Assessment of the depth of anaesthesia during inhalational and intravenous induction of general anaesthesia

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Abstract

Background: Tracheal intubation is one of the strongest stimuli during general anaesthesia and may result in an insufficient depth of anaesthesia. The aim of the study was to compare the clinical evaluation of the depth of anaesthesia with an evaluation using entropy during inhalational and intravenous induction of general anaesthesia.

Methods: This study involved 60 patients undergoing elective surgery under general anaesthesia. Patients were divided into two groups, group E (etomidate induction) and group S (sevoflurane induction). The systolic arterial pressure (SAP), heart rate (HR), response entropy (RE), and state entropy (SE) were determined at the following seven measurement points: before anaesthesia induction, at the loss of consciousness (LOC) point, before tracheal intubation, immediately after intubation, and 2 min, 4 min and 6 min after tracheal intubation. An increase in HR and/or SAP of more than 20% and/or the occurrence of lacrimation and/or perspiration in response to tracheal intubation was considered a marker of inadequate anaesthesia in the clinical evaluation. The depth of anaesthesia was considered insufficient according to entropy monitoring if the RE and SE were above 60.

Results: In clinical evaluation, insufficient anaesthesia in response to tracheal intubation was observed in all the patients in group E and in more than half of the patients in group S. At the same time, the majority of patients in both groups had entropy values that did not exceed the recommended value as an appropriate level of anaesthesia.

Conclusions: We found a discrepancy in the evaluation of the depth of anaesthesia based on clinical criteria compared with evaluations based on entropy values during both intravenous and inhalational induction of general anaesthesia.

Key words: entropy, depth of general anaesthesia, induction of general anaesthesia, inhalational, intravenous, etomidate, sevoflurane, tracheal intubation

A reliable assessment of the depth of anaesthesia during the induction of general anaesthesia is difficult. The use of striated muscle relaxants to facilitate tracheal intubation and excitation of the autonomic nervous system, which frequently accompanies intubation, can contribute to the misinterpretation of the depth of general anaesthesia. According to the 5th National Audit Project (NAP 5) carried out in the United Kingdom in 2011 to identify cases of accidental awareness during general anaesthesia, 47% of all reported cases occurred during the induction of general anaesthesia or immediately after, but before surgical manipulations [1].

One of the methods available to monitor the level of general anaesthesia is an entropy-based analysis of the bioelectrical cerebral cortex activity. Entropy is characterised by the following two parameters: state entropy (SE), consisting mainly of EEG signals and reflecting the cerebral cortex state; and response entropy (RE), consisting of both EEG and frontalis EMG signals [2]. SE and RE values within the range of 40–60 are considered sufficient for anaesthetic sleep, with a low probability of accidental awareness [3, 4].

The aim of the present study was to compare the assessment of the depth of anaesthesia using clinical parameters versus entropy during inhalational and intravenous induction of general anaesthesia.

METHODS
A prospective study was carried out; the study design was approved by the local bioethics committee (NKEBN/...
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The study encompassed 70 ASA I–III patients aged above 18 years of both sexes undergoing surgical procedures requiring general anaesthesia. Patients were randomly assigned to group S (inhaled induction with sevoflurane) or group E (intravenous induction with etomidate). The exclusion criteria were as follows: CNS disorders, alcohol or drug abuse, contraindications for etomidate or inhalational induction of anaesthesia, central neuraxial blockades and anticipated difficult airway access. In addition, at least two unsuccessful attempts of tracheal intubation were considered secondary exclusion criterion.

All the patients were pre-medicated with oral midazolam at a dose of 0.05–0.1 mg kg⁻¹. In group E, general anaesthesia was induced with etomidate at a dose of 0.3 mg kg⁻¹, whereas sevoflurane was administered in group S using the single- or multiple-breathe vital capacity method. During induction, 1–2 µg kg⁻¹ of fentanyl and 0.15 mg kg⁻¹ of cisatracurium were administered in both groups. All the patients underwent tracheal intubation 3 minutes after the administration of cisatracurium. Until intubation, face mask ventilation was applied using 100% oxygen (group E) or a mixture of sevoflurane and 100% oxygen to achieve the end-expiratory sevoflurane concentration of approximately 1.5 MAC, according to age (group S). After intubation, lung ventilation was initiated in both groups using the mixture of 30% oxygen and 70% air as well as sevoflurane at the end-expiratory concentration of approximately 1 MAC.

Vital and entropy parameters were continuously monitored. The heart rate (HR), non-invasive systolic arterial pressure (SAP), RE and SE were determined and analysed at the following measurement points: $T_1$ — before induction of anaesthesia, $T_2$ — on loss of consciousness (LOC), $T_3$ — immediately before tracheal intubation, $T_4$ — after tracheal intubation, $T_5$ — 2 minutes after, $T_6$ — 4 minutes after and $T_7$ — 6 minutes after tracheal intubation. The depth of anaesthesia was assessed by the anaesthesiologist based on haemodynamic changes and the presence of lacrimation and/or perspiration. Moreover, the values of RE and SE parameters were invisible for the anaesthesiologist and were recorded at appropriate measurement points.

The haemodynamic changes in response to tracheal intubation were considered significant when the HR and/or SAP increased by more than 20% compared to values recorded before laryngoscopy and tracheal intubation. The above clinically assessed changes as well as lacrimation and/or perspiration in response to tracheal intubation were considered evidence of an insufficient level of anaesthesia. Hypotension was defined as a decrease in SAP below 90 mm Hg and was treated with accelerated infusions of fluids. Values of RE and SE above 60 weighted in favour of insufficient depth of sleep, whereas those below 40 indicated too deep of a sleep.

The final statistical analysis was carried out in 60 patients. Ten patients were excluded from the final analysis, including three patients because invasive arterial pressure measurements could not be attained, three patients due to difficult airway access and four patients because of interruptions in the display of entropy parameters.

Statistica for Windows 9.1 software was used (Statsoft, Tulsa, OK USA). The data distribution was evaluated using Student’s t or the Mann-Whitney U tests; data were, respectively presented as a mean ± SD or median [quartile deviation]. Normal distribution of interval scale data was obtained by calculating common logarithms of the values. The interval scale data were compared using ANOVA and post-hoc Tukey’s HSD test, and the qualitative data were compared using the χ² or Fisher’s test. $P < 0.05$ was considered statistically significant.

**RESULTS**

The characteristics of the patients are presented in Table 1. In both groups haemodynamic and entropy parameters decreased until the airway was secured.

Significant haemodynamic changes in response to tracheal intubation were observed in all group E patients and in over half of group S individuals ($P = 0.0001$) (Fig. 1).

Only a low percentage of patients with significant haemodynamic changes had RE and SE values higher than 60 (Fig. 2).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group E</strong>&lt;br&gt;(n = 30)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Body mass (kg)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
</tr>
<tr>
<td>ASA scale (I/II/III)</td>
</tr>
</tbody>
</table>

Figure 1. Haemodynamic response to tracheal intubation in group E and S (inside the bars – the number of patients)
The haemodynamic response was increased in group E. There were no inter-group significant changes in RE and SE in response to the tracheal intubation, although the RE and SE values after intubation were higher in group E. The parameters analysed in both groups at the individual measurement points are presented in Table 2.

The presence of lacrimation and/or perspiration in response to the tracheal intubation was found in 17% of group E patients and in 3% of group S individuals \( (P = 0.19) \). Moreover, significant haemodynamic changes were observed in the patients of both groups, whereas the values of RE and SE did not exceed 60 in either group.

Pre-intubation hypotension was observed in 10% of group E patients and 43% of group S patients \( (P = 0.007) \) and post-intubation hypotension in 7% and 33%, respectively \( (P = 0.02) \). The percentages of patients with SE values lower than 40 at individual measurement points are presented in Fig. 3.

**DISCUSSION**

The provision of a sufficient depth of general anaesthesia is of the utmost importance. Anaesthesia that is too deep can be associated with cardiovascular instability, prolonged recovery from anaesthesia, cognitive disorders and increased postoperative mortality \([5, 6]\). Anaesthesia that is too light can lead to accidental awareness and result in permanent changes, such as sleep disorders, irritability, anxiety and posttraumatic stress, which can result in malpractice lawsuits against anaesthesiologists \([7]\). During the induction of general anaesthesia, laryngoscopy and tracheal

![Figure 2](image1.png)  
**Figure 2.** Percentages of patients with significant haemodynamic changes in response to tracheal intubation according to RE and SE values in group E and S (inside the bars — the number of patients)

![Figure 3](image2.png)  
**Figure 3.** Percentages of patients with SE values lower than 40 at individual measurement points in group E and S (inside the bars — the number of patients)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement point</th>
<th>T1</th>
<th>T2 (LOC)</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
<th>T7</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (min⁻¹)</td>
<td>Group E</td>
<td>70.6 ± 13.0</td>
<td>63.8 ± 9.5</td>
<td>60.3 ± 10.9</td>
<td>81.2 ± 17.6*</td>
<td>73.1 ± 15.1</td>
<td>66.8 ± 17.8</td>
<td>62.6 ± 10.3</td>
</tr>
<tr>
<td></td>
<td>Group S</td>
<td>72.6 ± 13.5</td>
<td>75.7 ± 15.3*</td>
<td>62.8 ± 10.5*</td>
<td>80.3 ± 17.6*</td>
<td>72.8 ± 17.5</td>
<td>64.7 ± 17.6</td>
<td>61.3 ± 9.9</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>Group E</td>
<td>145.6 ± 16.0</td>
<td>133.7 ± 18.0</td>
<td>116.7 ± 22.2*</td>
<td>167.3 ± 24.7*</td>
<td>141.5 ± 26.6</td>
<td>116.6 ± 22.0</td>
<td>106.5 ± 15.8</td>
</tr>
<tr>
<td></td>
<td>Group S</td>
<td>143.1 ± 25.9</td>
<td>124.8 ± 25.5*</td>
<td>98.9 ± 19.0*</td>
<td>121.2 ± 33.4*</td>
<td>112.9 ± 26.0*</td>
<td>104.2 ± 20.1</td>
<td>98.8 ± 17.3</td>
</tr>
<tr>
<td>RE</td>
<td>Group E</td>
<td>96.6 ± 3.9</td>
<td>78.2 ± 28.3*</td>
<td>39.2 ± 10.3*</td>
<td>46.3 ± 15.3</td>
<td>44.0 ± 10.7</td>
<td>42.6 ± 9.7</td>
<td>44.3 ± 10.8</td>
</tr>
<tr>
<td></td>
<td>Group S</td>
<td>97.3 ± 2.1</td>
<td>82.3 ± 21.3*</td>
<td>31.2 ± 12.3*</td>
<td>34.5 ± 15.4*</td>
<td>38.1 ± 13.2</td>
<td>44.3 ± 13.7</td>
<td>46.0 ± 12.8</td>
</tr>
<tr>
<td>SE</td>
<td>Group E</td>
<td>87.2 ± 3.2</td>
<td>69.8 ± 26.1*</td>
<td>37.2 ± 9.9*</td>
<td>41.7 ± 13.9</td>
<td>42.1 ± 10.5</td>
<td>41.6 ± 9.4</td>
<td>42.9 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>Group S</td>
<td>88.2 ± 2.0</td>
<td>75.4 ± 20.8</td>
<td>29.9 ± 12.0*</td>
<td>30.9 ± 12.2*</td>
<td>36.7 ± 12.4</td>
<td>43.0 ± 13.4</td>
<td>45.1 ± 12.5</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \) between group E and S at a given measurement point; *\( P < 0.05 \) compared to the previous measurement in the group; LOC — loss of consciousness; other abbreviations are explained in the text
intubation are two moments when the depth of general anaesthesia can become lighter [8].

In our study, haemodynamic and entropy parameters gradually decreased until the airway was instrumentally secured, which was consistent with previous findings [9, 10]. In response to tracheal intubation, significant haemodynamic changes were observed in both groups. An increase in SAP was found to be higher in the intravenous induction group compared to the inhalational group, which was also demonstrated in a study by Karpel and colleagues [11].

According to Wujtewicz [12], premedication with midazolam caused lesser haemodynamic responses to tracheal intubation, compared with patients given standard care. In our study, all patients were pre-medicated with midazolam, and the inter-group differences in haemodynamic responses seem to result predominantly from the type of induction of general anaesthesia.

Each case of lacrimation and/or perspiration was accompanied by significant haemodynamic changes. The haemodynamic response in those patients was significantly greater compared to patients without this type of reaction. Similar findings were reported by French researchers [13].

According to the criteria assumed, the clinically assessed insufficient depth of anaesthesia in response to tracheal intubation was demonstrated in all patients in the intravenous induction group and in over half of those in the inhalational induction group. It is known that the haemodynamic response comes from the subcortical region of the nervous system (brain stem and hypothalamus) and intravenous anaesthetics (e.g., etomidate), in contrast to inhalational anaesthetics, do not suppress these regions [14]. This can explain the significant haemodynamic changes in all the patients undergoing etomidate-induced general anaesthesia. The above-mentioned French authors, using the same clinical criteria, showed that after tracheal intubation 65% of patients were too lightly anaesthetised [13]. They used an infusion of remifentanil; therefore, it is likely that this lower percentage of patients compared to the percentage found in our study with the intravenous group might have resulted from weakened haemodynamic responses to the tracheal intubation caused by the continuous infusion of remifentanil [15]. According to some other authors, neither 1 MAC sevoflurane used for intravenous induction or maintenance of the end-expiratory sevoflurane concentration at 2 MAC fully prevented enhanced haemodynamic responses to intubation [16, 17]. In our study, the concentration of sevoflurane in the inhalational induction group before intubation was maintained at the level of 1.5 MAC, and significant haemodynamic responses were observed in over half of the patients.

The parameters of entropy did not increase in response to tracheal intubation in either group. Gao and co-workers, who induced general anaesthesia intravenously, did not find significant increases in SE and RE in response to intubation. In contrast, some authors observed an increase in one or both parameters of entropy [19, 20]. The RE parameter reflects both the EEG signal of the cerebral cortex and the frontalis EMG signal. The SE parameter consists mainly of the EEG signal and a small part of EMG in the range of 30–32 Hz. Thus, the striated muscle relaxants inhibiting the muscle activity can affect both entropy parameters [21]. According to our findings, RE and SE values after tracheal intubation were higher in the intravenous induction group compared to the inhalational induction group. All our patients received cisatracurium; therefore, the inter-group difference observed could have resulted from the effects of cisatracurium. The other researchers demonstrated that sevoflurane acting at the spinal cord level could suppress the motor reaction, thus modifying the values of entropy parameters [22, 23]. This could explain the lower RE and SE values observed in our study after tracheal intubation in the group of patients undergoing inhalational induction.

In the majority of patients with an insufficient level of general anaesthesia in response to the tracheal intubation found on clinical assessment, the parameters of entropy did not exceed the upper limit considered to be the proper level of anaesthesia. In approximately half of the group E patients as well as in over half of the group S patients, the parameters in question indicated an extremely deep anaesthetic-induced sleep. The presence of lacrimation and/or perspiration was also not accompanied by increased values of entropy parameters. Similar results were reported in other publications; despite the distinct haemodynamic response to the tracheal intubation, the parameters of entropy remained within the recommended limits in the majority of patients [13, 18]. The above confirms that the haemodynamic response to tracheal intubation does not have to indicate an insufficient level of anaesthetic sleep.

The reports suggesting that an excessive depth of anaesthesia could be associated with increased morbidity and long-term mortality in anaesthetised patients and cause marked impairments of cognitive function in elderly patients are alarming [24, 25]. The elderly show long-term cognitive deficits even at seemingly correct depths of general anaesthesia, assessed with the bispectral index for the general population [5]. It is implied that these values may be inappropriate to assess the level of anaesthesia in this specific population [26].

According to our findings, entropy-assessed levels of anaesthesia that were too deep throughout the study period were observed in over 60% of patients in the intravenous induction group and in 80% of those in the inhalational induction group. The anaesthesia level was assessed based on
Does spectral entropy reflect the M-Entropy guidance Awareness with recall during general The Bispectral index Peri-intubation hemodynamic changes during low Entropy indices vs the bispectral Anaesthesiol Intensive Ther 2014, vol. 46, no 4, 274–279

2. References:

2.1. Our study has some limitations, which include a wide age range of participants (i.e., 26–79 years), lack of post-operative conversations with patients to detect possible awareness incidents, possible effects of drugs (used for induction or taken by patients) on the parameters of entropy. Moreover, the criteria for insufficient anaesthesia that was selected for the clinical assessment could be another limitation. Various clinical criteria are used in different studies; therefore, the comparison of results can be hindered.

CONCLUSIONS

1. The clinical assessment of the depth of anaesthesia differed from the depth assessed with entropy, both during intravenous and inhalational induction of general anaesthesia.

2. Enhanced haemodynamic responses to tracheal intubation in the form of a significantly increased heart rate and/or arterial pressure as well as laceration and/or perspiration do not necessarily provide evidence of an insufficient level of anaesthetic sleep.

References:


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