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Comparison of Minimum Alveolar Concentration (MAC) Versus Entropy Using Sevoflurane in Patients Undergoing General Anaesthesia

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ABSTRACT
A successful GA is defined as a reversible combination of hypnosis, analgesia and suppression of reflex activity. In contemporary anaesthetic practices using a combination of drugs in a balanced manner, the traditional stages of anaesthesia may not be readily discernible. Inadequate GA can result in intraoperative awareness, while excessive dosage can cause delayed recovery and postoperative complications. Patients undergoing elective surgeries under general anaesthesia using sevoflurane, who were eligible for the study according to the above-mentioned eligibility criteria were included in the study. The study design, purpose, interventions, possible risks, adverse effects and possible outcomes were explained to each patient in his/her mother tongue and written consent was obtained. On comparing at all 3 settings of MAC, the study found positive correlation between both entropy levels, with statistical significance, thereby implying that the response entropy levels significantly increased with increase in the state entropy levels at all 3 different MAC settings.

INTRODUCTION

The determination of the depth of General Anaesthesia (GA) involves assessing the degree of suppression of the Central Nervous System (CNS) induced by the administered anaesthetic agent. The classic classification of anaesthetic states by Guedel, originally reliant on diethyl ether, involved evaluating indicators such as eyelash reflex, respiration, eyeball movements, and muscular activity. Despite a well-established comprehension of how GA drugs impact the brain's cortex and thalamic region, leading to unconsciousness, the precise underlying mechanism remains incompletely understood[1]. A successful GA is defined as a reversible combination of hypnosis, analgesia and suppression of reflex activity. In contemporary anaesthetic practices using a combination of drugs in a balanced manner, the traditional stages of anaesthesia may not be readily discernible. Inadequate GA can result in intraoperative awareness, while excessive dosage can cause delayed recovery and postoperative complications[1,2]. With the advancements in anaesthetic techniques, including intravenous agents and potent analgesics, it is crucial to accurately measure the depth of anaesthesia. Customizing this measurement is vital due to inter-patient variability. Excessive dosing can lead to complications like postoperative nausea, vomiting, delayed recovery and cognitive impairments. Conversely, insufficient dosing can result in intra operative awareness, accompanied by symptoms like increased heart rate, high blood pressure, tearing and sweating[3]. Establishing a suitable method for measuring the depth of anaesthesia is expected to reduce the occurrence of intraoperative awareness, promote quicker recovery and thereby diminish the human and financial burdens associated with anaesthetic care[3,4]. Bispectral Index (BIS) and Entropy have proven to be valuable tools for monitoring the depth of anaesthesia, displaying high specificity and sensitivity in evaluating consciousness during GA. Entropy utilizes data from the Electroencephalogram (EEG) and Frontal Electromyography (FEMG) to generate numerical values, namely State Entropy (SE) and Response Entropy (RE). These values offer insights into the patient's response to stimuli and the hypnotic effects of anaesthetic agents on the brain. SE, a stable EEG-based parameter, indicates the hypnotic effect of anaesthetic agents, while RE consistently remains equal to or higher than SE[5]. Minimum Alveolar Concentration (MAC), derived from the end-tidal concentration of volatile anaesthetics, is a widely used method for monitoring the depth of anaesthesia during GA[6]. The end-tidal concentration mirrors the concentration of inhaled anaesthetic exhaled from the lungs, assumed to be in equilibrium with brain anaesthetic levels. This assumption implies a uniform anaesthetic state across patients, regardless of brain health or physiological condition. However, relying solely on end-tidal concentration for preventing awareness might lead to over-administration in certain patients. Research on the relationship between end-tidal anaesthetic concentration and entropy is limited. Furthermore, entropy is not commonly available in many healthcare settings in India, often requiring technicians to rely solely on MAC to gauge the depth of anaesthesia. Hence, our study aimed to compare the correlation between MAC and entropy in patients undergoing GA with sevoflurane for the maintenance of anaesthesia.

MATERIALS AND METHODS

Study Area: Department of Anesthesiology.

Study Population: Patients aged between 21 and 50 years, of ASA Grading I-III undergoing elective surgeries under general anaesthesia using sevoflurane.

Study Design: Prospective Clinical Observational Study.

Sample Size Calculation: The sample size (n) was estimated to be 18, which was rounded to the final sample size of 30 subjects and was considered for the study.

Inclusion Criteria:

- Patients of either genders aged between 21 and 50 years.
- Patients with American Society of Anaesthesiology (ASA) Grade I-III.
- Patients posted for elective surgeries.

Exclusion Criteria:

- Patients under 20 years and >50 years of age.
- Patients with American Society of Anaesthesiology (ASA) Grade IV.
- Patient undergoing emergency procedures.
- Pregnant patients.
- Patients with significant pre-existing systemic diseases.
- Patients' refusal.

Patients undergoing elective surgeries under general anaesthesia using sevoflurane, who were eligible for the study according to the above mentioned eligibility criteria were included in the study. The study design, purpose, interventions, possible risks, adverse effects and possible outcomes were explained to each patient in his/her mother tongue and written consent was obtained. Routine pre-anaesthetic check-up was done prior to the surgery as per the routine preoperative protocol, by collecting basic demographic details, history of comorbid illness and drug therapy. All the patients were subjected to general and systemic examinations. Also airway assessment was carried out and documented. All the patients were kept fasting for at least 6 hours before surgery. On arrival to the operating room, monitors were attached. Electrocardiogram (ECG), Non-invasive BP, ETCO2, pulse-oximetry were connected. The entropy electrode (GE Health care) was applied on forehead of the patient in accordance with the manufacturer's instructions and was connected to the entropy monitor. Intravenous access was secured with 18/20 G intravenous cannula. Baseline vital parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SpO2) were noted.

RESULTS AND DISCUSSIONS

Table 1: Entropy Values Among the Study Subjects at Different MAC

Subjects (N=30)		At 0.8 MAC	At 1.0 MAC	At 1.3 MAC
State Entropy (SE)	**Mean**	55.30	45.77	40.23
	SD	4.50	2.78	3.59
	Median	56.50	46.00	41.00
	Minimum	44.00	40.00	32.00
	Maximum	61.00	51.00	45.00
Response Entropy (RE)	**Mean**	56.70	47.10	41.70
	SD	4.46	2.89	3.86
	Median	57.00	47.50	42.50
	Minimum	46.00	41.00	33.00
	Maximum	63.00	52.00	47.00

In the study, both state and response entropy values were recorded among all the subjects at different occasions where end-tidal concentration of anaesthetic being set to 3 different MAC i.e., 0.8, 1.0 and 1.3 MAC. As the MAC was increased from 0.8 to 1.0 and finally at 1.3, the mean SE got decreased, with the mean levels of 55.30±4.50, 45.77±2.78 and 40.23±3.59 respectively. Even the mean RE got decreased, with the mean levels of 56.70±4.46, 47.10±2.89 and 41.70±3.86 respectively.

Table 2: Comparison of State Entropy Values with Respect to Different MAC

State Entropy (SE)		Mean	SD	p-value#
Comparison_1	**At 0.8 MAC**	55.30	4.50	<0.001*
	At 1.0 MAC	45.77	2.78	
Comparison_2	**At 0.8 MAC**	55.30	4.50	<0.001*
	At 1.3 MAC	40.23	3.59	
Comparison_3	**At 1.0 MAC**	45.77	2.78	<0.001*
	At 1.3 MAC	40.23	3.59	

Paired t-test

* Statistically significant

The mean state entropy levels observed at different occasions where end-tidal concentration of anaesthetic being set to 3 different MAC i.e., 0.8, 1.0 and 1.3 MAC were compared to each other in the study. These 3 different mean levels were compared in 3 ways. As per first 2 comparisons, the mean SE of 55.30±4.50 at 0.8 MAC was significantly higher than either 45.77±2.78 at 1.0 MAC or 40.23±3.59 at 1.3 MAC. In last comparison, the mean SE of 45.77±2.78 at 1.0 MAC was also found to be significantly higher than 40.23±3.59 at 1.3 MAC. Thus in all 3 comparisons, the study found significant difference thereby confirming significant decrease in SE with increase in MAC.

Table 3: Comparison of Response Entropy Values with Respect to Different MAC

Response Entropy (RE)		Mean	SD	p-value#
Comparison_1	**At 0.8 MAC**	56.70	4.46	<0.001*
	At 1.0 MAC	47.10	2.89	
Comparison_2	**At 0.8 MAC**	56.70	4.46	<0.001*
	At 1.3 MAC	41.70	3.86	
Comparison_3	**At 1.0 MAC**	47.10	2.89	<0.001*
	At 1.3 MAC	41.70	3.86	

Paired t-test.

* Statistically significant.

The mean response entropy levels observed at different occasions where end-tidal concentration of anaesthetic being set to 3 different MAC i.e., 0.8, 1.0 and 1.3 MAC were compared to each other in the study. These 3 different mean levels were compared in 3 ways. As per first 2 comparisons, the mean RE of 56.70±4.46 at 0.8 MAC was significantly higher than either 47.10±2.89 at 1.0 MAC or 41.70±3.86 at 1.3 MAC. In last comparison, the mean RE of 47.10±2.89 at 1.0 MAC was also found to be significantly higher than 41.70±3.86 at 1.3 MAC. Thus in all 3 comparisons, the study found significant difference thereby confirming significant decrease in RE with increase in MAC.

In the study, the mean state entropy levels were compared with mean response entropy levels at different occasions where end-tidal concentration of anaesthetic being set to 3 different MAC i.e., 0.8, 1.0 and 1.3 MAC were compared to each other in the study. On comparing at all 3 settings of MAC, the study found positive correlation between both entropy levels, with statistical significance, thereby implying that the response entropy levels significantly increased with increase in the state entropy levels at all 3 different MAC settings.

In the present study, majority of the subjects belonged to ASA II (70.0%), followed by ASA I (23.3%) and ASA III (6.7%). Both state and response entropy values were recorded among all the subjects at different occasions where end-tidal concentration of anaesthetic being set to 3 different MAC i.e., 0.8, 1.0 and 1.3 MAC in the present study. As the MAC was increased from 0.8-1.0 and finally at 1.3, the mean SE got decreased, with the mean levels of 55.30±4.50, 45.77±2.78 and 40.23± 3.59 respectively. Even the mean RE got decreased, with the mean levels of 56.70±4.46, 47.10±2.89 and 41.70± 3.86 respectively. On further analysis, we found that, MAC value and entropy value at 0.8 MAC, minimum and maximum values and entropy values are very close with narrow range of SD. Similar results were found with 1 MAC and 1.3 MAC. Hence we feel that entropy values correspond to MAC values. It also establishes

Table 4: Correlation Between SE and RE at Different MAC

Subjects (N=30)			Response Entropy (RE)		
			At 0.8 MAC	At 1.0 MAC	At 1.3 MAC
					-
	At 0.8 MAC	Pearson Correlation	0.990	-	-
		p-value#	<0.001*		
State Entropy (SE)	At 1.0 MAC	Pearson Correlation	-	0.987	-
		p-value#		<0.001*	
	At 1.3 MAC	Pearson Correlation	-	-	0.991
		p-value#			<0.001*

*Statistically significant

that MAC values can be used as surrogate value for monitoring depth of anaesthesia in places where entropy or BIS monitor is not available. The relation in variation of MAC with both SE and RE was established to be statistically significant, thereby implying that both SE and RE decrease significantly with increase in MAC. The demographic values of our study are uniform and entropy values with respect to different MAC values are also found to have very narrow changes. They are almost comparable as seen by narrow changes in SD. Hence we suggest that these MAC can be used in places were entropy is not available. These findings are similar to the observations made from the previous studies such as Ellerkmann[7]. The performances of SE, RE and BIS to predict the estimated sevoflurane effect site concentration, obtained by simultaneous pharmacokinetic and pharmacodynamic modeling, were compared by calculating the correlation coefficients and the prediction probability. The authors proclaimed that SE and RE seemed to be useful electroencephalograph measures of sevoflurane drug effect. However, a study by Whitlock[8] has stressed on age-adjusted minimum alveolar concentration. Although a population relationship between ETAC and BIS was apparent, inter-individual variability in the strength and reliability of this relationship was large. Decrease in BIS with increasing ETAC were not reliably observed. According to the study, independent of pharmacokinetic confounding, BIS frequently correlated poorly with ETAC, was often insensitive to clinically significant changes in ETAC. BIS was therefore incapable of finely guiding volatile anesthetic titration during anesthetic maintenance. It was attributed to inter-individual variability.

CONCLUSION

The study established that there was significant inverse relation between MAC and entropy which was proven at different settings of MAC. As MAC increases depth of anaesthesia increases and it corresponds to lower SE and RE. Thus it is clear that the depth of anesthesia can be ascertained by using MAC values as a surrogate for entropy, in the places where entropy is not available to prevent awareness among the patients undergoing GA.

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