

# 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

Address for correspondence:  
Dr. Iti Shri,  
Department of Anesthesia,  
ESI PGIMS, Basaidarapur,  
New Delhi, India.  
E-mail: itishri\_2605@  
yahoo.com

**Madhu Gupta, Iti Shri, Prashant Sakia, Deepika Govil**  
Department of Anesthesia, ESI PGIMS, Basaidarapur, New Delhi, India

## ABSTRACT

**Background and Aims:** At equal minimum alveolar concentration (MAC), volatile agents may produce different bispectral index (BIS) values especially at low BIS levels when the effect is volatile agent specific. The present study was performed to compare the BIS values produced by sevoflurane and isoflurane at equal MAC and thereby assessing which is a better hypnotic agent. **Methods:** Sixty American Society of Anaesthesiologists I and II patients undergoing elective mastoidectomy were divided into groups receiving either isoflurane or sevoflurane, and at equi-MAC. BIS value was measured during both wash in and wash out phase, keeping other parameters same. Statistical analysis was performed using the Friedman two-way analysis and Mann–Whitney U-test. A  $P < 0.05$  was considered significant. **Results:** BIS value was significantly lower with sevoflurane at all MAC values as compared to isoflurane, except in the beginning and at MAC awake. However, both the drugs proved to be cardiostable. **Conclusion:** At equi-MAC sevoflurane produces lower BIS values during wash in as well as wash out phase as compared to isoflurane, reflecting probably an agent specific effect and a deficiency in BIS algorithm for certain agents and their interplay.

**Key words:** Bispectral monitoring, cardiostability, isoflurane, mean alveolar concentration, sevoflurane

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## INTRODUCTION

A satisfactory general anaesthetic state can be obtained with a balance of hypnotic drugs and analgesic drugs producing hypnosis, analgesia and reflex suppression. With the reports that the patients might recall events and conversation during the anaesthetised state, considerable efforts have been made to improve the methods of assessing the depth of anaesthesia. The bispectral index (BIS) of electroencephalograph (EEG) being one such effective tool in this armamentarium. It monitors the unawareness component of balanced anaesthesia, which is a cortical event and produces a single value (number).<sup>[1]</sup> BIS has been shown to correlate well with brain metabolism and accurately reflects the response of the brain to a variety of hypnotic agents like propofol, midazolam, alfentanil,<sup>[2]</sup>

and the inhaled anaesthetic agents like isoflurane,<sup>[2]</sup> sevoflurane.<sup>[3]</sup>

Anaesthetic agents vary in their relative hypnotic and immobilizing potentials. Therefore, equal minimum alveolar concentration (MAC) of various volatile anaesthetic agents may produce different BIS values.<sup>[4,5]</sup> The aim of the present study was to compare the BIS values at equi-MAC concentrations of isoflurane and sevoflurane.

## METHODS

This prospective randomised controlled study was approved by our Institutional Ethical Committee. A written and informed consent was obtained from 60 American Society of Anaesthesiologists (ASA)

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physical status grade I and II patients aged between 20 and 40 years, posted for elective mastoidectomy. With reference to the previous study,<sup>[4]</sup> a sample size of 30 per group was calculated based on the difference of 3 in BIS values at MAC 1.0 and 1.5 between both the groups, with a standard deviation of 4, at two sided  $\alpha$  error of 0.05, and a power of 80%. ASA grade III and IV patients, patients with uncontrolled hypertension, diabetes, cardiorespiratory disorders, neuropsychiatric disorders, renal or hepatic dysfunction, morbid obesity, history of alcohol or drug abuse and surgeries lasting <60 min were excluded from the study. This was a single-blinded study, where the care providers and then those assessing the outcomes were blinded to the purpose and the agent used respectively.

All patients were subjected to the pre-anaesthetic check-up that included medical history, physical examination, and clinical laboratory tests at which they were explained about the nature of the study.

The patients were pre-medicated with tablet diazepam 5 mg the night before and 2 h before surgery and were randomly allocated using a computer-generated number to either the isoflurane (I) or the sevoflurane (S) group, each having 30 patients. There were no losses after the patients were randomised and allocated in the respective group.

On arrival in the operating room, each patient was put on standard monitoring (Spacelabs Healthcare Ultraview® SL 2700 monitor) comprising of body temperature, non-invasive blood pressure, pulse oximetry (SpO<sub>2</sub>), end-tidal carbon dioxide (EtCO<sub>2</sub>), heart rate (HR) and electrocardiography and baseline readings were recorded.

Bispectral index monitoring was initiated using the Aspect 'Quatro' 4 point BIS sensor and the patient's awake BIS was recorded. The Spacelabs Healthcare 91482 BISx™ module version V1.00.13 acquires real-time EEG data and processes it into a BIS number between 0 and 100. The Spacelabs Healthcare 91518® multigas sidestream analyser was used to measure various inspired and expired gases and inhalational anaesthetic agents and also displaying MAC of the inhalational anaesthetic agents. The vapourisers used were Bleas Datum L® series isoflurane and sevoflurane vapourisers. Five minutes prior to induction both the groups were administered fentanyl 2 µg/kg intravenously (i.v.), and then induced with propofol 2 mg/kg i.v. and ventilated for 60 s after

injecting i.v. rocuronium 1 mg/kg to facilitate tracheal intubation. Anaesthesia was maintained in all cases with 66% nitrous oxide in oxygen and either isoflurane or sevoflurane according to the group of the patient. Patients were put to mechanical ventilation and EtCO<sub>2</sub> was maintained in the range of 32–35 mmHg. Total fresh gas flow was kept constant at 3 L/min. Injection rocuronium 0.1 mg/kg was administered at 1 twitch response on the train of four monitor. Supplemental doses of fentanyl 1.0 µg/kg i.v. was given if there was a persistent increase in HR (>100 bpm) or blood pressure (>20% of baseline values) in both the groups. Body temperature was maintained above 35.5°C in all cases.

The inspired and end-tidal concentrations of the inhalational agent and carbon dioxide were measured. 10 min after the incision, the end-tidal concentration of the inhaled anaesthetic agent was adjusted to 0.5 MAC and kept constant for 10 min (for BIS values to stabilize) and various parameters including the BIS were recorded. The BIS values were recorded only when the signal quality index was above 50%. Then the inspired concentration of the inhaled anaesthetic agent was increased to 1.0 and 1.5 MAC collecting the data each time at the end of 10 min. The concentrations were then decreased in the same graded manner from 1.5 MAC to 1 and finally to 0.5 MAC, recording the various parameters each time. After each increment or decrement of the inhaled anaesthetic agent, the concentrations were kept constant for 10 min to reduce the difference between the inspired and end-tidal concentrations of the agent to a minimum.

The inhalation agent was discontinued just before skin closure and the residual neuromuscular blockade reversed at the end of surgery. While the end-tidal concentration of the inhaled anaesthetic was decreasing, the patients were asked to open their eyes. After extubation, they were shifted to the post-operative care unit for monitoring vital parameters.

Patient data is presented as mean (standard deviation range). Two sample unpaired students *t*-test was used to compare demographic data and duration of surgery between the two groups. Friedman two-way analysis of variance was applied to see the trends of BIS values in each group. Mann–Whitney U-test was used to compare the BIS values between the two groups.  $P < 0.05$  was considered significant.

## RESULTS

The demographic characteristics and mean duration of surgery were comparable in both the groups [Table 1].

The haemodynamic parameters viz., HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure were recorded at various concentration of anaesthetic agent in both the groups I and S.

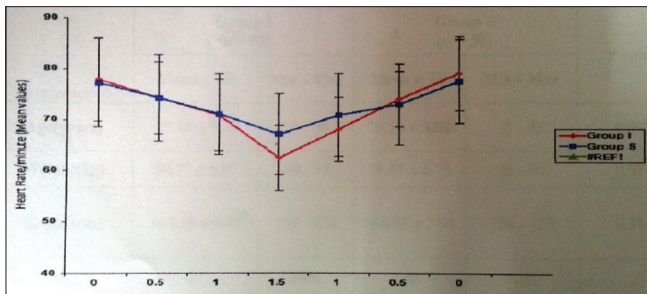
A significant reduction in HR was observed with isoflurane at a higher MAC of 1.5 ( $62.53 \pm 6.43$  vs.  $67.27 \pm 8.04$ ,  $P < 0.015$ ) [Figure 1], and a significant drop in SBP ( $P < 0.046$  at 1 MAC and  $< 0.027$  at

0.5 MAC) [Figure 2], DBP ( $P < 0.010$ , 0.001, 0.0004 at 1.5, 1.0, 0.5 MAC respectively) [Figure 3] and MAP ( $P < 0.001$ , 0.001, 0.004 at 1.5, 1.0, 0.5 MAC respectively) was recorded with isoflurane during reduction phase of MAC.

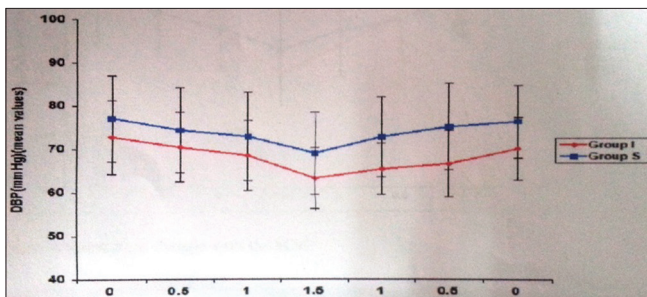
Bispectral index was recorded for both inhalational agents at the various MACs [Table 2]. BIS was significantly lower (40–55) with sevoflurane at almost all MAC values with  $P < 0.05$  [Figure 4].

## DISCUSSION

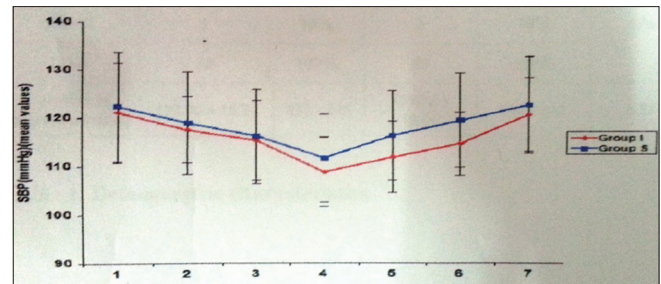
The neuro-physiologic properties of isoflurane and sevoflurane have been reported to be similar, both cause a dose-related depression of the central nervous system.<sup>[6,7]</sup> For isoflurane, 0.25 MAC produces amnesia. At 1MAC, both EEG frequency and voltage increase.



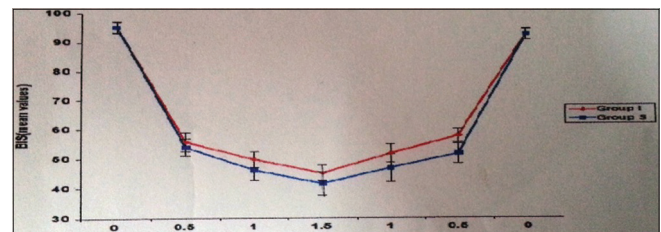
**Figure 1:** Comparison of heart rate (beats/min) changes with mean alveolar concentration values of isoflurane and sevoflurane



**Figure 3:** Comparison of diastolic blood pressure (mm Hg) changes with mean alveolar concentration values of isoflurane and sevoflurane



**Figure 2:** Comparison of systolic blood pressure (mmHg) changes with mean alveolar concentration values of isoflurane and sevoflurane



**Figure 4:** Comparison of bispectral index value changes with mean alveolar concentration values of isoflurane and sevoflurane

**Table 1: Demographic characteristics**

Parameter	Group I (n=30)		Group S (n=30)		P value
	Mean±SD	Min-max	Mean±SD	Min-max	
Age (years)	29.93±5.39	21-38	29.13±5.03	21- 39	
Weight (kg)	50.77±5.67	43-59	51.97±4.73	42-59	
Height (cm)	164.10±6.47	153-174	165.87±7.04	154-178	
Female	27	90%	27	90%	
Male	3	10%	3	10%	
Total	30	100%	30	100%	
ASA I	27	90%	27	90%	
ASA II	3	10%	3	10%	
Total	30	100%	30	100%	
Duration of surgery (minutes)	192.90±18.34	159-235	193.93±19.01	161-232	0.831

SD – Standard deviation, ASA – American Society of Anaesthesiologists

**Table 2: Comparison of BIS values at equi MAC value of isoflurane and sevoflurane**

MAC	Group I (n=30)		Group S (n=30)		P value
	Mean±SD	Min-max	Mean±SD	Min-max	
0.00	95.33±1.86	92-98	95.37±1.88	93-99	0.945
0.50	55.87±3.19	50-63	54.13±2.83	48-61	0.030
1.00	49.87±2.69	44-56	46.30±3.44	40-53	0.0003
1.50	45.17±2.76	39-51	41.63±3.97	34-48	0.0001
1.00	51.83±3.17	46-58	46.90±4.72	38-59	0.0001
0.50	57.90±2.28	53-65	51.83±3.36	46-57	<0.0001
0.00	92.77±1.94	89-96	92.73±1.80	90-96	0.945

SD – Standard deviation, BIS – Bispectral index, MAC – Minimum alveolar concentration

At deeper levels of anaesthesia, voltage and frequency decrease. Burst suppression occurs at 1.5 MAC, and an isoelectric pattern appears at 2.0 MAC.<sup>[8]</sup> Sevoflurane causes dose-related changes in EEG that parallel those found with isoflurane.<sup>[9]</sup> There have been studies comparing the effects of equi-MAC of sevoflurane and halothane<sup>[5,10]</sup> and isoflurane and halothane<sup>[4,11]</sup> on BIS, where sevoflurane or isoflurane had a greater decrement in the BIS values but there are very few studies comparing the effects of isoflurane and sevoflurane on EEG and other EEG parameters, which were mostly related to EEG spike activity during sevoflurane anaesthesia.<sup>[7]</sup> A lower BIS value was recorded in our study, at equi-MAC of sevoflurane as compared to isoflurane which was significant ( $P < 0.05$ ). This could have been due to the following reasons, although both of them have similar tissue-blood partition coefficient, MAC awake to MAC ratio; studies have been there where an increase in isoflurane concentrations from 0.79% to 1.26% was shown to cause a paradoxical arousal reaction as it results in the alpha and the beta waves in a pattern similar to that of light anaesthesia.<sup>[12]</sup> A similar paradoxical arousal in the mean BIS (A-1000 version 3.12) value from 35 to 46 was reported with the increase of isoflurane concentrations from 0.8% to 1.6%. BIS returned to baseline values with the return to 0.8%. It is possible that the paradoxical increase in BIS is related to continuous pre-burst EEG patterns consisting of high-frequency activity.<sup>[13]</sup>

Also, addition of 66% nitrous oxide could have resulted in the paradoxical effects. Both Porkkala *et al.*<sup>[14]</sup> and Yli-hankala *et al.*<sup>[15]</sup> have shown that nitrous oxide antagonised the depressant effects of isoflurane on the EEG. Sebel *et al.*<sup>[16]</sup> found that BIS values when isoflurane was used in combination with N<sub>2</sub>O were higher as compared with isoflurane when used alone. Analogous effects were observed by Glass *et al.*, who showed that the addition of nitrous oxide to propofol increased the BIS at which patients failed to respond to verbal commands.<sup>[3]</sup> While in a study by Nakayama

*et al.*,<sup>[17]</sup> that N<sub>2</sub>O with sevoflurane caused more reduction in BIS in comparison with sevoflurane alone that is, enhanced its hypnotic effect. Ozcan *et al.* found that N<sub>2</sub>O decreased both BIS and state entropy (SE) when added to sevoflurane, but not to propofol. This could result from a true additive effect and second gas effect of N<sub>2</sub>O that was unaccounted for despite a meticulous titration of sevoflurane using end-tidal gas monitoring.<sup>[18]</sup>

However, study by Tariq Al-Zahrani concluded that BIS during O<sub>2</sub>/N<sub>2</sub>O/sevo anaesthesia for lower segment caesarean section did not change significantly compared to O<sub>2</sub>/air/sevoflurane anaesthesia.<sup>[19]</sup> Barr *et al.* found no effect of N<sub>2</sub>O on the BIS when given alone or added to isoflurane.<sup>[20]</sup> In fact studies about nitrous oxide effects on BIS are conflicting, possibly reflecting an inadequate algorithm used to calculate BIS from EEG. These paradoxical changes could have resulted from an alteration in the relative  $\beta$  ratio with the nitrous oxide or on withdrawal of it.<sup>[21]</sup> These findings question BIS efficiency as anaesthetic monitor in patients receiving nitrous oxide as a sole agent or associated to other anaesthetic agents.

The BIS is determined both by degree of arousal and by direct effects of the anaesthetic agent on the EEG. At low concentrations, the predominant EEG determinant is arousal, and the BIS is less agent specific while at higher concentrations the effects of anaesthetic itself are greater. At low BIS numbers, the BIS may be more agent specific, and is tracking brain anaesthetic concentration rather than the real measure of arousal.<sup>[4]</sup>

We have used diazepam ensuring stable sedation at the time of measurement of the baseline values of BIS.

Premedication did not disturb the level of consciousness. It has already been shown that benzodiazepines do not shorten the time taken to achieve loss of consciousness with inhalational induction with sevoflurane.<sup>[22]</sup>

Our study also reinforces the idea that we can titrate the amount of anaesthetic given by monitoring BIS, thereby reducing the amount of drug administered and shortening recovery time;<sup>[23,24]</sup> reducing operation theatre pollution and averting even some side effects such as post-operative vomiting.<sup>[25]</sup>

As for haemodynamics a significant reduction in HR was observed with isoflurane at a higher MAC

of 1.5, and a significant drop in SBP, DBP and MAP was recorded with isoflurane during reduction phase of MAC. The comparative studies have shown that both sevoflurane and isoflurane have a similar haemodynamic profile<sup>[26,27]</sup> which does not correlate with our findings. A probable reason could be a slower wash out and carry over effect of isoflurane as compared to sevoflurane resulting into sustained haemodynamic alterations during continuous administration. However, at MAC awake both had comparable haemodynamic parameters. According to a study by Tanaka and Nishikawa<sup>[28]</sup> there occurred a rapid recovery of baroreflex sensitivities to conscious baseline level after sevoflurane anaesthesia because of its low blood-tissue solubility as compared to isoflurane. This was however later on again antagonised by Nagasaki *et al.*<sup>[29]</sup> Similarly in a study by Driessen *et al.*<sup>[30]</sup> horses under sevoflurane anaesthesia may require less pharmacological support in the form of dobutamine than isoflurane anaesthetised horses. This could be due to less suppression of vasomotor tone, at 1.2 MAC, and for the same degree of hypotension, tachycardia was more pronounced with sevoflurane than with isoflurane, consequently sevoflurane at low concentration may be less depressant to baroreflex function. So the clinical significance of our finding still needs to be validated, but in this conflicting state of affairs it is conclusively demonstrated that both isoflurane and sevoflurane are cardiostable as none of the patients in the either group had the requirement of parasympatholytics or vasopressors as demonstrated in other studies as well.

One of the limitations of our study is that it effectively demonstrates the oft repeated effects of isoflurane and sevoflurane with nitrous oxide on BIS and so a deficiency in BIS algorithm but it fails to demonstrate our primary aim of the assessment if one agent is a better sedative as compared to other, based on BIS values alone. Another limitation is the use of opioid that could have influenced our results. Use of fentanyl enhances the hypnotic effect of propofol and BIS failing to show this increased hypnotic effect. There is a paucity of literature on the effect of fentanyl on the inhalational anaesthetics but as stated, at hypnotic endpoint, low concentration of fentanyl 1–2 ng/ml have a minor effect on volatile anaesthetic dose and thereby probably not influencing the BIS values at the doses used in our study.

## CONCLUSION

Our study effectively demonstrates that at equi-MAC

sevoflurane produces lower BIS values, so better hypnotic agent as compared to isoflurane, probably an agent specific effect on BIS and a deficiency in the BIS algorithm for certain agents and their interplay. As for haemodynamics, HR and blood pressure were more stable with sevoflurane as compared to isoflurane. Also, use of BIS helps in careful titration of hypnotic agents and so an earlier recovery from anaesthesia. More studies with a bigger sample size are needed to validate our findings.

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## Announcement

### CALENDAR OF EVENTS OF ISA - 2015

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
30 <sup>th</sup> June 2015	Bhopal Award for Academic Excellence	Hony. Secretary, ISA
15 <sup>th</sup> August 2015	Prof. A. P. Singhal Life Time Achievement Award	Hony. Secretary, ISA
31 <sup>st</sup> October 2015	Dr. (Mrs.) Rukmini Pandit Award - Publication format along with Conference Presentation Certificate	Hony. Secretary, ISA
31 <sup>st</sup> October 2015	Y. G. Bhoj Raj Award - Best Review Article in IJA	Hony. Secretary, ISA
31 <sup>st</sup> October 2015	Dr. Kop's Award	Chairman Scientific committee of ISACON with a copy to Hony Secretary ISA
27 <sup>th</sup> November 2015	Dr. TN Jha Memorial & Dr. KP Chansoriya Travel grant	Hony. Secretary, ISA
27 <sup>th</sup> November 2015	Late Dr. Venkata Rao Memorial Oration	Hony. Secretary, ISA
27 <sup>th</sup> November 2015	Ish Narani Best Poster Award	Chairman Scientific Committee ISACON
28 <sup>th</sup> November 2015	ISA GOLDCON QUIZ Competition	Chairman Scientific Committee ISACON
28 <sup>th</sup> November 2015	Awards for	Hony. Secretary, ISA
	1. Best City Branch	
	2. Best State Branch	
	3. Best Metro Branch	
	4. Public Awareness Individual	
	5. Public Awareness City	
	6. Public Awareness State	
	7. Ether Day State	
	8. Ether Day City	
	9. Membership Drive % (State)	
	10. Membership Drive No.s (State)	
	11. Individual Drive	

**Dr. Venkatagiri K M**

"ASHWATHI", Opp. Ayyappa Temple, Nullippady, Kasaragod - 671121, Kerala

Email: [isanhq@gmail.com](mailto:isanhq@gmail.com) / [secretaryisanhq@gmail.com](mailto:secretaryisanhq@gmail.com) / [isanhq@isaweb.in](mailto:isanhq@isaweb.in) Mobile: 093880 30395