Original Article

A study of the relationship between Bispectral index and age-adjusted minimum alveolar concentration during the maintenance phase of general anesthesia in elective surgery

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Abstract

Background and Aims: Bispectral index (BIS) and minimum alveolar concentration (MAC) are commonly used to monitor the depth of anesthesia. The objective was to study the correlation between BIS and age-adjusted minimum alveolar concentration (aaMAC) during the maintenance phase of anesthesia. The influence of variables affecting BIS and or aaMAC was studied to determine an equation between BIS and aaMAC.

Material and Methods: This prospective observational study was carried out after institutional ethical approval in adult patients 18–60 years of either sex, ASA I and II posted for elective surgery under general anesthesia. Five minutes after airway management, BIS values and aaMAC equivalents were noted during the maintenance phase of anesthesia. aaMAC and corresponding BIS values were recorded every minute for periods, where the anesthetic agent concentration had remained the same during preceding 5 minutes till the switching off of the anesthetic agent. Age, sex, ASA status, use of nitrous oxide, inhalational agent, dose of midazolam, and opioid used were also recorded.

Results: BIS/aaMAC showed an inverse correlation. Increasing age, ASA II status, morphine equivalent >5, and use of nitrous oxide, sevoflurane, or isoflurane were associated with a higher BIS at equivalent aaMAC. Using the exchangeable correlation structure, a generalized estimation equation was obtained as the best predictor.

Conclusion: Factors affecting both aaMAC and BIS affect the relationship between the two, and although there are wide variations, BIS and aaMAC can be equated and values of either can be calculated if one is known using a generalized estimates equation.

Keywords: Bispectral index monitor, consciousness monitor, estimation techniques, general anesthesia, inhalation anesthesia, statistical factor analysis

Introduction

For over a century, inhaled anesthetic agents have been used to produce amnesia, prevent recall, and respond to noxious stimuli. The concept of minimum alveolar concentration (MAC) was introduced by Eger *et al.* in 1965 to monitor their relative potencies.[1] The concentration of the anesthetic agent required to suppress movement varies with the age of an individual; therefore, age-adjusted MAC (aaMAC) can better predict the depth of anesthesia.[2]

Historically, depth of anesthesia has usually been guided by intraoperative hemodynamic and end-tidal concentration of inhaled anesthetics. These being indirect indicators, may

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_153_23

How to cite this article: Kumar N, Bansal G, Jain A. A study of the relationship between Bispectral index and age-adjusted minimum alveolar concentration during the maintenance phase of general anesthesia in elective surgery. J Anaesthesiol Clin Pharmacol 2024;40:626-32.

Submitted: 07-Apr-2023 **Revised:** 15-May-2023
Accepted: 29-May-2023 **Published:** 23-May-2024

not reflect the actual depth. Bispectral index (BIS) gives an indication of the depth of anesthesia by processing the electroencephalographic waves.

A BIS value between 40–60 and aaMAC above 0.7 is expected to minimize the possibility of intraoperative awareness and is considered the adequate depth of anesthesia for routine surgeries.[3] An inverse correlation exists between BIS and aaMAC. The more the depth of anesthesia, the lower the BIS and the higher the aaMAC. The amount of anesthetic to be administered to maintain an adequate depth and prevent recall is therefore guided by the confines of BIS 40–60 and aaMAC >0.7.

An equation has been postulated by Whitlock *et al.*[4] to estimate the BIS from end-tidal concentration of an anesthetic agent expressed as aaMAC in patients at high risk of awareness.[4] However, the same cannot be validated for routine elective patients whose anesthetic conditions and requirements are different. With the advancement of technology and an increasing use of artificial intelligence in anesthesia, a mathematical relationship between aaMAC and BIS may be useful in developing an algorithm for closed-loop delivery of inhalational anesthesia. Therefore, this study was designed with a primary objective to study the relationship between BIS and aaMAC, and secondarily, their relationship with factors presumed to affect either BIS or aaMAC or both in patients undergoing elective surgery.

Material and Methods

This prospective observational study was carried out after approval by the Institutional Ethics Committee IEC No.: LHMC/ECHR/2016/42R1 dated: 02.11.2016 from November 2016 to March 2018 in adult patients 18–60 years of either sex, American Society of Anesthesiologists Physical Status (ASA) I and II posted for elective surgery under general anesthesia. Patients receiving total intravenous anesthesia, duration of surgery >2 hours, surgical procedures or positioning preventing BIS monitoring, and patients with a history of stroke or with any residual neurological deficit were excluded from the study. The trial was registered with CTRI (CTRI/2016/11/007432/ Dated: 04.11.2016; www.ctri.nic.in). Written informed consent for inclusion in the study was obtained from the patient. This study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013).

After a detailed pre-anesthetic checkup and investigations, adequate fasting, premedication, and a written informed consent for surgery and anesthesia, patients were shifted to the operating room. A pulse oximeter, electrocardiography, and noninvasive blood pressure were attached and readings were noted. Intravenous access was secured. Intravenous fluid was started. A BIS sensor (BIS Quatro) was applied to the forehead of each patient. Correct placement was confirmed and a baseline value was noted. All patients received general anesthesia with inhalational anesthetic agents as per the anesthesiologist in charge.

After induction of anesthesia and airway management, BIS values and aaMAC equivalents were noted during the maintenance phase of anesthesia (05 minutes after airway management to switching off of anesthetic agent before reversal). The aaMAC and corresponding BIS values were recorded every minute for periods where the anesthetic agent concentration had not increased or decreased by greater than 0.1 aaMAC during the preceding 5 minutes. Once the stability criteria were met, all the data points were included until the aaMAC again changed more than 0.1.

A record was also made of patient-related factors—age, sex, ASA physical status, and anesthesia-related factors—use of nitrous oxide, inhalational agent, total dose of midazolam and opioid used (expressed as morphine equivalent dose −100 μg of fentanyl = 10 mg morphine i.v = 10 morphine equivalent) which may influence the depth of anesthesia.

The primary objective was to study the correlation between BIS and age-adjusted MAC during the maintenance phase of anesthesia in elective surgery. The influence of other variables affecting BIS was also studied to determine an equation between BIS and aaMAC.

Statistical analysis

A previous study reported a correlation coefficient between BIS and MAC to be −0.16 (Whitlock *et al.*,[4] 2011). With this value of the correlation coefficient, the minimum required sample size at 85% power and 5% level of significance was found to be 348 patients. Therefore, 350 patients were observed for the present study.

Data were compiled, tabulated, and analyzed using Statistical Package for Social Sciences (SPSS) software version 15.0. The correlation between quantitative variables was evaluated using Spearman Correlation (rho) coefficient. Multivariate analysis was performed to obtain the predicting equation of BIS with aaMAC using factors which may affect either or both. A rho value of <0.4 was considered poor, 0.4–0.6 moderate, 0.6–0.8 good, and >0.8 as excellent correlation. A P value <0.05 was considered statistically significant.

Results

A total of 364 patients were recruited for the study. Four cases exceeded the time duration, there was equipment failure in eight cases, and two patients refused consent. Therefore, data from 350 patients were included in the final analysis.

The mean age of the study population was 36.58 ± 11.48 years with a median of 35 years (18–60 years). Patient characteristics are described in Table 1.

The opioid doses were converted to morphine equivalent, which ranged from 2 to 16, with a mean of 9.3 ± 2.1. The mean midazolam used was 0.34 ± 0.49 mg, with a maximum of 2 mg.

Each pair of BIS and aaMAC recorded for 350 patients was considered as a single datum point. With the method described, 17,791 data points were analyzed.

Bispectral index and aaMAC showed an inverse correlation. There was a wide distribution of BIS over a range of aaMAC. The Spearman correlation coefficient was rho −0.448, which was statistically significant ($P < 0.001$) and showed moderate correlation. The distribution of the range of BIS and aaMAC is depicted in Table 2. The line intersecting the graph represents the linearity [R Sq Linear = 0.211; Figure 1].

The relationship of patient factors such as age, gender, ASA status and anesthetic factors midazolam, use of opioids (as morphine equivalent), nitrous oxide, and volatile agents which may affect BIS with respect to BIS/aaMAC is described in Table 3.

Increasing age, ASA status II, morphine equivalent (ME) >5, use of nitrous oxide, sevoflurane, or isoflurane were associated with a higher BIS at aaMAC 1, which was statistically significant.

Based on the above parameters, generalized estimation estimates (GEE) were calculated using the exchangeable working correlation structure [Table 4]. A P value of <0.05 was considered significant. None of the variables except aaMAC were found to be statistically significant. The following equation was obtained as the best predictor:

BIS = 75.565 – 0.102 (age < 35) – 0.486 (female) +0.624 (ASA = II) – 0.859 (nitrous oxide not used) – 0.411 (midazolam >1 mg) +1.705 (opioid dose >5 morphine equivalents) – 0.236 (desflurane) +0.266 (isoflurane) – (21.582* aaMAC).

(Inhalational agent taken as constant is sevoflurane)

The GEE demonstrates that, on an average, for every 0.1 aaMAC increase during the maintenance phase of anesthesia, the BIS value will decrease by an estimated 2 units, and increasing MAC from 0.8 to 1.2 would decrease BIS by 8 units.

BIS has a clinical range of 40–60. Assuming the midpoint of 50, values of aaMAC are depicted in Table 5.

Table 1: Patients characteristics

Characteristics		No of patients (%)
Age	≥35	179 (51.1)
	<35	171 (48.9)
Gender	Male	67 (19.1)
	Female	283 (80.9)
ASA status	ASA I	272 (77.7)
	ASA II	78 (22.3)

Values are n (%). ASA: American Society of Anesthesiologists

Discussion

It is a known and logical fact that an increase in aaMAC would result in a lower BIS. Our study showed a moderate inverse correlation of 0.448 between the two. However, there are several factors which may independently affect either of the two values without having an impact on the other. We studied these various factors and tried to evaluate the effect of these factors on BIS and aaMAC. Failure to adjust the anesthetic requirements as per individual variations may lead to over and under dosage of drugs which may lead to intraoperative awareness or excessive anesthetic depth, which is harmful to the patient.[5] Patient's response to anesthesia changes over the course of the operation. There is, therefore, no correct

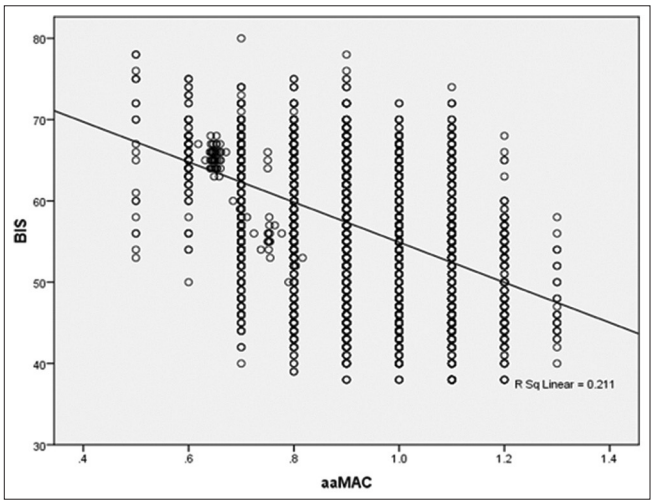

Figure 1: Correlation between BIS and aaMAC (n = 17791)

Table 2: Correlation between BIS and aaMAC (*n*=17791)

Variable	Median	Range	Minimum	Maximum	Percentile (25th, 75th)	rho	*P*
BIS	56	42	38	80	53,63	−0.448	<0.01*
aaMAC	0.9	0.8	0.5	1.3	0.8,1.0		

**Highly significant, Values are median (1Q, 3Q). BIS: bispectral index; aaMAC: age-adjusted minimum alveolar concentration*

Table 3: Correlation of factors with BIS and BIS/aaMAC

Variable		*n*	Mean±SD (BIS)	*P* (BIS)	rho	*P*
Age group	≥35 years	9070	56.88±6.65	0.001*	-0.462	0.01*
	< 35 years	8721	56.42±6.60		-0.431	
Gender	Male	3419	57.01±6.25	0.093	-0.452	0.795
	Female	14372	56.80±6.75		-0.448	
ASA	ASA I	13787	56.65±6.61	<0.001*	-0.416	<0.001*
	ASA II	4004	57.50±6.66		-0.546	
N_2O	Used	16277	56.88±6.63	<0.001*	-0.430	<0.001*
	Not used	1514	56.42±6.63		-0.622	
Morphine equivalent	≤ 5 ME	1040	55.00±7.02	<0.001*	-0.274	<0.001*
	> 5 ME	16751	56.95±6.59		-0.457	
Midazolam	≤ 1 mg	17548	56.86±6.65	<0.01*	-0.447	0.704
	> 1mg	243	55.02±5.06		-0.427	
Inhalational agent	Sevoflurane	14498	56.66±6.60	0.202	-0.461	Sevo: Des- <0.001*
	Desflurane	1979	56.64±7.09		-0.355	Des: Iso- <0.001*
	Isoflurane	1314	56.84±6.33		-0.455	Sevo: Iso- 0.795

**Highly significant, Values are Mean±SD. ASA: American Society of Anesthesiologists; N_2O: nitrous oxide; ME: morphine equivalents; Sevo: sevoflurane; Des: desflurane; Iso: isoflurane*

Table 4: Generalized estimation equation estimates

Parameter	Estimates	Std. error	95% Wald confidence Interval		*P*
			Lower	Upper	
Age group <35 years	-0.102	0.4347	-0.954	0.750	0.814
Female	-0.486	0.4841	-1.435	0.462	0.315
ASA II	0.624	0.4701	-0.297	1.545	0.184
Nitrous oxide is not used	-0.859	0.6065	-2.048	0.329	0.157
Midazolam >1 mg	0.411	1.1875	-1.916	2.739	0.729
Morphine equivalent >5	1.705	1.1228	-0.496	3.906	0.129
aaMAC (slope)	-21.582	1.4118	-24.349	-18.815	<0.0001*
Desflurane	-0.236	0.7712	-1.748	1.275	0.759
Isoflurane	0.266	0.7633	-1.230	1.762	0.728
Extrapolated intercept of the GEE equation on the BIS (y) axis	75.565	1.8035	72.031	79.1	<0.0001*

**Highly significant, Values are estimates (SE, 95% CI). ASA: American Society of Anesthesiologists; aaMAC: age-adjusted minimum alveolar concentration; GEE: generalized estimation equation; BIS: bispectral index*

Table 5: aaMAC at BIS 50

aaMAC at BIS 50		Minimum	Maximum	25th & 75th percentile
Mean±SD	0.968±0.13	0.6	1.3	0.9 and 1.1
Median	1.00			

Values are Mean±SD and Median (1Q, 3Q). aaMAC: Age-adjusted minimum alveolar concentration; GEE: Generalized estimation equation; BIS: Bispectral index

dose of anesthetic agents and their use in combination makes the task much more difficult.

For over a century, MAC remained the most commonly used measure of anesthetic potency for inhaled drugs when used alone or in combination with other inhalational agents.[1] It can be easily measured and is mandatory with a close circuit and the use of soda lime. Unfortunately, several patient factors and other anesthetic agents have an effect on its potency which cannot be measured.

Recently, bispectral index, a multiprocessor EEG parameter was developed to measure the effects of anesthetics on the brain hypnotic state and has proved to be a reliable method to assess brain function and allows the titration of hypnotics on cortical activity.[6] However, the use of depth of anesthesia monitoring like BIS to be used in all cases, or only those at higher risk of awareness continues to be debated, partly due to nonavailability and economic issues.

BIS and MAC both reflect the depth of anesthesia, reduce intraoperative drug consumption, reduce emergence and recovery time, improve patient satisfaction, and decrease the incidence of awareness and recall.[7-14] Nonavailability and cost prevent the widespread use of BIS, though MAC is commonly used. It has been further shown that the combination of the two may help provide a stable depth of anesthesia and reduce the incidence of awareness and recall.

In the absence of BIS monitoring, the value may be calculated using the equation provided by our study. All the patient and anesthetic factors that may affect either BIS or MAC were studied.

Age has an effect on MAC. Mean MAC decreases by approximately 1.8 per decade increase in age.[15] Mapleson[16] proposed a linear and parallel relationship between equi-MAC concentrations of inhalational agents and MAC and reported that for age >1 year, $\log_{10}$MAC decreases by 6% approximately per decade increase in age. Similar results were found by Tokuwaka[6] that increasing age >2 years leads to a decrease in MAC of sevoflurane to maintain BIS 50. This bias was removed from our study by including aaMAC instead of MAC. aaMAC is defined as $MAC_{40} * 10^{-0.00269(age-40)}$ as a function of MAC at the age of 40 years (MAC_{40}).[2] aaMAC with a combination of the inhalational agent is the sum of MAC fraction of volatile inhalation agent and nitrous oxide used.[17]

Gender on the other hand was not found to affect either MAC or BIS.

With increase in morbidity, the requirement for anesthetic agents should decrease, thus lowering BIS when compared to healthy individuals at equi-MAC concentrations. An opposite correlation was observed in our study, whereby BIS increased in ASA II patients as compared to ASA I patients. This could be due to the low distribution of data in ASA II status. Whitlock *et al.*,[4] on the other hand, described a decrease in BIS with ASA status >III.

The effect of nitrous oxide on BIS has been controversial, with studies both in favor and against it. The effect of nitrous oxide seems to be dose related. While 50%–70% N_2O does not change BIS, sudden interruption leads to a decrease in BIS as a consequence of increased activity of low-frequency α and ε waves.[18] BIS values were lower in our patients in whom nitrous oxide was not used, an observation supported by Mishra *et al.*[19] This could also be because the addition of nitrous oxide reduces the requirement of an inhalational agent, thus increasing BIS. Therefore, the use of nitrous oxide may increase BIS due to its direct effect on BIS and decreased requirement for the inhalational agent.

We observed a decrease in BIS with an increase in midazolam. Midazolam like other anesthetic agents produces dose-related changes on EEG and MAC probably because of an increased level of sedation, leading to a change of high-frequency alpha and beta power to low-frequency delta and theta power. Midazolam when used along with inhalational agents causes a decrease in MAC due to its synergistic action.[20] Due to its similar action on both BIS and aaMAC, midazolam did not have a statistically significant effect on the relationship between the two.

Although BIS is relatively insensitive to the addition of opioids, the effect as described in the literature seems to be variable based on the drug used.[21] Opioids cause minimal electrophysiological changes in the cerebral cortex and the subcortical area involved in the mechanism of action of opioids is not detected by EEG.[22,23] An opioid dose of almost five times the analgesic dose is required for the appearance of EEG depression.[24] Whitlock *et al.*,[4] however, found a decrease in BIS as they had used >50 morphine equivalents.

We found a dose-related effect—an increase in the opioid dose (fentanyl) led to an increase in BIS. Increasing the dose of opioids will lead to a decrease in inhalational agent requirement, thus causing an increase in BIS. This could also have been due to the influence on BIS through response to noxious stimuli, leading to cortical arousal thus causing an increase in BIS.[24] Thus, an increase in opioid dose affects the relationship between BIS and aaMAC due to a decrease in aaMAC.

Several authors have reported that at equi-MAC, BIS values are not the same for different inhaled anesthetics as each one of them has a different EEG signature.[24-27] We found similar findings in our study, desflurane causing a greater decrease in BIS compared to sevoflurane and isoflurane at equi-MAC concentrations.

Only one study conducted by Whitlock *et al.*[4] has determined a relationship between BIS and aaMAC and the influence of various other factors on BIS. Although the variables affecting BIS and MAC were not found to have a statistical significance in the GEE, they do affect the correlation between BIS and aaMAC.

They reported a weak correlation between the BIS and aaMAC, which is in contrast to the moderate correlation observed by us. They demonstrated that for every 0.1 aaMAC increase during the maintenance phase of anesthesia, the BIS

value will decrease by approximately 1.5 units whereas in our study we found that 0.1 increase in aaMAC led to a decrease in BIS by 2 units. They monitored the depth of anesthesia by either constant end-tidal anesthetic concentration or BIS, which was maintained by increasing or decreasing the inhalational agent. However, in our study there was no such restriction and the depth was decided by the consultant anesthesiologist taking into account either the clinical parameters and/or aaMAC and/or BIS. The major advantage of our study over that of Whitlock *et al*[4] is whereas they have used arbitrary cutoff points for variables included in the GEE, we have used median values. Another striking difference in their study was the inclusion of ASA III and IV patients, those posted for emergency surgery, inter-patient variability, and postoperative mortality. They disregarded the values falling to the extremes. We did not take into account postoperative data. The other major advantages of our study include that we have included routine elective surgery patients only and the effect of different inhalational agents has also been included in GEE.

The main limitation of our study was that it was an observational study. This was mitigated by taking into account anesthetic practice by different consultants. The administration of anesthetic agents was not guided by the BIS index value by all. This anomaly can be removed by setting a range of BIS and aaMAC to be maintained intraoperatively. This limitation is in fact the greatest strength of the study too. By studying the wide variation of anesthetics administered, the individual response of the patients will only strengthen the development of mathematical correlation, which would make the algorithm more robust and discern any deviations from the standard.

The two necessary criteria for depth of anesthesia monitor are: 1) correlation between BIS and aaMAC in individual patients; 2) minimal variation in concentration–response relationship between aaMAC and BIS in the same patient. The correlation for the former was moderate and given the variability of the sample, the latter would not have been representative in our study.

The results of the study might be subject to pharmacokinetic confounding; there is a delay between the equilibration of volatile anesthetic agents in the alveolus and at the effect site in the central nervous system. Surgical stimulation is an important confounder, which we could not include in the GEE. No inference can be drawn about the usefulness of BIS during the periods of induction and emergence since it was not the aim of our study.

To conclude, BIS and aaMAC are inversely related. Factors that affect aaMAC may also affect BIS and although there are wide variations, BIS and aaMAC can be equated. The aaMAC and magnitude of factors affecting MAC to achieve BIS_{50} can be calculated using the generalized estimates equation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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