



TO ASSESS THE CORRELATION BETWEEN MINIMUM ALVEOLAR CONCENTRATION (MAC) AND BISPECTRAL INDEX (BIS) AT AGE CORRECTED MAC (1 MAC) OF DESFLURANE – A PROSPECTIVE OBSERVATIONAL STUDY

Poornima Sapar., Hemlata Kapoor and Nitin Jadhav

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ABSTRACT

MAC is defined as the minimum alveolar concentration at a steady state of inhaled anaesthetic at 1 atmospheric pressure that prevents movement (e.g. withdrawal) in response to a standard surgical midline incision in 50% of a test population. It reflects the actions of an inhalation agent on spinal cord-mediated reflexes by measuring somatic responses and is not necessarily a surrogate for lack of awareness.

The minimum alveolar concentration (MAC) is widely known to decrease as age increases. Bispectral index (BIS) values provide a convenient method to avoid overdosage or underdosage of anaesthesia, especially in the elderly population. We assume that BIS values correlate with MAC values, provided we used age-corrected MAC for each of our patients, calculated using Mapleson formula. Elective surgeries requiring supraglottic airway insertion and belonging to American Society of Anesthesiologists physical status I and II were considered. We observed BIS values of each of our patients who were maintained on age adjusted MAC of desflurane. We then divided the study population into two groups: 18-40 years and 41-60 years. All 112 patients finished the study. BIS value at the end of 15 minutes in the age group 18-40 years was 43.2 with a standard deviation of 7.5, as compared in the age group of 41-60 years where it was 42.5 with a standard deviation of 7.4. In both the groups, BIS values remained within the normal range for general anaesthesia. The present study showed that there is positive correlation between BIS and MAC provided, age adjusted MAC value is calculated for all patients. It can hence, avoid the deleterious effects of both over and under administration of general anaesthesia.

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INTRODUCTION

Over the past 150 years since its introduction, general anaesthesia has become so safe that that the risk associated with it has become almost immeasurably small: less than one death solely attributable to anaesthesia occurs per 200,000 procedures. The discovery of ether anaesthesia was the result of a search for a means to eliminate a patient's pain response to noxious stimuli. The present-day definition of anaesthesiology provided by the American Board of Anesthesiologists states that "Anesthesiology is the practice of medicine providing insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures". Modern general anaesthetic techniques typically involve the co-administration of a hypnotic drug, an analgesic drug and a muscle relaxant. With discovery of multiple anaesthetic agents, the need arose to ascertain the potency of each agent. This led to the introduction of "minimum alveolar concentration" (MAC) values of various inhalational agents. In 1965, MAC was first defined by Eger as "minimum alveolar concentration of anaesthetic at 1 atmosphere, which produces immobility in 50% of subjects exposed to a noxious stimulus, usually a skin incision".

In the year 1996, Professor Mapleson concluded that from the age of 1 year onwards, \log_{10} MAC decreased with age at the same rate for all inhaled anaesthetics, and that the rate of decrease is 6% per decade of year of age. [1] Desflurane resists both *in vitro* [2] and *in vivo* [3] degradation to an extent greater than any other potent halogenated agent, making it the least degradable of the currently available halogenated agent. The blood/gas solubility of desflurane is 0.42. This low value allows anaesthetic alveolar concentration to remain near inspired concentration permitting a rapid and large change, with precise control of the anaesthetic depth and hence, early awakening. [4], [5] It is known to have a lower anaesthetic potency leading to a higher MAC value.

Comprehensive meta-analysis determined the relationship between MAC and age as:

$$MAC_{age} = MAC_{40} \times 10^{-0.00269(age-40)}$$

Hence, 1 MAC when defined in literature, is for 40 years.

And therefore, age corrected MAC is 1 MAC for that patient.

Awareness during general anaesthesia can be very distressing for a patient, particularly if accompanied by recall of the painful nature of surgery. [6] Conscious awareness without recall of pain is more common; it has been estimated at 0.1-0.7 MAC (1in 142-1000) [7].

The bispectral index (BIS) monitor displays a real-time electroencephalography (EEG) trace, acquired from a frontotemporal montage. The components of BIS include - a sensor, a digital signal converter, and a monitor. The sensor is applied to a patient's forehead to pick up the electrical signals from the cerebral cortex and transfer them to the digital signal converter, which then displays a number on the monitor. It outputs three other values, which are Signal Quality Index (SQI), Electromyography (EMG) and Suppression Ratio (SR). SQI is a dimensionless index between 0 and 100 which gives an indication of the accuracy of the BIS value. EMG gives an indication of the influence of muscle activity on BIS values. Suppression Ratio is a percentage of previous 63 seconds where EEG is isoelectric. Higher the SQI and lower the EMG, more reliable is the BIS value.

The monitor generates a dimensionless number on a continuous scale of 0-100, with 100 representing normal cortical activity and 0 indicating cortical electrical silence. As with any EEG signal, BIS is subject to interference and artefact, particularly from electromyography (EMG) activity, which can artificially elevate the recorded BIS. The display also shows a signal quality index, burst suppression along with an indicator of EMG interference.

The primary objective of the study is to assess the correlation between MAC and BIS at age corrected MAC of desflurane which is calculated using Mapleson formula as described above.

MATERIALS AND METHODS

Basic study design and sample preparation

The prospective, observational study was approved by the Institutional Ethics Committee of KokilabenDhirubhai Ambani Hospital and Medical Research Institute, Mumbai on May 14, 2018 (IEC – A Code: 012/2018). All patients received general anaesthesia with a supraglottic airway insertion, maintenance with air + Oxygen + Desflurane at age corrected MAC value. Vitals were recorded: blood pressure and BIS, 5 minutes apart (starting from a point when stable age corrected MAC value was achieved) and a total of three readings were noted. The study sample was then divided into two groups and correlation between MAC and BIS studied.

Protocol for the main experiment

All patients were visited a day prior to the surgery and a detailed pre-anaesthesia evaluation was done. Patients received the usual and customary care. No personal identifying information regarding the patient or anaesthesia provider was obtained, and therefore, patient and provider anonymity was maintained. Demographic information (age, sex, weight), American Society of Anesthesiologists physical status as per their medical conditions were recorded. All patients' blood investigations were confirmed and optimised, which included complete blood count, renal function test, viral markers, liver function test, chest X-ray, electrocardiogram, and wherever necessary – a 2-dimensional echocardiography and blood sugars. On the day of surgery, patients were instructed to take

their regular medication for systemic diseases, if any, and tablet Pantoprazole 40 mg with sips of water. All patients were kept nil by mouth for at least 6 hours prior to surgery. In the operating room, monitors were attached, and baseline parameters recorded. An appropriate gauge intravenous line taken and appropriate intravenous fluids started. All patients received injection Glycopyrrolate 0.2 mg and injection Midazolam 1 mg intravenously 10 minutes before the surgery. BIS sensor was then attached to patient's forehead after cleaning it with an alcohol swab and all its connections to digital sensor converter and the module checked. General anaesthesia induction performed with injection Fentanyl 3 mcg/kg, Propofol 2-2.5 mg/kg, maintenance with Desflurane as per age corrected MAC (calculated using Mapleson equation) and Oxygen.Atracurium 0.5-0.8 mg/kg was used for supraglottic airway insertion. After achieving age corrected MAC, BIS readings and blood pressure values were noted every 5 minutes. A total of three readings were recorded. Mapleson reported a meta-analysis and found that:

- Semi-logarithmic plots of MAC against age (age >= 1 year) for all inhalational agents are linear and parallel, and
- The available data can be represented by an equation, $MAC_{age} = MAC_{40} \times 10^{-0.00269(age-40)}$

which expresses MAC for a given age (MAC_{age}) as a function of that at 40 years (MAC₄₀).

Age corrected MAC (as per Mapleson formula):

AGE (years)	MAC value	Rounded off MAC value
18	0.595	0.6
19	0.591	0.6
20	0.587	0.6
21	0.584	0.6
22	0.580	0.6
23	0.576	0.6
24	0.573	0.6
25	0.569	0.6
26	0.566	0.6
27	0.562	0.6
28	0.559	0.5
29	0.555	0.5
30	0.552	0.5
31	0.549	0.5
32	0.545	0.5
33	0.542	0.5
34	0.538	0.5
35	0.535	0.5
36	0.532	0.5
37	0.529	0.5
38	0.525	0.5
39	0.537	0.5
40	0.519	0.5
41	0.516	0.5
42	0.512	0.5
43	0.509	0.5
44	0.506	0.5
45	0.503	0.5
46	0.500	0.5
47	0.497	0.5
48	0.494	0.5
49	0.491	0.5
50	0.488	0.5
51	0.485	0.5
52	0.482	0.5
53	0.479	0.5
54	0.476	0.5
55	0.473	0.5
56	0.470	0.5
57	0.467	0.5
58	0.464	0.5
59	0.461	0.5
60	0.458	0.4

Inclusion criteria

1. Men and women of age between 18-60 years undergoing elective surgeries requiring general anaesthesia with LMA.

2. Patients belonging to ASA physical status I and II.

Exclusion criteria

1. Pregnancy.
2. Patients undergoing an emergency surgery.
3. Hemodynamically unstable patients.
4. Patients belonging to ASA physical status III and above
5. Patients with neurological diseases.

Ethical considerations

Rights of the participants will not be violated and sufficient measures are described in the protocol for protecting confidentiality of data and privacy of research participant. Since this is an observational, non-interventional study; and we will not be disclosing any confidential data of the participants, our Institutional Ethics Committee has agreed to our request to grant waiver for informed consent.

Statistical analysis

Based on the literature *, it was found that, mean time-averaged BIS value recorded during 1 h surgical anaesthesia after a 15-minutes equilibrium phase was 37.0 with SD 4.9. For our sample size considering the expected mean BIS value at age corrected MAC value of Desflurane was found to be 38.5 with SD 4.9. With 90% power and 5% level of significance, total 112 patients will be enrolled in the study. Step wise calculation of sample size:

$$N = [(Z (1-\alpha/2) + Z (1-\beta) 2) * \sigma^2 / (\mu_1 - \mu_0)^2]$$

$$N = [(1.96 + 1.28)^2] * 4.9^2 / (38.5 - 37.0)^2$$

$$N = (10.50 * 24.01) / 2.25$$

$$N = 112$$

*Relationship of bispectral index to minimum alveolar concentration during isoflurane, sevoflurane or desflurane anaesthesia (Jin-Kyoung Kim, Duk-Kyung Kim and Myeong-Jin Le).

The numeric data will be summarized by descriptive statistics like; n, Mean, Standard Deviation (SD), median, minimum, maximum. For statistical significance of numeric type data, one sample t-test will be used for within group and two-sample t-test will be used for between groups. For ordinal type data, the analysis will be done by non-parametric test like Wilcoxon signed-rank test. The categorical data will be summarized by frequency count and percentage and significance will be analysed using chi-square/ fisher exact test. Correlation will be analysed by Pearson and Spearman correlation methods. A p-value less than 0.05 will be considering statistically significant.

RESULTS

112 patients were studied and all the patients completed the study. The demographic details of the patients were recorded. Maximum patients (27.7%) belonged to the age group 51-60 years (Fig.1). The average weight was 69.7 kg with a SD of +/-12.55 (Fig.2). Majority of the study sample (67%) belonged to ASA I physical status (Fig.3). Co-morbidities: 35.1% were hypertensive, 29.7% were diabetic, 16.2% were both diabetic and hypertensive, 10.2% were hypothyroid, and a small fraction had asthma (5.4%) and sarcoidosis (2.7%) (Fig.4). 79% of the patients required a MAC of 0.5, calculated as per age (Fig.5). Average systolic and diastolic blood pressure (mmHg) in the age group of 18-40 years at the end of 15

minutes was 100.5+/- 13.5 and 60.1+/- 10.6, respectively and in the age group 41-60 years was 98.6+/-15.1 and 63.5+/-11.2, respectively (Table.1 and 2). Average BIS at the end of 15 minutes in the age group 18-40 years: 43.2 and in 41-60 years: 42.5+/-7.4 (Fig.6).

Table 1 BP (mmHg) after 5 minutes, 10 minutes and 15 minutes in the study patients.

Blood pressure (mmHg)	Time	Number of Patient (N)	Mean ± Stander deviation	p-value
Diastolic blood pressure	After 5 minutes	112	65.4 ± 48.7	----
	After 10 minutes	112	60.8 ± 10.2	0.628
	After 15 minutes	112	61.9 ± 11.0	0.290
Systolic blood pressure	After 5 minutes	112	98.3 ± 11.8	----
	After 10 minutes	112	97.7 ± 12.9	0.324
	After 15 minutes	112	99.5 ± 14.4	0.452

Table 1 shows that the average diastolic blood pressure (mmHg) at the end of 5, 10 and 15 minutes was 65.4, 60.8, 61.9, respectively with a standard deviation of 48.7, 10.2 and 11.0, respectively. The average systolic blood pressure (mmHg) at the end of 5,10 and 15 minutes was 98.3, 97.7 and 99.5, respectively with a standard deviation of 11.8, 12.9 and 14.4.

Table 2 BIS and BP readings in two different age groups.

Age Group	Time of reading	BIS	BP (mmHg)	
			Systolic	Diastolic
18-40	5 minutes	39.8 ± 7.5	99.8 ± 11.4	59.5 ± 9.7
	10 minutes	42.2 ± 7.0	98.6 ± 13.0	59.7 ± 11.1
	p-value	0.00*	0.434	0.876
	15 minutes	43.2 ± 7.5	100.5 ± 13.5	60.1 ± 10.6
	P-value	0.00	0.654	0.714
41-60	5 minutes	39.7 ± 7.7	97.0 ± 12.1	70.6 ± 65.8
	10 minutes	41.7 ± 8.0	97.0 ± 12.7	61.8 ± 9.4
	p-value	0.016	0.965	0.308
	15 minutes	42.5 ± 7.4	98.6 ± 15.1	63.5 ± 11.2
	P-value	0.003	0.315	0.410

Table 2 shows that the average BIS reading in 18-40 years age group at the end of 5, 10 and 15 minutes was 39.8, 42.2, 43.2, respectively with a standard deviation of 7.5, 7.0 and 7.5, respectively. And in the second age group, it was 39.7, 41.7 and 42.5 with a standard deviation of 7.7, 8.0 and 7.4, respectively.

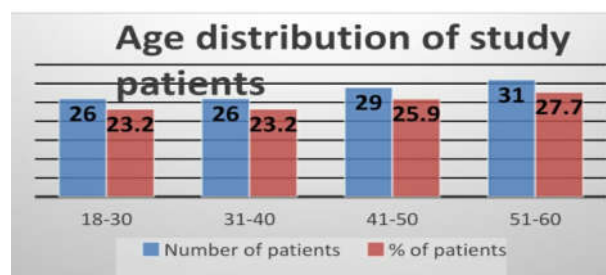


Fig 1 Bar diagram showing age distribution of the study population.

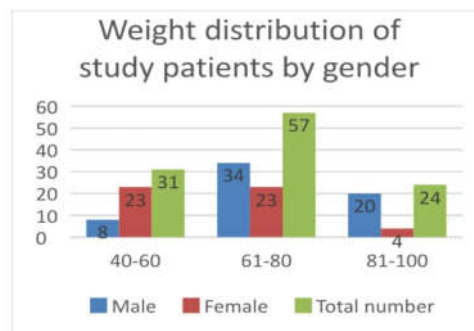


Fig 2 Bar diagram depicting weight distribution of the study population.

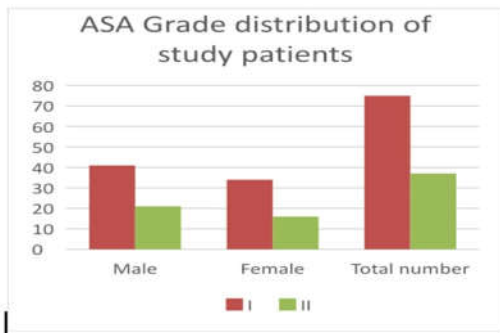


Fig 3 Bar diagram showing American Society of Anesthesiologists physical status distribution of the study sample.

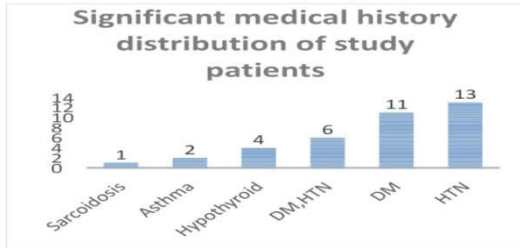


Fig 4 Distribution of the various co-morbidities in our study population.

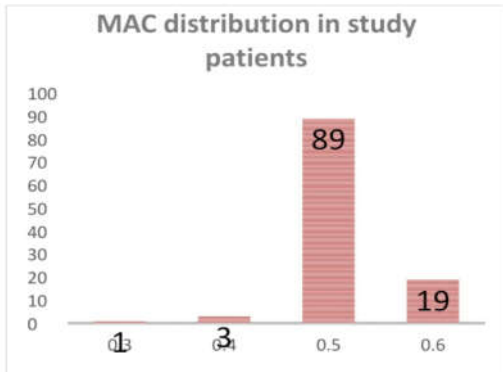


Fig 5 Bar diagram showing distribution of age corrected MAC values among the study population.

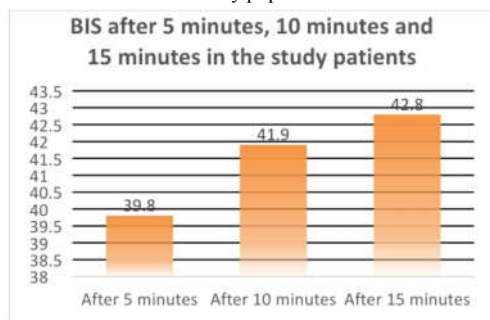


Fig 6 Bar diagram showing the average BIS values at the end of 5, 10 and 15 minutes.

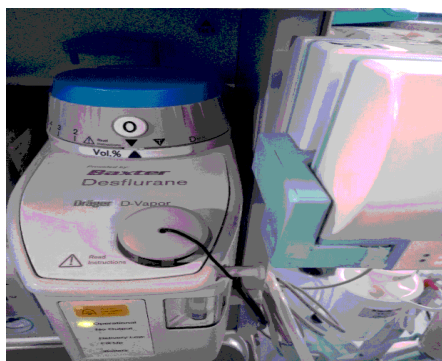


Fig 7 Desflurane Vapourizer.

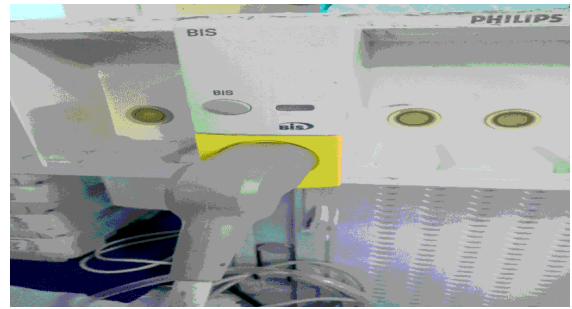


Fig 8 BIS module

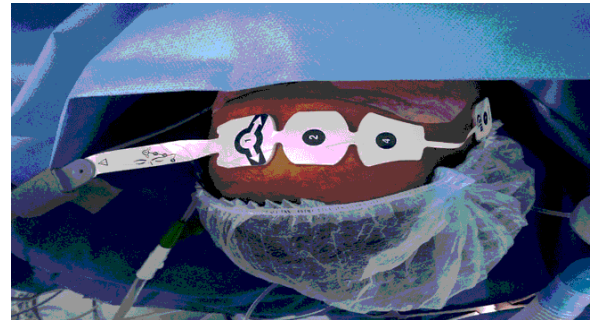


Figure 9 BIS sensor applied to patient's forehead.

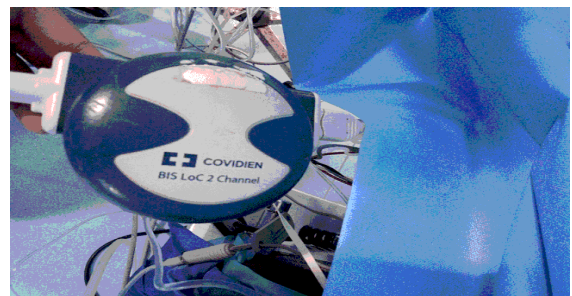


Figure 10 BIS digital signal converter.

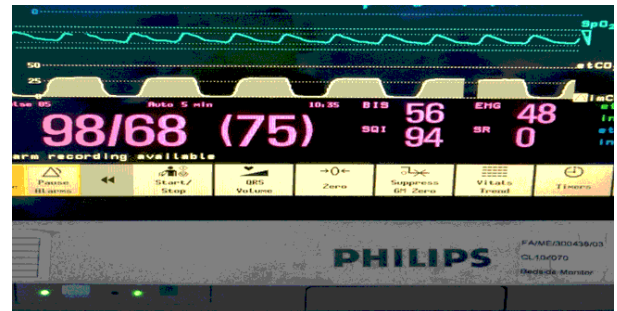


Figure 11 BIS values and components displayed on monitor



Figure 12 AMBU Auragain LMA.

DISCUSSION

The recent advances in medical science and availability of a wide variety of health care facilities has markedly increased the numbers of patients requiring general anaesthesia for surgical interventions. MAC is a measure of anaesthetic

potency. It is defined as the minimum alveolar concentration at a steady state of inhaled anaesthetic at 1 atmospheric pressure that prevents movement (e.g. withdrawal) in response to a standard surgical midline incision in 50% of a test population. It reflects the actions of an inhalation agent on spinal cord-mediated reflexes by measuring somatic responses and is not necessarily a surrogate for lack of awareness.

Inhalational agents have played a pivotal role in anaesthesia history. The first publicly demonstrated anaesthetic of the modern era, diethyl ether, was an inhalational anaesthetic. The attributes of a good agent, ability to rapidly induce anaesthesia, with limited side effects has led research efforts for over a hundred and fifty years. Desflurane, compared to other inhalations anaesthetic agents, offers the advantage of precise control over depth of anaesthesia along with a rapid, predictable, and clear-headed recovery with minimal postoperative sequelae, making it a valuable anaesthetic agent for maintenance in adults and paediatric patients in surgeries of all durations.

Achieving adequate depth of anaesthesia during surgical procedures is very important. Hence, assessment and monitoring depth of anaesthesia is fundamental to anaesthesia practice.

BIS PROFILE	STATE
100	Awake Responds to normal voice
80	Responds to loud commands or mild prodding/shaking
60	General Anaesthesia Low probability of explicit recall Unresponsive to verbal stimulus
40	Deep hypnotic state
20	Burst suppression
0	Flat line EEG

Figure 13 - BIS profile

The purpose of this study is to assess the correlation between bispectral index, which is the most commonly used depth of anaesthesia monitoring index, and age corrected MAC. In our study, we observed a positive correlation between BIS and age corrected MAC values as BIS values remained within a normal range of 40-60 for general anaesthesia if we used MAC calculated as per Mapleson equation. We conducted a study involving 112 patients, which involved males and females belonging to the age group 18-60 years undergoing elective surgeries requiring supraglottic airway insertion. Three readings of BIS values and systolic and diastolic blood pressures at those BIS readings were recorded following achievement of a stable age corrected MAC using the inhalational agent desflurane. Unlike in any of the studies we reviewed, an age corrected MAC value was calculated for each of our patients, using Mapleson equation.

We divided our study population into two age groups. It was noted that BIS value at the end of 15 minutes in the age group 18-40 years was 43.2 with a standard deviation of 7.5, as compared in the age group of 41-60 years where it was 42.5 with a standard deviation of 7.4. Systolic blood pressure at the end of 5 minutes was (mmHg) 98.3 with a standard deviation of 11.8, at the end of 10 minutes was 97.7 with a standard deviation of 12.9 and at the end of 15 minutes was 99.5 with a standard deviation of 14.4. The diastolic blood pressure (mmHg) at the end of 5, 10 and 15 minutes was 65.4, 60.8 and 61.9, respectively with a standard deviation of 48.7, 10.2 and 11.0, respectively. We did not observe any hemodynamic instability on administration of age corrected MAC values.

Sample size, age group distribution and average BIS

A similar study was conducted by Jin-Kyoung Kim *et.al* which aimed at understanding the relationship of bispectral index to minimum alveolar concentration at equipotent concentrations of three different inhalational agents, namely- isoflurane, sevoflurane and desflurane.^[8] Their study involved a sample size of 90 female patients belonging to age group 18-65 years and undergoing elective thyroidectomy. Patients were randomly allotted to isoflurane, sevoflurane or desflurane anaesthesia. Hence, each group had 30 patients. The primary study outcome was the time averaged BIS values of the three groups during the one-hour study period. They observed four parameters, namely – time averaged BIS, minimal BIS, duration of deep hypnosis and duration of adequate hypnosis for each of the three volatile agents. Time averaged BIS was lowest with desflurane (37+/-4.9), followed by isoflurane (39.6+/-5.1) and maximum was with sevoflurane (41.5+/-5.9). Minimal BIS values were also in the same order – lowest for desflurane (31.8+/-4.8), followed by isoflurane (33.7+/-4.8) and sevoflurane (35.0+/-6.0). Duration (min) of deep hypnosis (BIS < 40) was maximum for desflurane (40.2+/-20.7), followed by isoflurane (33.0+/-21.6) and sevoflurane (24.3+/-22.5). Duration (min) of adequate hypnosis (BIS 40-60) was maximum for sevoflurane (35.2+/-22.5), followed by almost equal duration for desflurane (27.3+/-22.4) and isoflurane (27.2+/-22.0). They concluded that the use of an equipotent MAC concentration of different volatile agents results in different BIS profiles. Our study also had an almost similar sample size and age group distribution. Time averaged BIS for desflurane in our study also reflected a similar value of 39.8 with a standard deviation of 7.6 after 5 minutes of achieving a stable age corrected MAC.

Confounding factors

A multicentre study was conducted by Sebel *et.al*, to understand confounding factors that affect BIS values^[9]. The study enrolled 300 patients, half of which were randomised to treatment group in which anaesthetic regimen was increased in order to lower the BIS and the other half belonged to the control group wherein, the BIS values were only noted and no change in the anaesthesia regimen done. BIS values were significantly higher in the control group (66+/-19) as compared to the treatment group (51+/-19). The movement response rate was significantly higher in the control group at 43% compared with 13% in BIS guided group. The study demonstrated that dosing anaesthetic drugs to lower BIS values achieved a lower probability of movement in response to surgical stimulation. In our study, we have used fentanyl for providing analgesia and propofol as an induction agent and anaesthesia was maintained by age corrected MAC of desflurane for each patient. Hence, avoiding any confounding factors that affect the BIS readings.

Usage of age corrected MAC values

The clinical characteristics of desflurane were studied by Rampil *et.al*, where in 46 patients belonging to American Society of Anesthesiologists physical status I or II undergoing elective surgery, were enrolled^[10]. Study population was divided into four groups – first one belonging to the age group 18-30 years, second one belonging to 31-65 years, third one receiving desflurane in 60% nitrous oxide/40% oxygen and the last group receiving desflurane in oxygen. The MAC of

desflurane in oxygen was 7.25+/- 0.0 in the age group 18-30 years and 6.0+/-0.29 in the age group 31-65 years. The addition of 60% nitrous oxide reduced the MAC to 4.0 +/- 0.29 and 2.83+/- 0.58 in the age group 18-30 years and 31-65 years, respectively. In our study, age corrected MAC was used for desflurane which was maintained in 50% oxygen/50% air.

Dependence of Mapleson equation

M. Sandin *et al* undertook a study to observe the effects of pain stimulus on bispectral index, heart rate and blood pressure at different minimal alveolar concentrations of sevoflurane^[11]. They studied 10 American Society of Anesthesiologists I physical status patients. The volunteers were spontaneously breathing under volatile agent sevoflurane in an air/oxygen mixture. At MAC of 1, there was noted a significant rise in BIS value, which decreased at 1.5 and at MAC value 2, variable response was seen in BIS profiles with periods of burst suppression and periods of high BIS values despite clinical signs of deep anaesthesia. In our study, we used the Mapleson equation to calculate MAC for each age and hence BIS values remained in the normal range for surgical anaesthesia of 40-60 following providing adequate analgesia for all the patients with fentanyl 3mcg/kg.

BIS guided anaesthesia

Faraz Shafiq *et al* studied the effects of bispectral index monitoring on isoflurane consumption and recovery profiles for anaesthesia in an elderly Asian population^[12]. 60 patients of 60 years and above participated and were divided into two groups – standard practice (SP) wherein, anaesthesia depth was maintained as a routine clinical practice and the group in which anaesthesia was maintained by monitoring the BIS score between 45-55. It was observed that the mean isoflurane consumption was lower (P=0.001) in the BIS group. Also, the time to eye opening, extubation and ready to shift was shorter (P=0.0001) in the BIS group. We got the values of BIS at age corrected MAC for every patient (using Mapleson formula) and divided the study sample into two age groups – 18 to 40 years and 41-60 years and observed a positive correlation between MAC and BIS as BIS remained within acceptable range in both the age groups for GA (40-60) after using age corrected MAC.

We conclude the study by observing that:

- On achieving age corrected MAC of Desflurane for all patients of our study population, BIS values remained within the normal range, and
- The BIS values were found to be within normal range in both the age groups on achieving steady age dependent 1 MAC values of desflurane. The age dependent decline of end-tidal MAC values showed BIS values within normal range. Hence, a positive correlation was observed between age corrected MAC and BIS across all age groups.

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