Non-instrumental clinical monitoring does not guarantee an adequate course of general anesthesia. A prospective clinical study

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Background. Clinical monitoring is the most common method of adjusting the appropriate level of general anesthesia. However, episodes of intraoperative awareness (AWR) are still reported, suggesting that clinical observations may not be sufficient in some cases. The objective of this study was to compare the efficacy of clinical and instrumental neuro-monitoring with auditory evoked potentials (AEP) in an intraoperative analysis of the proper level of general anesthesia.

Methods. Patients scheduled for elective surgery were randomly divided into two groups. Subjects in the first group underwent intravenous, in the second group volatile anesthesia. The adequacy of anesthesia was analyzed using clinical parameters. All the participants were instrumentally monitored with the autoregressive AEP index (AAI). After the anesthesia, patients filled out a questionnaire on possible AWR.

Results. Data of 208 patients (87 in the first, and 121 in the second group) were analyzed. Before surgery there were no changes in AAI values between groups (80 vs. 78, \( P = 0.5192 \)). The mean values of clinical parameters changed, but five minutes after the nociceptive stimuli. The mean values of AAI at analyzed time points were specific for general anesthesia. In patients under intravenous anesthesia, we found more episodes of too low (46/608 vs.15/847, \( P < 0.000 \)) anesthesia. One case of AWR was found in the TIVA group.

Conclusions. AAI index is good indicator of patients’ level of consciousness during general anesthesia. Standard clinical monitoring provides appropriate level of the procedure. However, it is insufficient during TIVA and does not prevent episodes of AWR.

Key words: volatile anesthesia, total intravenous anesthesia, intraoperative awareness, neuromonitoring, auditory evoked potential, AAI index

INTRODUCTION

The incidence of intraoperative awareness in patients undergoing surgical procedures under general anesthesia (GA) varies between 0.1–0.2 and 2.1–9.1 pro mille; a higher incidence is observed in cardiac surgery patients, women after caesarean sections, victims of multiple trauma as well as children. The difficulties in maintaining the proper level of general anesthesia arise from complex mechanisms involved in the physiology of dreams and consciousness, the multidirectional (including cardiodepressive) mechanisms of action of anesthetics, differences in pharmacokinetics and pharmacodynamics of anesthetics, genetic variability of patients as well as from experience of the anesthesiologist. Implicit and explicit recalls after procedure, resulting from too low level of anesthesia, may cause posttraumatic stress disorder (PTSD) and both acute and chronic mental disorders. These problems can affect from 4% to 70% of patients up to two years after the traumatic event. On the other hand, too deep a level of anesthesia can increase the incidence of postoperative cognitive decline, postoperative delirium, time of hospitalization and accelerate the onset of senile dementia. Analysis of the proper level of anesthesia is based on assessment of clinical parameters, autonomic and somatic reflexes. However, clinical parameters are not reliable indicators of adequate level of general anesthesia.

Currently, the role of instrumental monitoring in analysis of proper level of anesthesia is increasing. The mode of action of all these instruments relies on analysis of changes in brain functions due to anesthetics. The most common is analysis of spontaneous electroencephalogram (EEG) and/or evoked potentials. Instrumental neuromonitoring was recommended by the international associations of anesthesiologists. It was shown that monitoring of brain functions decreases the possibility of both intraoperative awareness and too deep a level of anesthesia. The costs of hospitalization and the incidence of postoperative nausea and vomiting were also decreased. Moreover, the patients’ postoperative level of consciousness was better.

The objective of the study was (1) to compare the value of basic clinical parameters and simultaneously recorded AEP for analysis of the depth of both total intravenous and volatile anesthesia, and (2) incidence of intraoperative awareness.
METHODS

The Ethics Committee of the Military Institute of Medicine (Warsaw, Poland) reviewed and approved this clinical investigation, which was registered at clinicaltrials.gov (NCT0333169).

A written, informed consent was obtained from all the subjects.

This project was planned as a prospective study. After commencement of the study its design was not modified.

The participants were hospitalized at the Department of Otolaryngology and at the Department of Neurosurgery of the Military Institute of Medicine, Warsaw, Poland. The inclusive criteria were (1) patients between 18 and 61 years old, (2) with preoperative health status I or II grade according to the American Society of Anesthesiologists (ASA) score, (3) scheduled for otorhinolaryngological (ear, nose, throat; ENT) procedures or discectomy.

The patients suffering from (1) hearing problems or tinnitus, (2) chronic inflammatory process of the ear, (3) epilepsy, (4) mental disorders, and (5) pregnancy were excluded from the study.

Two hundred and eight patients were assessed for eligibility. The participants were randomly (by flipping a coin) divided into one of the two groups, depending on the planned type of anesthesia:

1. Total intravenous anesthesia (TIVA),
2. Volatile anesthesia (VOL).

Benzodiazepines were not administered as premedication drugs.

In all the participants, continuous electrocardiogram, non-invasive blood pressure, pulse oximetry and end-tidal concentration of carbon dioxide were monitored.

Propofol as an induction agent of general anesthesia, fentanyl or remifentanil as an analgesic, and cisatracurium or vecuronium bromide as myorelaxant were administered. Anesthesia was conducted with continuous infusion of propofol according to the De Grood scheme28 (TIVA group) or sevoflurane (VOL group) with end-tidal concentration of volatile anesthetic below 0.8 and 1.2 minimum alveolar concentration (MAC). The patients were ventilated with a mixture of air and oxygen, with FiO₂ 0.5, and etCO₂ between 30 and 40 mmHg. The intraoperative administration of anesthetics was modified according to patients’ demands. The hemodynamic stability was maintained by optimization of the level of anesthesia. When the systemic blood pressure decreased below 30% in comparison to preoperative values, ephedrine hydrochloride was administered intravenously. Episodes of bradycardia (45/min and lower) were treated with intravenous administration of atropine sulphate. After the surgery and reversal of neuromuscular blockade the patients were extubated.

In all the participants an A-line ARX index (AAI) was continuously monitored with AEP Monitor/2 version 1.6 Danneter. The AAI is calculated from the middle-latency auditory evoked potentials waves, extracted from electroencephalographic signal using an autoregressive model with an exogenous input (ARX). The electrodes were placed on the forehead and in the region mastoid bone, and then the impedance of the electrodes was checked, the impedance of the electrodes was not greater than 5 kΩ.

Intraoperatively, auditory evoked potentials (AEP) with AAI were recorded every 1.1 s. Electroencephalogram with burst suppression (BS) analysis was recorded and updated every 0.5 s. Recorded data were blinded for anesthesiologists, so were not used for analysis of level of anesthesia during surgery. The alarm limits of recorded parameters were adjusted to correct the technical interferences.

Analyzed data were recorded in the following time points:

- T1 – after premedication, before the onset of anesthesia,
- T2 – during the induction of anesthesia (30 s after intravenous administration of hypnotic dose of propofol),
- T3 – just before the endotracheal intubation,
- T4 – 60 seconds after the endotracheal intubation,
- T5 – 5 minutes after the endotracheal intubation,
- T6 – at the beginning of surgery – just after skin incision,
- T7–T12 – every 5 min during the surgery and anesthesia,
- T13 – at the end of the surgery (after skin closure),
- T14 – before the extubation,
- T15 – just after the extubation,
- T16 – just after the return of consciousness of the patient.

After the surgery the participants were asked to answer the questions about the possibility of intraoperative awareness. This questionnaire was based on work of Brice29. The answers of the patients were classified according to Michigan Awareness Classification score30. Such score was shown in Table 1. This visit took place not earlier than 24 h after the anesthesia.

Statistical analysis

Collected data were archived with Microsoft Excel 2013 software. The data were analyzed using R statistical software (R Core Team R: A language and environment for statistical computing. Vienna, Austria 2014. http://www.R-project.org/).

The analysis of the data was begun by using the Shapiro–Wilk test to determine whether they were normally distributed. Demographic data were analyzed with descriptive statistics.

| Table 1. Michigan Awareness Classification Score. |
|---|---|---|---|---|
| Class 0 | No awareness |
| Class 1 | Isolated auditory perceptions |
| Class 2 | Tactile perceptions (e.g. surgical manipulation or endotracheal tube |
| Class 3 | Pain |
| Class 4 | Paralysis (e.g. feeling one cannot move, speak, or breathe) |
| Class 5 | Paralysis and pain |

An additional designator of “D” for distress is included for patient reports of fear, anxiety, suffocation, sense of doom, sense of impending death, etc.
The differences between the two groups were analyzed with a chi square test, Student’s t test and Mann–Whitney U test. Mean values of data in respective time points between two groups were analyzed with the Mann-Whitney U test, and inside each group with Wilcoxon signed rank test. 

\( P<0.05 \) was considered statistically significant.

RESULTS

Finally, data from 208 patients were analyzed. The characteristics of the participants are shown in Table 2. There were 25 ENT procedures, 27 discectomies in sacral-lumbar, and 35 discectomies in the cervical region of the vertebral column in the TIVA group. In the VOL group it was 24, 52, and 45 procedures, respectively.

There were no differences between groups in duration of anesthesia; mean time was 124±40 min in TIVA, and 113±30 min in VOL group. The time between the end of surgery and patient’s extubation was also similar in both groups, it was 9.6±3.1 min in TIVA and 9.4±2.9 min. The details of analyzed data (heart rate /HR/, systolic arterial pressure /SAP/, mean arterial pressure /MAP/, diastolic arterial pressure /DAP/, AAI, BS) in consecutive time points are presented in Table 3.

AAI readings above 25 (max. 51) in TIVA group were 46/608 (8%) of recorded values during conduction of anesthesia, in comparison to 15/847 (2%) in VOL group (\( P<0.0000 \)). In TIVA group we noted higher incidence of burst suppression episodes (29/608, 5%), in comparison to VOL group (49/847, 6%), but such difference was not statistically significant (\( P=0.3963 \)). The changes in AAI during anesthesia were shown in Fig. 1.

We found one case of intraoperative awareness. This case was 0.48% of the sample and 1.15% of patients in the TIVA group. Amongst the patients under volatile anesthesia no cases of intraoperative awareness were noted.

The incidence of dreaming during general anesthesia was also analyzed. Mean time between the end of anesthesia and collecting the questionnaire was 30 h.

In both groups, the percent of patients reported dreaming during anesthesia was similar (Table 4).

DISCUSSION

This is the first paper where in 208 patients the whole course of general anesthesia at 16 time points was analyzed and intravenous and volatile anesthesia were compared. We found, that clinical monitoring alone does not protect from both too shallow and too deep episodes of general anesthesia.

Our results and data from other authors are similar. The mean values of AAI before the surgery were comparable in both groups. It indicates, that the level of preoperative sedation in TIVA and VOL groups was comparable.

During induction of anesthesia rapid decrease of AAI was observed. The data of other authors also indicated

![Fig. 1. Changes of AAI values in study population.](image-url)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>TIVA</th>
<th>VOL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td>0.5192</td>
</tr>
<tr>
<td>(**)</td>
<td>(72.88-87)</td>
<td>(68-81)</td>
<td>0.4474</td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td>0.4703</td>
</tr>
<tr>
<td>(*)</td>
<td>(14)</td>
<td>(12)</td>
<td>0.0323</td>
</tr>
<tr>
<td>SAP</td>
<td></td>
<td></td>
<td>0.1447</td>
</tr>
<tr>
<td>(**)</td>
<td>(127-152)</td>
<td>(118-138)</td>
<td>0.4589</td>
</tr>
<tr>
<td>VOL</td>
<td></td>
<td></td>
<td>0.9022</td>
</tr>
<tr>
<td>(**)</td>
<td>(128-147)</td>
<td>(118-138)</td>
<td>0.9389</td>
</tr>
<tr>
<td>DAP</td>
<td></td>
<td></td>
<td>0.2482</td>
</tr>
<tr>
<td>(**)</td>
<td>(156-160)</td>
<td>(156-160)</td>
<td>0.5583</td>
</tr>
<tr>
<td>AAI</td>
<td></td>
<td></td>
<td>0.2482</td>
</tr>
<tr>
<td>(**)</td>
<td>(53-60)</td>
<td>(53-60)</td>
<td>0.5583</td>
</tr>
<tr>
<td>BS</td>
<td></td>
<td></td>
<td>0.0248</td>
</tr>
<tr>
<td>(*)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>0.0248</td>
</tr>
<tr>
<td>(**)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>0.0248</td>
</tr>
</tbody>
</table>

T1–T16 – analyzed time points; explanation in the text.

Data are presented as mean (SD) and median (Q1–Q3), for parametric (*) and nonparametric (**) data, respectively.

TIVA group – totally intravenous anesthesia group, VOL – volatile anesthesia group. SD – standard deviation; HR – heart rate (1/min); MAP – mean arterial pressure (mmHg); SAP – systolic arterial pressure (mmHg); DAP – diastolic arterial pressure (mmHg); AAI – autoregressive AEP index; BS – burst suppression.

*P* values refers to the comparison between TIVA and VOL group in every analyzed time points.

NA – not applicable.
Table 4. Intraoperative dreaming (based on the post anesthesia questionnaire survey).

<table>
<thead>
<tr>
<th>&quot;Dream&quot;</th>
<th>TIVA group</th>
<th>VOL group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>12/87 (13.8%)</td>
<td>16/121 (13.22%)</td>
</tr>
<tr>
<td>Positive / nice</td>
<td>9/87 (10.34%)</td>
<td>15/121 (12.4%)</td>
</tr>
<tr>
<td>Negative / unpleasant / bad</td>
<td>9/87 (10.34%)</td>
<td>15/121 (12.4%)</td>
</tr>
</tbody>
</table>

TIVA group – totally intravenous anesthesia group, VOL – volatile anesthesia group.

that AAI was one of the most sensitive variables of level of consciousness \(22,30-36\). The observations of others \(22,30-36\) showed the higher sensitivity of auditory evoked potentials in comparison to spontaneous electroencephalogram in evaluating the changes of consciousness. During induction of anesthesia, together with decrease in AAI, in both groups also heart rate and systemic blood pressure decreased. The observations of Freo et al. were similar \(32\). During induction of anesthesia, the AAI was always decreased; however other clinical parameters varied. Nishiyama et al. observed decrease in systolic blood pressure and AAI only; the frequency of heart rate was increased \(39\). In contrast, Milne et al. noted decrease of mean blood pressure and AAI, without changes in heart rhythm \(38\). Weber et al., in their study on the utility of AAI in analysis of the level of anesthesia found significantly decreased values of mean blood pressure, increased heart rate and decreased AAI (ref. \(40\)).

Before the endotracheal intubation, mean values of AAI in both groups were 16, which is characteristic for a deep level of anesthesia. This observation was confirmed by EEG analysis, and the highest observed number of burst suppression. It should ensure the adequate protection during endotracheal intubation. However, during intubation, both systemic blood pressure as well as AAI quickly increased in both groups. Only heart rate in the TIVA group did not change. The increase of AAI was significant in both groups, but mean index values did not exceed the limits of proper surgical anesthesia. It confirms the observations of Ekman et al. \(35\) that low records of neuromonitoring did not guarantee the absence of patient’s response to endotracheal intubation. Probably this was the result of reflex reaction at the level of the brainstem and hypothalamus. In the study of Allahyary et al. \(41\) the increased values of hemodynamic parameters during intubation were correlated with decreased AAI, probably as a result of increased concentration of volatile anesthetic. Chen et al. \(42\) found that the number of unwanted patients’ reactions to intubation was reduced when the neuromonitoring with AAI was used during anesthesia.

During the conduction of anesthesia the changes of AAI were similar in both groups. After the intubation, the values of AAI progressively decreased, until its final stabilization within the limits of surgical anesthesia was observed. However, there were more AAI readings above 25 in the TIVA group, in comparison to VOL group. The increase of AAI value above 25–30 may indicate the possibility of intraoperative awareness. AAI was more stable in VOL group. However, lower values of AAI during volatile anesthesia may indicate that volatile anesthetics were overdosed \(27\). Intraoperative monitoring of level of anesthesia can reduce the consequences of neurotoxicity of anesthetics \(14,15,43,44\).

Clinical parameters during conduction of anesthesia varied, probably as a result of administered doses of anesthetics. General anesthesia in the TIVA group was less stable; its level varied from very deep to much shallower. Although during intravenous anesthesia all drugs are administered continuously, the speed of infusion depended on the clinical status of the patients. The higher stability of volatile anesthesia probably arises from the monitoring of end-tidal concentration of volatile anesthetic. Good correlation between AAI and concentration of both volatile \(12,39,41,45,46\) and intravenous anesthetics \(21,37,38,47\) during anesthesia was observed. At the end of surgery, together with decreasing concentration of volatile anesthetics, both AAI values and clinical parameters increased till the reversal of anesthesia. The dynamics of these changes were similar in both groups. There were no differences in mean values of SAP, DAP and MAP between TIVA and VOL groups; the heart rate was higher in VOL, in comparison to TIVA group. Mean values of AAI after reversal of anesthesia was 60 in both groups, similarly to values observed before the induction of anesthesia. Because there was a good correlation between the level of conscience and AAI, use of neuromonitoring during anesthesia makes the prediction of the time of recovery over anesthesia more simple \(39,41,46,47\) and can reduce period between end of anesthesia and extubation \(22,27,31,46,49\).

The episodes of intraoperative awareness were surveyed using a questionnaire based on the work of Brice \(29\), because of its efficacy and large number of studies \(50\).

The highest detection of intraoperative awareness was noted when the questionnaire survey was carried out between 14 and 30 days after surgery \(50,51\). Sebel et al. \(7\) and Mashour et al. \(30\) found a higher detection of intraoperative awareness, when the survey took place between 7 and 14 days after the anesthesia, than immediately after the procedure (within 1 day). In our study the questionnaire survey was carried out usually 30 h after the anesthesia, because of logistic reasons in the hospital.

We found one case of intraoperative awareness, a woman who underwent intravenous anesthesia. This was a 57-year-old woman, in her case an ENT surgery was performed under total intravenous anesthesia. She did not remember any unpleasant feelings, such as fright or pain. The case was qualified as class 2 according to the Michigan Awareness Classification. The patient was informed about the possible consequences of this event and received some advice about the possible psychological support.

The anesthesia protocol of this woman was analyzed. After the induction of anesthesia (T4–T7), because of cardiovascular depression (SAP 90–80 mmHg, HR 40–50/minute) the level of anesthesia was made shallow; the doses of both remifentanil and propofol were reduced. After a few minutes (T10) the values of recorded clinical parameters quickly increased. The level of anesthesia was deepened, and the rest of the procedure was stable.
Probably, the patient’s memories were derived from this period of anesthesia (T8–T12). In this case the increase of AAI values to 41 (T9) was observed 5 to 7 min before the reaction of systemic blood pressure and changes in heart rate.

Many authors confirmed, that the higher incidence of such events was noted amongst patients during intravenous anesthesia without intraoperative neuromonitoring.\textsuperscript{52} The analysis of the records revealed that during anesthesia an AAI increased to 41; it was an effect of reduced doses of anesthetics in order to decrease the cardiodepression caused by too deep level of anesthesia. During general anesthesia, when the recorded values of AAI are between 30 and 50, there is an increased chance for intraoperative awareness. Intraoperative neuromonitoring for optimization of the level of intravenous anesthesia, together with clinical parameters, is often insufficient for protection of both systemic blood pressure and heart rate was noted.

An analysis of the level of anesthesia, based on clinical parameters, is often insufficient for protection of anesthetized patients from intraoperative awareness.\textsuperscript{5,7,20,51} especially during intravenous anesthesia. Hence, recommendations of intraoperative neuromonitoring for optimization of the level of intravenous anesthesia, together with continuous, concurrent clinical observation\textsuperscript{5,34,57}. Avidan et al.\textsuperscript{57,58} did not found differences in the number of intraoperative awareness between patients who underwent intraoperative neuromonitoring and those under volatile anesthesia, when the level of anesthesia was assessed by the end-tidal concentration of halogenated anesthetics.

Our results suggest that the anesthesia in VOL group was more stable, with AAI values at the lower limits of surgical anesthesia.

Thirteen per cent of participants had dreams under anesthesia, similar in both groups. This corresponds with the literature, where the incidence of dreaming during general anesthesia varies between 1% and 22% (ref.\textsuperscript{5,79,60}). The described patient who had an episode of intraoperative awareness reported no dreams under general anesthesia. In our study, intraoperative dreaming was included in a separate category, not related to intraoperative awareness.\textsuperscript{740,41}; however, some authors believe that their occurrence may result from inadequate level of anesthesia.\textsuperscript{59}

Our results are both interesting and clinically useful. However, this study has some limitations. The use of coagulation in the head region may interfere with monitoring of electroencephalography (EEG) and AEP. Moreover, one should realize that in two patients who were monitored in the same way, two distinct readings of AAI values may be received. It can result from complex mechanisms of consciousness, different mode of action of anesthetic drugs, as well as from the genetic diversity of the population. Intraoperative awareness is a devastating, but rare complication.

CONCLUSION

Clinical monitoring during volatile anesthesia provides adequate protection during surgery. During intravenous anesthesia, the observation of clinical parameters is insufficient for stable maintenance of anesthesia and does not prevent intraoperative awareness. Clinical monitoring itself does not exclude periods of too deep anesthesia. The AAI index is useful tool in monitoring patients’ level of consciousness during anesthesia.

ABBREVIATIONS

AAI, Autoregressive AEP index; AEP, Auditory evoked potentials; ASA, American Society of Anesthesiologists; AWR, Intraoperative awareness; BS, Burst suppression; DAP, Diastolic blood pressure; EEG, Electroencephalography; ENT, Ear, nose and throat; etCO\textsubscript{2}, End-tidal concentration of carbon dioxide; FiO\textsubscript{2}, Fraction of inspired oxygen; MAC, Minimum alveolar concentration; MAP, Mean arterial pressure; PTSD, Posttraumatic stress disorder; SAP, Systolic blood pressure; TIVA, Totally intravenous anesthesia; VOL, Volatile anesthesia.

Author contributions: KS: study design; acquisition and interpretation of data, drafting the work, and its critical revision; final approval; ZR: study design; interpretation of data; drafting the work, and its critical revision; final approval; DT: analysis and interpretation of data; drafting the work, and its critical revision; final approval.

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