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STUDY PROTOCOL

Monitoring the responses to nociceptive stimuli during general anesthesia based on electroencephalographic signals, an observational study.

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HYPOTHESIS

The Electroencephalogram (EEG), a direct measurement of brain activity, could contain information related to the probability of response of the patient to a noxious stimulation as well as being sensitive to changes in opioid concentrations. For this reason, the hypothesis is that there is a statistically measurable correlation between qNOX and rough clinical signs of insufficient anti-nociception such as movements during Laryngeal Mask Airway (LMA) insertion, skin Incision, LMA removal. It will reduce the problem of anticipating the nociception in patients undergoing general anesthesia.

STUDY OBJECTIVES

1) to compare two indexes of hypnosis, the qCON (Quantium Medical, Spain) with the Bispectral index (BIS™) (Covidien, Boulder CO. USA), in patients undergoing surgery under sedation and general anesthesia.
2) to assess the qNOX index of pain/nociception (Quantium Medical, Barcelona, Spain) and the qCON index of hypnosis.
3) to assess qNOX reliability as a specific indicator of response to nociceptive stimulation.

BACKGROUND AND SIGNIFICANCE

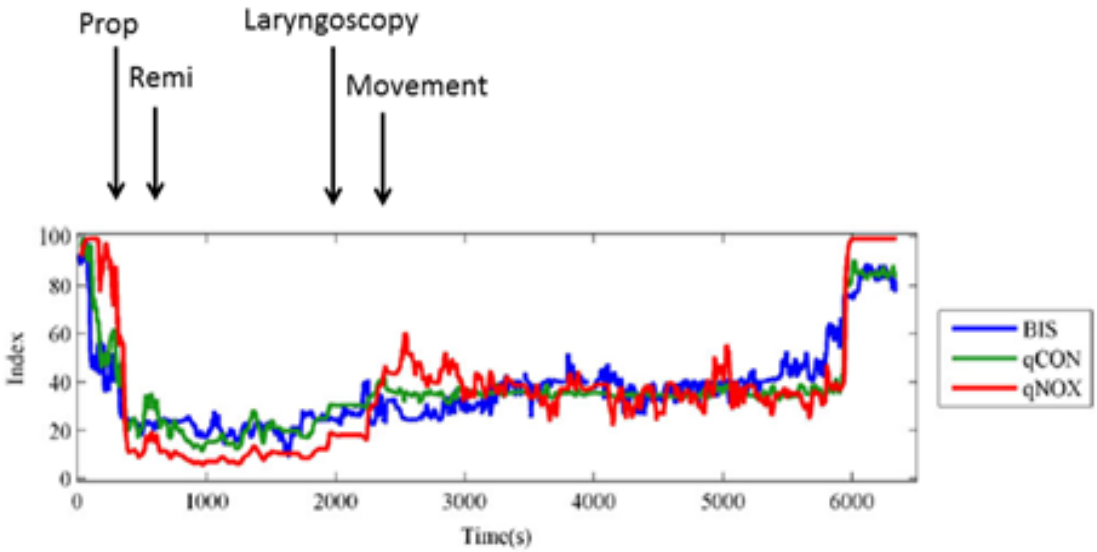
Monitoring the anti-nociceptive drug effect is useful because a sudden and strong nociceptive stimulus may result in untoward autonomic responses and muscular reflex movements [(1)]. Unopposed stimulation may also 'overrule' a state of stable unconsciousness, with resultant awakening and awareness. The traditional clinical use of systolic or mean blood pressure is actually still one of the methods in everyday use for this monitoring purpose [(2)]. Another cornerstone is the experience of which drugs and doses are effective in attenuating nociception. Alpiger and colleagues found that simple end-tidal monitoring of sevoflurane was a better predictor of nociceptive response than Auditory Evoked Potential [(3)].

Thus, monitoring the state of anti-nociception with objective, non-clinical methods is still in a state of testing and development, without well-documented and proven methods for consistent 'no-fuss' clinical daily use. Some methods, like those using systolic blood pressure, are based on the reduced sympathetic response from the Central Nervous System (CNS) when in a state of drug-induced anti-nociception during concomitant surgical stress. These include the pulse plethysmogram amplitude,[(4)] heart rate variability and/or amplitude,[(5-7)] pupillometry,[(8)] muscle tonus and skin conductance.[(9)] They all have limitations in interpretation, as the state of

sympathetic tone is strongly influenced by numerous factors, including hypovolemia, vasopressors, atropine and patient positioning. In addition, sympathetic tone is very unspecific in the awake or lightly sedated patient, as mood and subjective feelings have a strong impact.

Attempts are also been made on using the EEG for monitoring of anti-nociception. This approach has been challenged as difficult,[10] as most of the antinociceptive drugs effects are in the periphery, the medullary cord [11] or deeper cerebral layers, far from the EEG signals derived from the frontal cortex. However, EEG is a 'mirror' of what is going on in other parts of the CNS and peripheral nervous system. One problem is to elucidate how the EEG signals may be used in a sensitive and specific way to reflect anti-nociception. Concepts such as response-entropy, [9-12] Composite Variability Index [13] and BIS variability score [9] have been tested and launched.

Quantium Medical has an EEG-based algorithm with two outputs: the qCON for unconsciousness and the qNOX for anti-nociception.[14] This means that calculates and displays two indices. One, the qCON, is designed to provide information about the depth of the hypnotic state, similar to that provided by the BIS™ and Sedline™ monitor (Masimo, Irvine CA). The second index, the qNOX, is designed to provide information about the depth of the antinociceptive state. The qCON has shown a comparable performance with BIS, and qNOX has proved correlation with rough clinical signs of insufficient antinociception, such as movements during LMA insertion, laryngoscopy and tracheal intubation [14.] Figure 1 shows an example of the mentioned signals during a general anesthesia procedure.



Example of the three electroencephalographic indexes (Bis, qCON and qNOX).

STUDY METHODS:

I. Recruitment:

a) Study investigators will review the surgery schedule 10 days ahead and contact the potential subjects by email or mail with an invitation to participate in this study. If we don't get back from them potential subjects in 5 days we contact them by phone, following the phone consent script, and ask them if they are interested in the research study and if they agree we will answer all the questions and concerns and obtain the consent over phone or when the subjects come to the pre-operative area the day of the surgery. With the subjects approval, we will mail or email the study material packet containing the HIPAA and the informed consent form.

b) Investigators will explain the study protocol including the potential benefits and potential risks. Patients will be told that they have the right to choose or refuse the study without any loss and any penalty because their participation in this study is voluntary.

c) Only patients who have provided their written consent and indicated that they have been introduced to the study prior to meeting with the anesthesiologists on the day of surgery; will be able to participate and undergo screening procedures for this study.

d) Screening procedures will make sure patients meet all inclusion criteria. If patient meets all inclusion criteria, they will be accepted into the study.

II. Procedure for the preparation of the medical devices

1) The study investigator will prepare

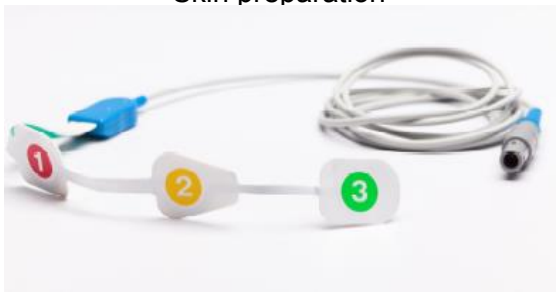
a) the PC.

b) the qCON-qNOX monitor and the BIS monitor (power supply unit and cables).

c) the skin preparation unit for each patient.

d) sensors for the qCON-qNOX and BIS monitor:

Skin preparation



2) The patient's cable will be connected to the qCON-NOX monitor and the qCON FTDI chip cable to the laptop USB port.
3) The qCON-NOX Display PC software will be checked if opens correctly, marks "Lead off" (because the electrodes are disconnected) and its files are saved. In addition, date and time will be well-adjusted.
4) After the electrodes are placed the qCON-NOX data will be displayed in one PC. Steps:
   a) open the software and select a COM port,
   b) press the start button,
   c) verify that files are being saved,
   d) verify that the impedances are below 15 and that the program state is running,

   On the uppers side are 5 parameters with different colors:

EMG: Electromyography signal power in a frequency band.

BSR (Burst suppression rate): % of time with isoelectric EEG in a window of 30 s.

SQI (Signal quality index): quality indicator signal. During acquisition this value should remain as high as possible (close to the value 100).

qNOX: index of pain.

qCON: index of anesthetic depth.

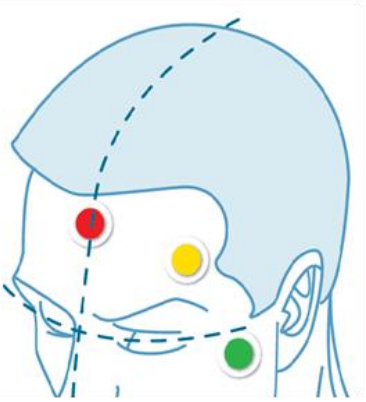
5) qCON-NOX Display PC during signal acquisition.

III. In the preoperative holding area:

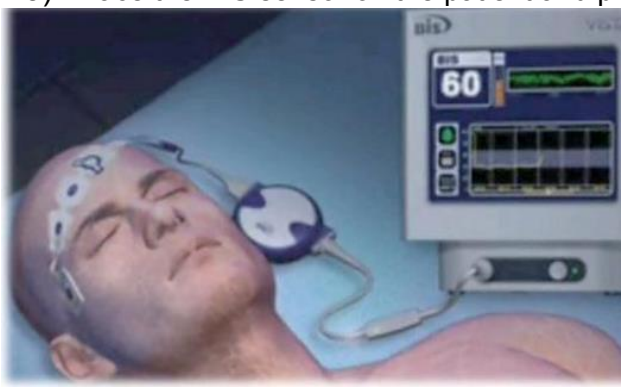
1) Collection of a detailed medical history including demographic information (e.g., age, weight, height, gender, ethnic origin).
2) Written informed consent will be obtained by one of the investigators.

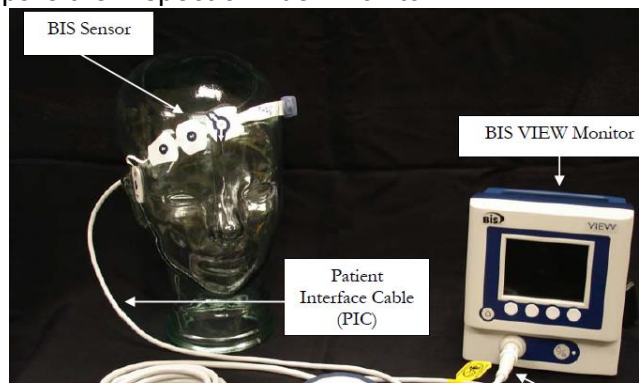
IV. During the intraoperative period:

1) Standard monitors: automatic blood pressure cuff, three-lead electrocardiogram, capnograph, pulse oximeter and BIS monitor will be applied.
2) The electrodes of the qCON-NOX monitor also will be placed, in a clean skin area of the forehead. The qCON-NOX monitor has a sensor with three electrodes: red, yellow and green. qCON-qNOX monitor sensors placement: at left side of the head, like is showing on the next pictures:



3) Place the BIS sensor on the patient and prepare the Bispectral Index monitor.





During the recording process:

4) When the recording process (BIS and qCON-NOX monitors) starts, the qCON-NOX Display PC will make an impedance measurement. If impedance values are high,

electrodes should be repositioned. In case they are repositioned twice and impedances remain higher than 15 kΩ, the patient will be withdrawn.

5) Data collection of the standard of care Anesthesia Technique chosen by the anesthesiologist:

I Premedication Standard Anesthesia Procedure:

Midazolam 20 ug/kg IV (1-2 mg IV)

II General Anesthesia with LMA

a. Induction with Fentanyl 50-100 Mcg,
b. Propofol, 1.5-2 mg/kg IV, with lidocaine, 30-50 mg IV followed by
c. Sevoflurane or desflurane 3% +
d. propofol 50-100 μg/kg/min for maintenance of anesthesia
e. For purposeful movements:
    i. Propofol 20-50 mg IV
    ii. Fentanyl 25-50 mcg, and if movements persist
    iii. Increase the inspired sevofulrane or desflurane concentration by 1-2%
f. Local anesthetics (lidocaine 2% and/or bupivacaine 0.5%) injected by surgeon as needed for analgesia locally during the operation
g. Ondansetron, 4 mg IV, and dexamethasone, 4 mg IV, administered before the end of surgery for antiemetic prophylaxis
h. Analgesics chosen by the anesthesiologist, will be given during the surgical procedure

V. At the end of surgery:

1) Record the time of the anesthetics discontinuation at skin closure
2) The exact time of the stimulation (verbal/noxious) and response of the patients during the awakening process must be recorded in the qCON-NOX Display Software.
3) The monitors will be disconnected from the patient once he/she is awake.
4) Patients will be transferred to the recovery room.

VI. Patient perioperative evaluations and data collected:

1) Response to noxious stimuli from induction to emergence (such as insertion of laryngeal mask [LMA placement], skin preparation, incision, skin suture, surgical events, closure, LMA removal or any other noxious stimuli.
    a) Number of coughs
    b) Cough severity will be graded as mild (1–2), moderate (3–5), or severe (>5)

c) Bucking
d) Gasps
e) Increase of heart rate, blood pressure and respiratory rate
f) Movements (movement in the period of 1 minute after applying the stimuli will be interpreted as a positive response to one of the nociceptive stimuli)

2) Vital signs (including MAP, and HR), at 5-10 min intervals throughout the intraoperative period
3) Dosages of anesthetics, analgesic, sedatives, local anesthetics, IV fluid therapy during the operation
4) Rescue bolus doses of propofol and/or fentanyl to treat coughing and/or movements.
5) Duration of surgery (from skin incision until closure) and anesthesia (from IV induction until discontinuation of the anesthetic drug)
6) BIS and qCON-qNOX monitors will be recorded throughout the intraoperative period and the recorded data will be archived for subsequent analysis. Also, the side where the BIS and qCON-qNOX electrodes were placed.
   Anesthesiologists will be blind to qCON-qNOX monitor; this one will be covered during all the procedure.
7) The exact time of the following stages of the surgery must be recorded in the qCON-qNOX Display Software (Also will be recorded in the data collection sheet):
   a) assessment of the level of consciousness of the patient using OAAS scale, [15]
   b) start of induction and end of induction,
   c) start and end of laryngeal mask placement,
   d) start and end of infusion pumps,
   e) response to noxious stimuli
   f) start and end of surgery
   g) emergence from anesthesia
8) Duration of surgery (from skin incision until closure)
9) Duration of anesthesia (from induction until discontinuation of the anesthetic drug)
10) LMA removal time
11) BIS and qCON-qNOX values at the time of rescue medication
12) Recovery times from discontinuation of anesthetic drugs until:
   a) eye opening
   b) following verbal commands

c) orientation to person, place and time
d) meeting discharge criteria (from PACU)

13) Requirements for "rescue" analgesic medication and antiemetic medication will be recorded before discharge.
14) Any side effects during the perioperative period.
15) Recall
16) Pain score at PACU

VII. DATA ANALYSIS

A power calculation will be pursued based on the following assumptions. We decide to have a power of 0.9 and a level of significance of 0.05. Previous experience showed that the standard deviation (SD) of the qCON is less than 24, and we consider a change of 15 as significant, hence the standardized difference is 15/24 = 0.625. According to Altman, [16] with these conditions the necessary sample size is 54 patients. Considering that some patients might be withdrawn because of high impedances of any of the monitors or any other technical issues, the number of patients to be monitored is 60.

The prediction probability (Pk) [17] will be used to assess the ability of the Bis, qCON and qNOX to predict the OAAS score and response to noxious stimulation. The Pk and its standard error (SE) will be calculated using the jackknife estimate which has the advantage that the variance can be estimated by the Student's t-distribution. The normal distribution using a Lilliefors test will be tested before using a Student's t-test (paired) to test for significance at $P < 0.05$. Also, the correlation between qCON-NOX, BIS, sevoflurane and desflurane drugs will be estimated using Pk. Finally, the Bland–Altman plot for (qCON+Bis)/2 vs. (Bis-qCON) will be presented.

VIII. INCLUSION AND EXCLUSION CRITERIA

1. Inclusion Criteria

Subjects may be included in the study only if they meet all of the following criteria:

1) Patients scheduled to undergo general surgical procedures with general anesthesia/LMA.
2) Willingness and ability to sign an informed consent document.
3) 18 – 80 years of age.
4) ASA Class I – III adults of either sex.

2. Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

1) Inability to consent

3. Withdrawal criteria

Subjects will be withdrawn from the study for the following reasons:

1) Electrodes should be changed when patient's skin impedance value exceeds 15 kΩ after conditioning skin properly. If after two changes of electrodes, impedance remains above 15 kΩ, patient will be excluded from the present study.

Observer's Assessment of Alertness/Sedation Scale (OAAS)

Table 1. Observer's Assessment of Alertness/Sedation (OAAS)[11]

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name	Normal	Normal	Clear, no ptosis	5
Lethargic response to name	Mild slowing	Mild relaxation	Glazed or mild ptosis	4
Responds to name only if called repeatedly	Slurring	Marked relaxation	Glazed or marked ptosis	3
Responds only after mild prodding	Not recognizable			2
No response to prodding or shaking				1

OAAS is the lowest score in any of the four categories.

OAAS score 5—awake and responds readily to name spoken in normal tone.

OAAS score 4—lethargic responses to name in normal tone.

OAAS score 3—responds only after name is called loudly and/or repeatedly.

OAAS score 2—responds only after name called loudly and mild shaking.

OAAS score 1—does not respond when name is called loudly and mild shaking or prodding.

OAAS score 0—does not respond to noxious stimulation.

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