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Monitoring of general anesthesia by qCON and qNOX indices versus conventional clinical parameters in urological surgery: A randomized controlled clinical trial

Himalaya Dutta[1], Suchismita Mallick[2], Baisakhi Laha[3], Sarbari Swaika[4], Uday Sankar Mandal[5], Sarmila Ghosh[6]

[1]Senior Resident, Department of Anaesthesiology, Barasat Government Medical College and Hospital, Barasat, [2]Associate Professor, Department of Anaesthesiology, Deben Mahata Government Medical College and Hospital, Purulia, [3]Associate Professor, Department of Anaesthesiology, IPGME&R, Kolkata, [4]Professor and Head, Department of Emergency Medicine, IPGME&R, Kolkata, [5]Associate Professor, Department of Psychiatry, Bankura Sammilani Medical College, Bankura, [6]Professor, Department of Anaesthesiology, Murshidabad Medical College, Murshidabad, West Bengal, India

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ABSTRACT

Background: Awareness during anesthesia is a major anesthetic concern. Depth of anesthesia is commonly assessed in clinical practice by the patient's clinical signs and symptoms such as blood pressure, heart rate variability, and body movement. At present, many studies have focused on qCON monitoring for sedative depth, but only a few studies have focused on qNOX monitoring for analgesic depth. **Aims and Objectives:** The aim of the present study was to evaluate the relative efficacy of qCON and qNOX versus commonly used vital signs such as blood pressure and heart rate in monitoring the anesthetic depth and analgesia. **Materials and Methods:** A total of 100 patients of either sex and of ASA Physical status I & II, scheduled for urogenital surgeries, were selected and randomly placed into two groups. Group A was monitored by conventional clinical technique and Group B was monitored by qCON and qNOX indices. The primary outcome was the total dose of propofol and fentanyl required to maintain the depth of anesthesia and analgesia. The secondary outcomes were propofol and fentanyl adjustment frequency, infusion duration, and quality of recovery from anesthesia. **Results:** Results showed statistically significant differences between the two groups in mean dose of both propofol (P = 0.000) and fentanyl (P = 0.006), adjustment frequency of both propofol (P = 0.000) and fentanyl (P = 0.010), time required to voluntary eye-opening (P = 0.000) and extubation time (P = 0.000) and visual analog scale score (P = 0.000). There was no statistically significant difference found in infusion duration (P = 0.317) and Ramsay Sedation Score (P = 0.709) between the groups. **Conclusion:** Using the qCON and qNOX indices, an anesthesiologist can monitor the depth of anesthesia and analgesia more effectively and can adjust the anesthetic or analgesic drug dosing in a better possible way with lesser requirement of drugs than with conventional clinical monitoring.

Key words: Conox monitor; Depth of anesthesia; Extubation time; Propofol; Fentanyl

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INTRODUCTION

As a dynamically developing field, anesthesiology aims to provide patients with maximum comfort during surgery without increasing the risk of any anesthesia-related adverse effects. To provide an optimal surgical plane of anesthesia, the concept of "depth of anesthesia" was introduced. To achieve adequate depth of anesthesia, proper drug dosing is most essential. Awareness and excessive sedation are on either side of the spectrum of inappropriate drug delivery.

Address for Correspondence:
Suchismita Mallick, Associate Professor, Department of Anaesthesiology, Deben Mahata Government Medical College and Hospital, Purulia - 700 019, West Bengal, India. **Mobile:** +91-7044441555. **E-mail:** suchismita2175@gmail.com

Inadequate depth of anesthesia leads to intraoperative awareness with recall, which increases the risk of post-operative complications (post-traumatic stress disorder).[1] Excessive drug delivery, on the other hand, can lead to increased depth of anesthesia interfering with patient recovery causing delayed reversal.[2]

Monitoring the depth of anaesthesia can help optimize the adequacy of the anaesthetic drug administration, reduce costs, and improve patient's outcome. Intraoperative digital EEG analysis to monitor the depth of anaesthesia aids the judicious use of anaesthesic drugs.[3,4] The CONOX is relatively a new device (vide figures 1 and 2) which can monitor both the depth of anaesthesia and analgesia. qCON is an index of the depth of anaesthesia, while qNOX is an index of predictive level of response to pain stimuli.[5] The qCON index has a value between 0-99, from isoelectric EEG to awake state. qNOX is an index ranging from 0-99. It correlates with patient's responsiveness to external stimuli or pain. Both indices are based on combination of different frequency bands derived from frontal EEG representing the bioelectrical activity of the brain.

Depth of anesthesia is commonly assessed in clinical practice by the patient's clinical signs and symptoms such as blood pressure, heart rate variability, and body movements, but these measures are difficult to express into a quantitative standard measure. At present, many studies have focused on qCON monitoring for sedative depth, but only a few studies have focused on qNOX monitoring for analgesic depth as well. Presuming that index of consciousness monitoring would help to control the depth of anesthesia and analgesia, in the present study, we applied qCON and qNOX indices. We evaluated the effectiveness of qCON and qNOX indices versus commonly used vital sign monitoring such as blood pressure and heart rate for monitoring the anesthetic depth and analgesia.

Aims and objectives

The objectives of the study are as follows:

1. To compare the efficacy of monitoring the depth of anesthesia and analgesia by qCON and q NOX indices with conventional methods in terms of the requirement of anesthetic and analgesic drug dosing.
2. To compare the recovery status, time to spontaneous eye opening, time to extubation, visual analog scale (VAS) score, and Ramsay sedation score between the groups.

MATERIALS AND METHODS

This study was a parallel group randomized controlled trial, conducted in a tertiary care referral institute from August 2021 to August 2022. The study was approved by the Institute's Ethics Committee IPGME&R/IEC/2021/045 and written informed consent was obtained from all the subjects who participated in the trial. The trial was registered before patient enrolment at the Clinical Trial Registry of India (CTRI/2021/08/035969) and was done in accordance with the principles of the declaration of Helsinki.

Patient allocation

A computer-generated randomization list was used and patients included in the trial were allocated to either of the two groups – one group monitored by qCON and qNOX, the other by conventional monitoring methods for depth of anesthesia and analgesia.

Group A was monitored by the conventional technique

Group B was monitored by the qCON and qNOX.

The trial was an openlabel trial; however, data were recorded by an independent observer.

Inclusion and exclusion criteria

Patients included in this study were aged between 18 and 65 years, body mass index (BMI) of 18–30 kg/m^2, with ASA I-II posted for elective urosurgical procedure.

Patients who had suspected inability to comply with the study process including language difficulties or medical history of concomitant disease, neurocognitive impairment, neurological and psychiatric diseases, patients with a history of drug abuse, pregnancy, allergy to the agents used in the study, cardiovascular diseases such as hypertension, hypotension, tachycardia, and bradycardia were excluded from the study.

Anesthesia and device performance

A routine pre-operative assessment of all the patients was done, explaining the anesthetic procedure. Preoperatively, fasting of 6 h was confirmed. IV cannulation was done after taking the patients in operation theater and standard ASA monitors were attached to all patients. In Group B, CONOX sensor strip was attached to the patient's forehead after cleaning with a wipe and connected to the CONOX monitor. The baseline values of qCON and qNOX were obtained just before anaesthesia. For Group A, the baseline values of heart rate and systolic and diastolic blood pressure were recorded. Patients were explained about the procedure once again.

Each patient was pre-medicated with injection Fentanyl (2 mcg/kg) and then induced with injection Propofol at 2 mg/kg. Tracheal intubation was performed when

satisfactory muscle relaxation was achieved with Inj. Atracurium 0.5 mg/kg. The patient was then placed on volume-controlled ventilation with a tidal volume of 8 mL/kg, a respiratory rate of 12/min, a respiratory ratio of 1:2, and an end-tidal carbon-dioxide ($P_{Et}CO_2$) kept between 35 and 45 mm of Hg. The maintenance of general anesthesia was initiated using Infusion Propofol at a dose of 50 mcg/kg/min and to maintain intraoperative analgesia, infusion Fentanyl was started at a dose of 1 mcg/kg/h.

Loss of response to verbal command and loss of eye-lash reflex was assessed during the transition from awake to anesthetized state, defining the state of loss of consciousness (LOC). Whereas the changes in the patient's vital parameters and the indices over the period of 1 min after applying the surgical stimuli were interpreted as the response to the nociceptive stimuli. All relevant clinical endpoints such as systolic and diastolic blood pressure, heart rate, and qCON and qNOX values in awake state, in the state of LOC, after applying the nociceptive stimuli and after extubation were monitored and charted down. The mean values of the qCON and qNOX were calculated over the 1-min period after the stimulus.

The qCON and qNOX indices were continuously monitored during surgery to keep the qCON and qNOX values between 40 and 60 in Group B and in Group A continuous hemodynamic monitoring was done to keep the vital parameters (heart rate, systolic and diastolic BP) within a range of 20% from baseline.

If there was an increase in qCON value intraoperatively more than 60, the dose of propofol was increased by a pre-calculated incremental rate (20% of the previous value). Moreover, in case of an increase in qNOX value intraoperatively, the dose of fentanyl was increased by a pre-calculated incremental rate (20% of the previous value) and adjusted accordingly.

At the time of conventional monitoring if there was an increase in heart rate and/or blood pressure more than 20% of the basal value, the dose of both propofol and fentanyl was increased by a pre-calculated incremental rate same as the indices guided monitoring.

At the end of surgery (after the completion of the skin suture), both infusions were stopped after which extubation was done. The time to spontaneous eye opening and extubation was recorded for all patients after the discontinuation of the infusions. Sedation level of each patient was assessed by Ramsay sedation scale (Patient's level of sedation is categorized into six categories ranging from Score 1 – anxious and agitation, Score 2 – tranquil, Score 3 –resonsive, Score 4 – brisk response to a light glabellar tap or auditory stimulus, Score 5 – sluggish response to glabellar tap or auditory stimulus, and score 6 – no response to stimulus). In the post-anesthesia care unit, patients were monitored for 1 h. At the end of 1 h, patients were assessed for adequacy of analgesia by the VAS scoring system.

Statistical analysis

Since our experience with this monitoring equipment is limited. Therefore, we did not apply for formal sample size calculation. We proposed to recruit 50 patients in each group. It was based on a previous study where a sample size of 34 was calculated assuming a difference in emergence (eye opening) of 3 min, an α error of 0.05, and 90% power.[6]

Data were entered into MS Excel (Microsoft Inc.) and cleaned. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then non-parametric test was used. The following statistical tests were applied

1. Quantitative variables were compared using the independent Mann–Whitney U-Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were correlated using the Chi-square test/Fisher's exact test.

$P<0.05$ was considered statistically significant.

RESULTS

During the study period, 100 ASA l and ll patients of both sexes and aged between 18 and 65 years undergoing elective uro-surgical procedure were enrolled. The CONSORT statement is shown in Figure 3.

Data from all 94 patients were collected and analyzed. The demographic characteristics are shown in Table 1. Higher median interquartile range (IQR) age is seen in Group B {39 (16.8)} compared to Group A {36.5 (21)}; however, the difference between the groups is not statistically significant (P=0.334). Statistically higher median BMI was seen in Group A {23.7 (2.4)} than Group B {(22.6 (3.9)}. There was no significant difference seen between the proportion of males and females between the intervention arms (P=0.534). No significant differences were seen between the proportion of patients in ASA Group 1 and ASA Group 2 (P=0.548).

Results showed statistically significant differences between the two groups in the mean dose of both propofol

(P=0.000) and fentanyl (P=0.006), in adjustment frequency of both propofol (P=0.000) and fentanyl (P=0.010), in time required to voluntary eye-opening (P=0.000) and in extubation time (P=0.000) (Figure 4) and VAS Score (P=0.000). There was no statistically significant difference found in infusion duration (P=0.317) and Ramsay Sedation Score (P=0.709) between the groups.

Adjustment frequency of fentanyl is listed in Table 2 and all other variables including propofol frequency of administration and mean dose of propofol are shown in Figure 4 and Table 3.

DISCUSSION

Intraoperative awareness with declarative memory of sensory perception is troublesome for patients undergoing general anesthesia. The incidence is approximately 1–2 per every 1000 patients. This rare but grievous adverse event can be extremely tormenting for both the patient as well as the anesthesiologist. Awareness during anesthesia may occur despite apparently sound anesthetic management and can be associated with intraoperative pain perception.[7]

The present study was conducted to compare the monitoring of depth of consciousness and depth of analgesia by qCON and qNOX indices as against conventional clinical parameters. In demographic data, we found statistically significance differences in BMI and height, but it was not significant clinically.

Melia et al., found that the qCON was able to predict LOC such as loss of verbal command and eyelash reflex while the qNOX was able to better predict response to noxious stimulation such as LMA insertion performed in a study and compared the qCON and qNOX indexes for the assessment of unconsciousness level and noxious stimulation response during surgery.[8]

The dose of propofol was comparable (P=0.11) in CONOX and the control group found in a study done by Jehosua et al.[9] In the same study, they found a significant difference (P<0.05) in the total dose of fentanyl between CONOX and control group.

The results were found similar with Jehosua et al., with respect to mean dose of fentanyl (P=0.006). However, a statistically significant difference in the mean dose of propofol (P=0.000) was observed which was not identical with the study. In the present study, the mean dose of propofol was 3463.6 (374.2) mcg/kg/h and 3960.2 (648.2) mcg/kg/h between qCON and qNOX group and the conventional group, respectively. The mean dose of fentanyl was 1.25 (0.18) mcg/kg/h and 1.32 (0.20) mcg/kg/h between qCON and qNOX group and conventional group, respectively. Adjustment frequency of both fentanyl (P=0.010) and propofol infusion was also found statistically significant in this study.

Oliveira et al., in their study, reviewed the time for spontaneous eye opening upon verbal command and time to tracheal extubation from the end of the last suture. There

Table 1: Demographic variables

Demographic Variables	Group A	Group B	P-value
Age (Median [IQR])	36.5 (21)	39.0 (16.8)	0.334
Gender			
Male	30	33	0.534
Female	20	17	
Height (m), (median [IQR])	1.54 (0.07)	1.6 (0.08)	0.001*
Weight (kg), (median [IQR])	57.5 (9.0)	55.0 (10.5)	0.203
BMI (kg/m^2), (median [IQR])	23.7 (2.4)	22.6 (3.9)	0.046*
ASA I	25	28	0.548
ASA II	25	22	

BMI: Body mass index, IQR: Interquartile range. *P-value were found significant in height and BMI

Figure 1: The conox monitor

Figure 2: The conox monitor with strips

Table 2: Comparison of frequency of fentanyl administration

Frequency of Fentanyl (times/sx)	Total	A n (%)	B n (%)	Chi-square test	P-value
0	10 (10.6)	3 (6.7)	7 (14.3)	13.372	0.010*
1	24 (25.5)	6 (13.3)	18 (36.7)		
2	36 (38.3)	20 (44.4)	16 (32.7)		
3	19 (20.2)	11 (24.4)	8 (16.3)		
4	5 (5.3)	5 (11.1)	0		
Total	94 (100)	45 (100)	49 (100)		

Study groups (A- Conventional group, B- qCON and qNOX group). (P values were significant in case of fentanyl frequency of administration)

Table 3: Comparison of outcome variables between the study groups

Variables	A median (IQR)	B median (IQR)	P-value
Infusion duration (h)	2.3 (1.1)	2 (0.8)	0.317
Mean dose of Fentanyl (mcg/kg/h)	1.32 (0.20)	1.25 (0.18)	0.006*
Adjustment frequency of Propofol (times/s)	2.0 (1.0)	1.0 (1.0)	0.000*
Mean dose of Propofol (mcg/kg/h)	3960.2 (648.2)	3463.6 (374.2)	0.000*
Voluntary eye opening (min)	8.0 (4.0)	5.0 (2.0)	0.000*
Extubating time (min)	11.0 (4.5)	7.0 (3.0)	0.000*
VAS Score	4.0 (2.0)	2.0 (3.0)	0.000*
Ramsay sedation scale	2.0 (2.0)	2.0 (0.0)	0.709

(A- Conventional group, B- qCON and qNOX group). VAS: Visual analog scale, IQR: Interquartile range, Mann Whitney U test done for comparison between the groups, Infusion duration, Mean dose fentanyl, Adjustment frequency propofol, Mean dose propofol, Voluntary eye-opening, Extubation time, VAS score was obtained at post-operative 1 h, Ramsay sedation scale was assessed just after tracheal extubation. (P-value were found significant in the comparison of following variables-mean dose of fentanyl, adjustment frequency of propofol, mean dose of propofol, voluntary eye opening, extubation time, VAS score)

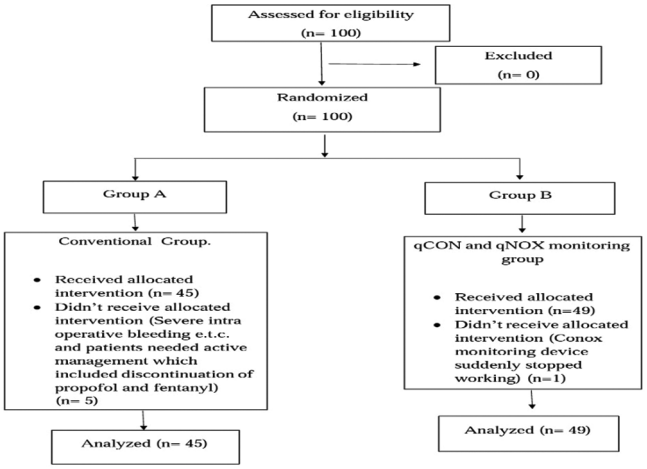

Figure 3: Consort flowchart of the study

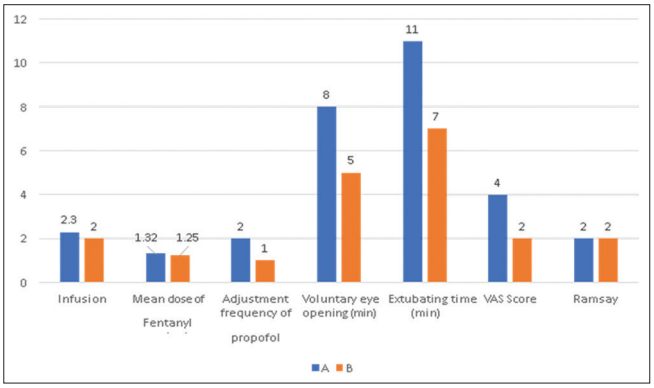

Figure 4: Multiple bar diagram showing comparison of outcome variables between the study groups (unit ignored)

was a reduction in time to eye-opening of 0.63 min in the BIS group than the conventional group but no statistically significant difference was seen. On the other hand, they found a significant reduction in time to extubation in the BIS-guided monitoring group.[10]

The result was found similar with Oliveira et al. with respect to the median time needed for extubation only. In this study, statistically significant difference in both the parameters [median time to voluntary eye opening and median extubating time was observed. The median time to voluntary eye opening was 5.0 (IQR-2.0) min and 8.0 (IQR-4.0) min in qCON-qNOX group and conventional group, respectively. The median time to extubate was 7.0 min and 11.0 min in qCON-qNOX group and the conventional group, respectively.

To compare the recovery status in both groups, we took the help of another two parameters – VAS Score and Ramsay Sedation Scale. It was observed that VAS Score at post-operative 1 h was found significantly lower in qCON-qNOX grouwp (P=0.000). However, the median value of Ramsay Sedation Scale was found comparable in both groups.

Limitations of the study

The few limitations of this study included low risk (ASA grade 1–20 patients) population sample and patients of similar cultural and socioeconomic backgrounds. Future studies on more samples of different ethnicities and cultural backgrounds and patients of higher risk groups and age groups can be studied on more samples of the population.

CONCLUSION

An anesthesiologist can continuously monitor the depth of anesthesia and analgesia of the patients using the qCON and qNOX indices and can adjust the anesthetic or analgesic drug dosing judiciously without excessive dosing. Patients monitored by these indices were found to have less anesthetic and analgesic requirement intraoperatively and better recovery status over the clinical parameter based monitored patients.

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Department of Anaesthesia, IPGMER.

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Authors Contribution:
HD – Literature survey, prepared first drift of manuscript, implementation of the study protocol, data collection, data analysis, and manuscript revision; **SM**- Definition of intellectual content, concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **BL**- Design of study, statistical analysis, and interpretation; **SS** – Definition of intellectual content, design of the study, review a manuscript, literature survey and preparation of figures, coordination, and manuscript revision; **USM** – Statistical analysis and interpretation, manuscript preparation, and editing; **SG** – Design of study, statistical analysis, and interpretation review manuscript.

Work attributed to:
Institute of Post Graduate Medical Education and Research, SSKM Hospital, Kolkata 700020, West Bengal, India.

Orcid ID:
Himalaya Dutta - https://orcid.org/0009-0007-0274-7326
Suchismita Mallick - https://orcid.org/0000-0001-9913-0080
Baisakhi Laha - https://orcid.org/0000-0002-6260-020X
Sarbari Swaika - https://orcid.org/0000-0002-0525-8460
Uday Sankar Mandal - https://orcid.org/0000-0002-2886-8333
Sarmila Ghosh - https://orcid.org/0009-0007-0568-4930

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