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Effect of BIS monitoring on sevoflurane consumption in patients undergoing breast cancer surgeries under general anesthesia—a prospective observational study

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Abstract

Background: The bispectoral index (BIS), a parameter derived from electroencephalogram, has been used to assess the depth of anesthesia. The objectives of this study were to evaluate the effect of BIS monitoring on sevoflurane consumption and recovery profile at the end of anesthesia. After obtaining Institutional Review Board approval and written informed consent, 25 American Society of Anesthesiologists (ASA) physical status classification 1 and 2 patients undergoing breast cancer surgeries who had BIS monitoring in addition to standard ASA monitoring (BIS GROUP) were compared against 25 controls (control group). In the control group, adequate depth of anesthesia was maintained using routine clinical parameters like heart rate (HR), mean arterial pressure (MAP), and minimum alveolar concentration (MAC) of sevoflurane, while in the BIS group, it was maintained by keeping the BIS score between 40 and 60 (mean 50). Data including demographics, sevoflurane consumption, hemodynamic variables, and recovery profile at the end of anesthesia was assessed in terms of time for eye opening (TEO), time for motor response (TMR), time for extubation (TE), and modified Aldrete scoring (MAS).

Results: The mean sevoflurane consumption was lower ($P = 0.019$) in the BIS group. TEO ($P = 0.001$), TMR ($P = 0.0001$), and TE (0.003) were shorter in the BIS group. Difference in MAS between the 2 groups was not statistically significant ($P = 0.085$).

Conclusions: BIS monitoring during anesthesia resulted in significant reduction in the sevoflurane consumption. Patients who had BIS monitoring awoke earlier and had better recovery profile at the end of anesthesia.

Keywords: Bispectral index, Sevoflurane consumption, Breast cancer surgery

Background

Expeditious recovery and shorter hospital stay are necessary to improve efficiency of an ambulatory health care facility and to reduce health care costs. One of the major factors that determine the speed of recovery from anesthesia is the choice of anesthetic technique. General anesthesia is still the most common anesthetic technique used (Oliveira et al., 2017; Scott & Kelley, 2010). The main targets of anesthesia are to provide hypnosis, analgesia, neuromuscular blockade, and prevention of reflex responses. Currently, hypnotic level during anesthesia is mainly monitored by hemodynamic responses and measurement of minimum alveolar concentration (MAC) of the inspired and expired inhalation anesthetics (Shafiq et al., 2012). The monitoring of inhalational anesthetic concentration using MAC value provides a way to

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observe the continuous brain concentration of volatile anesthetics once equilibration between the alveolus, blood, and brain concentration is achieved, but it is not always reliable to evaluate the brain status of anesthetized patients, and moreover, this application mostly supplants the true needs of the patient (Karaca et al., 2014). Excessive and inadvertent usage of these inhalation agents may cause significant morbidity because of its side effects like hypotension, tachycardia, and delay in recovery (Shafiq et al., 2012).

Despite remarkable improvements in the assessment of the cardiovascular and respiratory system changes during anesthesia, the impact of inhalational agents on central nervous system and its functioning always remained as a challenge. This led to the emergence of electroencephalography (EEG)-based indices like bispectoral index (BIS) monitor to assess the depth of anesthesia. BIS monitoring may thus act as an additional vital sign that allows the clinicians to deliver anesthesia in keeping with the patients need and to assess and respond befittingly to the patient's clinical condition during surgery. It is thus very useful for the titration of volatile anesthetic agents more precisely than what is possible by routine clinical parameters (Shafiq et al., 2012).

The monitoring has shown convincing proof in preventing surplus exposure to higher concentrations of anesthetic agents and thus helps to achieve faster emergence, rapid turnover, and shorter duration of stay in post-anesthesia care unit (Shafiq et al., 2012; Tang et al., 1999). Though there are several studies mentioning the use of BIS monitor as a tool to assess the depth of anesthesia, adequate literatures are not there to support the use of BIS monitor to decrease sevoflurane consumption. Hence, this study adds to the insight that BIS monitor helps to decrease inhalation agent consumption to significant levels.

The objective of doing this study was to evaluate the effect of BIS monitoring on sevoflurane consumption and recovery profile in patients undergoing breast cancer surgeries under general anesthesia.

Methods

After getting approval of the hospital institutional review board (IRB No: 11/2016/05), this study was performed in 50 ASA 1 and 2 patients of age group 40–70 years undergoing breast cancer surgeries over a period of 1 year from June 2017 to June 2018. Hospital Ethical Committee clearance was waived by the Institutional Review Board as it did not involve any newer intervention rather than applying BIS leads over the forehead. The cost of the BIS electrode was also not charged from the patients as it was covered by the hospital health insurance scheme. The study was commenced after obtaining informed consent from the patients. Patients with altered renal function tests and hyper-reactive airways, who are allergic to any of the drugs used for surgery, and have altered mental function, Alzheimer's disease, cerebral palsy, and psychiatric illness were excluded from the study.

The sample size was calculated on the basis of a study by Shafiq et al. assuming the power of the study as 80% and confidence level as 95%. The estimated effect size was 1.1929 (Shafiq et al., 2012). Twenty-five ASA I and II patients undergoing breast cancer surgeries who had BIS monitoring in addition to standard ASA monitoring (BIS group) were compared against 25 controls (control group). The sevoflurane consumption and recovery profile in the study group were noted. Data obtained from the study group was compared against the control group. Twenty-five patients who fulfilled the inclusion and exclusion criteria were included in the control group. In the control group, titration of agent concentration was based on intraoperative clinical parameters and MAC value of sevoflurane (Baxter Company, USA). A thorough preoperative check-up, general and systemic examination, and routine investigations were done. All the patients were kept nil per oral 6 h for solid foods and 2 h for clear liquids on the day of surgery. Premedication was given to all patients with pantoprazole 40 mg and alprazolam 0.5 mg on the previous day night and also on the morning of the day of surgery. In the operation theater, all patients were monitored using standard monitors like electrocardiogram (ECG), pulse oximeter, non-invasive blood pressure monitor (NIBP), and end-tidal carbon dioxide monitor ($ETCO_2$). BIS monitoring leads were kept ready for the BIS group population (A-2000; Aspect Medical Systems, Natick, MA). After securing intravenous access, diclofenac 75 mg was given intravenously (IV) as pre-emptive analgesia for all patients in the holding room. After shifting to operation theater, patients were pre-medicated with midazolam 1 mg IV and fentanyl 2 mcg/kg IV. Patients in the BIS group had continuous BIS monitoring by applying BIS sensors on the forehead and temple regions before induction. BIS values were then recorded. All patients were preoxygenated with 100% oxygen for 3 min at 8 L/min followed by induction with propofol 2 mg/kg IV. Propofol was then titrated against the response of the patient, until the clinical signs showed the onset of anesthesia, the end point being the loss of verbal contact with the patient. Lignocaine1.5 mg/kg was given IV 90 s before intubation to attenuate the hemodynamic stress response. Muscle relaxation was achieved using vecuronium 0.1 mg/kg IV after ensuring the adequacy of mask ventilation. The airway was then secured appropriately using endotracheal tubes. All patients were mechanically ventilated to keep their $ETCO_2$ between 35to 40 mm Hg.

Maintenance of anesthesia was done using air-oxygen-sevoflurane with an FIO_2 0.4. Fresh gas flow was then reduced to 2 l/min. Sevoflurane concentration was then adjusted using routine clinical parameters like heart rate (HR), blood pressure (BP), and minimum alveolar concentration (MAC) values in the control group, while in the BIS group, sevoflurane was titrated by keeping the BIS value between 40 and 60 with a mean of 50.

Intraoperative hypertension was defined as blood pressure greater than 25% of baseline and tachycardia as heart rate greater than 20% of baseline (Orhon et al., 2013). During intraoperative hypertension episodes, the depth of anesthesia was adjusted with the boluses of fentanyl 25–50 μg with additional top-up doses 0.02 mg/kg of vecuronium depending upon the situation, as per the judgment of primary anesthetist. Intraoperative hypotension was defined as MAP less than 25% of the baseline or an absolute value less than 60 mmHg and was treated with boluses of ephedrine 6 mg or phenylephrine 50–100 mcg. Bradycardia was defined as HR less than 50/min, and all symptomatic bradycardia were treated with IV atropine 0.6 mg boluses.

Patient's demographic data and other relevant information were recorded. Patients were monitored throughout the surgery and hemodynamic recording was done continuously with ECG, SPO_2, $ETCO_2$, and NIBP every 3 min interval till the discontinuation of sevoflurane. For plotting graphs, readings were taken from the monitor's trends option every 10 min interval. Measurement of intraoperative sevoflurane consumption in milliliters was calculated as follows:

Usage of sevoflurane = PFTM/2412d (Dion's equation) (Singh et al., 2013).

where the variables represent

P is the vaporizer dial concentration in percent

F is the total fresh gas flow in L/min

T is the time during which the concentration P was maintained in minutes

M is the molecular mass of sevoflurane in grams

d is the density of liquid sevoflurane in g/ml.

Mean consumption of sevoflurane in milliliters during the procedure was calculated. Sevoflurane was continued till the closure of skin incision in both the groups. The time of discontinuation of sevoflurane was noted. Residual neuromuscular blockade was reversed with glycopyrrolate 20 mcg/kg and neostigmine 0.05 mg/kg. Patients in both the groups were extubated when they fulfilled the subjective and objective criteria for extubation. From this point, the recovery profile of the patient was noted in terms of the following:

1. Time for eye opening—TEO (defined as time from discontinuation of anesthetic agent to the eye opening on verbal command) (Shafiq et al., 2012).
2. Time for motor response—TMR (defined as time from discontinuation of anesthetic agent to hand squeezing on verbal command) (Shafiq et al., 2012).
3. Time for extubation—TE (defined as time from discontinuation of anesthetic agent to extubation of endotracheal tube) (Shafiq et al., 2012).
4. Modified Aldrete scoring (MAS) at the post-anesthesia care unit (PACU) (Shafiq et al., 2012).

All patients received adequate post-operative analgesia with optimal doses of inj. diclofenac, inj. paracetamol, or inj. tramadol either alone or in combination to keep the visual analog scale score (VAS) < 3/10. At the time of discharge from the recovery room and 24 h after surgery, patients were asked whether they dreamt or recalled any intraoperative events.

Outcomes

Primary outcome—To evaluate the efficacy of BIS monitoring on sevoflurane consumption in patients undergoing breast cancer surgeries under general anesthesia.

Secondary outcome—To evaluate the recovery profile of patients in terms of time for eye opening, time for motor response, time for extubation, and modified Aldrete score.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 11.0. Data variables including age, weight, height, heart rate, mean blood pressure, sevoflurane consumption, and recovery profile were expressed as mean ± standard deviation (SD). Significance difference for continuous variables was tested using Student's t test (normally distributed) or Mann-Whitney U test (non-normal), and chi-square tests (categorical) were applied to compare different variables between the BIS group and the control group respectively. P value of less than 0.05 was considered as statistically significant.

Results

A total of 55 patients were enrolled in the study, among which three patients were removed as two of them did not meet the inclusion criteria of the study and one patient refused to participate in the study. Hence, 52 patients were then allocated and divided into 2 groups (BIS group and control group), among which one patient from BIS group was lost to follow-up as intervention was discontinued due to prolonged duration of surgery and one patient from the control group was lost to follow-up due to technical failure to collect data, and so the final analysis was made from 50 patients (Fig. 1).

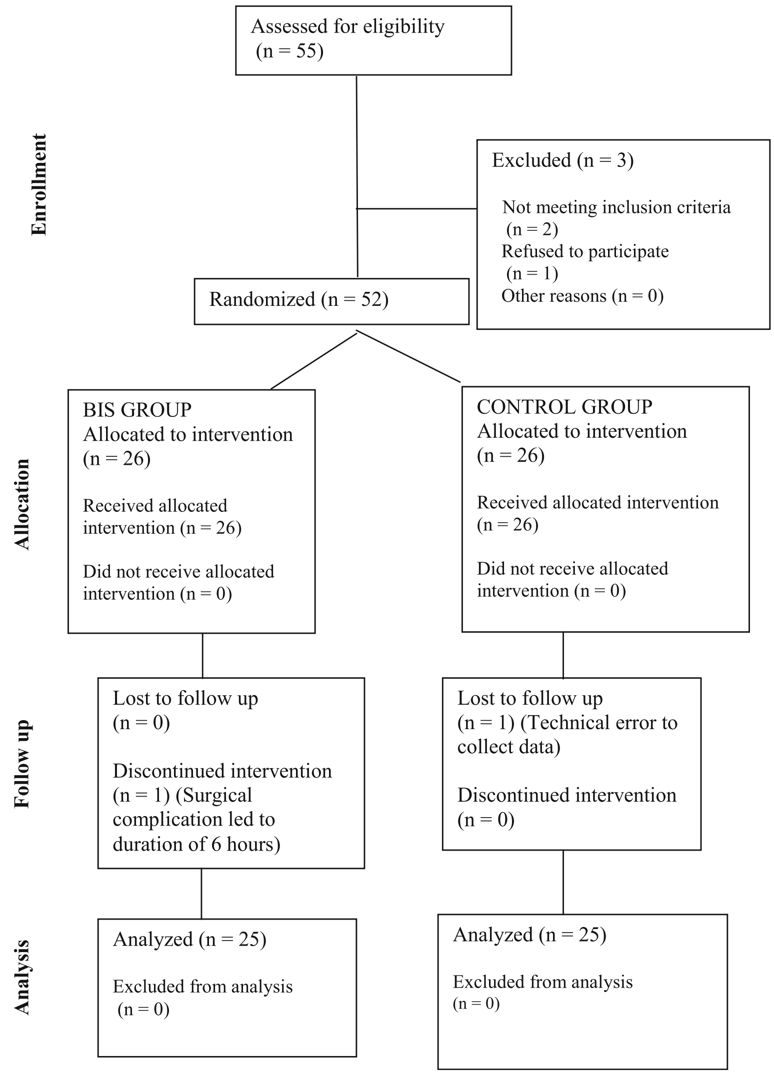

Fig. 1 CONSORT diagram

Comparison of demographic data between the two groups is expressed as mean with standard deviation (SD). There was no statistically significant difference in the demographic data between the two groups (Table 1). The baseline HR and MAP was measured just before induction and noted. There was no significant difference in the heart rate (HR) (Fig. 2) and mean arterial pressure (MAP) (Fig. 3) at 10-min interval during the maintenance of anesthesia between the two groups. Student's *t* test was used for all the variables except those HR 100, HR 110, MAP 100, MAP 110, and MAP 120, for which Mann-Whitney *U* test was used.

The primary objective of the study was to find out the sevoflurane consumption in both groups. The amount of

Table 1 Demographic data comparison

Variables	*Group*		*P value*
	Control group (N = 25)	*BIS group (N = 25)*	
Age (years)	51.12 ± 10.89	55.28 ± 9.22	0.152
Weight (kg)	64.24 ± 13.73	66.37 ± 12.49	0.534
Height (cm)	157.78 ± 7.43	158.38 ± 9.88	0.791
BMI (kg/m^2)	26.6 ± 3.46	26.46 ± 3.49	0.831
Duration of surgery (min)	92.80 ± 18.45	88.80 ± 17.67	0.438

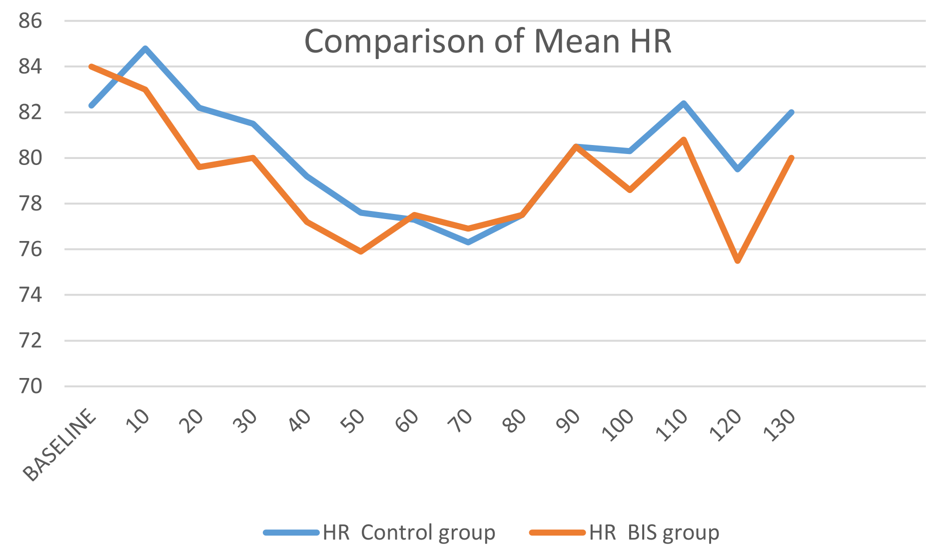

Fig. 2 Comparison of mean heart rate (HR) between the control group and BIS group

sevoflurane consumed by each patient in each group was calculated using Dion's equation, and the mean value was obtained which was 9.6 ± 2.66 ml in the control group and 8.16 ± 1.17 ml in the BIS group. Hence, there was significant reduction in the sevoflurane consumption in the BIS group (Fig. 4). The difference was statistically significant with a *P* value of 0.019.

Regarding recovery profiles, there was significant difference in time for eye opening between the control group and the BIS group (5.80 ± 3.12 min versus 3.24 ± 1.30 min) with a *P* value of 0.001. Time for motor response also showed significant difference between the control group and the BIS group (8.40 + 3.40 min versus 5.20 + 1.35 min) with a *P* value of 0.0001. The time taken to extubate the patients was more in the control group than the BIS group (5.36 ± 2.05 vs. 3.80 ± 1.47 min) with a *P* value of 0.003. Difference in modified Aldrete score was not statistically significant ($P = 0.085$) between the two groups (Table 2) (Fig. 5). At the time of discharge from the recovery room and 24 h after surgery, patients were asked whether they dreamt or recalled any intra-operative events, and none of them had a positive response.

Discussion

The study conducted and revealed that use of BIS monitor helped to significantly reduce the consumption of sevoflurane with a better recovery profile in patients

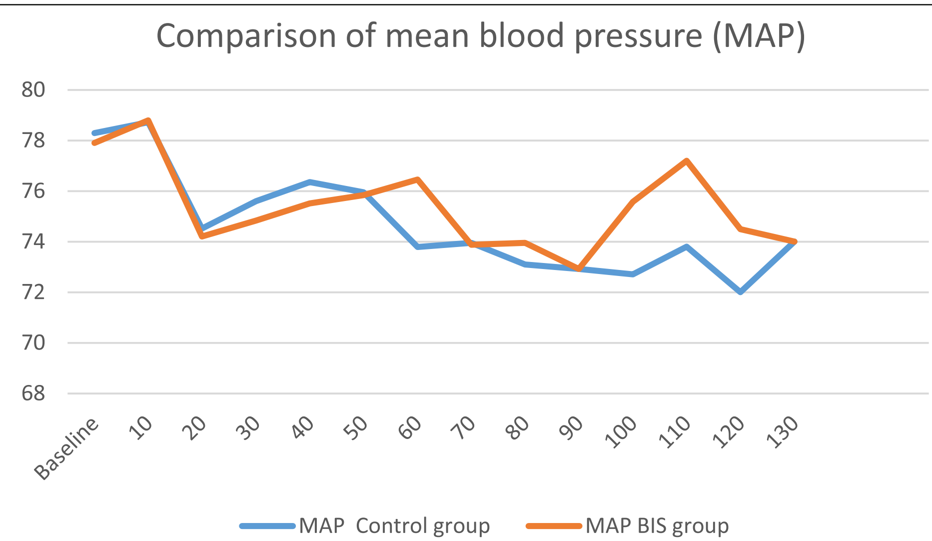

Fig. 3 Comparison of mean blood pressure (MAP) between the control group and BIS group

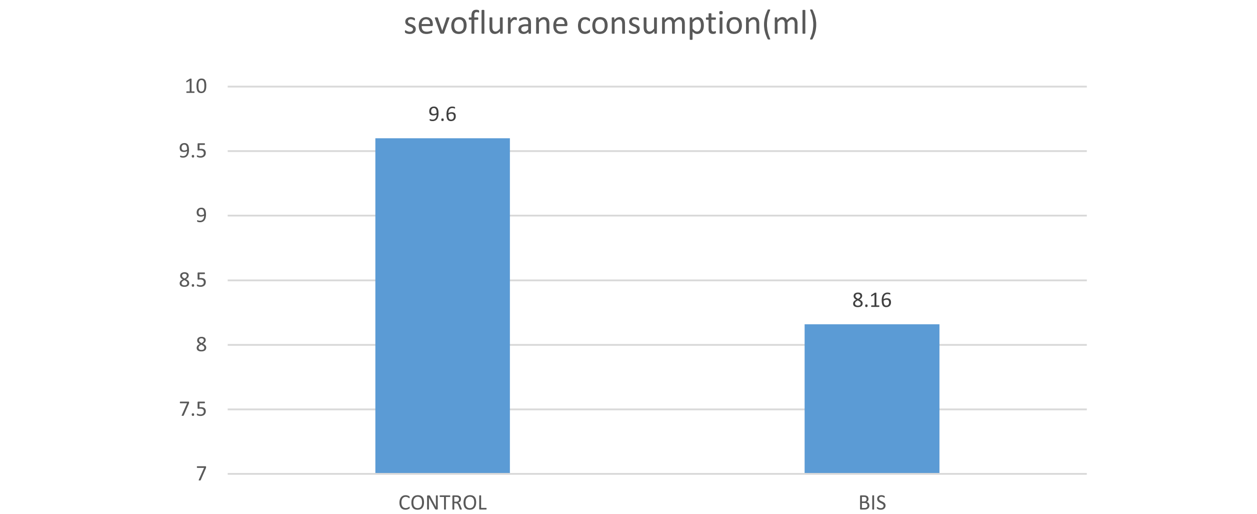

Fig. 4 Comparison of mean blood pressure (MAP) between the control group and BIS group

undergoing breast cancer surgeries under general anesthesia. General anesthesia is a reversible state of controlled unconsciousness achieved with the administration of combination of drugs (Emery et al., 2010). The traditional practice of assessment of depth of anesthesia is by monitoring the routine clinical parameters and MAC value of inhalation agents. Minimum alveolar concentration (MAC) is defined as the minimum inhaled anesthetic concentration required to prevent movement in response to a defined noxious stimulus in 50% of subjects at one atmospheric pressure (Emery et al., 2010). The immobilizing effect of the inhalation agent involves actions in the spinal cord whereas sedation/hypnosis, amnesia, and other cognitive functions involve supraspinal mechanisms that communicate with the endogenous memory, sleep, and consciousness pathways and networks. Minimum alveolar concentration, which is based exclusively on motor response, might not proportionately reflect other components of anesthesia like sedation and hypnosis (Emery et al., 2010). Even today, many of the anesthesiologists adjust the doses of anesthetic agents by monitoring the hemodynamic parameters and the MAC value of inhalation agent, and this mostly supplants the true needs of the patient. This can result in deleterious consequences like early postnatal neurotoxicity and apoptotic cell death leading to reperfusion injury, excess excitatory neurotransmitter release leading to long term functional neurologic consequences in children, interaction with GABA receptors and central cholinergic pathway causing post-operative cognitive dysfunction, myocardial depression, and decreased myocardial contractility, and peripheral vasodilation causing hypotension (Emery et al., 2010).

Table 2 Comparison of recovery profile between two groups (group 1 = control group, group 2 = BIS group)

Recovery profile	*Group*	*N*	*Mean*	*Standard deviation*	*P value*
TEO	1	25	5.80	3.122	0.001
	2	25	3.24	1.300	
TMR	1	25	8.40	3.403	0.0001
	2	25	5.20	1.354	
TE	1	25	5.36	2.059	0.003
	2	25	3.80	1.472	
MAS	1	25	7.92	0.572	0.085
	2	25	8.16	0.374	

TEO time for eye opening, *TE* time for extubation, *TMR* time for motor response, *MAS* modified Aldrete scoring

Thus, excessive and injudicious use of inhalation agents leads to significant morbidity and delay in recovery which could be controlled with BIS monitoring technique. Moreover, using minimum possible concentration of volatile anesthetics titrated to patient requirement with BIS monitor can possibly help to prevent the occurrence of post-operative cognitive dysfunction which is currently gaining attention in a big worry (Chan et al., 2013).

The bispectoral index (BIS) is an empirically derived scale that was proposed by Aspect Medical Systems (later purchased by Covidien) in 1994, as a novel way to monitor level of consciousness and depth of sedation among patients receiving general anesthesia. The EEG in near real time is processed by the algorithm, and an index value between 0 and 100 is computed that indicates the patient's level of consciousness. A value of 100 corresponds to being completely awake, whereas 0 corresponds to a profound state of coma, unconsciousness, or absence of brain activity that is reflected by an isoelectric or flat EEG.

Elderly population undergoing elective hip or knee replacement showed 30% reduction in isoflurane usage in

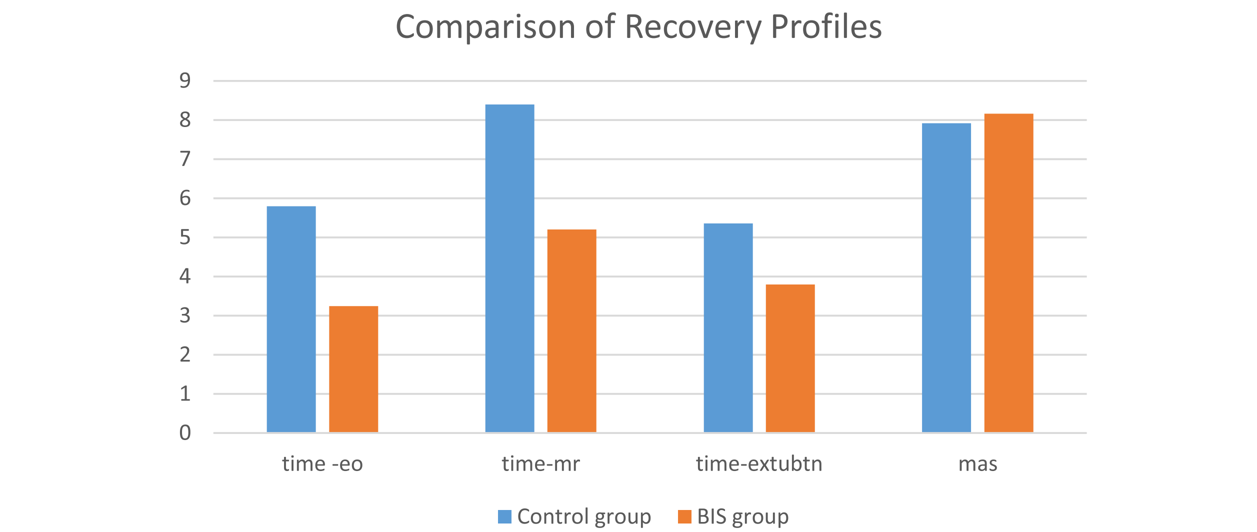

Fig. 5 Comparison of recovery profiles between the control group and BIS group

the BIS group (Wong et al., 2002). Young females undergoing gynecological surgeries showed that BIS monitoring reduced sevoflurane and desflurane usage by 30–38% (Song et al., 1997).

The results of our study indicated that BIS monitoring helps to significantly reduce sevoflurane consumption. The intraoperative hemodynamic variables including HR and MAP did not show any significant difference between the two groups in our study which indicated adequate depth of anesthesia was maintained in spite of significant reduction of the sevoflurane usage in the BIS group.

Now, we are in the era of fast track surgeries, and a speedy recovery is important after surgery. In our study, there were significant reductions in time to eye opening, time to motor commands, and time for extubation between the BIS group and the control group. The BIS group patients showed significant reduction in the time of arrival in PACU; hence, these patients became eligible for the discharge sooner than the control group (Gan et al., 1997). The elderly patients showed statistically significant reduction in time for good recovery using BIS monitor (Wong et al., 2002). Regardless of the anesthetic used, BIS-guided anesthesia reduced recovery times, which is the time to open eyes, in response to the voice command, extubation, and orientation (Punjasawadwong et al., 2014; Kreuer et al., 2003; Dagtekin et al., 2007).

In our study, there was no statistically significant difference in the modified Aldrete scoring system between the two groups. BIS monitoring did not influence the Aldrete scoring system (Song et al., 1997; Guignard et al., 2001; Pavlin et al., 2001). The cost of getting BIS monitor and BIS electrodes is a major hindrance in developing countries for the uniform provision of this monitoring (Scott & Kelley, 2010). Implementation of this monitoring may however reduce the overall cost by reduction in the inhalation agent usage which further reduces theater pollution and help with better recovery profile and earlier discharge of the patient (Kamal et al., 2009).

There were few limitations for the study. Firstly, the study was not blinded. Secondly, the study was confined to breast cancer surgeries alone and most of the cases lasted for less than 2 h. Observations cannot be generalized to all type of surgeries and anesthesia protocols. Further research is needed with a larger sample size that includes the general population of surgical patients undergoing various types of major and minor surgeries under general anesthesia with BIS monitoring. Its impact may be in the form of variation in the depth of anesthesia requirement for the particular procedure, leading to difference in the anesthetic agent consumption. Different studies have also measured the postoperative cognitive dysfunctions and incidences of awareness in their work; however, this was not our objective and requires a large sample size for finding such rare incidences, and finally other factors affecting recovery after general anesthesia such as blood loss, temperature, fluids, and electrolyte imbalance were not considered.

Conclusions

In addition to the monitoring of awareness during anesthesia, the information given by the BIS monitor permits for better adjustment of anesthetic management. The potential advantage of implementing BIS monitoring is critical. Drug savings combined with improved recovery will enable patients to go home faster with fewer residual drug effects. Hence, from our study, it was concluded that the recovery variables were shorter with BIS monitoring which in turn made significant savings in sevoflurane consumption and influenced the speed of recovery after breast cancer surgeries under general anesthesia.

Abbreviations
MAC: Minimum alveolar concentration; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; BIS: Bispectoral index; DOA: Depth of anesthesia; EEG: Electroencephalogram; MAS: Modified Aldrete score; GABA: Gamma amino butyric acid; CNS: Central nervous system; ECG: Electrocardiogram; EMG: Electromyogram; ASA: American Society of Anesthesiologists; NIBP: Non- invasive blood pressure; IV: Intravenous; VAS: Visual analog scale; PACU: Post-anesthesia care unit; SPSS: Statistical Package for Social Sciences; SD: Standard deviation

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Authors' contributions
AN is the guarantor and done the concepts, design, definition of intellectual content, literature research, clinical studies, experimental study, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. SP and SR done the concepts, design, definition of intellectual content, literature research, data acquisition, manuscript preparation, manuscript editing and manuscript review. RCK done the concepts, design, definition of intellectual content, manuscript editing and manuscript review. JKKM done data analysis and statistical analysis. All authors have read and approved the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board (IRB), Regional Cancer Centre, Thiruvananthapuram. IRB no. 11/2016/05. Hospital Ethical Committee clearance was waived by the Institutional Review Board as it did not involve any newer intervention rather than applying BIS leads over the forehead. The cost of the BIS electrode was also not charged from the patients as it was covered by the hospital health insurance scheme. The study was commenced after obtaining written informed consent from the patients.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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