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Research Article

Effect of Use of Entropy Monitoring on Consumption of Sevoflurane Inhalational Agent in Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery: A Randomized, Double Blinded, Controlled Study

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ABSTRACT

Background: Monitoring the depth of Anesthesia using Entropy modality is essential and resourceful as it allows for more accurate hypnotic drug administration and decreased anesthetic drug consumption and shortens the recovery time. This study was performed to evaluate the effect of entropy monitoring on Sevoflurane consumption in patients undergoing Off Pump Coronary Artery Bypass Graft Surgery.

Methods: A total of 60 patients of ages between 40 – 70 years and of either sex with American Society of Anesthesiologist (ASA) grade 2 and 3, planned for Off Pump Coronary Artery Bypass Graft Surgery were randomly allocated to two groups in this Randomized Controlled Trial. In the control group i.e. Group B, Sevoflurane was titrated according to changes in clinical parameters (Heart Rate (HR) and Blood Pressure (BP) changes within 20% of baseline values) and in the study group i.e. Group A, Sevoflurane was titrated to maintain State Entropy (SE) values between 40-60 accordingly. Response Entropy (RE) and State Entropy (SE) values were continuously recorded in both the groups but were displayed on the monitor only in the study group and were not displayed to the anesthesiologist in the control group. The entropy values, Sevoflurane Consumption and recovery times were compared amongst the two groups. Patients in both the groups were ventilated on Volume Control Mode of ventilator with 100% oxygen @ 2L/min.

Results: There were no significant results in terms of age, sex, ASA Grade and NYHA Grade amongst the two groups. Sevoflurane consumption and time of recovery were significantly reduced in the study group i.e. Group A than the Control group i.e. Group B (p value <0.001; Sevoflurane consumption: 7.03±0.67 ml/hr vs 12.42±0.68 ml/hr; Recovery Time 6.47±0.65 hr vs 12.05±1.11 hr). Response and State Entropy values were lower in the control group than the study group ($p < 0.001$) during the maintenance phase of anesthesia. Systolic Blood Pressure values during skin incision, sternotomy and at the time of completion of all grafts were significantly lower in study group as compared to the control group.

Conclusion: Monitoring the Depth of Anesthesia using Entropy Monitoring leads to significant reduction in Sevoflurane consumption and significant faster recovery rate from surgery.

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General anesthesia comprises of various components like loss of consciousness, loss of reflex response, amnesia, muscle relaxation and analgesia. All these are imperative for carrying out any surgical procedure smoothly and effectively especially long surgical procedures like Off – Pump Coronary Artery Bypass Graft Surgery. This surgery is indicated in coronary artery disease caused by narrowing or blockage of the coronary arteries supplying the heart which presents as unstable angina or myocardial infarction. This surgery is performed when multiple arteries are blocked at multiple sites and non - invasive procedures no longer play a role. Thus, this procedure stands as a life - saving procedure for the patient. Thus, measuring the depth of anesthesia becomes crucial because a deeper plane of anesthesia would lead to side effects like post-operative nausea and vomiting, cognitive dysfunction and delayed recovery and on the other hand, a lighter plane would cause intra operative awareness [1].

In olden days, depth of anesthesia was measured using the PRST Score i.e. Pressure, Rate, Sweating, Tear Production and it would indicate a lighter plane of anesthesia if patient had intra operative Hypertension, Tachycardia, Sweating or Lacrimation. As technology advanced, newer modalities like isolated forearm technique, spot Electroencephalography, Bispectral Index (BIS), Mid Latency Auditory Evoked potentials (MLAEP) and Entropy came into practice and were found to be more effective ways of monitoring the depth of anesthesia [2].

Entropy monitoring works on the principle of assessing the degree of irregularity in the electroencephalography (EEG) signals and Frontal Electromyography (FEMG) signals of the brain under General Anesthesia [3]. As the drug concentration in the brain increases, the irregularity in the EEG signals decreases and Entropy is the measure of that irregularity and it is very useful nowadays because it gives a quantitative estimation of the depth of anesthesia in terms of Response Entropy (RE) and State Entropy (SE). It is measured via a 3 – electrode sensor applied to the patient's forehead and it gives a score between 0 – 100 where 0 indicates comatose state and 90-100 indicate awake state. A score between 40-60 is considered optimum for general anesthesia [4-7].

RE is based on both EEG and FEMG signals and provides patient's response to external stimuli. The higher frequency FEMG signals have a faster reaction time in RE (<2 seconds) compared to SE (15-30 seconds) [8]. SE is a more stable parameter and changes with the changes in the hypnotic effects of the anesthetic drugs. Both RE (0-100) and SE (0-91) are standardized, dimensionless values between 100 and 91 (awake) and 0 (no EEG and FEMG activity) with RE>SE [8]. RE is always higher than SE and the difference between the two is <10 [1]. SE is calculated as a frequency range between 0.8 – 32 Hz and primarily includes components from the EEG. RE is determined in the range of 0.8 – 47 Hz and simultaneously registers EEG of brain and FEMG of facial muscles. RE approximates SE when FEMG power is equal to 0 [9]. When SE is in the recommended range for adequate anesthesia but RE increases 5 – 10 U more, this indicates that patient's responsiveness to surgery can be interpreted as a sign of uncovered nociception and an indicator of FEMG activity [9-10].

Anesthetic management of Off – Pump Coronary Artery Bypass Graft Surgery poses a significant challenge. There are various events during the entire surgical procedure where hemodynamic fluctuations are expected which are namely at the time of the induction of anesthesia, intubation, positioning the heart for various graft placements, sternotomy, sternal wiring, and extubation etc. As heart is functioning on a limited cardiac reserve, it becomes prudent to keep the hemodynamic parameters as stable as possible. This can only be ensured if there is adequate depth of anesthesia which is monitored using entropy all throughout the surgery.

In previous studies conducted, the use of these modalities like BIS, Entropy etc. have proven useful in administering accurate amounts of anesthetic drugs and thus have saved the patients from unnecessary intra – operative awareness or post – operative side effects from anesthetic drug overdose as well as prevented any hemodynamic instability [10-11].

Out of these, most of the studies have been conducted using BIS modality and nearly all of them have concluded that use of BIS allowed anesthesiologist with precise decision making in balancing the dose of anesthetic drugs [12] and it also led to decreased volatile anesthetic drug consumption and shorter recovery times [13]. Entropy is a newer and more advanced modality over BIS and a study conducted comparing BIS and Entropy in patients undergoing coronary artery bypass graft surgery showed an advantage of using Entropy over BIS as Entropy showed significantly less interference from FEMG signals and a superior resistance against artifacts as compared to BIS and thus is more suitable for monitoring the depth of anesthesia in cardiac surgery patients [14].

Some studies have evaluated the impact of entropy monitoring on intravenous anesthetic drug requirements in Coronary Artery Bypass Graft Surgery and have concluded that entropy monitoring significantly reduced intravenous anesthetic drug dose requirements [15-16]. However, lesser evidence is present for the same in volatile anesthetic agents.

A few studies on the subject have used end tidal Sevoflurane concentration [17] or difference in vaporizer weights [18] but neither have given accurate estimation of volatile anesthetic agent consumption.

The present randomized controlled study tested the hypothesis that the use of Entropy Monitoring in Off –

Pump Coronary Artery Bypass Graft Surgery is associated with decrease in Sevoflurane consumption compared with the controlled clinical practice group. We used GE Healthcare Ventilator and monitor (Helsinki, Finland) with entropy module which allowed precise measurement of the anesthetic gas consumption. Other outcomes were also recorded like recovery time which was noted as the time to eye opening on command and hemodynamic changes.

Methods

This prospective, interventional, randomized, double blinded, controlled single site study was conducted in the department of Anesthesiology, in cardiac surgery operation theatre with due permission from Institutional Ethics Committee and review board and written informed patient consent. From December 2020-May 2021, 60 patients with ASA grade of 2 and 3 and New York Heart Association (NYHA) grade of 1, 2 and 3 within the age groups of 30-70 years of either sex who were planned for off-pump Coronary Artery Bypass Graft surgery under General Anesthesia with Ejection fraction > 45% were enrolled into the study.

The patients provided written informed consent. Patients suffering from Diabetes Mellitus, Electrolyte disturbances, bleeding disorders, heart failure or Ejection Fraction <45% or having any valvular lesions or deranged liver or renal functions or any respiratory illness or patients on sedatives and hypnotics pre-operatively or with altered sensorium, psychiatric illness or drug/alcohol abuse and the patients who gave refusal to informed consent were excluded from the study.

60 patients were equally and randomly divided into two groups of 30 using computer generated form of randomization. Group A belonged to patients who underwent Entropy Monitoring with entropy values displayed on the monitor and titration of sevoflurane was done according to the target range of Entropy values of SE i.e. 40-60 and the difference between RE and SE below 10 throughout the entire duration of surgery. Group B belonged to patients with entropy values recorded but not displayed on the monitor and titration of Sevoflurane was done according to changes in clinical parameters (±20% of baseline values) throughout the entire duration of surgery. The recorded entropy values were later used for making comparison with Group A and draw conclusions.

Patients were asked to consume nothing by mouth for at least 8 hours preoperatively. All anticoagulants like Aspirin and clopidogrel were stopped 7 days prior to surgery. Patient was prescribed Tab. Alprazolam 0.5mg at bed time on the night before surgery to alleviate anxiety associated with surgery. Patient's consent and pre anesthetic check up was checked. In operating room, 20–gauge peripheral venous cannula was inserted into the right antecubital vein. All patients were infused with Ringer Lactate fluid in peripheral line.

5 lead Electrocardiogram (ECG) leads and pulse oximeter were attached. Then, preferably, right femoral artery cannulation was performed and Central Venous Catheterization in Right Internal Jugular vein was done under Local anesthesia. Baseline data in the form of Heart Rate (H.R.), Systolic Blood Pressure (S.B.P.), Diastolic Blood Pressure (D.B.P.), Mean Arterial Pressure (M.A.P.) and oxygen saturation were recorded.

Entropy Electrodes were placed on the patient's forehead after carefully wiping and drying the skin of forehead with spirit swab. In group A patient, entropy values were displayed on the monitor and recorded and Sevoflurane dosage was titrated accordingly and in Group B patients, entropy values were recorded but not displayed on the monitor and thus Sevoflurane dosage was titrated according to changes in the clinical parameters.

Patients were pre oxygenated simultaneously for 3-5 minutes. Injection (Inj.) Midazolam (0.15mg/kg) iv, Inj. Fentanyl Citrate (3□g/kg) was given as pre- medication.

Patients were induced with Inj. Etomidate (0.3 mg/kg) and Inj. Rocuronium (0.9mg/kg). Patients were intubated with an appropriate size Endotracheal Tube. Patients were maintained with 100% Oxygen at 2L/min, Inj. Vecuronium, Inj. Midazolam and Inj. Fentanyl Citrate in order to maintain End – Tidal CO2 (ET CO2) less than 35-40mmhg.

Surgery was performed on beating heart without using Cardiopulmonary Bypass (CPB) pump i.e. Off – Pump Coronary Artery Bypass Grafting (OP-CABG).

In both groups Entropy values (Response Entropy and State Entropy) were calculated by the plug - in module of the same GE Healthcare machine monitor as well as Heart Rate (H.R.), Systolic Blood Pressure (S.B.P.), Diastolic Blood Pressure (D.B.P.), Mean Arterial Blood Pressure (M.A.P.), and Oxygen saturation were recorded pre operatively and thereafter at specific times till the end of surgery.

Statistical Analysis

The primary objective of this study is to demonstrate that the amount of Sevoflurane consumed is significantly reduced through use of Entropy Monitoring in Off Pump Coronary Artery Bypass Graft surgery. Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by students t-test. Probability (P value) was considered to be significant if less than 0.05.

Results

60 patients posted for Off Pump Coronary Artery Bypass Graft Surgery were screened and analyzed. They were divided into two groups of 30 each.

Demographic Profile

As (Table 1) suggests, there was no significant difference found in age wise distribution, sex wise distribution, distribution according to ASA grade or according to NYHA grade and duration of surgery.

Table 1- Demographic profile

Parameter	Study Group (A)	Control Group (B)
AGE (Y)	59.77±9.53	58.93±8.29
SEX (M/F)	26/4	25/5
ASA GRADE (2/3)	23/7	23/7
NYHA GRADE (1/2/3)	3/17/10	3/16/11

Note – Data expressed as mean ± standard deviation.

Duration of surgery

As, (Table 2) suggests, there was no significant difference in the duration of surgery in between the two groups as well.

Table 2- Duration of Surgery (min) in Study Group a Vs Control Group B

	Group A		Group B	
	Mean	SD	Mean	SD
Mean Duration of Surgery	218.93	25.39	226.83	26.09
Median	210		225	
Results (p value)	0.239 (NS)			

S = Significant; NS = Non Significant

Amount of Sevoflurane consumed

According to (Figure 1), Sevoflurane consumption was calculated in terms of ml/hr and it was found that Sevoflurane uptake was significantly higher in control group (Group B) than in the study group (Group A) (12.42±0.68 ml/hr in control group vs. 7.03±0.67 ml/hr in study group; p<0.001).

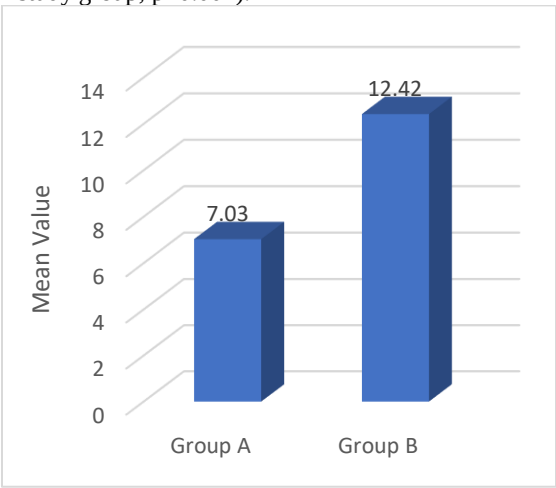

Figure 1- Amount of Sevoflurane Consumed (ml/hr) in the Study Group A vs Control Group B

Time of recovery

The time of recovery from Sevoflurane Anesthesia which was assessed as the time (in hours) taken for eye opening on command was significantly longer in the control group (Group B) than in the study group (Group A) (12.05±1.11 hours in control group vs 6.47±0.65 hours in the study group; p<0.001) as shown in (Figure 2). None of the patients recalled any intra operative events.

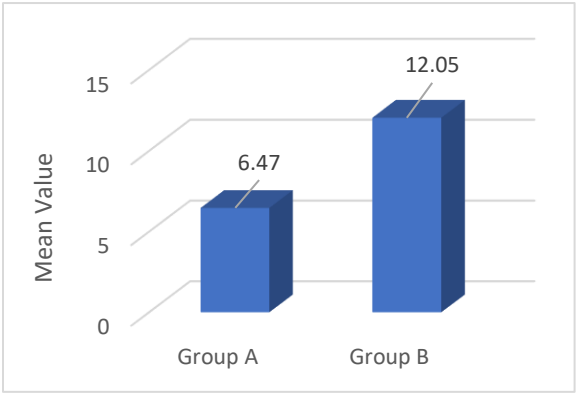

Figure 2- Time of Recovery (hours) in Study Group A vs Control Group B

Response Entropy and State Entropy

Response Entropy (RE) and State Entropy (SE) values were recorded pre operatively, at the time of induction and at every 30 second interval post induction till 5 minutes and after that at several instances in the surgery. Before Induction of anesthesia, RE was 98.77±1.07 and SE was 90.27±1.11 in the Entropy group i.e. the study group (Group A) and RE was 98.33±1.12 and SE was 90.00±1.58 in the control group (Group B). It was also found that mean values of RE and SE recorded at 1.5 minutes after induction and from 4.5 minutes post induction till the completion of surgery were significantly lower in the control group (Group B) than the study group (Group A). Desired values of RE and SE were achieved at 3.5-4.0 minutes as shown in (Figure 3-4) respectively.

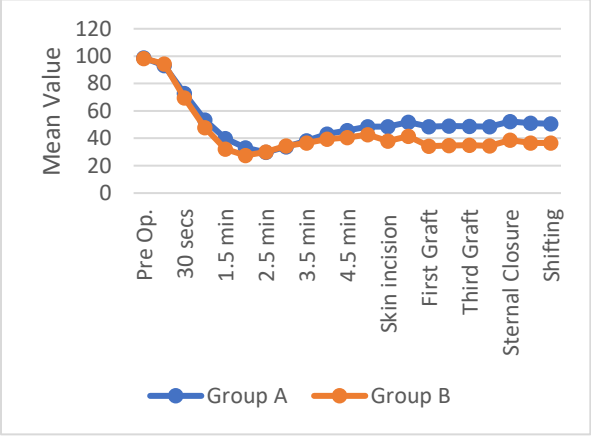

Figure 3- Response Entropy values pre operatively and at various intervals during surgery in Study Group A and Control Group B

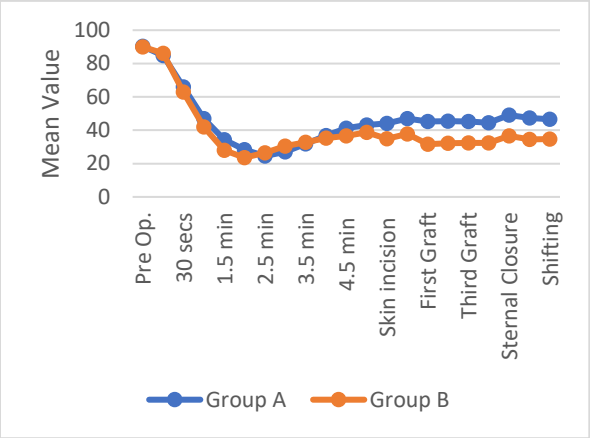

Figure 4- State Entropy values pre operatively and at various intervals during surgery in Study Group A and Control Group B

Hemodynamic changes

As suggested by (Figure 5-6), There were significant differences between the SBP values at the time of first skin incision and sternotomy and at the time of completion of all the grafts in between the groups and the values being significantly higher in the control group (Group B) than the study group (Group A). MAP was significantly higher at the time of completion of all the grafts in the control group (Group B) as compared to the study group (Group A). There was no significant difference in the Heart rate in between the two groups however, there was one incident of intra operative tachycardia in one patient in the control group and was managed by Inj. Esmolol. One episode of hypotension occurred in one patient in study group and five patients in control group and was managed by Inj. Noradrenaline. One episode of hypertension occurred in three patients in control group and six patients in study group and was managed by increasing sevoflurane concentration in control group and by Inj. Nitroglycerine in study group if entropy values were in the desired range.

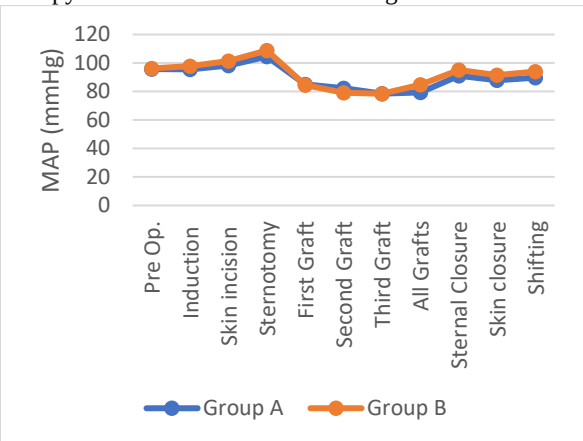

Figure 5- Mean Arterial Pressure (MAP) (mmhg) values pre operatively and at various intervals during surgery in Study Group A and Control Group B

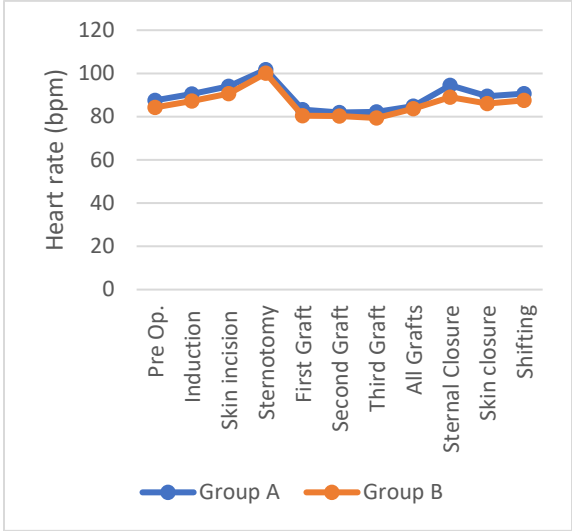

Figure 6- Heart Rate (beats/min) values pre operatively and at various intervals during surgery in Study Group A and Control Group B

Midazolam and Fentanyl consumption

No changes were seen in the amount of consumption of Inj. Midazolam and Inj. Fentanyl as they were repeated at equal time intervals in both the groups.

Discussion

In this study, entropy monitoring was compared to standard clinical practice to assess the depth of Anesthesia and to assess Sevoflurane consumption and recovery time from Anesthesia. We found that assessment of depth of Anesthesia using Entropy monitoring resulted in significantly lower Sevoflurane consumption and significantly shorter time of recovery from Anesthesia as compared to standard clinical practice group. This reduction in Sevoflurane consumption and recovery time was reflected in the State Entropy (SE) values of the study group which were higher than in the control group.

In olden days, depth of Anesthesia has widely been assessed by changes in clinical parameters and assessing the PRST Score, isolated forearm technique [2], jaw thrust, pain on surgical stimuli and trapezius squeeze test [19].

However, with the advancement of technology and further studies on the subject, newer modalities like spot Electroencephalogram (EEG), BIS, MLAEP, Entropy came into use [2]. Since Anesthetic drugs tend to have a major impact on the brain, any modality that could assess the depth of Anesthesia using brain's electrical activity would prove to be more reliable.

Coronary Artery Bypass Graft surgery is indicated in patients of Coronary Artery disease and patients who have a risk or might actually suffer from Myocardial Infarction pre – operatively and/or intra – operatively.

Cerebral activity of brain can be adversely affected especially during coronary artery bypass graft surgery as the massive hemodynamic changes or intra – operative myocardial Infarction might lead to altered anesthetic depth and exposing the brain to varied depths of Anesthesia [20]. Deeper than required plane of Anesthesia will lead to intra operative hypotension and post-operative nausea and vomiting and delayed recovery whereas lighter than required plane of Anesthesia will lead to inadequate depth of Anesthesia with recall of intra operative events and hemodynamic changes. Thus there is an indispensable need of monitoring the depth of anesthesia in CABG surgery.

Multiple studies have shown that lower BIS values and hypotension is associated with higher morbidity and mortality in the long run [21-23]. Inhalational agents are known to have promoted Alzheimer's disease in the elderly however, no such studies are conducted using Entropy yet [24].

Entropy monitoring has had a positive impact on the reduction in amount of induction agents as well. Saranjit Singh et al in their study concluded Entropy as a reliable indicator to assess the depth of Anesthesia for Laryngeal Mask Airway (LMA) placement during Sevoflurane and propofol Anesthesia [1].

Baulig W et al conducted a study where they compared Spectral Entropy and Bispectral Index Electromyography in CABG surgery for assessing the depth of anesthesia and concluded that RE and SE showed less interference from FEMG signals and superior resistance against artifacts as compared to BIS and hence proved to be a better tool for monitoring the depth of Propofol–Ramifentanil anesthesia [14].

There have been studies where Entropy Monitoring was used in CABG surgery but only the dosage of intravenous anesthetic (mainly propofol) and analgesic drugs was assessed and no such effect on inhalational agents was seen. Jiahai M et al concluded in their study that Entropy Monitoring reduced propofol and sufentanil dosage for patients undergoing Off Pump Coronary Artery Bypass Graft Surgery [16]. Ahmed Said et al concluded in their study that Entropy monitoring for cardiac patients undergoing Coronary Artery Bypass Graft (CABG) surgery reduced propofol consumption and maintained a fair hemodynamic profile during induction of General Anesthesia [15]. Considering the poor condition of heart due to myocardial infarction and limited cardiac reserve and contractility and the adverse effects of propofol if administered without managing the adequate dosage would lead to hemodynamic instability chiefly hypotension and the heart could succumb to further unpropitious conditions intra and/or post operatively. This signifies to need to adapt to better agents for maintaining the depth of anesthesia which could be by the use of Inhalational anesthetic agents as they have a lesser adverse effect profile on heart.

A study conducted by Bignami E et al through a survey at 64 Italian Cardiac centres concluded that risk adjusted mortality may be reduced by the use of Volatile anesthetic agents in patients undergoing coronary artery bypass graft surgery and also that the longer the agent is administered, the better is the outcome [9]. Another study which compared Propofol and Sevoflurane use in CABG surgery by De Hert SG et al arrived at the conclusion that Sevoflurane had cardio - protective properties as it preserved Left Ventricular function after Cardio Pulmonary Bypass with less evidence of myocardial damage and significantly less cardiac Troponin I release in the first 36 hours post operatively [25]. A similar finding was observed by Guarracino F et al in their study except that it was done using desflurane [26].

As Vakkuri A et al suggested, two parameter entropy could prove better than single parameter BIS as it has RE covering nociception and SE covering Hypnosis and thus would aid the anesthesiologist in administering analgesic or hypnotic drug as and when each is required [6]. This could play a vital role in CABG surgery. However, further studies are needed to be done to give a definitive clue.

Many studies have assessed the outcomes of BIS and Entropy on anesthetic agent consumption and have found positive results. Aime et al concluded that use of BIS or spectral Entropy monitoring led to 29% decreased Sevoflurane consumption [27]. Apart from this, Hor et al also concluded that use of Entropy monitoring was associated with 30% reduction in Sevoflurane uptake and faster extubation rates [3]. A study conducted by Ellerkmann RK et al concluded that electroencephalographic effects of increasing or decreasing dosage of Sevoflurane could be attributed to Entropy Monitoring [26]. However, no such studies have come to our notice where entropy monitoring was used to assess sevoflurane uptake in Coronary Artery Bypass Graft Surgery.

There are other studies that have also shown significant reduction in Sevoflurane consumption [17-18, 27] however, their method of calculation of Sevoflurane was different. They either calculated it using expired Sevoflurane fraction [18] or by weighing the vaporisers at the beginning and at the end of surgery [27]. Nevertheless, our Anesthesia workstation was of GE Healthcare and it precisely calculated and displayed Sevoflurane consumption at the completion of surgery. If not, it could be calculated using Dion's formula [28].

Shafiq et al concluded that use of BIS in elderly Asian population resulted in 40% reduction in Isoflurane consumption and significant shorter recovery time in study group at the end of Anesthesia [29]. However, Goyal KA et al, in their study concluded that use of Entropy monitoring does not change the amount of Isoflurane consumed or resulted in clinically significant faster recovery [28].

The incidence of hypertension was more in the study group as compared to the control group because in control group, intra operative hypertension was treated with increasing Sevoflurane concentration assuming the patient to be in a lighter plane of Anesthesia. On the contrary, in the study group, if the Entropy values were in the desired range of 40-60, lighter plane of Anesthesia was ruled out and intra operative hypertension was treated with drugs like Inj. Diltiazem or Inj. Nitrogylcerine. For similar reasons, incidences of hypotension were more in the control group as compared to the study group due to overuse of Sevoflurane agent. Hence, Entropy monitoring worked as an aid to the anesthesiologist in better ascertaining the cause of intra operative hemodynamic disturbances and manage accordingly [3].

None of the patients in either groups reported any recall of intra operative events suggesting adequate anesthetic depth however further studies need to be done on the subject. According to the results of our study it would not be wrong to ascertain that the patients in the Control group received more than required dosage of anesthetic agent due to lack of entropy monitoring guided titration of Sevoflurane and could lead to more gross hemodynamic changes and cardiac depression. Also, significant longer recovery time which was estimated by the time taken (in hours) for eye opening on command was seen in control group which could be possible as the patients in this group were exposed to higher concentration of sevoflurane compared to the study or entropy group.

One more thing to note in this study is that Inj. Midazolam and Inj. Fentanyl were administered at equal time intervals to all the patients of both groups irrespective of Entropy values or Sevoflurane concentration so that the depth of Anesthesia can only be used to assess Sevoflurane consumption [3].

Patient and surgery related characteristics were similar in both groups like pre - operative anticoagulation therapy, duration of surgery, equal number of grafts, uneventful surgery and complete revascularisation with no signs of ischaemia. This implies that our results are majorly derived from the effect of the anesthetic drug being studied and not patient or surgery related events [25].

Limitations

Due to unavailability of Flo-trac system, there was no monitoring of cardiac output, stroke volume or systemic vascular resistance. Also, no monitoring for Myocardial Infarction was done. None of the patients with co morbidities or very low ejection fractions were studied as those comprise high risk patients and a study conducted on those would prove to be fruitful. Also, patients undergoing CABG surgery using CPB were also not studied as it is used sometimes when grave hemodynamic instability warrants the need for CPB as surgery is no longer possible on beating heart. Hence further studies are needed in these areas so majority of the patients could be benefitted.

Conclusion

In conclusion, monitoring the depth of Anesthesia using Entropy Monitoring was associated with significant reduction in consumption of Sevoflurane and faster recovery times.

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