An Entropy-Based Prospective Randomized Controlled Trial to Evaluate the Analgesic and Hypnotic Effects of Equipotent Doses of Sevoflurane and Isoflurane in Patients Presenting for Spine Surgeries

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Abstract

Objectives  Minimal alveolar concentration (MAC) of anesthetic agents has been considered a suitable measure of the potency of inhalational anesthetics. Furthermore, it is assumed that equi-MAC concentrations of different anesthetic agents have a similar potency in suppressing responses to painful stimuli. Isoflurane and sevoflurane are two commonly used volatile anesthetic agents in spine surgeries. Therefore, these agents’ hypnotic and analgesic potencies should be distinguished and comprehended for the optimal administration of anesthesia. Consequently, we undertook this study to compare the analgesic and hypnotic potencies between these agents at equi-MAC concentrations, using the entropy monitor.

Materials and Methods  Forty patients undergoing lumbar spine surgery were randomly assigned to two groups receiving either isoflurane (n = 20) or sevoflurane (n = 20). After induction, maintenance of anesthesia was done with age-corrected 1.0 MAC of either isoflurane or sevoflurane. A standardized noxious stimulus was provided to all the patients after achieving a steady state of 1.0 MAC. The state entropy (SE), response entropy (RE), and RE–SE were recorded at baseline, prestimulus, and poststimulus time points in both groups.

Statistical Analyses  Data are presented as frequency and percentages for categorical variables and mean ± standard deviation for continuous variables. The comparison of categorical variables between the two groups was made using the Fisher’s exact test, and the Student’s t-test was used for continuous variables. A p-value of < 0.05 was considered to be statistically significant.

Keywords
► entropy
► analgesia
► isoflurane
► sevoflurane


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Introduction

General anesthesia consists of the four components of hypnosis, analgesia, immobility, and the maintenance of homeostasis. Therefore, monitoring the respective components would allow tailoring drug administration to facilitate balanced anesthesia when a clinician pharmacologically induces this reversible state of unconsciousness.\(^1\)

Minimal alveolar concentration (MAC) of anesthetic agents has been considered a suitable measure of the potency of inhalational anesthetics. Furthermore, it is assumed that equi-MAC concentrations of different anesthetics have a similar potency in suppressing responses to painful stimuli.\(^2\) However, MAC as a measure of potency has been questioned since the suppression of mobility is mediated by spinal α-motor neuron depression and not the area of its hypnotic action, that is, the cerebral cortex.\(^3\) However, the fact that we can quantify MAC for various volatile anesthetics allows us to compare various effects of these anesthetic agents at equi-MAC concentrations (e.g., 0.5 MAC, 1.0 MAC, and 2.0 MAC).

Isoflurane and sevoflurane are two commonly used volatile anesthetic agents in spine surgeries. These agents’ hypnotic and analgesic potencies should be distinguished and comprehended for the optimal administration of anesthesia. We undertook this study to compare the analgesic and hypnotic potencies between these agents using the entropy monitor. A quantitative comparison of their hypnotic and analgesic effects can help us choose the ideal inhaled anesthetic in our clinical practice.

Materials and Methods

After obtaining approval from the institutional ethics committee, a prospective randomized study was initiated. Consenting patients aged between 18 and 60 years scheduled for elective lumbar disc surgery were included in the study. Patients with American Society of Anesthesiologists physical status classification of III and higher, neurologic or psychiatric ailments, obesity and underweight patients, alcohol or drug abuse, any medications affecting the nervous system, that is, sedatives, anxiolytics, prior chronic usage of analgesics were excluded from the study. Using a web-based response, a random-permuted block randomization algorithm randomly allocated the patients into two groups (isoflurane and sevoflurane groups) of 20 each. Allocation concealment was ensured with opaque serially numbered envelopes containing protocol with the name of the agent to be used.

Results

At age-corrected 1.0 MAC, there was no significant difference in the SE, RE, and RE–SE in both the groups at any time point.

Conclusion

Our study shows that during a steady state of age-corrected 1.0 MAC single-agent anesthesia, sevoflurane and isoflurane have comparable analgesic and hypnotic potencies as measured by entropy indices when a standardized nociceptive stimulus is provided.

Premedication drugs such as anxiolytics and anticholinergics were avoided in the study population. In the operating room, standard preinduction monitoring, comprising electrocardiography, noninvasive blood pressure, and pulse oximetry (SpO\(_2\)), was attached. According to the manufacturer’s instructions, the entropy electrode was applied to the patient’s forehead and connected to the monitor (M-Entropy module for S/5 Anesthesia Monitor, GE Healthcare). State entropy (SE) and response entropy (RE) and the difference between them (RE–SE) were surrogate measures to assess the hypnotic and analgesic levels, respectively. General anesthesia was induced with Inj. propofol 2 mg/kg and tracheal intubation was facilitated with Inj. succinylcholine 2 mg/kg. In addition, lignocaine 2 mg/kg was administered to blunt the autonomic responses to intubation. The peripheral nerve stimulator electrodes were placed over the ulnar nerve on the volar aspect of the distal forearm. A train-of-four (TOF) count of 0 was ensured prior to intubation using a neuromuscular monitor device (M-NMT MechanoSensor, GE Healthcare, Finland). Hemodynamic surges during laryngoscopy and intubation were promptly treated with a titrated dose of esmolol. After intubation, mechanical ventilation with air:O\(_2\) (1:1) mixture was initiated. Temperature and end-tidal CO\(_2\) monitoring was instituted to ensure normothermia and normocarbia.

At this juncture, the volatile anesthetic agent was introduced by overpressurization to target an age-corrected MAC of 1.0. End-tidal anesthetic concentration was continuously measured using the gas analyzer (GE Datex Ohmeda S5 Anesthesia Monitor). The noxious stimulus was provided after 20 minutes to ensure the steady-state concentration of the volatile agent and to avoid the residual effects of propofol. We also confirmed a TOF count of 4 prior to the stimulus. The noxious stimulus was provided to the subject by tetanic stimulation (square wave, 70 mA stimulus, 30-second duration at 50 Hz), and the postnoxious stimulus study parameters were obtained. Opioids were administered after the recording of the poststimulus values.

The study parameters, namely, heart rate (HR), mean arterial pressure (MAP), SE, RE, and RE–SE were recorded at three time points: before anesthetic induction, prior to providing noxious stimulus, and after application of noxious stimuli. The baseline and prenoxious stimulus values were recorded as the mean values calculated over 1 minute. The postnoxious stimulus values were the maximal readings recorded within 1 minute of the stimulus application.

During the study duration, hemodynamic derangements were promptly managed. If the entropy values were > 70,
additional sedatives/analgesics would be administered, and such patients were excluded from the study.

**Statistical Analysis**

The primary outcome of interest was the measure of analgesia, that is, RE–SE. Since there has not been any previous study comparing analgesic properties of isoflurane and sevoflurane using entropy indices, the power analysis for sample size calculation was based on the RE–SE difference considered significant between any two anesthetic agents. Therefore, a difference of 4, derived from previous studies, was utilized. The study was designed to have a power of 90% to detect a statistical significance of 0.05 in the RE–SE difference between isoflurane and sevoflurane groups. To meet these criteria, we included 20 subjects in each group. Statistical analyses were performed using the SPSS 17.0 version. Data are presented as frequency and percentages for categorical variables and mean ± standard deviation for continuous variables. The Shapiro–Wilk's test was used to confirm the normalcy of distribution for categorical variables. The comparison of categorical variables between the two groups was made using the Fisher's exact test, and the Student's t-test was used for continuous variables. A p-value of < 0.05 was considered to be statistically significant.

**Results**

Fifty-six patients presenting for spinal surgery were screened for the study. Twelve patients were ineligible based on the exclusion criterion (Fig. 1). One patient withdrew consent and was excluded from the study. Therefore, 21 subjects were included in each group. Two patients (one from each group) were excluded from the study because of the administration of fentanyl. Thus, data of 20 subjects in each group were taken for final analysis (Fig. 1). Patient baseline demographic characteristics and entropy indices were comparable between groups (Table 1).

The baseline, prenoxious, and postnoxious variables were evaluated (Table 2) for both groups. The baseline hemodynamic values before the induction were comparable between the two groups (Table 2). At age-corrected 1.0 MAC, there was no significant difference in the prestimulus hemodynamic variables between both the groups (HR p = 0.06, MAP p = 0.17). Similarly, there was no statistically significant difference in the prestimulus RE, SE, RE–SE between the isoflurane and sevoflurane groups (RE p = 0.46, SE p = 0.07, RE–SE p = 0.06; Table 2).

During the poststimulus period, there was a significant increase in HR in the isoflurane group compared with the...
Table 1 Demographic details of patients in both the groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (isoflurane)</th>
<th>Group 2 (sevoflurane)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (mean ± SD)</td>
<td>45 ± 12</td>
<td>41 ± 14</td>
<td>0.33</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>12:8</td>
<td>10:10</td>
<td>0.75</td>
</tr>
<tr>
<td>Height (cm) (mean ± SD)</td>
<td>159 ± 12</td>
<td>155 ± 10</td>
<td>0.26</td>
</tr>
<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>69 ± 15</td>
<td>73 ± 18</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
Note: *p* < 0.05 is considered statistically significant.

Table 2 Hemodynamic and entropy indices of both the groups

<table>
<thead>
<tr>
<th>Variables (mean ± SD)</th>
<th>Group 1 (isoflurane)</th>
<th>Group 2 (sevoflurane)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>88 ± 20</td>
<td>80 ± 14</td>
<td>0.15</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94 ± 10</td>
<td>96 ± 12</td>
<td>0.5</td>
</tr>
<tr>
<td>RE</td>
<td>96 ± 2</td>
<td>95 ± 3</td>
<td>0.3</td>
</tr>
<tr>
<td>SE</td>
<td>90 ± 3</td>
<td>89 ± 2</td>
<td>0.3</td>
</tr>
<tr>
<td>RE–SE</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>1</td>
</tr>
<tr>
<td>Prenoxious stimulus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>78 ± 12</td>
<td>71 ± 10</td>
<td>0.06</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>85 ± 8</td>
<td>81 ± 8</td>
<td>0.17</td>
</tr>
<tr>
<td>RE</td>
<td>38 ± 5</td>
<td>37 ± 5</td>
<td>0.46</td>
</tr>
<tr>
<td>SE</td>
<td>38 ± 5</td>
<td>35 ± 4</td>
<td>0.07</td>
</tr>
<tr>
<td>RE–SE</td>
<td>0.2 ± 3</td>
<td>1.7 ± 2</td>
<td>0.06</td>
</tr>
<tr>
<td>Postnoxious stimulus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>103 ± 15</td>
<td>95 ± 9</td>
<td>0.05*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>100 ± 8</td>
<td>97 ± 9</td>
<td>0.39</td>
</tr>
<tr>
<td>RE</td>
<td>59 ± 5</td>
<td>56 ± 5</td>
<td>0.06</td>
</tr>
<tr>
<td>SE</td>
<td>48 ± 5</td>
<td>46 ± 5</td>
<td>0.12</td>
</tr>
<tr>
<td>RE–SE</td>
<td>11 ± 3</td>
<td>10.45 ± 4</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Abbreviations: bpm, beats per minute; HR, heart rate; MAP, mean arterial pressure; RE, response entropy; SE, state entropy.
* *p* < 0.05 is considered statistically significant.

Sevoflurane group (103 ± 15 vs. 95 ± 9, *p* = 0.05) (*Table 2*). However, there was no significant difference in the MAP values between both groups (*p* = 0.39). Though the SE, RE, and RE–SE increased linearly during the poststimulus period in both the groups, there was no statistically significant difference between the two groups (SE *p* = 0.12, RE *p* = 0.06, RE–SE *p* = 0.63) (*Table 2*). RE–SE was >10 in both the isoflurane and sevoflurane groups (*Table 2*). RE–SE was 10.45 ± 4 in the sevoflurane group compared with 11 ± 3 in the isoflurane group (*p* = 0.63).

**Discussion**

The main aim of our study was to compare the analgesic and hypnotic potencies of isoflurane and sevoflurane at age-corrected 1.0 MAC in response to a standardized noxious stimulus. We found that isoflurane and sevoflurane had comparable analgesic and hypnotic potencies before and after providing the noxious stimulus.

Electroencephalographic (EEG) activity can assess and measure the hypnotic states and the cortical response to noxious stimulation. Time–frequency balanced spectral entropy (M-Entropy) is one of the EEG-based monitors used to monitor the neurophysiological response to anesthesia. The SE index is calculated for frequencies between 0.8 and 32 Hz, reflecting the EEG activity and the time windows for measuring the SE index vary between 15 and 60 seconds. The RE index is calculated for frequencies between 0.8 and 47 Hz and reflects EEG and frontal electromyographic (fEMG) activity. The time windows for measuring the SE index vary between 2 and 15 seconds. The difference between RE and SE indicates EMG activity alone and can be a measure of nociceptive–antinociceptive balance. We used entropy indices as surrogate measures for hypnosis and analgesia.
The potential of entropy monitor to reflect nociceptive–
antinociceptive balance has been explored by many studies
in the past. Guerrero et al, in their observational, prospective
study using 3 and 4% sevoflurane anesthesia, found that
the difference between RE and SE increased significantly af-
after a noxious stimulus. Aho et al also had similar results
wherein deepening the plane of anesthesia produced a simulta-
nous decrease of RE and SE values with a concurrent dominance
of low-frequency EEG. However, the application of a noxious
stimulus induced an increase in RE and RE–SE values.
Wheeler et al, using sevoflurane anesthesia, observed that
noxious stimulus was associated with a concurrent increase
in SE and RE and increased autonomic responses in terms of
HR and BP. They also noticed that RE increased initially
followed by SE, supporting the relationship between fEMG
and patient arousal. In the calculation of RE, 2 seconds is used
to assess fEMG compared with 15 to 60 seconds for measur-
ing brain electrical activity; this could be the plausible
reason for the delay in the rise of SE.

Our study is the first to compare the analgesic potency
of isoflurane and sevoflurane with entropy indices. RE and SE
increased after the noxious stimulus, and RE–SE was > 10 in
both the isoflurane and sevoflurane groups. These findings
are similar to that of Mathews, who successfully integrated
RE–SE into an automated algorithm for opioid administra-
tion. It further concurred with the results of Gruenewald
and Ilies, where RE–SE of < 10 was associated with a signifi-
cant reduction in opioid consumption.

The similarity noted in the entropy indices of sevoflurane
and isoflurane could be due to the similar EEG effects of these
agents. Schwender et al calculated the spectral edge frequen-
cy (SEF), total power, and relative power of the delta, theta, α,
and β in the EEG. They found that at equi-MAC levels,
isoflurane and sevoflurane had equipotent EEG suppres-
sion. Rehberg obtained concentration-response curves
for these agents and compared the dose for SEF reduction
with equi-MAC values. Their findings also demonstrated that
the EEG-slowing effect of these agents is not different from
the potency measured by MAC.

We used the entropy indices to compare the hypnotic
potencies of isoflurane and sevoflurane at equi-MAC values.
Our study results have shown that both SE and RE were
comparable in the isoflurane and sevoflurane groups at an
age-corrected MAC of 1.0. Eger defined MAC as the minimum
alveolar concentration of inhaled anesthetic required to
prevent 50% of subjects from responding to a standard
painful stimulus (initial skin incision) with "gross purposeful
movement." However, one major limitation in using MAC as
hypnotic potency is that this "gross purposeful movement" is
produced at the spinal (motor neuron) level and is indepen-
dent of cerebral function. Thus, the MAC awake concept was
introduced as the monitor of cerebral cortical state. MAC
awake expresses the anesthetic concentration at which
consciousness might be regained; it was defined as the
anesthetic concentration needed to suppress a voluntary
response to verbal command in 50% of patients. The ratio
of MAC awake to MAC describes the emergence from
anesthesia.

We compared sevoflurane and isoflurane as these both
agents had a similar MAC awake to MAC ratio. It is noted that
isoflurane, sevoflurane, and desflurane have comparable
MAC awake/MAC ratios. The ratio is higher for halothane,
which is reflected by studies showing increased bispectral
index (BIS) and entropy values for halothane compared with
isoflurane and sevoflurane at similar anesthetic concentra-
tions. Therefore, further studies are required to elucidate
whether agents with comparable MAC awake/MAC ratios
have similar potencies with respect to hypnosis, analgesia,
and immobilizing properties.

The results of our study should be interpreted keeping in
mind the limitations of entropy monitor as surrogate meas-
ures of hypnosis and analgesia. In one study, there was an
increase of SE, RE, and RE–SE during intubation in patients
receiving propofol anesthesia. They analyzed the absolute
values and the raw EEG data and found that the increase of RE
was soon followed by an increase in SE values, decreasing the
RE–SE difference. They presumed that the cause of the rise in
SE was not because of EEG activation but could be attributed
to the intense EMG activity changing the EEG spectrum at
20 Hz. It must be noted that all activity below 32 Hz is
regarded as EEG in entropy analysis. It is possible that SE can
capture the EMG activity as there is an overlap of the
frequencies captured by SE and RE. However, there was an
increase in SE and RE in our study with a concomitant
increase in RE–SE above 10 during the noxious stimulus.

Few studies have shown a lack of RE to painful stimulus in
fully paralyzed patients. Kawaguchi et al showed that muscle
relaxants suppressed the change in entropy to intubation in a
dose-dependent manner. Xing et al found that muscle
relaxants significantly reduced spectral entropy changes in
response to a noxious stimulus. These studies suggest that
the values of RE and RE–SE are purely EMG related, and
consequently, these indices are unreliable in a complete or
incomplete neuromuscular blockade. We ensured a TOF of 4
prior to recording prenoxious and postnoxious values to
remove the confounding factor of effects of neuromuscular
blockade on the study.

We had compared the effects of isoflurane and sevoflur-
ane at 1.0 MAC and found that they produce similar entropy
indices. Similarity, Kim et al reported similar BIS values for
these agents at 1 MAC. However, another study demon-
strated that sevoflurane produced lesser BIS/more hypnosis
than isoflurane both at wash-in and wash-out phases of
anesthesia. Kurehara et al evaluated the BIS values in
patients anesthetized with sevoflurane and isoflurane.
They found that at 1.2 MAC, both anesthetics produced the
same BIS values. However, increasing the anesthetic concen-
tration to 2.0 MAC decreased the BIS values in patients
anesthetized with isoflurane; however, it had no effect in
those anesthetized with sevoflurane. Moreover, it is to be
noted that a study by Ryu et al, which compared desflurane
and sevoflurane (agents with similar MAC awake/MAC ratio),
found that they produced different levels of hypnosis as
measured by BIS. Further studies comparing these agents’
hypnotic and analgesic effects at increasing MAC levels
would throw light on this.
Randomized double-blind trials are considered a superior study design since randomization, and double blinding eliminates confounding variables. In our study, though patients were blinded to the agent they were administered, the anesthetists who provided anesthesia and recorded the values were not blinded. This could have led to bias, though strict study protocol adherence and withdrawal criterion was followed in the study. Also, the primary outcome of interest was study protocol adherence and withdrawal criterion was followed in the study. Also, the primary outcome of interest was the measure of analgesia, and the sample size was calculated based on the same and not for the measure of hypnosis. However, the SE (a measure of hypnosis) of iso
to the measure of analgesia, and the sample size was calculated. Also, the primary outcome of interest was study protocol adherence and withdrawal criterion was followed in the study. Also, the primary outcome of interest was the measure of analgesia, and the sample size was calculated based on the same and not for the measure of hypnosis. Hence, we believe the study results are valid not just for the measure of analgesia but also for hypnosis.

Conclusion
In conclusion, our study shows that during a steady state of age-corrected 1.0 MAC single-agent anesthesia, sevoflurane and isoflurane have comparable analgesic and hypnotic potencies as measured by entropy indices when a standardized nociceptive stimulus is provided.

Funding
None.

Conflict of Interest
None declared.

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