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Comparison of the qNOX, qCON and Bispectral (BIS) index responses to noxious stimuli during surgery

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Abstract

Background: Monitoring a patient's level of anti-nociception during surgery can minimize autonomic and muscular responses to intraoperative stimuli. Electroencephalogram (EEG)-based tools like Bispectral Index (BIS) (Covidien, Boulder CO, USA), Conox (Fresenius Kabi A. G. Bad Homburg, Germany), and SedLine monitor (Masimo Corp., Irvine, CA, USA) might provide insights into depth of hypnosis (sleepiness) and responses to noxious surgical stimuli. The Conox (qCON and qNOX) was designed to independently assess both sedation and nociception during surgery. The objective of this observational study was to simultaneously compare the responses to specific events during surgery using the qCON, qNOX and BIS index monitors.

Methods: Prior to induction of anesthesia, 59 consenting adult patients undergoing general anesthesia with a laryngeal mask airway (LMA) were simultaneously monitored using BIS and Conox monitors. Monitoring was continuous from induction of anesthesia until return of consciousness after surgery. Both the surgical and anesthetic teams were blinded to the qCON and qNOX values during the operation. Baseline values were recorded prior to and after induction of anesthesia, as well as responses to LMA insertion, and noxious events during surgery (e.g., local anesthetic infiltration, skin incision, painful manipulations during the operation, and skin closure), removal of the LMA device, and upon return of consciousness after the operation.

Results: The prediction probabilities (Pk) show significant concordance among comparisons of qCON vs BIS (Pk=0.821, $p<0.01$), qCON vs qNOX (Pk=0.827, $p<0.01$), and qNOX vs BIS (Pk=0.743, $p<0.05$) during anesthesia. During LMA insertion, there were no significant differences in heart rate (HR), mean arterial pressure (MAP), BIS, or qCON values in patients who moved vs. those who did not move; however, qNOX values were significantly higher ($p<0.05$) in "movers" compared to "nonmovers". During noxious stimulating events during the operation, there was no significant difference in qCON nor BIS values when comparing movers and nonmovers. However, HR, MAP, and qNOX were significantly higher in movers compared to nonmovers ($p<0.05$). These findings suggest that qNOX may be capable of serving as a surrogate for sympathetically-mediated responses to noxious stimuli. Logistical regression analysis showed that qNOX was the most accurate predictor of intraoperative movement. The BIS values and hemodynamic changes in HR and MAP were less predictive of patient movements during surgery.

Conclusion: Although there was a strong correlation between BIS and qCON in monitoring hypnotic levels, however, the qNOX values provide useful information for predicting movements in response to noxious stimuli during anesthesia. These preliminary data suggest that higher qNOX values appear to more reliably correlate with inadequate analgesia than either the BIS or qCON values.

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Introduction

The ability to monitor both the hypnotic and anti-nociceptive effects of anesthetic medications would potentially allow anesthesiologists to improve their administration of commonly used anesthetic and analgesic drugs during surgery [1]. In clinical practice, achieving an adequate depth of anesthesia has traditionally been achieved by observing the patient's hemodynamic and respiratory responses to induction of anesthesia and stimulating surgical events [2]. Assessing hypnosis and nociception in patients receiving general anesthesia is difficult due to blunting of the sympathetic response by anesthetic and analgesics drugs.

There have been many different strategies for evaluating the stress response during surgery, including measurements of hormonal levels (e.g., catecholamines, cortisol) pulse plethysmograph amplitude [3], heart rate variability and/or amplitude [4], pupillometry [5], muscle tonus, skin conductance [6], the analgesia/nociception index (ANI) [7], and the nociception level (NOL) index [8,9]. All of these assessment tools have limitations as the state of sympathetic tone is strongly influenced by numerous other factors. Changes in standard hemodynamic variables is the most commonly used method for assessing the depth of anesthesia and analgesia [2,10,11].

Adrenergic stimuli produce arousal reactions which can be observed using cortical EEG electrodes. These EEG based monitoring systems have been used as a surrogate measure of the autonomic and hemodynamic responses to stimuli [12]. The bispectral (BIS index monitor (Covidien, Boulder CO, USA) utilizes EEG signals from the frontal cortex to assess the hypnotic effect of anesthetic drugs [13]. EEG-derived methods (e.g., response entropy (RE), state entropy [14], and BIS) [6] have been developed to monitor anesthesia depth and detect nociceptive responses. BIS and RE provide scores between 0 and 100, indicating the patient's level of consciousness [15].

In contrast to the BIS monitor, the Conox monitor displays two indices based on an EEG-based algorithm. The qCON index is alleged to monitor consciousness and the qNOX index values are alleged to reflect the state of anti-nociception during an operation [16]. Thus, the qCON index is designed to provide information regarding the depth of the hypnosis similar to the EEG-based BIS and Sedline monitors (Masimo, Irvine CA). The qNOX index was designed to provide information about the state of anti-nociception (e.g., responsiveness to noxious stimuli). The qCON has been shown to achieve a comparable performance level to the BIS monitor in determining the depth of hypnosis [17]. On the other hand, the qNOX index has been shown to possess predictive value regarding whether or not the patient would move in response to a noxious stimuli (e.g., laryngeal mask airway[LMA] insertion, laryngoscopy for tracheal intubation) [16]. Thus, the EEG-based BIS and qCON indices were designed to provide information regarding the depth of sedation and hypnosis, while the qNOX index was designed to provide information regarding the adequacy of analgesia (i.e., degree of antinociception prior to painful stimuli during the operation).

This observational clinical study was designed to compare the indices of hypnosis, namely the BIS and qCON values, in patients undergoing general anesthesia. In addition, we assessed differences between the BIS, qCON and qNOX indices to determine if the qNOX index possessed unique predictive value regarding responses to specific noxious stimuli during surgery (e.g., LMA insertion, incision).

Methods

This study was approved by Cedars-Sinai Medical Center's Institutional Review Board (IRB) with # Pro00043738 and with clinical trials registration (http://www.clinicaltrials.gov) # NCT02928172. After obtaining informed consent, 69 patients scheduled to undergo elective surgery were enrolled in this study. Inclusion criteria were age 18-80, either gender, American Society of Anesthesiologists (ASA) physical status I-III. Exclusion criteria included the inability to consent. Withdrawal criteria included conversion to endotracheal tube and EEG malfunction which required electrodes to be changed when the patient's skin impedance value exceeds 15kO after proper skin cleaning more than two times. Of the 69 subjects initially enrolled, seven had their procedure rescheduled, canceled or moved to another operating room, and three patients were removed from this study due to EEG malfunction or incomplete data collection.

In the pre-operative holding area, written consent was obtained by one of the investigators followed by collection of a detailed medical history including demographic information (e.g., age, weight, height, gender). Prior to the patient being brought into the operating room, the Conox software was checked to confirm that the program was running properly. The anesthesiologist and the surgical team were blinded to the Conox monitor values during the operation. In the operating room, standard monitoring devices including automatic blood pressure cuff, three-lead electrocardiogram, capnograph, pulse oximeter, and BIS monitor were placed on the patient. Additionally, the Conox sensor was placed on a cleaned skin area of the forehead. on the opposite side of the BIS sensor.

A standardized induction technique consisting of 1-2 mg of IV midazolam, 50-100 ug fentanyl, 1.5-2 mg/kg IV propofol containing 30-50 mg IV lidocaine, sevoflurane

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(1-3%) or desflurane (6-8%) with propofol 50-100 ug/kg/min for maintenance of anesthesia. An LMA device was inserted in all cases. For purposeful movements during the case, the anesthesiologist administered 25-50 mg of IV propofol and if the movement persisted, 25-50 ug of fentanyl was administered and if movements persisted, the sevoflurane or desflurane concentration was increased by 1%. Local anesthetics (e.g., lidocaine 2% and/or bupivacaine 0.5%) were injected by the surgeon as needed for local analgesia during the operation. For antiemetic prophylaxis, ondansetron (4 mg IV) and dexamethasone (4 mg IV) were administered before the end of the surgery. All of the monitors were disconnected after the patient was awake, and the patient was subsequently transferred to the PACU.

The standardized perioperative evaluation and data collection included: (1) response to specific noxious stimuli from induction to emergence: (a) LMA insertion and removal, skin preparation, incision and closure, surgical events, coughing (frequency with severity graded as mild, moderate or severe), bucking, gasps (b) movement in a period of 1 minute after applying stimulation (2) vital signs at 5-minute intervals throughout the intraoperative period including heart rate, blood pressure, and respiratory rate, (3) Intraoperative medication (a) dosages of anesthetics, analgesics, sedatives, IV fluid therapy, rescue bolus doses of propofol and/or fentanyl, (4) time stamps of the following: (a) start and end of surgery and anesthesia, (b) stages of surgery, (c) start and end of LMA placement, (d) response to noxious stimuli, (e) emergence from anesthesia, (f) BIS and qCON, qNOX values at the time of rescue medication (of note, all movement responses were documented at the exact time they occurred), (5) 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, (6) requirements for 'rescue' analgesic medication and antiemetic medication before discharge, (7) side effects during the perioperative period, (8) recall, and (9) pain score at PACU. The responses to LMA placement and surgical stimuli were analyzed separately.

Data analysis

A sample size of 54 subjects was determined using a power analysis based on a previous study demonstrating that a standard deviation (SD) of the qCON is <24, we considered a change of 15 to be significant, with a power of 0.9 and significance level of 0.05 (Altman's nomogram). Due to the possibility of patient withdrawal the actual sample size of patients to be monitored was increased to 60. The prediction probability (Pk) was utilized to evaluate the effectiveness of the BIS, qCON and qNOX in predicting the response to noxious stimulation. Pk and its standard error (SE) were computed using the jackknife estimate, which allowed for estimation of variance using the student's t-distribution. Before conducting a paired Student's t-test to assess significance at $P < 0.05$, a Lilliefors test was performed to check for normal distribution. Additionally, Pk was used to determine the correlation between qCON-NOX, BIS, and qNOX. Finally, a Bland-Altman plot comparing (qCON+BIS)/2 to (BIS-qCON) were presented.

A binary logistic regression model, eq.1, was performed to model the probability of movement response for the hemodynamic parameters and the EEG indices = *logit* (p)= $p/(1-p) = \beta_0 + \beta_1\chi$. The variables in the equation that were assessed including measurements: at 5-minute intervals throughout the case, at LMA insertion and removal, and rough clinical signs when movement was observed with no-movement response used as a control. The sampling of the EEG was carried out at single measurements with no averaging.

Results

A total of 69 subjects was initially enrolled of which seven had their procedure rescheduled, canceled or moved to another operating room, and three patients were removed from this study due to EEG malfunction or incomplete data collection, hence a total of 59 patients were included in the statistical analysis. The mean age (years) was 51.5± 14 (21-79), 76% were female, and the mean BMI was 26± 5.6 (Kg/m^2). Patients underwent general 8 (13.6 %), gynecological 43 (73%), urological 6 (10%), and orthopedic 2 (3.4 %) surgeries. Other basic demographic data are presented in table 1.

Table 1: Demographic characteristics of adult patients undergoing elective surgery under general anesthesia using a laryngeal mask airway (LMA) device for airway management.

	Female (n=45)	**Male (n=14)**
Age (years)	53 ± 13	51 ± 20
Race/ethnicity		
White/Asian/Black/Hispanic (n)	35/3/4/3	11/0/2/1
BMI (Kg/m^2)	26 ± 6	27 ± 5
ASA (1/2/3) (n)	9/33/3	5/8/1
Smoker (Yes/No) (n)	1/44	1/13
Alcohol (Yes/No) (n)	10/35	4/10
Motion Sickness (Yes/No) (n)	3/42	0/14
PONV (Yes/No) (n)	5/40	0/14
Type of surgery (n)		
General	1	7
Gynecological	43	-
Urological	1	5
Orthopedic (tendon repair)	0	2
Intraoperative variables		
Surgery Duration (min)	40±33	51±25

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Anesthesia Duration (min)	63±36	83±39
Medication		
Fentanyl (µg)	78±28	83±26
Propofol (mg)	383±219	582±315
Ondansetron (mg)	4+0	4+0
Dexamethasone (mg)	4.5+1.4	4+0
Ketorolac (mg)	30+0	30+0
Lidocaine (mg)	48±15	55±18
IV Fluids (ml)	719±228	715±230
PACU variables		
Duration of PACU stay	120±48	125±52
Max pain score at PACU	2.1 +2.9	2.4+2.9
Opioid analgesics (IV Morphine equivalents)	4.5±3.8	4.9±2

Numbers (n), means values ± standard deviation (± SD). BMI (body mass index), ASA (American Association of Anesthesiologist), PONV (postoperative nausea and vomiting).

The Bland-Altman plot (**figure 1**) show significant agreement when comparing the BIS, qCON, and qNOX indices. Using 803 instances when qCON and BIS were both measured, the prediction probability showed significant agreement between those indices (Pk = 0.821; p<0.01). Using 811 instances when qCON and qNOX were both measured, the prediction probability showed significant agreement between those indices (Pk = 0.827; p<0.01).

During LMA insertion, there were 16 patients who showed clinical responses (movers) and 43 patients who did not (nonmovers). There were no significant differences in heart rate (HR), mean arterial pressure (MAP), BIS, and qCON when comparing movers and nonmovers during LMA insertion (**figure 2**). However, the qNOX was significantly higher (p<0.05) in movers compared to nonmovers during LMA insertion.

There were 21 occurrences where patients showed clinical responses (movers) during intraoperative events (LMA placement, incision, and suturing) and 63 occurrences where patients did not show clinical responses during intraoperative events, including skin preparation, local infiltration, incision, and suturing. There was not a significant difference in qCON when comparing movers and nonmovers during intraoperative events (**figure 3).** HR, MAP, BIS, and qNOX values were significantly higher (p<0.05) in movers compared to nonmovers during intraoperative events. Additionally, qNOX was found to have the greatest difference comparing movers to nonmovers (p<0.01).

Post-LMA insertion clinical signs are shown in figure 4. The red dots indicate the events where the patient moved, and in blue similar events where the patients did not move. The dots were scattered around the 1 and 0 lines only for better graphical presentation.

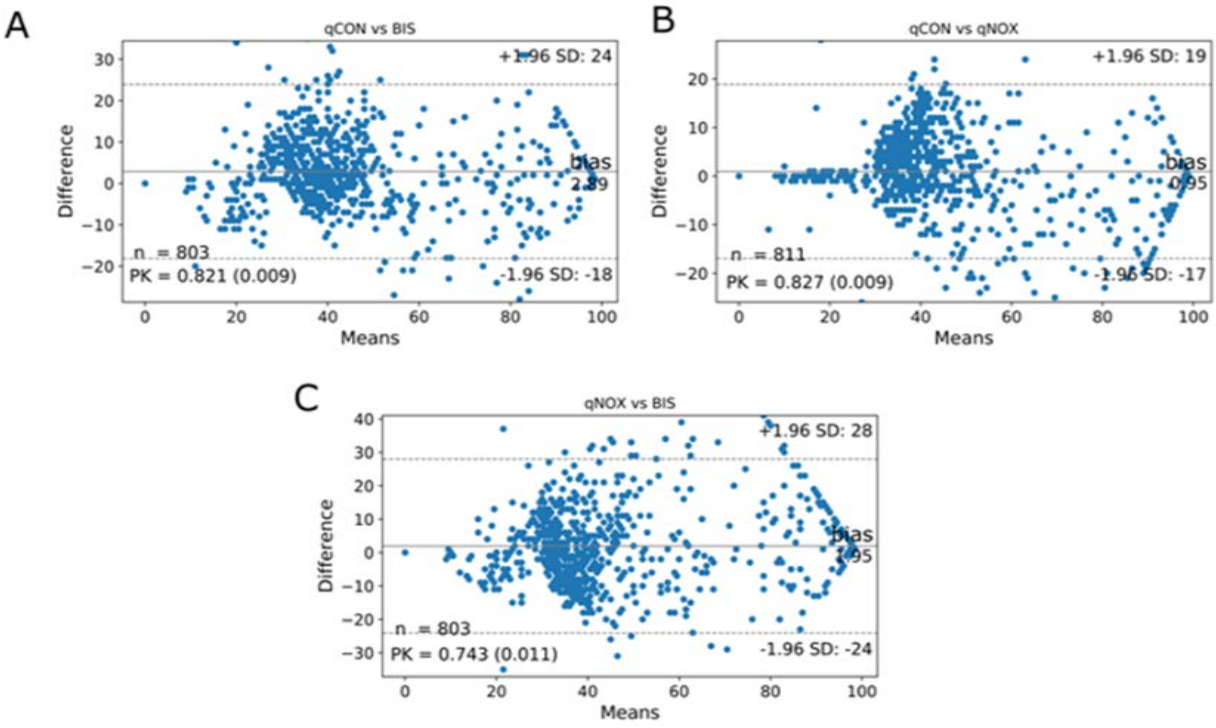

Figure 1: Bland-Altman plot showing the level of agreement between (A) qCON and BIS, (B) qCON and qNOX, and (C) qNOX and BIS. All plots show statistically significant agreement between the indices (p value <0.05).

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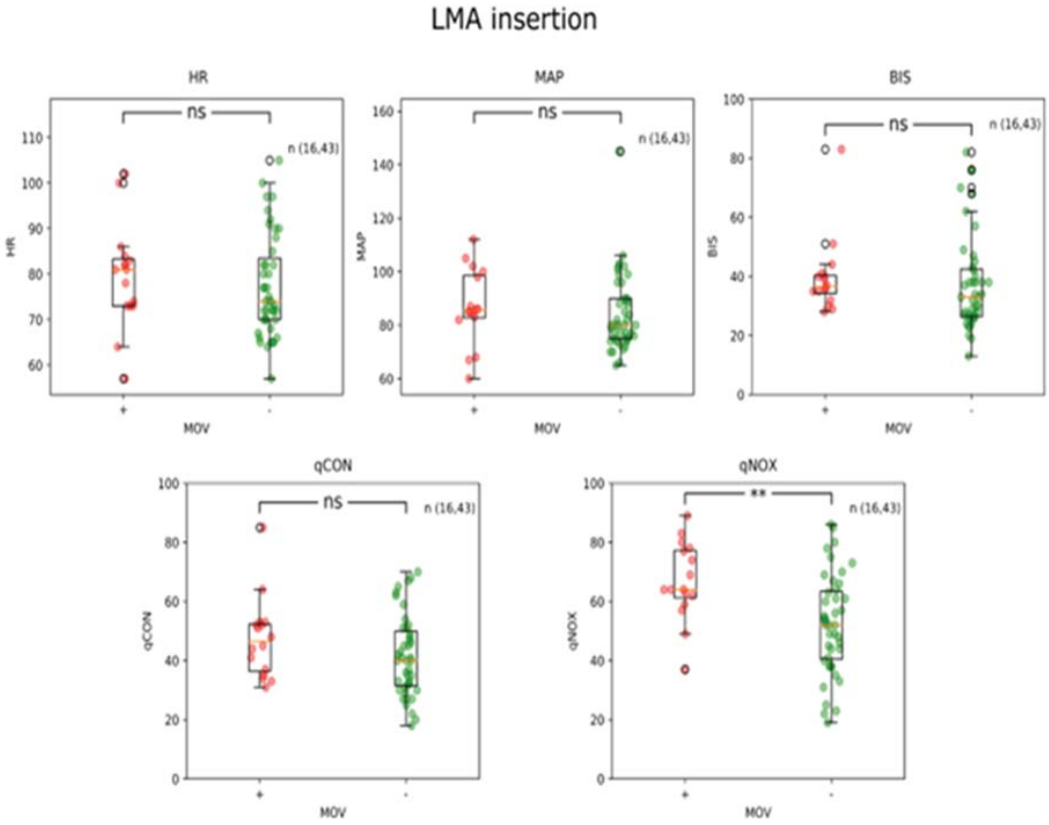

Figure 2: Mann Whitney U analysis showing the differences in measurements of depth of anesthesia between movers (red; n=16) and nonmovers (green; n=43) during laryngeal mask airway (LMA) insertion. There was no difference in heart rate (HR), mean arterial pressure (MAP), bispectral index (BIS), and qCON when comparing movers and nonmovers. qNOX and qNOX-qCON were significantly different when comparing mover and nonmovers. ns = not significant; *p value <0.05; **p value = 0.01; ***p value < 0.01

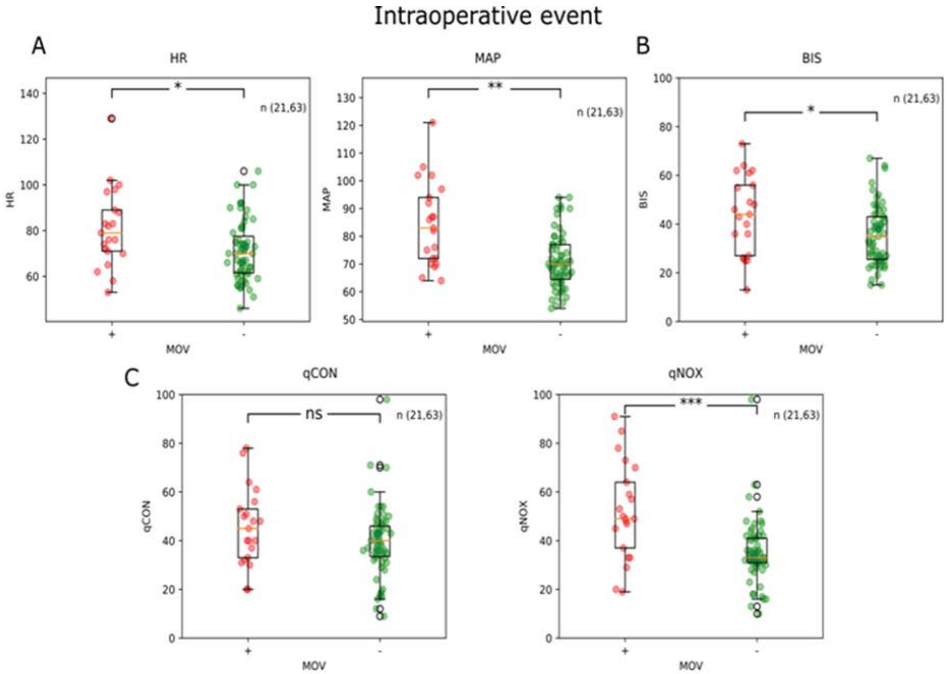

Figure 3: Mann Whitney U analysis showing the differences in measurements of depth of anesthesia between movers (red; n=21) and nonmovers (green; n=63) during intraoperative events. There was no difference in qCON when comparing movers and nonmovers. Heart rate (HR), mean arterial pressure (MAP), bispectral index (BIS), qNOX and qNOX-qCON were significantly different when comparing mover and nonmovers. ns = not significant; *p value <0.05; **p value = 0.01; ***p value < 0.01.

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Clearly, those intraoperative periods where patients moved had higher qNOX values with respect to similar events without movement. The corresponding logistic regressions of intra operative movements are shown in figure 5.

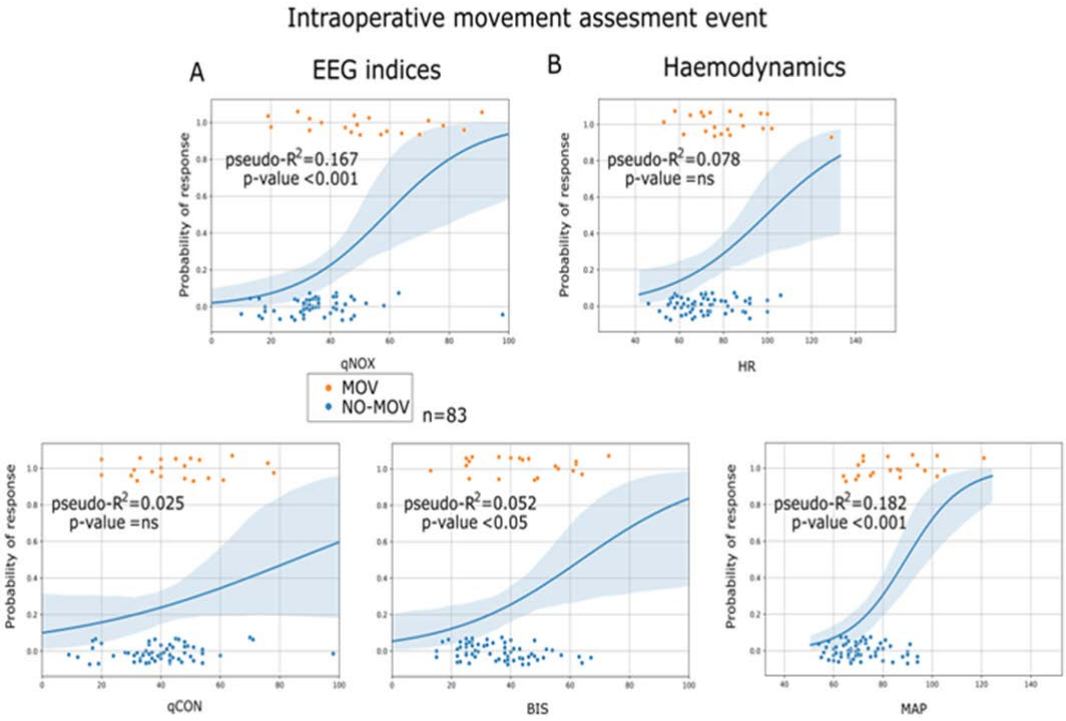

Figure 4: Probability responses to LMA insertion. Hemodynamics and EEG indices preceding LMA insertion. Logistic regression significance p-values.

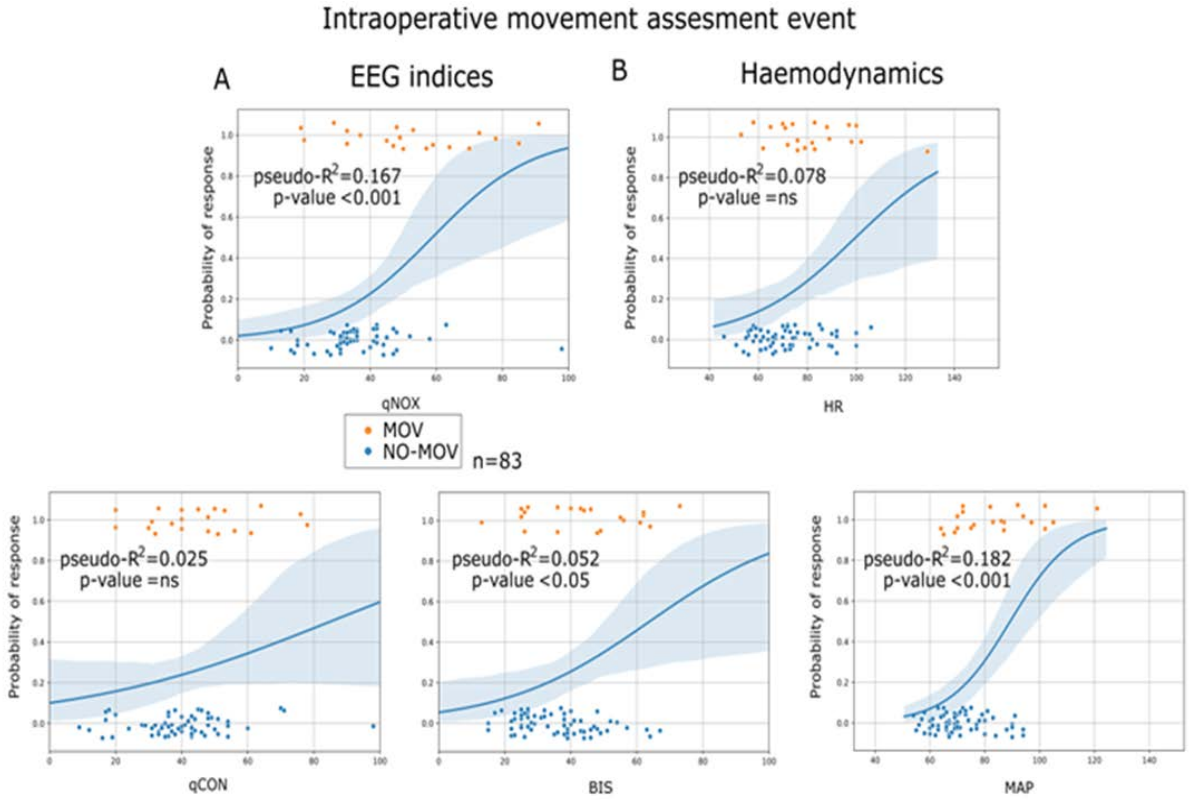

Figure 5: Probability responses during maintenance. Hemodynamics and EEG indices.

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The probability responses for all measured values (LMA and intraoperative clinical occurrences) are show in **Figure 6**. Fourteen patients showed skin discomfort to the BIS sensor whereas for the Conox sensor this was only the case for two patients.

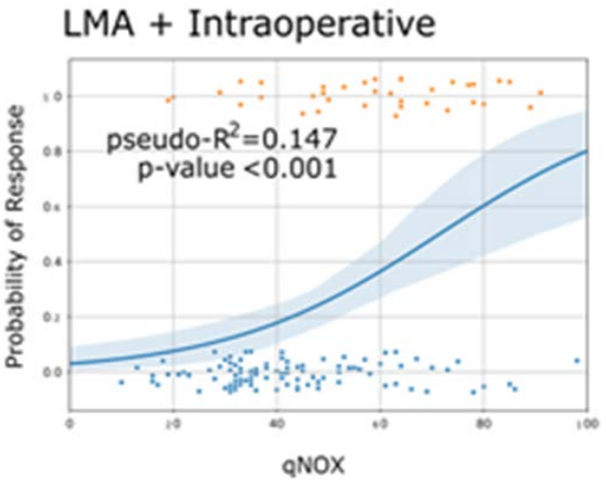

Figure 6: EEG indices on the probability response during LMA and maintenance.

Discussion

The published literature indicates that the values of these indices change predictably with variations in consciousness level and different noxious stimuli [18]. For example, it has been reported that higher values of qNOX and qCON at induction and extubation compared to all other time points [19]. However, determining the optimal dosage of anesthesic and analgesics in unconscious patients who cannot verbally communicate information about their comfort level or degree of discomfort (pain) while under general anesthesia remains a challenge for practitioners. The two Conox indices have been used to monitor the depth of anesthesia in patients undergoing several surgical procedures [20,21]. For example, the Conox monitor was use in patients undergoing laparoscopic cholecystectomies to compare the efficacy of sevoflurane and desflurane [20]. In patients undergoing gynecological laparoscopy, the indices were used to adjust the concentrations of sevoflurane and remimazolam to improve the anesthesia management [21]. In urological surgery, the qCON and qNOX indices were more effective in maintaining the depth of anesthesia and analgesia and adjusting anesthetic and analgesic drugs dosing compared to conventional clinical monitoring [22]. The Conox monitor was used to manage the administration of opioids and non-opioid analgesics, aiming to enhance the quality of anesthesia and analgesia [23,24]. Contradicting these observations, a study of patients undergoing elective cardiac surgery did not support the statement that signs of nociceptive stimulation were predictive of postoperative pain [25,26]. However, the authors suggested this could be due to the compounding effects of qNOX processing and the use of muscle relaxants [25]. Also, in a study of patient undergoing elective major abdominal surgery the qNOX failed to demonstrate any predictive value with postoperative pain [26].

The results from this observational study demonstrated a correlation between qCON and BIS indices for monitoring the depth of hypnosis (Figure 1), consistent with previous studies [16,17]. Although BIS and qCON are different EEG based algorithms, they appear to correlate well with each other in reflecting the level of hypnosis during an operation under general anesthesia. Previous studies have assessed the post-operative clinical utility of intraoperative BIS guided monitoring. These studies have shown better post-operative outcomes, like decreased recovery time, decreased intraoperative patient awareness, and increased patient satisfaction when this monitor was used during anesthesia [16,27,28]. The strong agreement between BIS and qCON in this study allows us to make a reasonable inference that qCON-guided monitoring may offer similar benefits.

Our analysis also found that the BIS, qCON and qNOX indices showed strong agreement with each other in the absence of noxious surgical stimulation as shown in figure 1. However, qNOX was significantly lower than BIS and qCON in non-moving vs. moving patients in response to specific stimuli during the operation. While the BIS and qCON values were not statistically different between movers vs. nonmovers (Figures 2 and 3). This finding provides evidence to support the concept that hypnosis and analgesia (anti-nociception) reflect two distinct endpoints and there is value in quantifying and monitoring both values independently. This is further supported by our finding that an increasing difference between qNOX and qCON in Figures 2 and 3) is also associated with movement in response to noxious stimuli. These findings support the conclusion that qNOX values are a more predictive of in response to noxious stimuli during anesthesia (e.g., LMA insertion and other intraoperative events (e.g., skin incision), consistent with the findings from earlier studies [16,17,29]. In fact, the qNOX index appeared to be a potentially useful indicator of adequacy of nociception during surgery as it was the only EEG-based index that was significantly higher in movers compared to nonmovers during both LMA placement and other specific painful intraoperative events (e.g., incision, local infiltration).

Hemodynamic measures, like HR and MAP, were recorded in this study to assess their value in predicting a response to noxious stimuli but we did not find correlation that could suggest a response to a noxious stimuli. These hemodynamic measures have traditionally been used to identify the level of nociception during a surgical procedure. Additionally, EEG -based monitor of nociception (e.g., ANI, BIS) are commonly employed [2,10,11]. Monitoring EEG-based endpoints may prove useful in detecting inadequate analgesia during noxious intraoperative events, but they are

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not as helpful in detecting inadequate analgesia (movements) during LMA insertion. This is perhaps a consequence of the combination of medications given during induction of anesthesia that alter these hemodynamic measures render these indices point unreliable in predicting level of anti-nociception. In any event, these hemodynamic measures are still a tool that an anesthesia provider can use in conjunction with qNOX. In addition to monitoring response to noxious stimuli, monitoring the depth of hypnosis is also important to avoid the trauma associated with being awake and aware during an operation.

Limitations

1. **Sample Size and Generalizability**: The study had a small sample size of 59 patients. Future research should include larger sample sizes and diverse populations with additional comorbidities and different airway management methods to improve generalizability.
2. **Subjective Movement Determination**: Movement was determined subjectively rather than using electromyography (EMG). Although experienced anesthesia providers monitored patients, future studies should consider objective measures like EMG.
3. **Data Documentation**: Data was recorded every five minutes and at the time of any patient movement. A continues data recording could more precisely determine if specific changes in qNOX predict movement in response to noxious stimuli.
4. **Focus of the Study**: The study compared indices for monitoring depth of hypnosis and nociception but did not examine the effects of specific anesthetic agents or long-term post-operative outcomes.
5. **Post-Operative Outcomes**: We did not research the qNOX-guided analgesia affects post-operative pain, recovery time, risk of falls, post-operative psychosis, and patient satisfaction.

Conclusion

In this observational study, BIS and qCON showed strong agreement in monitoring the depth of hypnosis. This study also provides evidence validating the use of qNOX for the monitoring anti-nociception. The qNOX index appears to be a surrogate measure for the level of anti-nociception that is distinct from the BIS and qCON indices and an increase in qNOX in response to painful stimuli may indicate inadequate analgesia. Overall, this study adds to the existing body of literature that provides support for monitoring both the level of hypnosis and nociception independently throughout the surgical procedure. The BIS, qCON, and qNOX indices are valuable tools that anesthesia providers could use to supplement information from traditional hemodynamic monitoring, to ensure an adequate depth of anesthesia during surgical procedures under general anesthesia.

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