

Can changes in skin impedance be used to monitor sedation after midazolam and during recovery from anaesthesia?

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Skin impedance during anaesthesia

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Summary

It has been suggested that sympathetic activity, measured as changes in electrical skin impedance (SI), can be used to assess the adequacy of general anaesthesia. Our prospective study investigated if measurements of skin impedance can determine levels of sedation induced by midazolam. Twenty-seven patients scheduled for arthroscopy requiring general anaesthesia were served as their own control. These were blinded to the order of injections by telling them that they will be randomly administered a placebo (saline) or sedative agent. A DM 3900 multimeter was used for SI measurements. The degree of sedation was measured using the modified Observer's Assessment of Alertness and Sedation (mOAAS) scale. Resting SI values were noted, and all participants were then administered the placebo followed 5 minutes later by midazolam 2 mg i.v. Five minutes after that, patients were administered standard general anaesthesia with propofol, oxygen, nitrous oxide 60%, and isoflurane 1 MAC via a laryngeal mask, and sufentanil 5 – 10 µg. SI significantly increased after administration of midazolam an induction of anaesthesia. There were no significant differences between pre-administration (baseline) and placebo and end of surgery and end of anaesthesia with closed eyes. There were highly significant differences ($p < 0.001$) between pre-administration vs. midazolam, placebo vs. midazolam, pre-administration vs. induction of anaesthesia. We found no correlation between mOAAS and SI. There were no significant changes between the end of surgery and the end of anaesthesia with closed eyes, but SI significantly decreased ($p < 0.01$) after eyes opened.

Key words

Anaesthesia – midazolam – skin impedance – sedation

Introduction

Sedation is frequently used for a variety of procedures performed outside the operating rooms by non-anaesthetists. Usually, anxiolysis is preferable to sedation since sedation may interfere with recovery after short procedures and may bring the risk of inadvertent deep sedation with loss of airway patency. Unfortunately, although anxiolytic sedatives are widely used in clinical practice, the methodology for assessing the treatment effect of these compounds has not been well developed. Psychological tests like the Hamilton Anxiety Rating Scale (HARS), the Wang Anxiety Rating Scale (WARS), or the Zung Self-Rating Anxiety Scale (SAS) have been used to assess changes in anxiety, but they were developed to measure the effect of long-term therapy and are rather cumbersome and difficult to use in routine clinical practice.

Tests such as the Ramsay sedation scale (RSS), the Richmond Agitation–Sedation Scale (RASS), and the Observer’s Assessment of Alertness and Sedation (OAAS) scale are commonly used in perioperative clinical settings, but they focus mainly on the level of sedation and not the level of anxiolysis. There are few methods available for assessing the onset and intensity of sedation. A bispectral index (BIS) monitor is commonly used as an objective measure of the “alert” state, although mainly during general anaesthesia. A large meta-analysis concluded that its use for sedation was largely unreliable (Shetty *et al.* 2018, Zhang *et al.* 2019).

There have been several studies demonstrating a correlation between the level of anxiety and changes in skin impedance. Changes of skin impedance were first used in criminology in 1897. In 1921 August Larson combined changes in SI with changes in heart rate, respiratory rate, and blood pressure to create a device for use by law enforcement (Marsh 2019, Widacki 2015). This method has been validated many times, and these devices, polygraphs, are still used as “lie detectors.” More recently, several studies have demonstrated a correlation between changes in skin impedance and the degree of sedation, the bispectral index, reaction to stimulation, pain, and motor activity (Cowen *et al.* 2015, Gjerstad *et al.* 2007, Winterhalter *et al.* 2008, Winterhalter *et al.* 2009, Winterhalter *et al.* 2010). A change in skin impedance is a complex response to sympathetic nervous system (SNS) activity and depends on emotional states like fear, anxiety, and pain. SNS activity can be measured using secretions from eccrine sweat glands. Various drugs like sedatives, opioids, and anaesthetics act through central

mechanisms that depress SNS activity, which is then followed by changes in skin impedance (Gjerstad *et al.* 2007, Winterhalter *et al.* 2010).

The present double-blind study was designed to refine the methodology for evaluating the effect of sedative and anxiolytic agents by assessing drug-related SNS-mediated changes in SI.

The primary aim of our study was to determine if skin impedance can be used as an objective measurement of the level of sedation compared to the, more or less, subjective OAAS. The OAAS was chosen because the scoring system was initially introduced to assess sedation with benzodiazepines, which were used (midazolam) in our study. The OAAS categories were responsiveness, speech, facial expression and eye appearance, and each of the categories was scored on 5 dimensions. The OAAS scale was found to have high discriminatory power for the different levels of sedation (Chernik *et al.* 1990), but may vary between assessors. Modified OAAS (mOAAS) (Nonaka *et al.* 2018) was used in our study because of better reflection of changes during deep level of sedation and anaesthesia (Appendix 1). Midazolam was used in our trial because it is the most commonly used drug to reduce anxiety before anaesthesia and surgery.

A secondary study goal was to investigate if skin impedance can help to determine the level of onset and recovery from general anaesthesia.

Methods

The study was approved by the Ethics Committee of the University Hospital Kralovske Vinohrady and is registered at ClinicalTrials.gov as NCT03791424.

Subjects

The study was performed on adult patients scheduled for knee arthroscopy under general anaesthesia. Consent was obtained the day before surgery during the pre-anaesthetic visit. Exclusion criteria were a previous history of taking drugs affecting mental functions, history of mental illness, an implanted electrical device, allergy to benzodiazepines, myasthenia

gravis, an American Society of Anesthesiologists (ASA) classification of ASA 3 or higher. All patients consented to not use any medication for sedation or anxiety, opioid analgesics, ethanol, and/or illicit drugs within 24 hours before surgery. Patients were instructed that they would be administered, in random order, a sedative agent or placebo, and would be observed for their level of sedation.

Measurements

After arrival at the operating theater and venipuncture, two standard AgCl ECG electrodes (Medico Electrodes International Ltd.) size 27 mm x 35 mm were attached to the palm side of the second and third finger of the non-dominant hand. A DM 3900 Multimeter (Mastech) was used to measure SI. The device was controlled and approved for use on humans by the Department of Medical Biophysics and Informatics of the Third Faculty of Medicine of Charles University.

As described above, the modified OAAS (mOAAS) scale was used as a standard tool to measure sedation levels. It was administered at the same times as the SI measurements were taken. The person providing the mOAAS assessment was also blinded to the order of midazolam and placebo injection, and only the anaesthesiologist administering the injections knew the order of drugs.

Data recording: Participants were given 10 minutes to acclimate to the test situation. The resting SI value for each patient was noted. Despite the instructions to the contrary, all patients were administered the placebo first, followed 5 minutes later by midazolam 2 mg i.v., so they could serve as their own controls. After another 5 minutes, patients were administered standard general anesthesia with propofol, oxygen, nitrous oxide 60%, and isoflurane 1 MAC (adjusted to the age and BMI of the patient) via a laryngeal mask, and sufentanil 5 – 10 µg as needed. Monitoring was routine for this type of surgery (i.e., ECG, non-invasive blood pressure, capnography, and pulse oximetry). SI and OAAS were recorded at the end of the surgery (i.e., after stopping the volatile anaesthetic agent), then with zero exhaled isoflurane (i.e., the end of anaesthesia with eyes closed) and the end of anaesthesia with the patient's eyes open and verbally engaged.

Statistical analysis

SI values before placebo administration (baseline), 5 minutes after placebo, 5 minutes after midazolam, 5 min. after induction, at the end of the surgery, zero exhaled isoflurane after anaesthesia with closed eyes, and after eyes opened were recorded. Changes in SI values compared to baseline data were used for analyses using a one-way ANOVA with the post-hoc Tukey's test. These relative changes allowed us to compare the course of changes independently of the absolute values. Pearson's correlation coefficients were used to analyze the relationship between mOAAS and SI values. P-values < 0.05 were considered statistically significant.

Results

All 30 patients eligible for the study consented, but because of two postponed surgeries, only 28 patients were analyzed. There were 14 men and 14 women. The mean age was 39.8 years (standard deviation (SD) was 9.3 y), the mean BMI was 26.2 kg/m² (SD = 4.4 kg/m²), and the mean duration of surgery was 25.5 min. (SD = 16.5 min).

Primary Outcome Measures

SI significantly increased after administration of midazolam and induction of anaesthesia, although the inter-individual baseline skin impedance values differed greatly from patient to patient. For this reason, percent changes from baseline were used instead of absolute values. There were no significant differences between pre-administration vs. placebo and end of surgery vs. end of anaesthesia with closed eyes. Highly significant differences were seen between the first two and the last measured points (i.e., 5 minutes after placebo and 5 minutes after midazolam, and end after anaesthesia with eyes open) and the fourth and fifth measured points (i.e., at the end of surgery vs. zero exhaled isoflurane, end of anaesthesia with closed eyes) – $p < 0.001$ for all comparisons. Additional significant differences involved comparison between measurements at 5 minutes after induction and 5 minutes after placebo ($p = 0.02$), and at the end of surgery ($p = 0.003$) and at zero exhaled isoflurane, end of anaesthesia with eyes closed ($p = 0.01$) (Fig. 1). There was a slight correlation between the mOAAS and SI. The mOAAS decreased from approximately 5.0 before the administration of midazolam to 4.2 after midazolam administration. Correlations between relative skin impedance and

mOAAS are shown in Fig. 2. There was some gender difference in the relative changes in skin impedance. Except of CE ($p < 0.05$), all of them were statistically non-significant (Fig. 3).

Secondary outcome measures

There were no significant changes between the end of surgery and the end of anaesthesia with eyes closed, but SI significantly decreased ($p < 0.01$) after eyes opened.

Discussion

Assessments of the depth of sedation are usually dependent on verbal or motor responses to various stimulations and are dependent on the subjective skills of the assessor. The use of stimuli can potentially result in patient responses that disrupt the procedure for which the patient is sedated. Various objective methods have been tried to assess the level of anxiolysis and light sedation. The goal is to find an objective measure of the level of consciousness, which, if valid, would improve the quality of conscious sedation (Chisholm *et al.* 2006). Ideal monitoring of sedation levels would have several potential advantages over observational clinical sedation scoring systems: it would be objective, quantitative, easy to use, free of observer bias, economical, and non-invasive. Objective monitoring usually uses EEG-based measurements, which were developed mainly to avoid alertness during general anaesthesia. There are some works comparing subjective and objective methods like the bispectral index (BIS) monitor or the Patient State Analyzer; however, for the area of clinical interest, i.e., mild sedation, they are not sufficiently sensitive (Chisholm *et al.* 2006). Very similar results were obtained by Haberland *et al.* (2011), who used BIS to assess levels of sedation in children (Haberland *et al.* 2011). Correlations between BIS and clinical observations were statistically significant, but only moderately so. There were several children observed to be in deep sedation while the BIS monitor showed alertness. Results of the Cochrane review (Shetty *et al.* 2018) also found that BIS measurements had little value relative to ICU sedated patients. Recently, two monitors for measurement pain, depth of analgesia and anaesthesia using relative changes of SI as a part of global calculated scale e.g. NOL index (PMD-200TM, Medasense, Ramat Gan, Israel) and NFSC index (Skin Conductance Algesimeter,

MedStorm innovations, Oslo, Norway) has introduced to clinical practice, but they are intended for monitoring of reaction to pain stimulation during surgery (Rogoyov and Vanek 2020).

Our results showed that skin impedance could be used to measure levels of anxiety and sedation. Changes in skin impedance can provide complex information regarding anxiety or fear and depressed levels of consciousness.

Sympathetic activation by cortical and subcortical areas in the brain produce changes in sweat gland activity, which are exclusively innervated by the SNS (Gjerstad 2012). There is a direct correlation between eccrine sweat gland activity and skin impedance (Winterhalter *et al.* 2008). There is also a direct correlation between the discharge rate during sympathetic nerve stimulation and the amplitude of simultaneously measured skin impedance changes (Bach 2014). There have been several attempts to use skin impedance to assess specific parts of this complex state, but the results were inconsistent. Measurements of skin impedance or conductance have also been used to assess pain intensity or the quality of analgesia. Storm *et al.* recommended using skin conductance, instead of heart rate, blood pressure, and electroencephalographs (EEG), as a more sensitive tool for measuring pain perception since it is independent of anaesthesia level and muscle relaxation (Storm 2008). Czaplik *et al.* tried using changes in skin conductance as a way to target acute pain therapy in the post-anesthesia care unit; however, they failed to find any long-term correlation between the numeric pain rating scale and the number of fluctuation in skin conductance (NFSC) (Czaplik *et al.* 2012). They concluded that there are many other factors affecting SI results, e.g., anxiety, level of sedation, disorientation, shivering, etc., and that this method works best for sedated patients. Similar results were seen in other studies. Ledowski *et al.* demonstrated a high correlation between NFSC and pain ratings, although with several limitations, mainly the fact that many drugs used for sedation and anaesthesia may influence the result (Ledowski *et al.* 2007). In a later study from 2010, Ledowski *et al.* failed to find any correlation between stress hormones levels and skin conductance (Ledowski *et al.* 2010). More recently, Valkenburg *et al.* (Valkenburg *et al.* 2012) drew similar conclusions with infants, and Günther *et al.* found the same with ICU adult patients (Gunther *et al.* 2013). The latter concluded that NFSC might be more influenced by anxiety and stress than by pain intensity. These findings support our opinion that factors responsible for skin impedance changes are complex, and SI is probably best suited for objective assessment of anxiety and sedation level. The interpretation of the

differences between men and women (Fig. 3) is difficult. We can only speculate that it is a result of different sympathetic nerve regulation (Hinojosa-Laborde *et al.* 1999, Kittnar 2020, Ueno *et al.* 2003). Gender differences were described also in pain perception and the reasons are probably multifactorial (Rokyta and Yamamotova 2013).

Several studies measured skin impedance during anaesthesia and compared it to ECG methods. Winterhalter *et al.* demonstrated that skin impedance correlated to the depth of sedation during targeted-controlled infusion of propofol and was correlated with both BIS and mOAAS values in 22 patients and 8 healthy volunteers. In a second study, Winterhalter *et al.* measured skin impedance changes during anaesthesia induction with fentanyl and etomidate and compared the results with BIS values. In spite of using different drugs and a slightly different protocol (i.e., concentrating mainly on the induction of anaesthesia), their results correspond with our findings (Winterhalter *et al.* 2009, Winterhalter *et al.* 2010).

We did not confirm the usefulness of skin impedance measurements for assessing depth and emergence from anaesthesia; however, Gjerstad *et al.* (Gjerstad *et al.* 2007) found a correlation between NFSC and Response Entropy (RE), which measures electromyographic and electroencephalographic activity from electrodes placed on the forehead. However, in this study, changes in skin impedance during emergence from anaesthesia were slower than RE changes. In one of their 20 patients, the NFSC was unchanged 1 min after extubation.

Limitations

Our study has several limitations. The first is a study design in which the same patients were used for both placebo and active treatment. However, the variability in absolute values of skin impedance made it the only method suitable for testing the difference between the placebo and active treatment. The second limitation involved the interpretation of values. A high level of inter-individual variability prevents the use of absolute values, and the percentage change over time had to be used. In the context of the comparability of skin impedance measurements, relative changes from an individual patient's baseline value had to be used. Another issue, which was mentioned by several other authors, involved minor differences linked to the electrodes, e.g., changes in hydration under electrodes, an absence of sweat gland activity, and sweat accumulation under electrodes during heavy perspiration. For the

purpose of our study, the administration of atropine and other drugs used during the maintenance of anaesthesia and emergence from anaesthesia with theoretical exception of small dose of sufentanil in all patients were not relevant to the outcomes, as they were not used.

Conclusions

Changes of skin impedance can be used as a simple and economical method to measure the onset of anxiolysis and sedation induced by midazolam; additionally, SI correlated with mOAAS scores. However, until this use of SI will be more and deeply studied, we cannot recommend it for the assessment of the depth of anaesthesia and for predicting emergence from anaesthesia.

Conflict of Interest

There is no conflict of interest.

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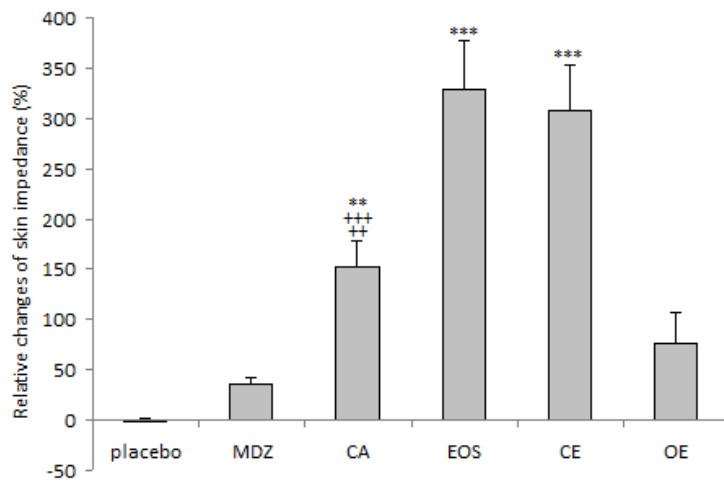


Fig. 1. Relative changes in skin impedance from base line (i.e., prior to placebo administration)

Legend: placebo - 5 minutes after placebo, MDZ - 5 min after midazolam, CA - 5 min after induction, EOS - at the end of surgery, CE - zero exhaled isoflurane, end of anesthesia with eyes closed, OE - end of anesthesia, eyes open. Bars represent means with whiskers showing \pm standard errors of means (**... $p < 0.001$ vs. placebo, MDZ, and OE; **... $p = 0.003$ vs. EOS; +++... $p = 0.01$ vs. CE; ++... $p = 0.02$ vs. placebo)

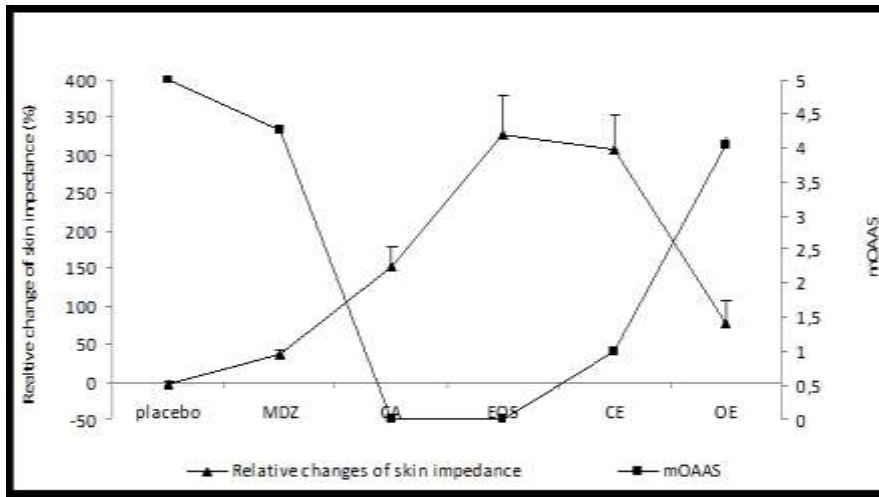


Fig. 2. Correlations between relative skin impedance and mOAAS. Bars represent means with whiskers showing \pm standard errors of means

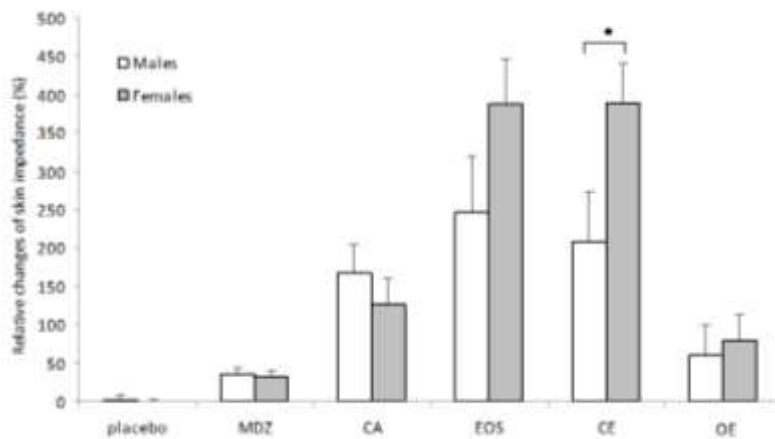


Fig. 3. Gender differences relative to changes in skin impedance. Bars represent means with whiskers showing \pm standard errors of means (*... $p = 0.05$)

Appendix 1

Modified Observer's Assessment of Alertness/Sedation Scale (mOAAS). Available via license: [CC BY-NC-ND](#)

Scores	Description
5	Fully awake. Responds readily to name spoken in normal tone
4	Drowsy. Lethargic responds to name spoken in normal tone
3	Eyes closed. Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to deep stimulus