Pre induction BIS value was found to be in between 96-98 in all four groups. After administration of different inhalational anaesthetic agents at their 1 MAC end tidal concentration mean BIS value for halothane was 57.0 ±3.51, for isoflurane 48.0±2.29, for sevoflurane value was 40.65± 2.07 , and for desflurane BIS value 35.60± 4.68 (Table 2) .

BIS values at end-tidal concentration of 1 MAC of the different agent in different groups were compared using One way Analysis of Variance (ANOVA) as appropriate, and Bonferroni test was performed for post hoc comparisons within and between groups assuming equality of variances, showed that the difference is significant between halothane and isoflurane, halothane and desflurane, halothane and Sevoflurane, isoflurane and desflurane, isoflurane and Sevoflurane and desflurane and Sevoflurane ($p<0.001$) Table 2.

Table 1: Demographic profiles

Variables	Halothane	Isoflurane	Sevoflurane	Desflurane	Total (In 4 Groups)	p-value
Age-years * (media-range)	36.52±9.351	34.14±8.286	38.48 ± 9.177	37.62±9.889	36.69±9.269	0.103
Weight-kg* (mean ± SD)	58.14±8.595	57.22±9.706	55.88±10.756	56.44±9.119	56.92±9.544	0.666
Height-cm * (mean ± SD)	157.864±7.629	157.564±8.562	155.094±9.7031	157.626±8.2877	157.037±8.588	0.330
Sex-ratio ** (male/female)	12/38	14/36	10/40	12/38	48/152	0.832
ASA class ** (I/II)	43/7	44/6	46/4	45/5	178/22	0.797

*ANOVA Test, ** Chi Square Test

Table 2: Descriptive statistics of BIS value at 1 MAC end tidal concentration of halothane, isoflurane, Sevoflurane and desflurane in all study groups (normally distributed data)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Sevoflurane	50	40.6493	2.07360	.29325	40.0600	41.2386	34.87	46.33
Desflurane	50	35.5987	2.50596	.35440	34.8865	36.3109	31.20	42.87
Halothane	50	57.0093	3.51559	.49718	56.0102	58.0085	49.33	63.40
Isoflurane	50	48.0013	2.29464	.32451	47.3492	48.6535	42.73	54.87
Total	200	45.3147	8.50347	.60129	44.1290	46.5004	31.20	63.40

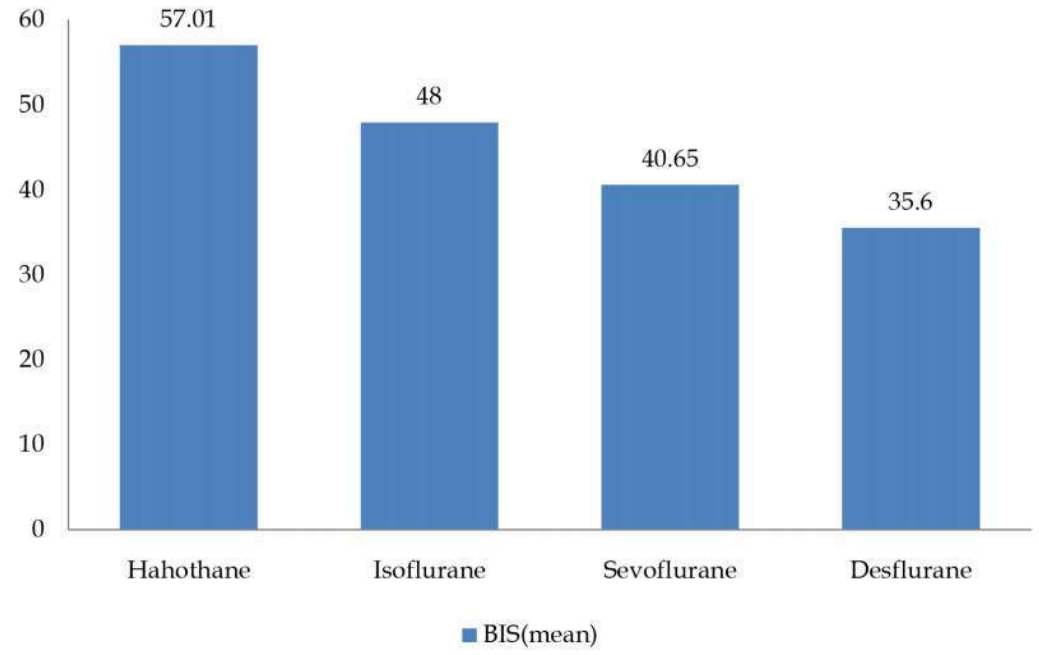

Fig. 1: BIS value at 1 MAC end tidal concentration of halothane, isoflurane, Sevoflurane and desflurane

At a relatively equipotent doses, the mean BIS value for halothane {57.0±3.51} was significantly higher than isoflurane {48.0±2.29}, Sevoflurane {40.65±2.07} and desflurane {35.60±4.68}.

Discussion

Our study was planned to establish the relationship between BIS value of various inhalational agents halothane, isoflurane, sevoflurane and desflurane at equi MAC, value i.e. at 1 MAC.

The result of our study showed that at 1 MAC end tidal concentration of halothane, isoflurane, sevoflurane and desflurane the BIS value were agent specific and at their 1 MAC end tidal concentration mean BIS value for halothane was 57.0±3.51, for isoflurane 48.0±2.29, for sevoflurane value was 40.65± 2.07, and for desflurane BIS value 35.60±4.68.

On comparison, the BIS value of different anaesthetic agents was found to be statistically significant between the groups, i.e between halothane and isoflurane ($p<0.005$) , halothane and sevoflurane ($p<0.005$), halothane with desflurane ($p<0.005$), isoflurane with sevoflurane ($p<0.005$), isoflurane with desflurane ($p<0.005$) and sevoflurane with desflurane ($p<0.005$).

At 1 MAC value the volume concentration of halothane (0.32±0.05), isoflurane (0.48±0.04) sevoflurane (0.78±0.11) and desflurane (2.65±0.45) produced BIS value of 57.0±3.51, 48.0±2.29, 40.65± 2.07, 35.60±4.68 respectively. The volume concentration of MAC value of different inhalational agents were found to be inversely related to their BIS value.

Various inhalational agents produce specific pattern of EEG and this could contribute to the fact that inhalational agents produce drug specific BIS value at equivalent MAC. BIS utilizes different information from raw EEG. Power and frequency, beta activation and burst suppression are integrated in single number [2].

As anaesthesia deepens the amplitude of high frequency components fall with an increase at lower frequencies , these changes are agent dependent [3].

However, halothane and sevoflurane differently affect the total spectral power and median power of EEG [4].

Halothane produces relatively fast EEG rhythms whereas isoflurane produces mainly slow waves. In addition isoflurane produces burst suppression within the clinical dosage range whereas halothane does not [5,6].

These known differences of halothane and isoflurane on EEG are expected to influence the BIS value differently at a similar depth of anaesthesia. Halothane is known to have a greater analgesic and immobilizing effect (through its spinal action) as compared to isoflurane [7].

Also results can be partly explained by the nature of the BIS and how the algorithm was derived The BIS is determined both by degree of arousal and by direct effects of anesthetic agents on the EEG. At low concentrations (high BIS numbers), the predominant EEG determinant is arousal, and the BIS is less agent specific. At high concentrations (low BIS numbers), the effect of arousal are less, and effect of anaesthetic agents itself are greater [8].

So there is inverse relation between concentration of inhalational agents and BIS value. Further the drug specific BIS value is also strengthened by the fact that the four volatile anesthetics tested, enhanced Gabaergic synaptic inhibition between interneurons. Differential effects on IPSC amplitude and on the prolongation of these currents were observed for each agent, similar to effects observed for CA1 pyramidal neurons [9].

Thus, hippocampal interneuron circuits are depressed by these anesthetics in an agent-specific manner, consistent with a multisite agent-specific theory of anesthetic action [10]. So specific effect on mechanisms underlying EEG generation induced by each anesthetic agents may cause the difference between the BIS value produced by different inhalational agents [10].

Gupta M et al performed a study to compare the hypnotic effects of sevoflurane and isoflurane by analysing the BIS values produced by the two agents. Sixty patients undergoing elective mastoidectomy were allocated into groups receiving either isoflurane or sevoflurane. BIS value was measured at equi-MAC during both wash in and wash out phase. They found that BIS was significantly lower with sevoflurane compared to isoflurane at almost all MAC values [11].

A study conducted by Tirei and wodey et al found that EEG bispectrum is agent dependent and sevoflurane and halothane show different patterns in the EEG bispectrum corresponding to their respective frequencies of coupling [12].

The BIS value under 1 MAC halothane anesthesia to be distinctly higher 62 (43-80), than desflurane, 34 (18-64) , and sevoflurane 40 (20–60), which correlates with our result that at 1 MAC of end tidal concentration, the BIS value for halothane was 57.0±3.51, for sevoflurane value was 40.65±

2.07, and for desflurane BIS value 35.60±4.68. They concluded that the difference between BIS value found in sevoflurane and halothane is not dependent on depth of anesthesia but is attributable to the different pharmacologic effect on EEG frequency.

A study was conducted by HA Samarkandi on paediatrics population to correlate the bispectral index, with end-tidal concentration of inhalation anesthetics. His results reflected the effect of different pharmacokinetic properties of the three anesthetics, with the slowest-and therefore most incomplete-cerebral uptake for halothane, and the fastest for desflurane, with isoflurane in between. As a consequence BIS values for desflurane were significantly lower than for isoflurane and halothane, and BIS for isoflurane was lower than for halothane [26].

He also found that volume concentration of the MAC value is inversely related to BIS value , that at a relatively equipotent doses, the mean BIS value for halothane (60.4±5.6) was significantly higher than isoflurane (45.5±9.2) and desflurane (38.5±9.2) $p<0.001$) which corroborates closely with finding of our result that at a relatively equipotent doses, the mean BIS value for halothane (57.0± 3.51) was significantly higher than isoflurane (48.0±2.29) and desflurane (35.60±4.68).

In a study Davidson and colleagues also found that BIS value obtained under halothane were higher than those under isoflurane at 1 MAC [13].

Similar study reported by Edwards and colleagues showed that mean BIS value of halothane was approximately 15 points higher than with sevoflurane [14].

Also Davidson and Czarencki in a study done on paediatrics population found that at 1 MAC, BIS value of halothane is significantly higher than isoflurane [8].

Result of these study closely corroborates with our study. Neerja Bharti et al in 2007 found the BIS value of halothane and isoflurane at 1 MAC end tidal anesthetic agents to be 54.2±3.7 and 42.4±5.8 respectively [20]. dwards, J.J. par Soto, R.G. par, found that BIS values during surgical levels of halothane anesthesia are significantly higher than those found at equipotent concentrations of sevoflurane [16].

Umamaheswara Rao GS, Ali Z, Ramamoorthy M, Patil J. 2007, concluded, BIS values are significantly lower under isoflurane compared with halothane anesthesia at similar MAC concentrations [17].

For a given anesthetic agent and a given MAC concentration, the BIS values are similar during wash-in and wash-out phases of anesthesia. Hildebrand S chwab, et al. in 2004 studied that at equal multiples of the minimum alveolar concentration, sevoflurane produced lower bispectral index (BIS) values than did halothane [18].

It was found that BIS values in awake patients did not differ between the sevoflurane and halothane groups. At 1MAC with neuromuscular blockade, BIS values for patients anesthetized with halothane exceeded those for patients anesthetized with sevoflurane (p - 0.0001). This finding adds to other evidence indicating that BIS is drug specific. The results of all these studies corroborated well with our findings.

However, BIS has Considerable Limitations [19]

Odri A et al. [20], 2008, reported a case in which there was falsely elevated BIS value, during general anaesthesia, neither neuromuscular blockade nor clinical signs of awareness was present, they attributed it to high-electromyographic activity and electric artefacts, such as extracorporeal-circulation machine and tourniquet, and patient did not complain of recall post operatively. Under some circumstances a BIS value predicted unawareness when awareness did exist [23] Avidian et al. [22], conducted a study and found that patient had awareness inspite of BIS value remaining within normal range, and they proposed that protocol based on end-tidal anesthetic gas (ETAG) measurement is better than BIS-based protocol.

BIS is drug specific, so no specific value guarantees adequate depth of anaesthesia with all anaesthetics [24].

In our study we failed to find an effect of neuro muscular blockade on BIS value, as muscle activity was minimised at 1 MAC and was not further decreased by neuromuscular blocking agents. Another limitation of BIS is that BIS value does not predict likelihood of movement [25].

From this study we can say that at one hand halothane at one MAC is insufficient for prevention of awareness, on other hand desflurane and sevoflurane are more than sufficient at 1 MAC concentration, and infact will delay the recovery period, increase the incidence of nausea and vomiting and increase the cost. With the background knowledge that BIS is specific for each inhalational agent and correlating the BIS value with end tidal concentration, we can prevent awareness and also reduce the recovery time and cost of inhalational anaesthetic agents.

Thus we conclude that halothane produces greater BIS value than isoflurane which is greater than sevoflurane and which produces greater BIS value than desflurane. And this result is consistent with the finding of other studies that BIS value for inhalational anesthetic agent is drug specific.

References

1. Degoute CS, Macabeo C, Dubreuil C, Duclaux R, Banssillon V. EEG bispectral index and hypnotic component of anaesthesia induced by sevoflurane: comparison between children and adults. Br J Anaesth. 2001 Feb;86(2):209-12.
2. Matsuura T, Oda Y, Tanaka K, Mori T, Nishikawa K, Asada A. Advance of age decreases the minimum alveolar concentrations of isoflurane and sevoflurane for maintaining bispectral index below 50. Br J Anaesth. 2009 Mar;102(3):331-5.
3. Prabhakar H, Ali Z, Bithal PK, Rath GP, Singh D, Dash HH. Isoflurane and sevoflurane decrease entropy indices more than halothane at equal MAC values. J Anesth. 2009; 23(1):154-7.
4. Fahlenkamp AV, Peters D, Biener IA, Billoet C, Apfel CC, Rossaint R, et al. Evaluation of bispectral index and auditory evoked potentials for hypnotic depth monitoring during balanced xenon anaesthesia compared with sevoflurane. Br J Anaesth. 2010 Sep; 105(3):334-41.
5. Belda E, Blissitt KJ, Duncan JC, Laredo FG, Escobar Gil de Montes M, Clutton RE. The bispectral index during recovery from halothane and sevoflurane anaesthesia in horses. Vet Anaesth Analg. 2010 Jan; 37(1):25-34.
6. Avidan MS, Jacobsohn E, Glick D, Burnside BA, Zhang L, Villafranca A, et al. Prevention of intraoperative awareness in a high-risk surgical population. N Engl J Med. 2011 Aug 18;365(7):591-600.
7. De Mattos-Junior E, Ito KC, Conti-Patara A, de Carvalho Hda S, Reinoldes A, Caldeira Jde A, et al. Bispectral monitoring in dogs subjected to ovariohysterectomy and anesthetized with halothane, isoflurane or sevoflurane. Vet Anaesth Analg. 2011 Sep;38(5):475-83.
8. Lloyd-Thomas AR, Cole PV, Prior PF. Quantitative EEG and brainstem auditory evoked potentials: comparison of isoflurane with halothane using the cerebral function analyzing monitor. Br J Anaesth. 1990 Sep;65(3):306-12.
9. Yli-Hankala A, Eskola H, Kaukinen S. EEG spectral power during halothane anesthesia.Acomparison of spectral bands in the monitoring of anaesthesia level. Acta Anaesthesiol Scand 1989;33:304-08.
10. Jinks SL, Martin JT, Carstens E, Jung SW, Antogini JF. Peri- MAC depression of a nociceptive withdrawal reflex is accompanied by reduced dorsal horn activity with halothane but not isoflurane. Anesthesiology 2003;98:1128-38.
11. Gupta M, Shri I, Sakia P, Govil D. Comparison of equi-minimum alveolar concentration of sevoflurane and isoflurane on bispectral index values during both wash in and wash out phases: A prospective randomised study. Indian J Anaesth 2015;59:79-84
12. Eger EI, 2nd. Age, minimum alveolar anaesthetic concentration, and minimum alveolar anaesthetic concentration-awake. Anesth Analg. 2001 Oct;93(4): 947-53.
13. Rosow C, Manberg PJ. Bispectral index monitoring. Anesthesiol Clin N Am 2001;19:947–66.
14. Constant I, Dubois MC, Piat V, et al. Changes in electroencephalogram and autonomic cardiovascular activity during inductionof anesthesia with sevoflurane compared with halothane in children. Anesthesiology 1999;91:1604–15.
15. Katoh T, Suzuki A, Ikeda K. Electroencephalographic Derivatives as a Tool for Predicting the Depth of Sedation and Anesthesia Induced by Sevoflurane. Anesthesiology. 1998;88(3):642-50.
16. Nishikawa K, Maclver MB. Agent-selective Effects of Volatile Anesthetics onGABAA Receptor– mediated Synaptic Inhibition in Hippocampal Interneurons. Anesthesiology 2001;94:340-7.
17. Martin- Cancho MF, Lima JR, Luis L, Crisostomo V, Lopez MA, Ezquerra LJ, et al. Bispectral index, spectral edge frequency 95% and median frequency recorded at varying desflurane concentrations in pigs. Res Vet Sci. 2006 Dec;81(3):373-81.
18. Tufano R, Palomba R, Lambiase G, Giurleo LG. [The utility of bispectral index monitoring in general anaesthesia]. Minerva Anestesiol. 2000 May;66(5): 389-93.
19. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 2000;93:1336–44.
20. Bharti N, Devrajan J. Comparison of Bispectral Index Values Produced by Isoflurane and Halothane at Equal End-tidal MAC Concentrations. Indian J Anaesth 2007;51:401.
21. Schneider G, Gelb AW, Schmeller B, et al. Detection of awareness in surgical patients with EEG-based indices: bispectral index and patient state index. Br J Anaesth 2003;91:329–35.
22. Samarkandi AH. The bispectral index system in pediatrics—is it related to the end-tidal concentration of inhalation anesthetics?. Middle East J Anesthesiol. 2006;18(4):769-78.
23. Schneider G, Gelb AW, Schmeller B, et al. Detection of awareness in surgical patients with EEG-based indices: bispectral index and patient state index. Br J Anaesth 2003;91:329–35.
24. Edwards JJ, Soto RG, Bedford RF. Bispectral Index values are higher during halothane vs. sevoflurane

anesthesia in children, but not in infants. Acta Anaesthesiol Scand 2005;49:1084–7.

25. Davidson AJ, Huang GH, Rebmann CS, Ellery C. Performance of entropy and Bispectral Index as measures of anaesthesia effect in children of different ages. Br J Anaesth 2005;95:674–9.
26. Banks MI, Pearce RA. Dual actions of volatile anesthetics on GABA IPSCs: Dissociation of blocking and prolonging effects. Anesthesiology 1999;90: 120–34.