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ORIGINAL ARTICLE

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Effect of atracurium and rocuronium on the state and response entropy during isoflurane anesthesia: randomized prospective study

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Abstract

Background Several researches have examined the impact of inhalation anesthetics, intravenous anesthetics, and muscle relaxants on spectral entropy, but many did not evaluate the extent of neuromuscular block. Besides, they did not inspect the impact of distinct degrees of neuromuscular blockade on spectral entropy under dissimilar saturations of isoflurane inhalation. Hence, this study has evaluated variant degrees of minimum alveolar concentration (MAC) to estimate the isoflurane concentration, along with various levels of neuromuscular blockade.

This study aims to evaluate the effect of muscle relaxants (atracurium and rocuronium) on entropy readings (state, response entropy, and response-state difference) during isoflurane anesthesia.

This is a prospective randomized study, as forty patients have been included and divided into two study groups: patients in group A received atracurium, while patients in group R received rocuronium. Under 50% and 100% neuromuscular blockage, state and response entropy were observed at MACs of 0.8% and 1%, respectively.

Results There was a positive correlation between state (SE) and response entropy (RE) at baseline, different MACs, and different trains of four (TOF) for both atracurium and rocuronium. State and response entropy decreased with increasing MAC of isoflurane ($P < 0.001$), while atracurium and rocuronium at TOF 50% and 100% showed no effect on SE, RE, or RE-SE ($P > 0.05$).

Conclusions State and response entropy can be used effectively to evaluate the depth of anesthesia at different isoflurane MAC and atracurium or rocuronium doses.

Registration number ClinicalTrials.gov identifier: NCT 05097508, Registered October 5, 2021 (prospectively registered), http://www.ClinicalTrial.gov

Keywords Entropy, Atracurium, Rocuronium, Isoflurane

Background

Intraoperative awareness with clear recollection is a sporadic phenomenon with potentially catastrophic cognitive effects. Research revealed that it only happens at a frequency of 0.1–0.2%; patients stated a diversity of events varying from ambiguous, illusive states to broad awake, paralyzed, and agonized states from the surgery. Generally, this is due to the administration of insufficient

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anesthetics compared to the patient's needs. Anesthetic factors (i.e., use of muscle relaxants, total intravenous anesthesia, technical errors), surgical factors (i.e., cardiac surgery, trauma/emergency, C-sections), and patient factors (i.e., decreased cardiovascular reserve, history of substance abuse, previous history of intraoperative awareness) are factors that increase the risk of awareness under general anesthesia (Almeida 2015)

Entropy is an effective detector for evaluating the depth of anesthesia; moreover, entropy is an accurate method for evaluating consciousness level during anesthesia and retrieves electroencephalogram (EEG) and frontal electromyography (FEMG) data to transform those into digital results, state entropy, and response entropy. The RE is based on both EEG and FEMG signals and anticipates the patient's reaction to external stimuli and detects early awakening. The SE is a reliable measure established on the EEG and can evaluate the hypnotic potency of anesthetic agents. RE is usually greater than or equivalent to the state entropy range (Patel et al. 2013).

Entropy is a measure of irregularity in any signal. Under general anesthesia, EEG transforms from erratic to more steady forms as the anesthesia intensifies. Furthermore, FEMG pacifies as the deeper parts of the brain are progressively saturated with anesthetics. The entropy calculates these changes by estimating the irregularity of EEG and FEMG signals. State entropy consists of the entropy of the EEG signal counted to 32 Hz. Response entropy comprises further higher frequencies up to 47 Hz. Therefore, the fast frontalis EMG (FEMG) signals allow a rapid response time for RE. Response entropy (ranges 0–100) conveys activation of facial muscles (FEMG). Facial muscles give an early lead of emergence or arousal, which causes a rapid upstroke in RE. State entropy ranges from 0 to 91. Entropy measures the activity of brain, which is the field of action of numerous anesthetic drugs, so it aids in titrating drug doses and helps in smooth and fast patient turnover. The clinical target scope for entropy values is 40–60, and RE and SE values around 40 reveal a lower possibility of consciousness (Bharadwaj et al. 2016).

Employment of muscle relaxants is essential to maintain skeletal muscle immobilization and promote mechanical ventilation during general anesthesia; these muscle relaxants suppress frontal muscle activity and thus alter EEG monitoring. Atracurium and rocuronium are the most used muscle relaxants in our facility, hence the need to study their effect on entropy (Dian et al. 2019).

Given the abovementioned data, we hypothesized that SE and RE will decrease with increasing isoflurane anesthesia, while non-depolarizing muscle relaxants (such as atracurium and rocuronium) will not affect entropy readings at different degrees of muscle relaxation.

Methods

Ethics statement

This randomized clinical study has been performed in Ain Shams University Hospitals between October 2021 and February 2022. The identification code in the ClinicalTrials.gov database is NCT 05097508. This study has been permitted by the Research Ethical Committee of Ain Shams University under the number. Every patient provided written informed consent prior to enrollment. This study adheres to CONSORT guidelines.

Study protocol

Inclusion criteria

Forty male patients aged between 20 and 50 years with American Society of Anesthesiologists physical status (ASA) I to II.

Exclusion criteria

Patients receiving any neuropsychiatric medications, undergoing neurosurgical operation, BMI above 40, or had any drug addiction were excluded from this study.

Patients' recruitment and randomization

Randomization was performed using computer-generated random number tables in opaque, sealed envelopes prepared by an anesthesiologist who was not part of the study. The randomization was performed in a 1:1 ratio. Group assignments were enclosed in sealed, opaque, sequentially numbered envelopes by a junior anesthesiologist not involved in the study. All the attending anesthesiologists, the patients, and the data collectors were blinded to group assignments throughout the entire study period. On the scheduled day of operation, the junior anesthesiologist opened each envelope just before induction of general anesthesia, prepared the induction dose and the infusion solution of muscle relaxants, and handled it to anesthesiologist, who was then planning to collect the perioperative data. At the end of our study, the anesthesiologist was informed about the nature of the muscle relaxant needed to complete the operation safely including maintenance and reversal drugs.

Forty patients were randomly divided into 2 equal groups by a computer-generated random numbers table, each consisting of 20 patients, namely group A and group R.

- Group A: Patients who received atracurium
- Group R: Patients who received rocuronium

Study intervention

No premedication was given. After the patients were admitted to the operating room, a venous cannula was

inserted. Data from standard monitoring, including noninvasive arterial blood pressure, oxygen saturation, end-tidal oxygen concentration (ETO2), and end-tidal carbon dioxide concentration (ETCO2) were gathered. Neuromuscular blockade was constantly evaluated by acceleromyograph using the train-of-four-watch SX system (made in Ireland), starting when the patients were unconscious. RE and SE were monitored using a Datex Ohmeda Entropy Module (M-Entropy) and the Entropy Sensor system (made in Finland). Baseline RE and SE were recorded. Anesthesia was induced with propofol (doses of 2–3 mg/kg) and fentanyl as analgesia (doses of 1–2 mg/kg). Tracheal intubation was promoted with rocuronium (0.6 mg/kg) or atracurium (0.5 mg/kg) after an acceleromyograph count of 0. Anesthesia was sustained with isoflurane in an air-O2 mixture (FiO2 0.6, 2 L/min). Mechanical ventilation was sustained at a tidal volume of 5–7 ml/kg. Ventilator frequency was aligned for the preservation of an ETCO2 of 35–40 mmHg. After reaching equilibrium for 30 min, SE, RE, and the difference between them were recorded at MAC 0.8 and MAC 1 at two levels of muscle relaxation assessed by TOF values of 50% and 100%. Rocuronium (dose 0.01–0.012 mg/kg/min) or atracurium (dose 0.005–0.01 mg/kg/min) was continually infused and adjusted until 50% and 100% depression of T1 (first twitch by acceleromyograph) was noticed. In case of hypotension (drop in blood pressure 20% of baseline reading), 10–30 mg of ephedrine will be given intravenously by titration, and in case of bradycardia (heart rate less than 60 bpm), when it is accompanied by hypotension or any evidence of reduced perfusion, 0.01–0.02 mg/kg of atropine will be administered. The whole experiment ended prior to the start of surgery.

Measured outcome

The primary outcome was to evaluate the correlation between SE and RE, including the RE-SE difference, at different degrees of neuromuscular block (at TOF 50% and 100%) during different MACs of isoflurane anesthesia (MAC 0.8% and 1%).

Statistical analyses

Sample size

Using PASS 11 program for sample size calculation and according to Kawaguchi et al. (Kawaguchi et al. 2009) and Aho et al. (Aho et al. 2011), the expected spectral entropy among study groups = 52 ± 6.5 and 62 ± 10, sample size of 20 patients can detect the difference between two groups regarding spectral entropy after surgery with power 90% and *x*-error 0.05.

Statistical method

Data were analyzed using Statistical Package for Social Science (SPSS) version 22.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were used. Independent-sample *t*-test of significance was used when comparing between two means. Chi-square (χ^2) test of significance was used to compare proportions between two qualitative parameters. Pearson's correlation coefficient to analyze the degree of association between two parametric variables and the confidence interval was set to 95%, and the margin of error accepted was set to 5%. The *P*-value was considered significant when *P*-value < 0.05 and highly significant when *P*-value < 0.001. *P*-value > 0.05 was considered non-significant.

Results

Patients have been enrolled in the study based on the inclusion and exclusion criteria. The total number of patients manifesting the studied pathology was 55, but a number of these were banned from the study protocol ($N = 15$). After applying the randomization protocol, 20 patients were assigned to group A and 20 patients to group R; no events have been reported in either of these groups that could have led to the omission of certain patients from the study (Fig. 1).

Demographic characteristics are comparable in both groups (Table 1).

Concerning state and response entropy correlation, for the atracurium group (group A), RE correlates strongly with SE at MAC 0.8% isoflurane ($r = 0.8881$) but correlates moderately at MAC 1% ($r = 0.6876$) at TOF 50%. While at TOF 100%, RE strongly correlates with SE at MAC 0.8% and 1% isoflurane ($r = 0.8446$ and 0.7756, respectively) (Fig. 2).

For the rocuronium group (group R), RE strongly correlates with SE at MAC 0.8% and 1% isoflurane at TOF 50% ($r = 0.9329$ and 0.960, respectively). At TOF 100%, RE also strongly correlates with SE at MAC 0.8% and 1% isoflurane ($r = 0.8977$ and 0.8622, respectively) (Fig. 3).

There is no consequential variation in RE-SE between groups (all *p*-values > 0.05) (Table 2).

At TOF 50% and 100%, increasing isoflurane concentration decreased entropy readings (*p*-value < 0.001). While at different MACs of isoflurane (0.8% and 1%), neither atracurium nor rocuronium affects entropy readings (Tables 3 and 4).

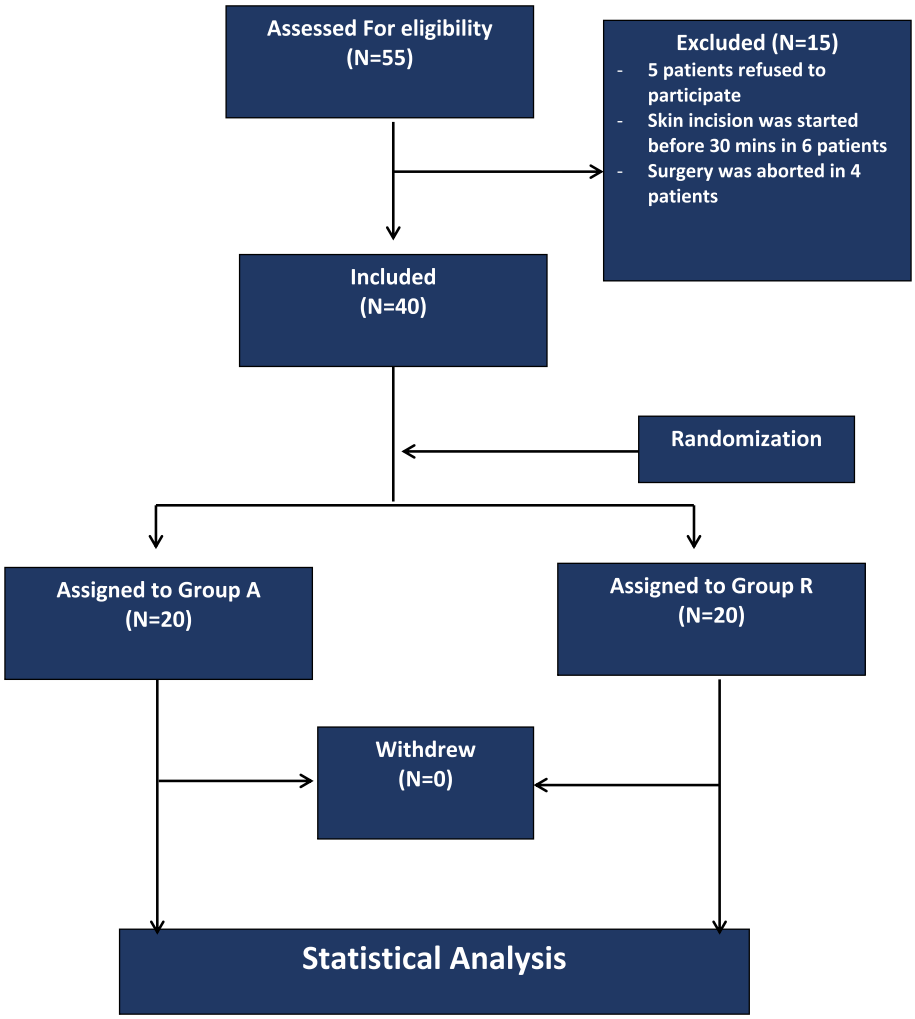

Fig. 1 Patient flowchart

Table 1 Comparison between groups concerning demographic data

Demographic data	Atracurium group ($n = 20$)	Rocuronium group ($n = 20$)	*p*-value
Age (years)	36.1 ± 10.3	38.8 ± 8.12	#0.37
BMI (kg.m^{-2})	25.38 ± 4.1	25.14 ± 2.2	#0.81
ASA (I/II;*n*)	12/8	11/9	^1
SABP (mm Hg)	127.85 ± 19.2	135.7 ± 16.4	#0.17
DABP (mm Hg)	68.6 ± 14.02	72.95 ± 10.88	#0.28
MABP (mm Hg)	88.35 ± 14.65	93.87 ± 12	#0.2

Data expressed as mean ± SD

ASA American Society of Anesthesiology, *BMI* body mass index, *DABP* diastolic arterial blood pressure, *MABP* mean arterial blood pressure, *SABP* systolic arterial blood pressure

Independent *t*-test

^ Chi-square test

Discussion

Entropy (SE/RE) and the bispectral index (BIS) are common technologies for monitoring anesthesia depth. Ellerkmann et al. examined the dose-response correlation of the entropy module during anesthesia with sevoflurane, which corresponded to the BIS monitor, and concluded that the Entropy Module is an aid monitor for assessing the electroencephalographic effects of increasing and decreasing sevoflurane; these sevoflurane electroencephalographic effects were seen symmetrically by the Entropy Module as by the BIS® monitor (Ellerkmann et al. 2004).

Describing the effect of isoflurane on entropy, Goyal et al. calculated the impact of entropy monitoring on isoflurane expenditure and anesthesia recovery time as the period from eye opening on demand to extubation time was much briefer in entropy group contrary to clinical group (Goyal et al. 2017). Also, Talawar et al. found

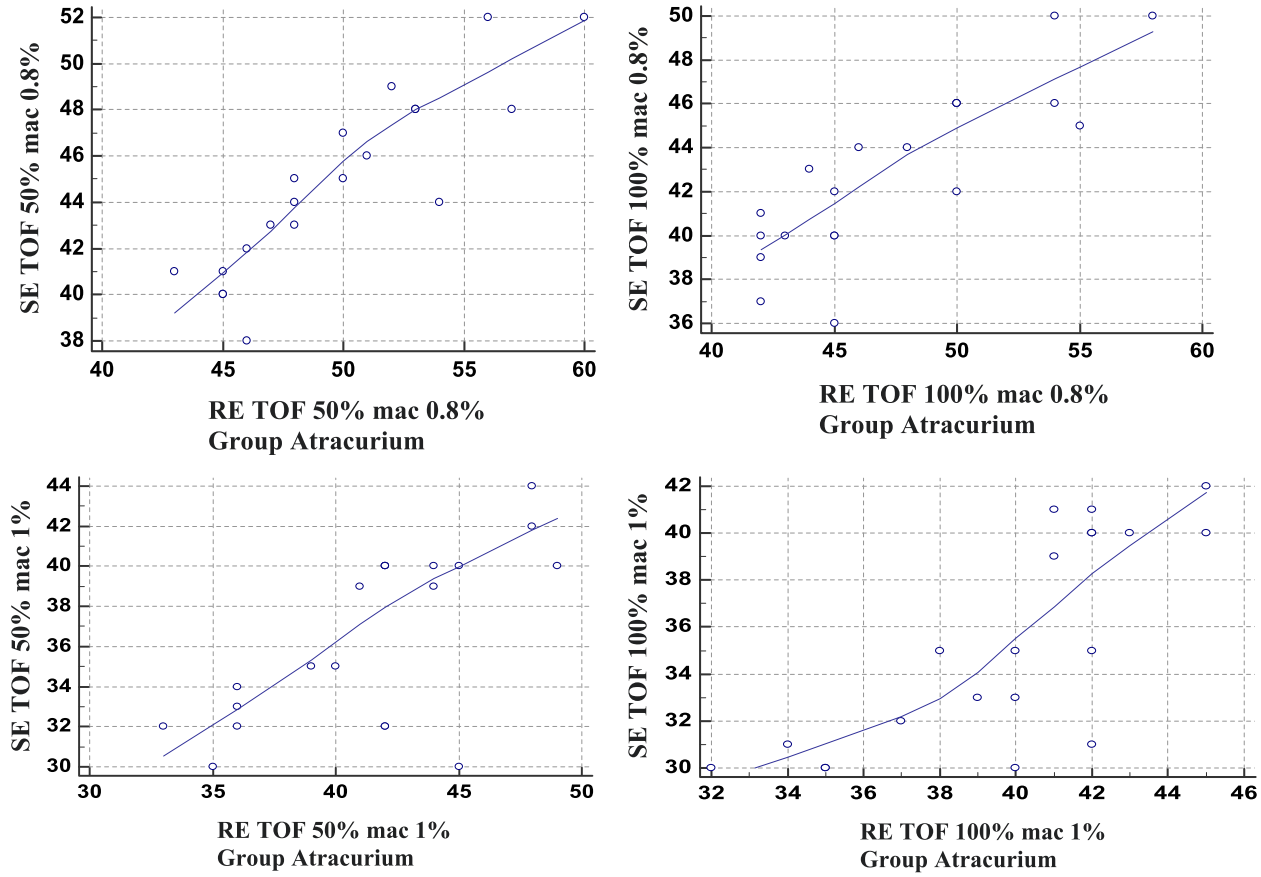

Fig. 2 Correlations between RE and SE at MAC 0.8% and 1% with TOF 50% and 100% of atracurium group

that awakening from anesthesia was faster in the entropy group than in the control group, and end-tidal isoflurane concentrations were lower in the entropy group (Talawar et al. 2010).

SE and RE correlations had been identified. In patients who were not taking neuromuscular blockers, Aho et al. discovered that increasing RE was followed by increasing SE in response to noxious stimuli. While NMBAs decreased the RE, SE, and RE-SE response, this inhibition is dose dependent, which contradicted our results (Aho et al. 2009). Rather, recent study by Dinu et al. proved that there is a positive correlation between RE and SE after induction of general anesthesia and before noxious stimuli (Dinu et al. 2020).

Correlations between isoflurane concentration and SE and RE have been presented. Duan Li et al. used the Spearman's rank correlation coefficient to measure the extent of the relationship between the entropy measures and isoflurane end-tidal concentrations, and a negative correlation surfaced between the isoflurane concentration and the calculated EEG value (Li et al. 2013).

The effect of muscle relaxants on entropy remains argumentative. Ekman et al. supported our results, whereas NMB did not affect BIS or Alaris auditory-evoked potential index (AAI) in lack of noxious stimulation. That case could be interpreted by the decline in EMG action of the frontal muscles in patients under general anesthesia without nociceptive stimulus (Ekman et al. 2007).

On the other hand, Inoue et al. hinted that BIS is altered by muscle relaxants in mildly sedated patients but not during deep sedation, although muscle relaxants did not affect cardiovascular stability during either mild or deep sedation (Inoue et al. 2006). The effects of electromyograph activity and neuromuscular blockade on BIS or entropy rely on consciousness level. During alertness, the influence of EMG was apparent on the BIS but not on entropy. During sedation, the BIS was diminished with a reduction in BIS value regardless of NMB, but NMB reduces entropy readings, although the level of reduction in entropy after muscle relaxants was corresponding to that after infusing a placebo. No impact of the EMG was noticed on either the BIS or entropy during general anesthesia as stated by Jin et al. (Jin et al. 2021). In contrast to Aho et al. study that showed during sevoflurane-N_2O anesthesia, both EEG and EMG arousals were seen. But EMG arousal was abolished

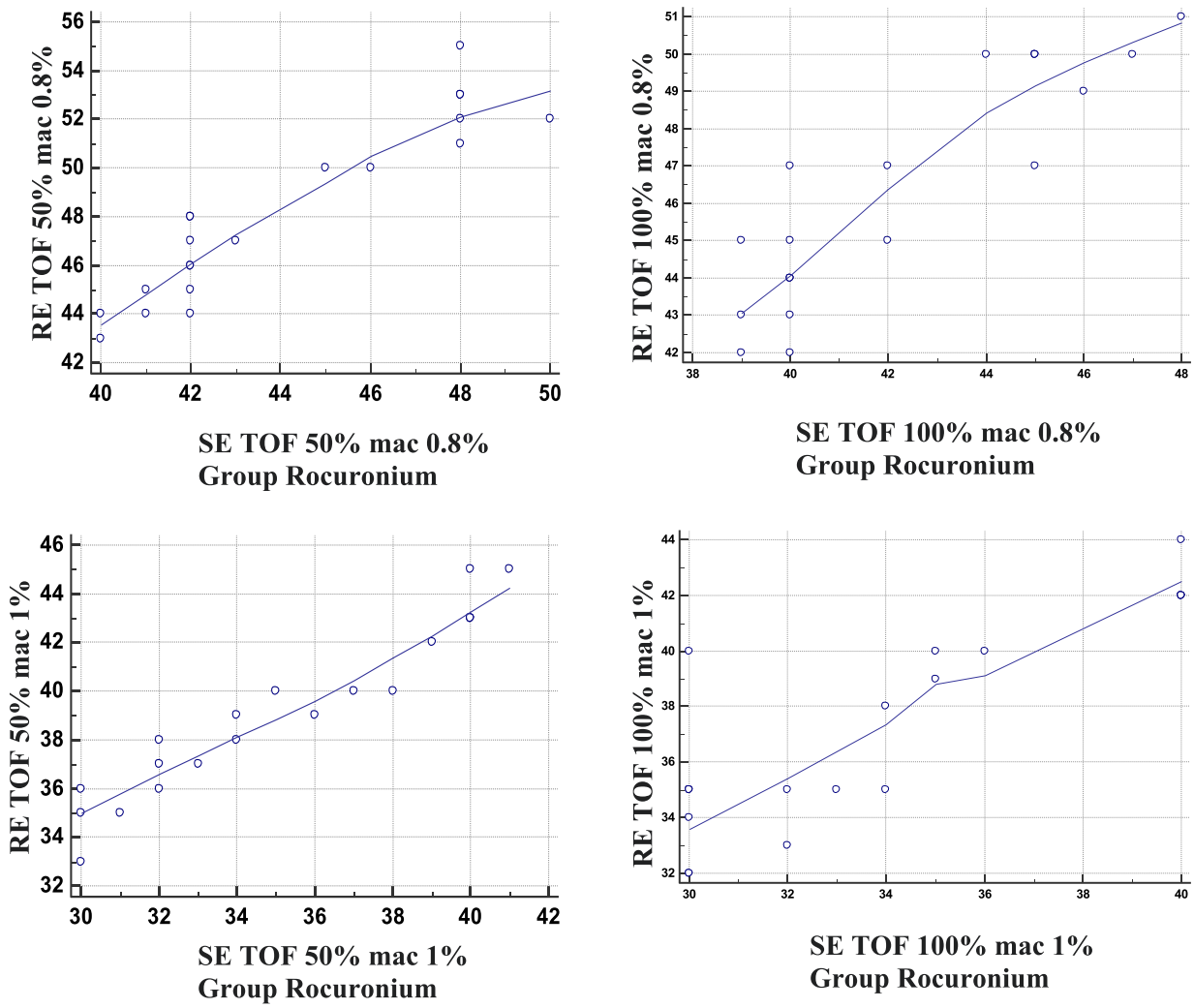

Fig. 3 Correlations between RE and SE at MAC 0.8% and 1% with TOF 50% and 100% of rocuronium group

Table 2 RE-SE difference at different MAC and TOF

	Atracurium group Mean ± SD	Rocuronium group Mean ± SD	*p*-value
Difference 50% mac 0.8%	5.05 ± 2.11	4.15 ± 1.31	0.1
Difference 100% mac 0.8%	4.65 ± 2.64	4.0 ± 1.52	0.35
Difference 50% mac 1%	4.8 ± 2.98	3.9 ± 1.07	0.2
Difference 100% mac 1%	4.3 ± 2.81	3.1 ± 1.59	0.1

by rocuronium at the train of four-level 0/4 (Aho et al. 2011). Even Punj et al. showed that entropy is a better guide for endotracheal intubation than TOF (Punj et al. 2019).

We believe that the main merits of the current study are the fact that SE and RE correlate with each other, and both were minimally affected by muscle relaxants (atracurium and rocuronium), and accordingly, using entropy is effective in determining depth of anesthesia at different levels of muscle relaxants. However, our study has certain limitations. Firstly, the sample size was minimal, with only 20 participants for each group, so we recommend that the number of participants could be escalated in our further studies to enhance the

Table 3 SE and RE at different MAC and TOF of atracurium group

	TOF_50%_mac_0.8%	TOF_100%_mac_0.8%	*p*-value
SE	44.8 ± 3.94	42.85 ± 3.86	0.12
RE	49.85 ± 4.59	47.50 ± 4.90	0.13
	TOF_50%_mac_1%	TOF_100%_mac_1%	*p*-value
SE	36.45 ± 4.36	35.4 ± 4.49	0.46
RE	41.45 ± 4.55	39.75 ± 3.58	0.197
	TOF_50%_mac_0.8%	TOF_50%_mac_1%	*p*-value
SE	44.8 ± 3.94	36.45 ± 4.36	**< 0.001***
RE	49.85 ± 4.59	41.45 ± 4.55	**< 0.001***
	TOF_100%_mac_0.8%	TOF_100%_mac_1%	*p*-value
SE	42.85 ± 3.86	35.4 ± 4.49	**< 0.001***
RE	47.50 ± 4.90	39.75 ± 3.58	**< 0.001***

* Indicates comparison between mac 0.8 and mac 1% showed significant value at both TOF 50% and 100%

Table 4 SE and RE at different MAC and TOF of rocuronium group

	TOF_50%_mac_0.8%	TOF_100%_mac_0.8%	*p*-value
SE	44.0 ± 3.24	42.30 ± 2.99	0.09
RE	48.15 ± 3.62	46.40 ± 3.1	0.11
	TOF_50%_mac_1%	TOF_100%_mac_1%	*p*-value
SE	35.2 ± 3.9	34.05 ± 4.02	0.36
RE	39.2 ± 3.46	37.5 ± 3.8	0.15
	TOF_50%_mac_0.8%	TOF_50%_mac_1%	*p*-value
SE	44.0 ± 3.24	35.2 ± 3.9	**< 0.001***
RE	48.15 ± 3.62	39.2 ± 3.46	**< 0.001***
	TOF_100%_mac_0.8%	TOF_100%_mac_1%	*p*-value
SE	42.30 ± 2.99	34.05 ± 4.02	**< 0.001***
RE	46.40 ± 3.1	37.5 ± 3.8	**< 0.001***

* Indicates comparison between mac 0.8 and mac 1% showed significant value at both TOF 50% and 100%

verification of the results. Secondly, the authenticity of our study may have been restricted by the single-center study design. Thirdly, we did not investigate the impact of opioids on spectral entropy. Lastly, we did not explore the effect of muscle relaxants on entropy readings during noxious stimuli.

Conclusions

Response entropy and state entropy declined with escalating isoflurane concentrations. While neuromuscular blockade (atracurium and rocuronium) did not alter entropy readings (SE, RE, and RE-SE) without noxious stimulation, accordingly, entropy can be used effectively as a monitor of the depth of anesthesia for patients anesthetized by isoflurane under different MACs and at different degrees of muscle relaxants.

Abbreviations

ASA	American Society of Anesthesiologists physical status
EEG	Electroencephalogram
ETCO2	End-tidal carbon dioxide concentration
ETO2	End-tidal oxygen concentration end-tidal carbon dioxide concentration
FEMG	Frontal electromyography
MAC	Minimum alveolar concentration
RE	Response entropy
SD	Standard deviation
SE	State entropy
SPSS	Statistical Package for Social Science
TOF	Train of four

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Authors' contributions
MB designed the study, revised literature, followed the patients, and critically reviewed the manuscript. HE designed the study, analyze the data, and wrote and critically revised the manuscript. TA and MI revised literature followed the patients. NH collected the data, performed the analysis, and wrote the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due (publishing the clinical data about any study conducted in our hospitals and approved by the institutional ethical committee is against the policy of the faculty of medicine, Ain Shams university unless there is a reasonable request) but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
After approval of the ethical committee in Faculty of Medicine, Ain Shams University number FMASU M D 146/2020, this observational prospective study was conducted over 40 male patients between October 2021 and February 2022. Every patient provided written informed consent prior to enrollment. The identification code in the ClinicalTrials.gov data base is NCT 05097508.

Consent for publication
Not applicable

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

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