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Amount of Desflurane Consumed in Entropy-guided vs. Minimum Alveolar Concentration Guided Administration in Major Abdominal Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: Conventional titration of volatile anesthetics relies on Minimum Alveolar Concentration (MAC) and hemodynamic parameters. Entropy uses electroencephalogram signals to monitor depth of anesthesia. Desflurane offers rapid emergence but carries higher costs. Literature comparing desflurane consumption between entropy-guided and MAC-guided titration in major abdominal surgeries remains limited.

Methods: In this single-center, single-blind, randomized controlled trial, 48 patients (ASA I–II, aged 18–65 years) undergoing elective major abdominal surgery lasting more than 4 hours were randomized into two groups. In the MAC group, desflurane was titrated to maintain a MAC of 0.8–1.2 based on hemodynamics. In the Entropy group, titration was adjusted to maintain entropy values between 40 and 60. Primary and secondary outcomes included total desflurane consumption, mean end-tidal desflurane concentration, time to awakening and extubation, incidence of emergence agitation, and hemodynamic stability.

Results: Baseline characteristics were similar between groups. Desflurane consumption was significantly lower in the entropy-guided group compared to the MAC group (230±86ml vs300±83ml(p=0.006)). Recovery was significantly accelerated with entropy guidance; time to spontaneous eye opening was (319±141sec vs 481±182sec(p=0.013) and time to tracheal extubation was (450±196 sec vs 621±277sec(p= 0.01) .No significant differences were observed in hemodynamic parameters or postoperative cognitive outcomes.

Conclusion: Entropy-guided desflurane administration significantly reduces total anesthetic consumption and accelerates recovery offering a cost-effective strategy for prolonged abdominal surgeries.

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Keywords: Desflurane, Entropy Monitoring, General Anesthesia, Volatile Anesthetic Consumption, Enhanced Recovery.

INTRODUCTION

Hypnotic state of a patient during surgery can be evaluated in real time by quantifying the electroencephalogram (EEG) signals. Titration of the dose of an anesthetic agent based on the EEG signals ensures prevention of awareness and pain during surgery due to inadequate dosage of anaesthetic agents, and at the same time is helpful in avoiding hemodynamic instability due to its excessive administration.[1] The standard practice involves use of the concept of Minimum Alveolar Concentration (MAC). It is an indirect method of assessing the depth of anaesthesia at cerebral level which is the effect site. Titration of age adjusted MAC between 0.8 to 1.2 is based on haemodynamic parameters such as heart rate and blood pressure which depends on several other factors such as blood loss during major abdominal surgery. Thus, maneuvering MAC based on haemodynamic parameters becomes inefficient in setting of major abdominal surgeries. [2]

Entropy is an EEG based technology that integrates two methods, namely, the deciphering of EEG signals and changing into numerical values and, Electromyography (EMG) of facial muscles. It has two components: State entropy (SE) which includes EEG analysis and, Response entropy (RE) which includes both EEG and EMG activity.[3]

Major abdominal surgeries are often of long-duration, thus large amount of inhalational agent is used, which translates into higher cost. Furthermore, these surgeries are usually associated with blood loss and haemodynamic alterations, thus titrating depth of anaesthesia assumes crucial importance. Standard method of utilizing MAC towards achieving this goal may not be accurate.[2]

Desflurane is an excellent inhalational agent owing to its short half-life, which allows precise control of the depth of anaesthesia, but it is expensive.[4] Benefits of entropy guided administration of desflurane have been shown in terms of time to awakening, prevention of emergence agitation, reduction of cost in children undergoing short procedures and may contribute to lesser environmental pollution.[5] However, there is paucity of literature on entropy guided desflurane consumption in adults undergoing prolonged procedures.[5]

This randomized control trial was designed to study the effect of entropy guided administration on amount of desflurane consumed in adults undergoing major abdominal surgery as well as its impact on time to awakening, recall and emergence agitation, and compare it with MAC guided administration.

METHODOLOGY

In this single blind randomized control trial after Institutional review board (IRB) approval, Clinical trial registry of India registration (CTRI/2023/02/049808) was done and written informed consent was taken from each patient.

Patients aged 18–65 years undergoing elective major abdominal surgery with expected duration of more than 4 hours and American Society of Anesthesiologists physical status (ASA) I or II were included in the study. Patients with history of any disabling central nervous or cerebrovascular disease, hypersensitivity to opioids, history of substance abuse, treatment with opioids or any psychoactive medication or who had deviation from the standard care of anesthesia were excluded.

Forty-eight adult patients were randomly allocated into the two groups, entropy-guided group (Group E) and MAC-guided group (Group M) using computer generated random numbers. Demographic characteristics like age, sex, weight, height and body mass index (BMI) were recorded. Baseline heart rate and mean arterial pressure were noted in the operating room before the induction of anaesthesia. In both the groups, patients were administered subarachnoid block. After confirming free flow of cerebrospinal fluid (CSF), morphine 5mcg/kg was given intrathecally along with 1.0 ml bupivacaine (Heavy) 0.5%.

Entropy sensors were placed in the patients in Group E prior to anaesthetizing the patient. Radial artery catheter was placed according to the standard protocol. General anesthesia was induced with IV propofol 2 mg/kg, IV fentanyl 2 µg/kg and the trachea was intubated with an appropriate size tube using rocuronium 0.6 mg/Kg. Lungs were mechanically ventilated with a tidal volume of 6-8 mL/kg, with the ventilatory rate adjusted to maintain an end-tidal carbon dioxide concentration of 30–35 mm Hg. Intravenous atracurium infusion 5 µg/kg/min was started.

Anaesthesia was maintained with 8% desflurane in air and oxygen mixture with fractional inspired concentration of oxygen (FiO2) of 0.5. Fresh gas flow rate was set to 4 L/min initially until the difference between the inspiratory and end-expiratory desflurane concentrations were equal to or <0.4%; following which fresh gas flow rate was reduced to 1 L/min and the dial setting was decreased to 6 % in both the groups.

Tachycardia was managed with fentanyl 0.5µg/kg bolus, followed by esmolol in increments of 10-20 mg bolus IV if needed. Hypotension was treated with IV fluid bolus of 250 ml and a decrease in desflurane concentration, and finally, by ephedrine 3–6 mg IV or phenylephrine 50–100 µg IV if necessary. In case of bradycardia, atropine 0.5–1 mg IV was administered.

The titration of desflurane during maintenance of anaesthesia in the two groups was as follows:
Group M: In this group after achieving a MAC of 1 initially, further titration of desflurane was guided by change in heart rate or blood pressure. Any increase or decrease in heart rate or blood pressure by 20% of baseline, desflurane dial setting was increased or decreased by 1 % respectively to keep MAC between 0.8 to 1.2.

Group E: In this group after achieving MAC of 1 initially, desflurane concentration was adjusted to keep SE and RE values in the range of 40–60 during the procedure. Desflurane concentration was titrated with an increment or decrement of 1% with any increase in SE to more than 60 or decrease in SE to less than 40 respectively

Muscle relaxant infusion was started in all patients after induction and was discontinued when the abdominal muscle closure was started. For postoperative analgesia, IV paracetamol 1g, and for antiemetic prophylaxis, ondansetron 4mg were administered 20 minutes prior to the end of the surgery. Desflurane administration was discontinued at the end of skin closure, and fresh gas flow was increased to 6 L/min of air-oxygen mixture in the ratio of 70:30. Residual neuromuscular blockade was reversed with glycopyrrolate 0.5mg IV and neostigmine 2.5mg IV. Tracheal extubation was performed once the spontaneous eye opening, purposeful limb movement, and ability to follow verbal commands were achieved. Time to tracheal extubation i.e., time from stopping of desflurane to extubation was noted.

Time to awakening was defined as the time duration between discontinuation of desflurane and spontaneous eye opening, the onset of sustained purposeful limb movements or phonation. Subsequent recovery was assessed according to the modified Steward recovery score. The time to achieve a maximal Steward score was noted, and the patient was transferred to the post-anaesthesia recovery area. Postoperatively, the patients were assessed for residual sedation after 12 hours by the modified Ramsay sedation score. On the first postoperative day, patients were interviewed about intraoperative awareness using Michigan awareness scale and postoperative cognitive function was assessed by Mini Mental State Examination (MMSE) questionnaire. Pain was assessed by the numerical rating scale (NRS) with a scale from 0-10, (0 indicating no pain and 10 worst possible pain) every 30 min for the first 2 h. Patient with a score of 4 or more was administered boluses of 0.5 µg/kg) fentanyl IV every 15 min till the pain subsided.

Sample size calculation:
Assuming that the mean desflurane consumption in MAC guided group is 25.3 ±8.11ml and the same in the entropy group is 18.7 ±5.07 ml with an alpha error of 5% and power of 80%, we needed to enroll 48 patients i.e., 24 in each group. So, it was decided to enroll 48 patients i.e., 24 in each group. The patients were randomly allocated by computer-generated random numbers using sealed opaque sequentially numbered envelops.

Statistical analysis
Data were transferred to a computer hard disk using the software program GE Datex-Ohmeda S/5 Collect (version 4.0) for offline analysis. All the variables were reported on an Excel data sheet. The desflurane consumption per hour per kg body weight was calculated using the software program GE Datex-Ohmeda.Quantitative data with normal distribution are presented as mean ± standard deviation and analyzed by independent t test. Qualitative categorical data are presented as frequency and percentage. Fisher's exact test was used to test the proportion between groups. $P < 0.05$ was considered a statistical significance. All analyses were performed on an intention-to-treat basis.

RESULTS
A total of 60 patients were assessed for eligibility. Seven did not meet inclusion criteria. Five patients were excluded. Two patients declined to participate, 2 were previously treated with opioids for pain, and one had hypersensitivity to opioids. Forty-eight patients were randomized into 2 groups each consisting of 24 patients. (Figure1).

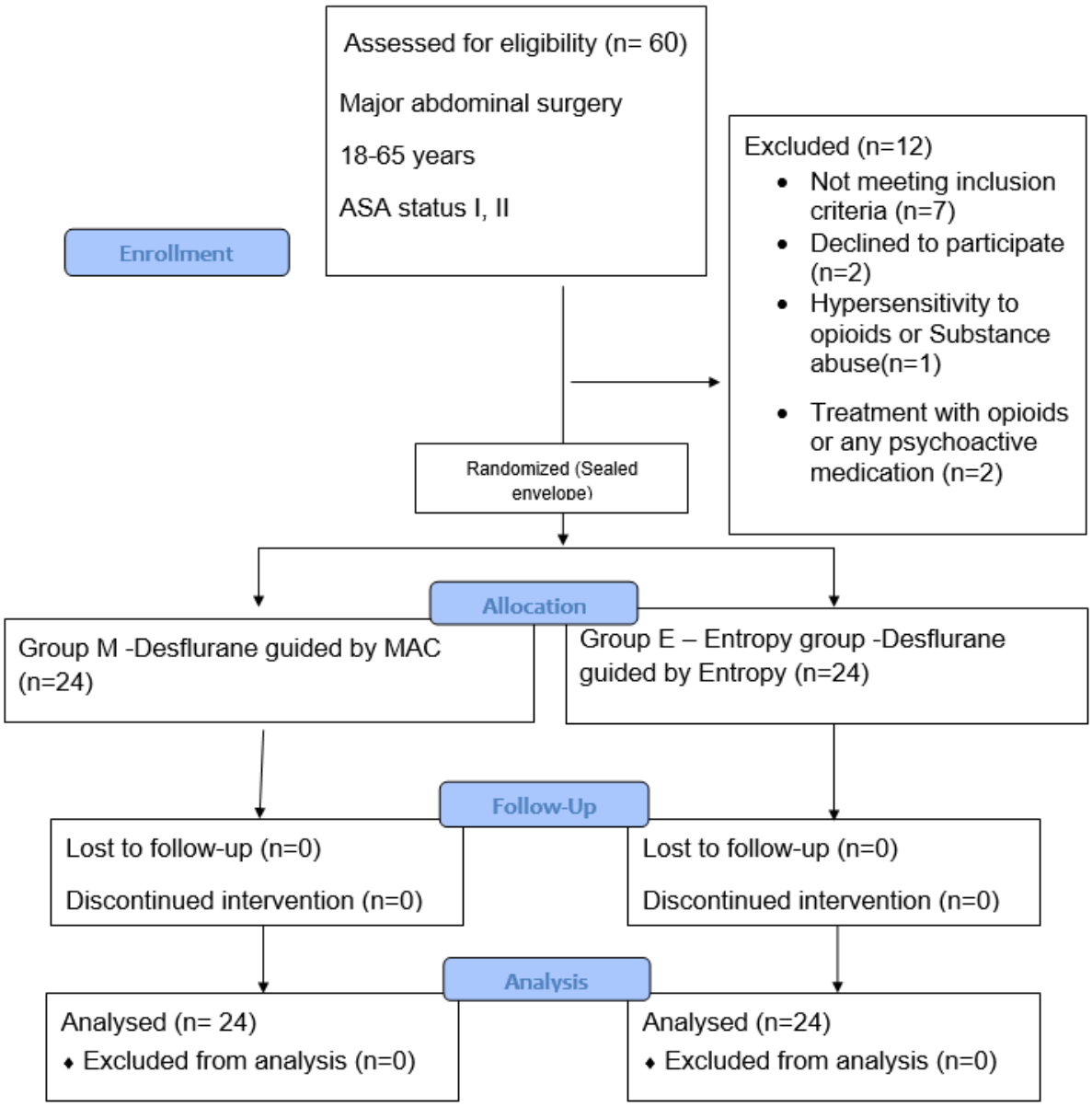

Figure 1

CONSORT DIAGRAM:

The two study groups, Group E and Group M were comparable with respect to age, gender, weight, height, BMI and body surface area and ASA. There was no difference in the types of surgery performed (P=0.6). The most common surgery was liver resection in group E while pancreatic resection was most common in group M. The demographic parameters are presented in table 1.

Table 1: Comparison of demographic variables between the groups

	Group E n=24	Group M N=24	P value
Age (years)	48.6±14.2	47±13.5	0.6
Sex female/male	9/15	7/17	0.7
Weight (Kg)	66.1±14.3	63.9±10.9	0.1
Height (cm)	161±11.4	162±10	0.65
Body Mass Index	25.4±5.2	24.0±2.7	0.25
Body Surface Area	1.84±0.24	1.83±0.20	0.48
ASA grade1/2	12/12	18/6	0.13
Comorbidities y/n	10/14	6/18	0.35
Type of surgery			
Liver resection	11	8	

Liver cyst deroofing	2	1	
Pancreatic resection	6	11	
Biliary surgery	2	1	
Gastrointestinal	1	3	
Others	2	0	

P< 0.05-statistically significant; ASA (American Society of Anesthesiologists) E- Entropy; M- MAC; Data presented as mean± Sd

Intraoperative variables were taken into account. The duration of anaesthesia in group E was 514±125 minutes and in group M it was 531±141minutes, the difference was not significant (p=0.61). Time to spontaneous eye opening was 319±141 seconds in group E while 481±182 seconds in group M, the difference was statistically significant (p=0.013; CI 66.61 to 256.30). Time to tracheal extubation was 450±196 seconds in group E and 621±277 seconds in group M, the difference was significant (p=0.01; CI 31.25 to 310.25). Average end-tidal desflurane concentration (Et Des) concentration in Entropy group E was 4.47 ±0.47 and in group M it was 5.13±0.59, the difference was significant (p=0.001; CI 0.35 TO 0.97). Results are shown in table 2.

Table 2: Intraoperative and recovery parameters

Intraoperative Variables	Group E N=24	Group M n=24	P value
Duration of anaesthesia (min)	514±125	531±141	0.61
Average end-tidal desflurane concentration (%)	4.47 ±0.47	5.13±0.59	0.001
Time to spontaneous eye opening (seconds)	319±141	481±182	0.013
Time to tracheal extubation (seconds)	450±196	621±277	0.01
Vasopressor requirement	4/24	3/24	1.0

Data presented as mean ± SD

Average blood pressure and heart rate were compared at different time points between the groups. There was no difference in the blood pressure and heart rate (Figure 2 and 3).

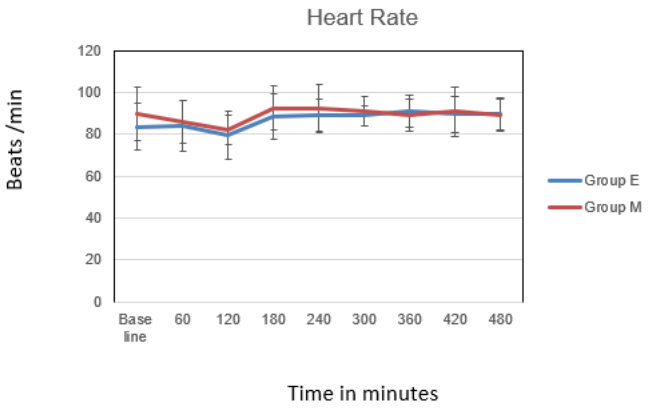

Figure 2: Average heart rate at different intervals

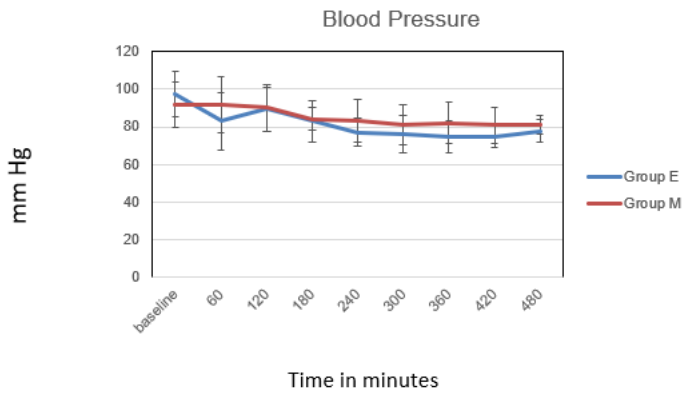

Figure 3: Average mean blood pressure at different time points

Total consumption of desflurane was 230± 86 ml in group E vs 300± 83 ml in group M. The difference was statistically significant (p=0.006; CI 20.60 to 119.48). When consumption was normalized for weight, time, and BSA the difference remained statistically significant. The average cost of desflurane in group E was INR 9084± 3412 vs INR 11844± 3292 in group M. The difference was statistically significant (p=0.006; CI 811.90 to 4708.78). Desflurane consumption related parameters are shown in table 3.

Table 3: Desflurane consumption and cost

	Group E n=24	Group M n=24	P value	95% CI of difference
Desflurane consumption (ml)	230±86	300±83	0.0.006	20.60 to 119.48
Desflurane consumption (ml/kg)	3.63±1.6	4.93±1.8	0.001	0.28 to 2.31
Desflurane consumption (ml/kg/min)	0.006±0.0028	0.01±0.0056	0.021	0.00009010 to 0.005443
Cost (INR)	9084± 3412	11844± 3292	0.006	811.90 to 4708.78

INR: Indian Rupees, Data presented as mean ±SD

There was no difference in the drowsiness after extubation (0 in group E vs 2 in group M, p=0.48) and in emergence agitation (2in group E vs. 4 in group M; p=0.42) between the two groups. Likewise, there were no differences in the Steward score, Michigan awareness classification score, modified Ramsay sedation score, numerical rating score and MMSE score (Table 4).

Table 4: Post extubation and postoperative parameters.

	Group E n=24	Group M n=24	P value
Drowsiness after tracheal extubation	0	2	0.48
Steward score	5.9± 0.8	5.7± 0.75	0.27
Emergence agitation (n)	3	5	0.7
Michigan awareness classification score (mean)	0	0	
Mini Mental State Examination score	29.5± 0.65	29.4± 0.6	0.26
Modified Ramsay sedation score	1.8±0.4	1.75±0.6	0.15
Numerical Rating Scale score	3.1±0.86	2.7±1.1	0.13

Data presented as mean ± SD

DISCUSSION

In this clinical study, we compared the consumption of desflurane between entropy-guided and MAC-guided administration. Results demonstrate that entropy guided administration of desflurane is associated with less consumption which translates into less cost. Furthermore, entropy guidance facilitates quicker recovery from anaesthesia in terms of time to spontaneous eye opening and time to tracheal extubation.

This was a randomized control trial where patients undergoing major abdominal surgery were recruited. The study is unique as the surgeries were of long duration (523± 132 minutes). The patients had uniform baseline characteristics which allowed for accurate comparisons. The amount of desflurane was calculated using software in the anaesthesia machine which is more accurate than weighing of vaporizers.

The consumption of desflurane was lower in the group E. This held true when normalized for weight, BSA, and duration of surgery. The average cost saving was INR 2760 per case. Similarly, Et Des values were significantly lower in group E. To the best of our knowledge, there are no studies on adult patients undergoing long (lasting for more than 4 hours) surgeries which has specifically looked at the desflurane consumption using entropy guidance. In a study by Mishra et al, desflurane consumption was significantly lower in children undergoing ophthalmic procedures lasting for less than 1 hour.[5] In the study by Ibrahim TH et al the consumption of desflurane was significantly low in the BIS guided group vs standard care group. The duration of surgery was shorter compared to the current study and the patient population was morbidly obese patients undergoing bariatric surgery.[6] There are several studies using other agents which have also shown benefit. Aime et al showed that there was 29% less consumption of sevoflurane when entropy was used to guide administration.[7] In a study by El Hor et al the consumption of sevoflurane was significantly low compared to the control group.[8] Entropy measures the degree of disorder of EEG. Increasing depth of anaesthesia- more regular patterns of EEG -decreasing the entropy value. This allows more accurate titration of the anaesthetic agent by directly monitoring the hypnosis component (EEG) than MAC. As desflurane is expensive but at the same time has several advantages, the present study is relevant as judicious use can be facilitated by entropy guidance.

The time to spontaneous eye opening and time to tracheal extubation were significantly less in Group E. This is logical as with accurate titration, only the minimum required quantity of inhalational agents were administered. In the study by Mishra and coworkers using desflurane in children, LMA removal time was significantly lower in the entropy guidance group.[5] In the study by Ibrahim et al, the time to spontaneous eye opening and time to tracheal extubation were shorter in the BIS guided group.[6] Chen et al using sevoflurane showed that the time to spontaneous eye opening was significantly less in entropy guided group, whereas time to tracheal extubation was similar.[9] Since desflurane is associated with faster wakeup and washout, the concentration is kept at a higher level in patients where neuromonitoring is not used. This is further substantiated by significantly higher Et Des values in the MAC arm vs. entropy arm. One of the benefits of using desflurane is faster emergence from anaesthesia which is further facilitated by the use of entropy.

There was no difference between the groups in terms of blood pressure and heart rate. There was no difference in the vasopressor requirement between the groups. In the study by Mishra et al and Ibrahim et al, similar findings were observed.[5,6] In contrast, the study by El Hor et al reported that the standard care group had higher incidence of hypotension (3 vs 0).[8] Several factors apart from depth of anaesthesia determine the haemodynamics such as blood loss, fluid shifts, sepsis, etc. Any deviation in the haemodynamics is promptly corrected using interventions, hence getting a difference in hemodynamics is unlikely.

There was no difference in the drowsiness and emergence agitation. In the Study by Chen et al, entropy guided administration decreased emergence agitation,[9] while in the study by Mishra et al[5] there was no difference between the groups. Emergence agitation is multifactorial and the incidence is less in most of the studies. This study was probably not powered enough to capture the difference, if any.

Similarly, there was no difference in the recall and cognitive function after the surgery. There used to be a concern that lower amount of inhalational agent may be associated with recall but it has been refuted in several studies.[10] Although there was no incidence of recall in this cohort of patients, this study was not powered enough to capture this as the incidence is low. Postoperative cognitive dysfunction is a debatable entity. The contribution of inhalational agent to the occurrence of postoperative cognitive dysfunction is not conclusively proven and its etiology seems multifactorial.[11] Larger study with longer follow- up will give more insight into this entity.

There were several limitations of the study. The sample size was small, so some of the parameters which have low incidence could not be captured. In the MAC-guided arm, the entropy monitoring was not done so the entropy values could not be compared between the groups.

SUMMARY AND CONCLUSION

Entropy guidance reduces the amount of desflurane consumed in adult patients undergoing major abdominal surgery and saves the cost. Time to spontaneous eye opening and time to tracheal extubation is less with entropy guidance, hence the recovery is faster. There was no effect of entropy guidance on haemodynamics, emergence agitation, drowsiness after extubation, recall, pain scores, and cognitive function.

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