

AT EQUI-MAC VALUES, DO INHALATIONAL ANAESTHETICS PRODUCE EQUAL ENTROPY INDICES- PROSPECTIVE RANDOMISED STUDY USING ISOFLURANE, SEVOFLURANE AND HALOTHANE

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ABSTRACT

BACKGROUND

Minimal alveolar concentration has been used to measure the potency of inhalational anaesthetics. It is supposed that equi-MAC concentrations of different anaesthetics have a similar potency in suppressing responses to painful stimuli. The Minimum Alveolar Concentration (MAC) of an inhaled anaesthetic at 1 atmosphere prevents movement in 50% of patients to skin incision and is used to quantify inhaled anaesthetic potency.⁽¹⁾ MAC-awake is the MAC of an inhaled anaesthetic that prevents appropriate response to command in 50% of subjects. As a fraction of MAC, MAC-awake differ among anaesthetics.

The aim of this prospective randomised study was to compare three anaesthetics- halothane, isoflurane and sevoflurane in terms of their equi-MAC entropy values.

MATERIALS AND METHODS

After getting approval from Research Methodology and Human Ethical Committee of Government Medical College and informed consent from the patients, 30 adult patients undergoing spine surgery were enrolled for this study. After premedication, the baseline monitors were attached. The spectral entropy electrode was applied on forehead of the patient in accordance with manufacturer's instructions and connected to entropy monitor. The indices, response entropy and state entropy were read manually and recorded. Before induction of general anaesthesia, baseline HR, SBP, DBP, ETCO₂, SPO₂ were recorded along with response entropy and state entropy. General anaesthesia was induced, the heart rate, mean arterial pressure, response entropy and state entropy were noted as end tidal concentration of inhaled anaesthetics increased from 0.5 to 0.75, 0.75 to 1.0 and 1.0 to 1.5 MAC (wash-in). The values were again noted when MAC decreased from 1.5 to 1.0, 1.0 to 0.75 and 0.75 to 0.5 (wash-out). Steady state of 20 minutes was allowed at each target concentration before data were recorded to ensure equilibration of anaesthetic to brain.

Statistical Analysis- Data was analysed using Statistical Package for Social Sciences (SPSS) version 10. Data was expressed in frequency, percentage, mean and standard deviation. Mean age, weight, sex and values for heart rate, mean arterial pressure, response entropy and state entropy in the three groups was compared by one-way analysis of variance and chi square test. Post-hoc testing was done using Scheffe's method. P values of less than 0.05 were considered significant.

RESULTS

Reduction heart rate is noted in a dose-dependent manner in all groups. The systolic blood pressure decreases in a dose-dependent manner for all the agents, but not statistically significant. There was a statistically significant difference between the inhalational agents for DBP at different MAC values ($p < 0.05$). MAP was found to decrease in a dose dependent manner for all inhalational agents. During wash-out phase at 1 MAC, there was a statistically significant difference between the MAP values obtained with halothane and sevoflurane ($p < 0.05$). Dose dependent reduction of response entropy was seen with all the inhalational agents. The RE of sevoflurane was found to be the lowest at all MAC. Entropy values during wash-in and wash-out were comparable for all agents at 1 and 0.75 MAC. There was a statistically significant difference between the entropy indices of all inhalational agents at all MAC values ($p < 0.05$). At 1.5 MAC (wash-in), SE of 30.9 ± 4.6 and 25.2 ± 3.1 was obtained with isoflurane and sevoflurane. With halothane, a higher value of 46.4 ± 3.7 was obtained. At all MAC, there was a statistically significant difference between the SE values of the three inhalational agents ($p < 0.05$).

CONCLUSION

We recorded the entropy values of three volatile agents for comparison, unlike most of the studies done in the past with two agents. Through entropy, we measured two indices; SE, which quantifies cortical cerebral activity (Hypnosis) and RE, which evaluate Electromyography (EMG) activity (subcortical component). It was observed that, under anaesthesia the difference between RE and SE remained at less than 10, indicating adequate analgesia. Entropy values of halothane were found to be higher than isoflurane and sevoflurane at all MAC levels. The clinical implication of our study is that adjusting the administration of anaesthetic agents based on entropy values may be inappropriate, as halothane results in higher entropy of EEG compared to sevoflurane or isoflurane at equivalent MAC values. As halothane produces higher entropy indices there will be a tendency to increase its concentration, so as to achieve adequate levels of entropy. This may indirectly affect systemic and intracranial haemodynamics. Our study like previous studies shows that entropy is specific for each drug and that equi-MAC values of inhalational agents do not produce same entropy indices.

KEYWORDS

MAC, Entropy, BIS, EEG, Halothane, Isoflurane, Sevoflurane.

HOW TO CITE THIS ARTICLE: Parameswaran S, Christudas J. At Equi-MAC values, do inhalational anaesthetics produce equal entropy indices- prospective randomised study using isoflurane, sevoflurane and halothane. J. Evolution Med. Dent. Sci. 2017;6(31):2545-2551, DOI: 10.14260/Jemds/2017/551

Financial or Other, Competing Interest: None.
 Submission 30-01-2017, Peer Review 05-04-2017,
 Acceptance 12-04-2017, Published 17-04-2017.

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DOI: 10.14260/jemds/2017/551



BACKGROUND

Minimal alveolar concentration has been used to measure the potency of inhalational anaesthetics. It is supposed that equi-MAC concentrations of different anaesthetics have a similar potency in suppressing responses to painful stimuli.

The Minimum Alveolar Concentration (MAC) of an inhaled anaesthetic at 1 atmosphere prevents movement in 50% of patients to skin incision and is used to quantify inhaled anaesthetic potency.⁽¹⁾ MAC-awake is the MAC of an inhaled anaesthetic that prevents appropriate response to command in 50% of subjects. As a fraction of MAC, MAC-awake differ among anaesthetics. Desflurane, isoflurane and sevoflurane have MAC-awake/MAC ratios (approximately 0.34) that are smaller than the ratios for halothane (0.55) and nitrous oxide (0.65). These differences suggest that desflurane, isoflurane and sevoflurane are more powerful hypnotic drugs than halothane or nitrous oxide.

Entropy and BIS monitoring are relatively new methods of assessing depth of anaesthesia. The commercially available Datex-Ohmeda module calculates entropy over time windows of variable duration and reports two separate numerical values on a scale between 0 and 100. The maximum value of the Response Entropy (RE) is 100, and the maximum value of the State Entropy (SE) is 91. Numbers close to 100 mean that the patient is conscious and numbers close to zero denote very 'deep' anaesthesia. A clinically practical level of anaesthesia is achieved when the value is between 40 and 60. When the RE and SE values are identical (subtracted value 0 - 3), the level of anaesthesia can be considered 'adequate.' A slow increase in the difference between the RE and SE values during anaesthesia is a sign of frontal muscle EMG activity, which in turn is a sign of 'inadequate' anaesthesia.

Recently, attempts were made to see whether equi-MAC concentrations of various anaesthetics produced similar BIS values.⁽²⁾ Limited data allow a comparison of BIS values during anaesthesia with different inhaled anaesthetics at equal MAC multiples. Kurehara et al⁽³⁾ found no significant differences in BIS values for sevoflurane and isoflurane at 1.2 MAC. This finding parallels the nearly equal MAC awake/MAC ratios of sevoflurane and isoflurane. However, the MAC awake/MAC ratio of halothane exceeds that of sevoflurane, and Schwab et al found that halothane produces greater BIS values than sevoflurane at comparable MAC.⁽⁴⁾

Aim of Study

Primary

To compare the entropy values of volatile anaesthetic agents at their equivalent MAC values.

Secondary

Comparison of entropy indices specific volatile agents at equi-MAC concentration during wash-in and wash-out phases. Role of entropy monitoring in adjusting the concentration of volatile agents during administration. Compare the haemodynamic responses of inhalation agents at equi-MAC concentration.

MATERIALS AND METHODS

After getting approval from Research Methodology and Human Ethical Committee, informed consent from the patients, thirty adult patients undergoing spine surgery were enrolled for this study.

All patients were pre-medicated with intravenous glycopyrrolate 0.2 mg and ondansetron 4 mg one hour before surgery. The spectral entropy electrode was applied on forehead of the patient in accordance with manufacturer's instructions and connected to entropy monitor.

Before induction of anaesthesia, baseline HR, SBP, DBP, ETCO₂, SPO₂ were recorded along with response entropy and state entropy.

General anaesthesia was induced with thiopentone sodium 5 mg/kg and fentanyl 2 µg/kg IV. Tracheal intubation was with succinylcholine 2 mg/kg IV. Muscle relaxation was facilitated with vecuronium 0.08 mg/kg IV. Based on computer-generated randomisation table, patients received halothane, isoflurane or sevoflurane for maintenance of anaesthesia in a N₂O:O₂ mixture 4:2. Constant fresh gas flow of 3L/minute was maintained throughout the surgery. Mechanical ventilation was started to adjust ETCO₂ between 34 and 36 mmHg. Intermittent boluses of vecuronium 0.002 mg/kg were administered to assist ventilation. Whenever heart rate and mean arterial pressure exceeded 20% of baseline, fentanyl 1 µg/kg/hr was administered. Blood pressure was increased with bolus injection of ephedrine if values decreased by 20% from the initial MAP.

The heart rate, mean arterial pressure, response entropy and state entropy were noted as end tidal concentration of inhaled anaesthetics increased from 0.5 to 0.75, 0.75 to 1.0 and 1.0 to 1.5 MAC (wash-in). And also, when MAC decreased from 1.5 to 1.0, 1.0 to 0.75 and 0.75 to 0.5 (wash-out). Steady state of 20 minutes was allowed at each target concentration before data recording to ensure equilibration of anaesthetic to brain.

Statistical Analysis

Sample size used was based on following studies and calculations

1. In the study of Kaskinoro et al (2011), spectral entropy and BIS values were tested to differentiate consciousness from unconsciousness during increasing doses of three different anaesthetic agents. Thirty healthy male volunteers aged 19 - 30 years were recruited and divided into three 10 volunteer groups to receive either dexmedetomidine, propofol or sevoflurane in escalating concentrations at 10-minute intervals until LOC was reached.
2. Schmidt et al in 2004 recorded state entropy, response entropy, BIS and sedation level in 20 patients during minor gynaecological surgeries.

Study Design
 Prospective randomized study

Study population

Sample size calculation

$$N = \frac{(Z\alpha + Z(1-\beta))^2 \sigma^2}{d^2}$$

$$(Z\alpha + Z(1-\beta))^2 = 7.9$$

σ = standard deviation = 2.03

d = difference between entropy indices

Entropy of sevoflurane = 89.8

Entropy of halothane = 87.0

Entropy of isoflurane = 87.6

Mean difference between entropy indices = 1.87

Hence, $N = \frac{7.9 \times 2 \times 2.03 \times 2.03}{1.87 \times 1.87} = 18.6$

Data was analysed using Statistical Package for Social Sciences (SPSS) version 10. Data was expressed in frequency, percentage, mean and standard deviation. Mean age, weight, sex and values for heart rate, mean arterial pressure, response entropy and state entropy in the three groups was compared by one-way analysis of variance and chi square test. Post-hoc testing was done using Scheffe's method. P values of less than 0.05 were considered significant.

Inclusion Criteria

Thirty adult patients (ASA-PS I and II) aged 18 to 50 years undergoing spine surgery.

Exclusion Criteria

Patients with obesity (BMI > 30), on hypnotics and antidepressants with cardiac or neurological diseases, alcoholics or other illicit drug users, on beta-blockers.

RESULTS

Thirty patients (25 males, 5 females) were enrolled in the study. The groups did not differ in demographic characteristics.

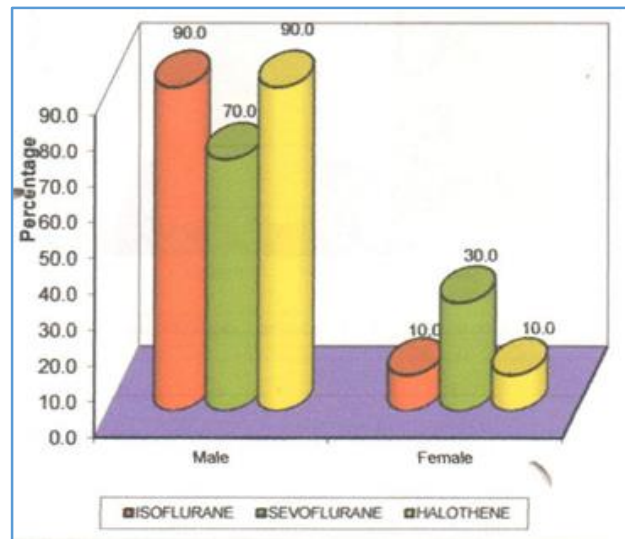


Figure ii. Comparison of Sex based on Group

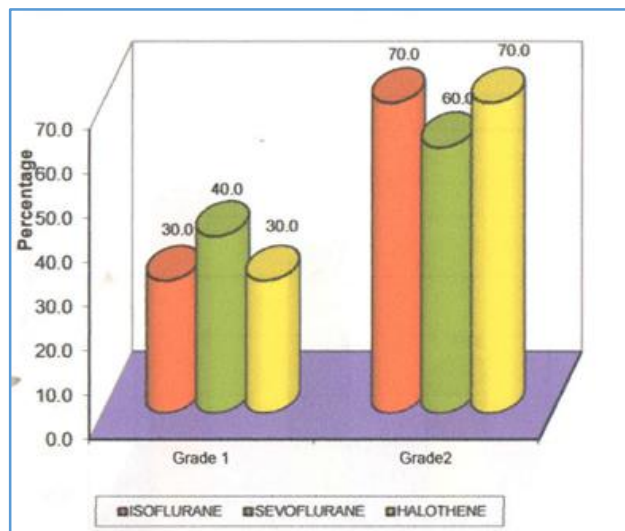


Figure iii. Comparison of ASA-PS based on Group

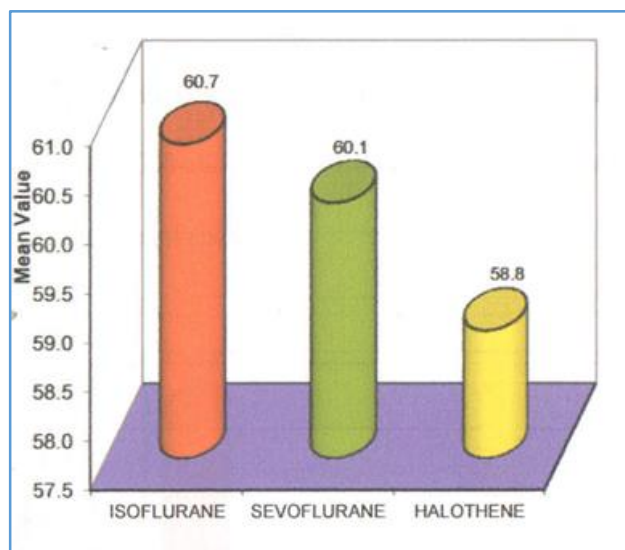


Figure iv. Comparison of Weight based on Group

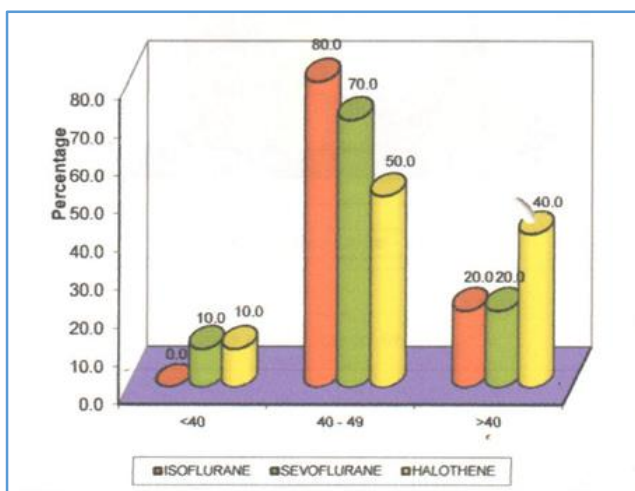


Figure i. Comparison of Age based on Group

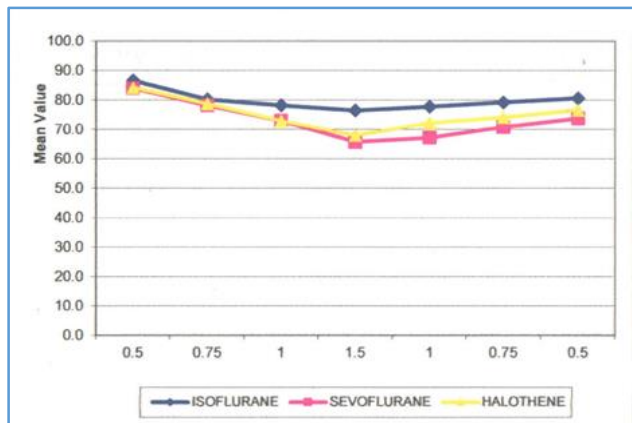


Figure v. Comparison of HR based on Group for different MAC

HR had decreased in a dose-dependent manner for all the groups. (The difference was not statistically significant, $p > 0.05$).

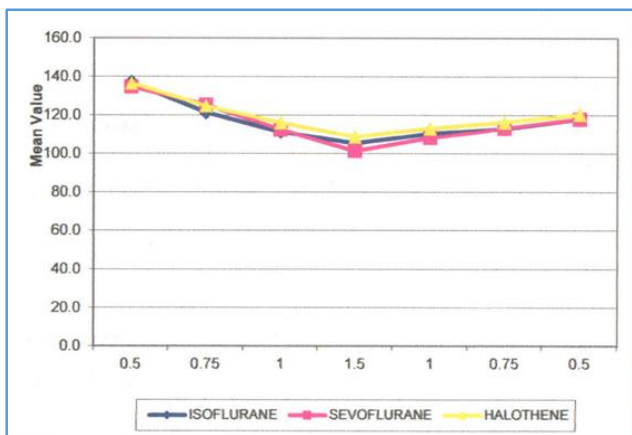


Figure vi. Comparison of SBP based on Group for different MAC

The systolic blood pressure decreases in a dose-dependent manner for all the agents. Under different MAC values, difference between the groups was not statistically significant ($p > 0.05$).

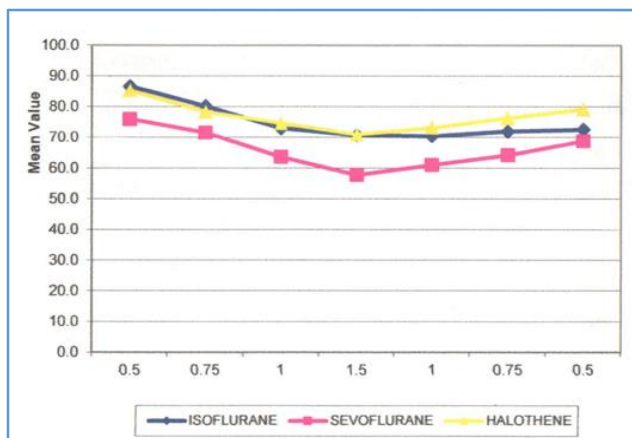


Figure vii. Comparison of DBP based on Group for different MAC

In contrast to SBP, there was a statistically significant difference between the inhalational agents for DBP at different MAC values ($p < 0.05$). Sevoflurane produced DBP values of 76 ± 10.3 and 57.8 ± 7.3 , which was lower than DBP of 86.6 ± 7.4 and 70.8 ± 10.2 obtained with isoflurane at 0.5 and 1.5 MAC ($P < 0.05$). During wash-out phase, there was a statistically significant difference in the DBP values between sevoflurane and halothane ($p < 0.05$). Sevoflurane produced lower DBP values compared to halothane.

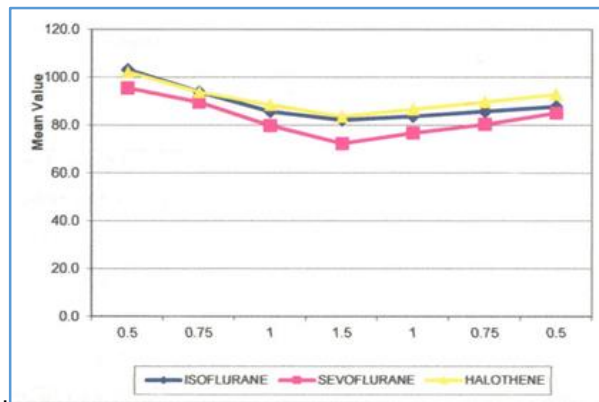


Figure viii. Comparison of MAP based on Group for different MAC

MAP was found to decrease in a dose dependent manner for all inhalational agents. During wash-in, there was a statistically significant difference between the MAP values obtained with halothane and sevoflurane ($p < 0.05$).

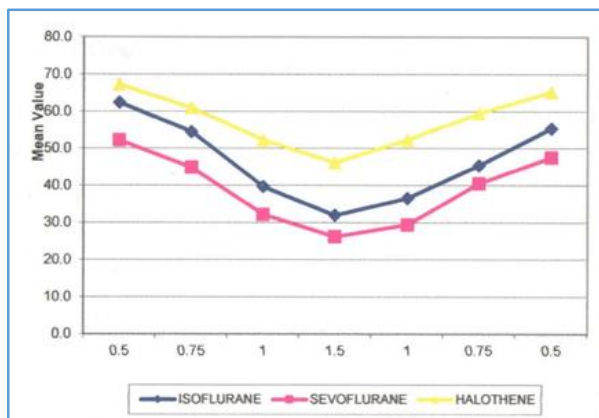


Figure ix. Comparison of RE based on Group for different MAC

Dose dependent reduction of response entropy was seen with all the inhalational agents. During wash-in, the RE for isoflurane at 0.5 MAC was 62.4 ± 5.1 , whereas at 1 MAC it was 39.7 ± 5.4 . It further reduced to 32 ± 4.2 at 1.5 MAC.

The RE of sevoflurane was found to be the lowest at all MAC. During wash-in at 0.5 MAC, the RE was 49.2 ± 6.6 . It reduced to 31.3 ± 4.9 and 25.2 ± 3.1 at 1 and 1.5 MAC respectively. Halothane produced much greater entropy indices than isoflurane and sevoflurane at all MAC values. During wash-in, RE at 0.5, 1, 1.5 MAC was 67.2 ± 6.8 , 61 ± 6.3 , 52.3 ± 4.7 respectively.

Entropy values during wash-in and wash-out were comparable for all agents at 1 and 0.75 MAC. There was a statistically significant difference between the entropy indices of all inhalational agents at all MAC values ($p < 0.05$).

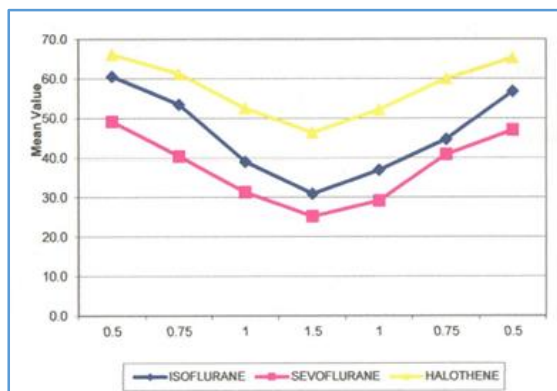


Figure x. Comparison of SE based on Group for different MAC

SE values decreased in a dose dependent manner for all the agents. Isoflurane at 0.5 MAC produced SE value of 60 ± 5.9 . With increasing MAC during wash-in phase, entropy was reduced to 31.3 ± 4.9 at 1 MAC and 25.2 ± 3.1 at 1.5 MAC. Halothane produced higher entropy values at all MAC levels. At 0.5 MAC, halothane produced entropy values of 66.2 ± 6.1 , it reduced to 52.6 ± 5.9 at 1 MAC and 46.4 ± 3.7 at 1.5 MAC.

SE values for isoflurane and sevoflurane were comparable at 1 MAC and 1.5 MAC during both wash-in and wash-out phases. Isoflurane and sevoflurane produced an SE of 39 ± 6.2 and 31.3 ± 4.9 at 1 MAC (wash-in). With halothane a higher SE value of 52.6 ± 3.5 was obtained.

At 1.5 MAC (wash-in) SE of 30.9 ± 4.6 and 25.2 ± 3.1 was obtained with isoflurane and sevoflurane. With halothane, a higher value of 46.4 ± 3.7 was obtained. At all MAC, there was a statistically significant difference between the SE values of the three inhalational agents ($p < 0.05$).

DISCUSSION

Vakkuri et al validated spectral entropy as an accurate assessment of anaesthesia depth. They ran spectral entropy on 70 patients who had received sevoflurane, propofol or thiopental.⁽⁵⁾ RE and SE distinguished very well between conscious and unconscious states and showed high sensitivity and specificity in the detection of LOS. RE decreased earlier than BIS and SE during the patients' emergence from anaesthesia.



Figure xi. Replica of the First Inhaler used in Anaesthesia

The SE, RE, BIS and sedation level were recorded for 20 patients during minor gynaecologic surgery.⁽⁶⁾ A record was made every 20s during step-wise increase of propofol until the patients lost response.

In the study of Kaskinoro et al,⁽⁷⁾ spectral entropy and BIS values were tested to differentiate consciousness from unconsciousness during increasing doses of three different anaesthetic agents. Because of wide inter-individual variability, BIS and entropy were not able to reliably differentiate consciousness from unconsciousness during and after stepwise increasing concentrations of these anaesthetics.

BIS and entropy monitors have been compared in a couple of studies and have been found to detect different sedation levels reliably; however, variation in the performance between BIS and SE were reported; in some of these studies BIS has been better and in others SE and in some studies there have been no differences between these two commercial indices. When comparing propofol sedation with nitrous oxide sedation, SE and RE do not decrease when N₂O is used.⁽⁸⁾ In another study because of large intra- and inter-individual variability, neither BIS nor entropy were able to predict the sedation level.⁽⁹⁾

In our study, we found that all inhalational anaesthetic agents produced decreasing entropy values with increasing MAC. Also, entropy values were less during sevoflurane and isoflurane anaesthesia than halothane anaesthesia at equivalent MAC levels. It was noted that entropy values were comparable in the isoflurane and sevoflurane groups. The difference in entropy values can be explained based on the differential effects of halothane, isoflurane and sevoflurane on EEG. In 2001, Professor Eger published a comprehensive review of MAC determinations. This review also considered data on MAC_{aw}, which was first described in 1970. It was defined as the alveolar concentration of agent, which was midway between that permitting response to command and that preventing it. Each alveolar (end-tidal) concentration was recorded after a 15-min period of constant alveolar concentration maintained by controlled ventilation (slow wash-out). This was done to ensure equilibrium between the alveolar and brain concentrations of agent. The finding was that MAC_{aw} was 0.5 - 0.6 of MAC, but that when patients were allowed to wake up breathing air spontaneously (fast wash-out) then considerably lower values were obtained. This difference was attributable to failure of equilibrium between brain and alveolus. Eger concludes that for desflurane, isoflurane and sevoflurane, MAC_{aw} is one-third of MAC. This figure is clearly of clinical importance.⁽¹⁰⁾ Our study supports the hypothesis that sevoflurane and isoflurane produce a greater hypnotic effect than halothane, and it parallels the finding that the MAC-awake/MAC ratio is larger for halothane (0.55) than for sevoflurane (0.34) and isoflurane (0.41). It is clear that at equi-MAC concentrations, isoflurane and sevoflurane produce a greater hypnotic effect than halothane.

Another point is that BIS and entropy incorporates different information from the raw EEG. Sevoflurane and isoflurane produces burst suppression within the clinical dosage range, whereas halothane does not. This difference is especially important for BIS values less than 30 when the burst suppression ratio (i.e. the time ratio of total EEG suppression for a given time period) is linearly correlated with the BIS value.⁽¹¹⁻¹⁵⁾

These known differences in the effects of halothane, isoflurane and sevoflurane on EEG are expected to influence the entropy value differently at a similar depth of anaesthesia.

Bharthi et al showed that the BIS values were less during isoflurane anaesthesia than during halothane anaesthesia at equivalent MAC levels and is probably consistent with the greater metabolic suppression caused by isoflurane and also its ability to produce a higher degree of suppression brain electrical activity than halothane. Halothane is known to have a greater analgesic and immobilising effect (through its spinal action) as compared to isoflurane. The BIS does indeed selectively measure the hypnotic or obtunding aspects of anaesthesia rather than the immobilising action of anaesthesia.

BIS is less agent specific with low concentration of anaesthetics. This is consistent with the findings that BIS-awake values were similar between the agents. As the concentration increases, the effects of arousal are less and the effects of anaesthetics are greater and the BIS may be more agent-specific. In a previous study in children, Davidson et al also reported significant low BIS values with isoflurane than halothane at 1 MAC, but not at awakening.

BIS values in a range of 40 - 60 have been proposed for producing adequate degree of hypnosis during anaesthesia. In a study by Bharthi et al, the entropy value at 1 MAC of halothane (54.2 ± 3.7) and isoflurane was 42.4 ± 5.8 , which shows the possibility that 1 MAC of isoflurane is more than enough for adequate hypnotic effect. In our study, SE at 1 MAC for halothane, isoflurane, sevoflurane was 52.6 ± 3.5 , 39 ± 6.2 , 31.3 ± 4.9 . This finding is consistent with the fact that the use of BIS monitoring for titration of anaesthetic agent reduces intraoperative anaesthetic consumption. Vakkuri and colleagues showed that titration of propofol-alfentanil-N₂O anaesthesia by using RE/SE monitoring (SE target 45-65, RE-SE target < 10) decreased propofol use and hastened early recovery without increasing adverse intra- or post-operative reactions.

Kurehara et al investigated the BIS values in patients anaesthetised with sevoflurane and isoflurane, two drugs that have the same MAC-awake/MAC ratio. At 1.2 MAC both anaesthetics produced the same BIS values. However, increasing the anaesthetic concentration to 2 MAC decreased BIS values only in patients anaesthetised with isoflurane; it had no effect in those anaesthetised with sevoflurane. This finding does not support our notion that the MAC-awake/MAC ratio reflects the hypnotic potency of inhaled anaesthetics and contrasts with our finding that an increase in halothane, isoflurane and sevoflurane from 1 MAC to 1.5 MAC proportionately decreased BIS values. These conflicting results suggest the possibility that the parallel of MAC-awake/MAC ratios and the hypnotic effect of anaesthetics as defined by BIS values may not consistently extend to deeper levels of anaesthesia.

Part of the power of MAC is the ease and precision with which immobility can be measured for all inhaled anaesthetics. At 1 MAC, 50% of patients move in response to a noxious stimulus and almost all will move at 0.8 times MAC.⁽⁵⁾ The level at which 50% of patients will appropriately respond to command (MAC-awake) is even clearly lower for both sevoflurane (0.34 times MAC) and halothane (0.55 times MAC). Thus, absence of movement after a noxious stimulus in

the unparalysed patient anaesthetised with an inhaled anaesthetic indicates that the anaesthetic concentration is clearly in excess of the concentration that allows appropriate response to commands. Consequently, it may be expected that the anaesthetic concentration is sufficient to suppress awareness. Therefore, the immobile, unparalysed patient primarily anaesthetised with an inhaled anaesthetic rarely if ever would subsequently remember the surgery. MAC provides the clinician therefore with a valuable tool to judge "depth of anaesthesia" and indirectly the production of amnesia.

However, when neuromuscular blocking drugs are used lack of movement cannot predict awareness in the anaesthetised patient. In this situation, use of the BIS/entropy monitor particularly trends of change of values is expected to add information on depth of anaesthesia, providing a combination of sensitivity and specificity equal to or better than other commercially available depth-of-anaesthesia monitors.⁽¹⁶⁾ Moreover, the entropy monitor can be used both during inhaled and IV anaesthesia, whereas MAC only applies to inhaled anaesthetics. The addition of N₂O increases BIS values during isoflurane anaesthesia and probably also during anaesthesia with other anaesthetics. This is consistent with a modest capacity of N₂O to antagonise the amnestic effect of isoflurane. Similarly, the addition of ketamine to a propofol-based anaesthetic increases BIS and entropy values. In addition, Schneider et al found significantly different BIS values in patients receiving sevoflurane/remifentanil compared with patients receiving propofol/remifentanil at the same level of anaesthesia.⁽¹⁷⁾

In our study, we failed to find an effect of neuromuscular blockade on entropy values during halothane, isoflurane or sevoflurane anaesthesia. We suggest that muscle activity was minimised at 1 MAC, and was not further decreased by the administration of neuromuscular blocking drugs.

In our study, all the anaesthetic agents produced dose-dependent reduction in the entropy indices. Maksimow and Colleagues have shown that calculated entropy values corresponding to SE correlate with CBF and thus presumably with neuronal function during sevoflurane and propofol anaesthesia. The correlation extended to deep (1.5 - 2 MAC/EC₅₀) levels of anaesthesia.⁽¹⁸⁾

Some limitations should be considered for the interpretation of the results of our study. First, different anaesthetics have different pharmacokinetic properties. Because of its higher tissue/blood partition coefficient, time to equilibration is longer for halothane than for sevoflurane; but even for halothane the equilibration of the brain as part of the vessel rich group is completed after 20 minutes (Equilibration half-time of 2 minutes). We allowed an equilibration time of 20 minutes, so we are of the opinion that non-equilibration can be ruled out. An additional limitation is that we initially did not adjust the MAC of both inhaled anaesthetics to the age of each patient. But age did not differ between groups and hence we suggest that this factor has not affected our results. Also, the age adjustment algorithm is derived from meta-analysis and may not be clinically relevant for individual patients.

We conclude that halothane produces greater entropy values than sevoflurane at comparable MAC levels. This result is consistent with the finding in other studies that BIS and

entropy values for inhaled and other anaesthetics are drug specific.

CONCLUSION

We recorded the entropy values of three volatile agents for comparison unlike most of the studies done in the past with two agents. Through entropy, we measured two indices; SE, which quantifies cortical cerebral activity (hypnosis) and RE, which evaluate Electromyography (EMG) activity (Subcortical component). It was observed that under anaesthesia the difference between RE and SE remained at less than 10, indicating adequate analgesia. Entropy values of halothane were found to be higher than isoflurane and sevoflurane at all MAC levels.

The clinical implication of our study is that adjusting the administration of anaesthetic agents based on entropy values may be inappropriate, as halothane results in higher entropy of EEG compared to sevoflurane or isoflurane at equivalent MAC values. As halothane produces higher entropy indices there will be a tendency to increase its concentration, so as to achieve adequate levels of entropy. This may indirectly affect systemic and intracranial haemodynamics. Our study like previous studies shows that entropy is specific for each drug and that equi-MAC values of inhalational agents do not produce same entropy indices.

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