



Intraoperative Nociception Monitoring by qNOX Score Using Three Different Doses of Fentanyl

Alisha Kaur, Nandita Mehta, Sunana Gupta

Abstract

Background: The qCON and qNOX scores in the conox monitor measures depth of anaesthesia and analgesia respectively. qNOX, a parameter extracted from the raw EEG could predict the likelihood of movement response to different anaesthetic and surgical stimuli. Various workers have used various doses of fentanyl to find an optimal dose that will achieve adequate analgesia and at the same time will reduce the occurrence of its side effects. **Purpose:** Primary objective was to study and compare the effect of three different doses of fentanyl on nociception score qNOX and secondary objective was to compare the number of doses of Inj paracetamol used and extubation time in three groups. **Material and Methods:** Study was done in ninety patients scheduled for elective surgery under general anaesthesia who were randomly assigned to group I, II and III to receive fentanyl in the dose of 1, 1.5 and 2 microgram/kg respectively. Parameters recorded were values of qNOX scores at various time intervals, number of patients requiring Inj paracetamol intraoperatively, extubation time and any side effect of study drug in all the three groups. **Results:** The mean values of qNOX score and Inj paracetamol required intraoperatively was highest in the group of patients who received fentanyl in the dose of 1 mcg/kg and lowest in patients who received fentanyl in the dose of 2 mcg/kg. The difference between all the three groups was statistically significant ($p < 0.05$). The mean extubation time was insignificant between group 1 and II, Group II and III but was significant between I and III ($p < 0.05$). **Conclusion:** Fentanyl in a dose of 2 micrograms per kg was able to achieve desired qNOX scores intraoperatively without any serious side effects.

Key Words

Nociception, Fentanyl, qNOX, qCON

Introduction

Adequate analgesia and awareness prevention are two important components of balanced anaesthesia. Different methods have been used to monitor nociception and awareness under general anaesthesia. Pain is, by its very nature, subjective, per se non-existent, and hence, unmeasurable in anaesthetised subjects but pathophysiological response to pain called as nociception can be measured. Nociception, in contrast to pain, is not a subjective feeling, but the physiological encoding and

processing of nociceptive stimuli (1).

Traditionally nociception is estimated by evaluating hemodynamic responses, along with sweating, lacrimation, increase in pupil diameter or movement. In the last few years various nociception monitors have been introduced whose purpose is to measure the nociceptive stimulus suppression level. These monitors ensure appropriate blockage of the body reaction to nociception (2,3).

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CONOX monitor (qCON 2000 plus, Quantum medical, Barcelona, Spain) is depth of anaesthesia monitor. It measures qNOX which is the probability of a patient to respond to noxious stimuli in addition to qCON which indicates the patient's level of consciousness. Fentanyl is the most common opioid used for intraoperative analgesia. Since there is a wide range in the dose of fentanyl used for intraoperative analgesia, varying from as low as 1 microgram/kg to 5 microgram/kg, we planned a study to compare and evaluate the effect of three different minimum doses of fentanyl on qNOX values as measured by the CONOX monitor.

Material and Methods

After obtaining approval from the Institutional Ethics Committee, the present study was undertaken in the Department of Anaesthesiology and Intensive Care, ASCOMS and Hospital, Jammu for a period of one-year w.e.f. November 2018 to October 2019, in 90 patients. Informed written consent was obtained from the patients preoperatively. Patients were divided according to computer generated table of randomization into three equal groups with thirty patients in each group.

Group I (n=30) - received fentanyl at 1 µg/kg.

Group II (n=30) - received fentanyl at 1.5 µg/kg.

Group III (n=30) - received fentanyl at 2 µg/kg.

The inclusion criteria were ASA grade I and II patients, of either gender, age group between 18-65 years, scheduled for surgeries under general anaesthesia.

Patients excluded from the study were ASA grade III and IV, age <18 years and >65 years, patients with clinical record of psychiatric or neurological disease, patients on medications which affect the central nervous system, drug or alcohol abusers, known hypersensitivity or intolerance to fentanyl and other opioid analgesics, head injuries and increased intracranial pressure.

All patients underwent a pre anaesthetic check up one day prior to surgery which included a detailed history, a thorough physical examination (general and systemic) and routine investigations. All patients received tab. alprazolam 0.25 mg and tab pantoprazole 40 mg night before surgery and were kept fasting for six hours prior to surgery.

On the morning of surgery, a peripheral I/V line was established with 18G cannula in pre operative room. On arrival in the operating room, standard clinical monitoring devices were applied (NIBP cuff, ECG, pulse oximeter). Disposable sensors of CONOX monitor were applied to patient's forehead. CONOX monitor was connected to

the sensor (which had been applied to the patient's forehead). Baseline value of NOX were recorded. Anaesthesia was induced with fentanyl at 1 µg/kg, or 1.5 µg/kg, or 2 µg/kg i/v depending on the group followed by propofol at 2.5 mg/kg intravenously. Laryngoscopy and tracheal intubation were facilitated with rocuronium at 0.6 mg/kg. qNOX values was recorded just before laryngoscopy and 5 minutes after tracheal intubation and every 15 minutes thereafter till surgery is completed. All patients received diclofenac 75 mg i/v infusion immediately after induction. Anaesthesia was maintained with isoflurane at 1-1.5% inspired concentration in combination with N₂O (66%) and O₂ (33%) and intermittent doses of Inj rocuronium.

If NOX values were persistently >60 for more than 5 minutes, an infusion of paracetamol 1 gm was given over 20 minutes and number of patients requiring this was noted. All patients received i.v ondansetron at 0.1 mg/kg 10-15 mins before the end of surgery to reduce post operative emesis. All inhaled anaesthetics were discontinued on the completion of skin closure. Neostigmine at 50 µg/kg and glycopyrrolate at 10 µg/kg were given to antagonize residual neuromuscular block.

The following parameters were recorded intraoperatively:

1. Baseline qNOX values were recorded. After that qNOX values were recorded before laryngoscopy, 5 minutes after intubation and every 15 minutes thereafter till the end of surgery.
2. Number of patients requiring paracetamol infusion for analgesia (if NOX persistently >60).
3. Extubation time: Time from skin closure to the removal of endotracheal tube.
4. Side effects related to the study drug like respiratory depression, pruritis, skeletal and thoracic muscle rigidity etc.

Statistical Analysis:

At the end of the study all the data was compiled and analyzed statistically. Comparison of mean value among the two groups was done using students *t*-test and percentage comparison was done using the chi square test. To compare more than two variables ANOVA test was used. The *p* value of less than 0.05 was considered statistically significant

Results

Data from 90 patients was analysed. Patients in the three groups were comparable with respect to the baseline

Table 1: Demographic Parameters

Variable	Fentanyl 1 mcg/kg (n=30)	Fentanyl 1.5 mcg/kg (n=30)	Fentanyl 2 mcg/kg (n=30)
Age (in years) Mean ± SD	44.46 ± 11.6	45.16 ± 13.08	42.2 ± 12.91
Sex Male: Female Ratio	15:15	16:14	15:15
ASA I/II	20/10	13/17	21/9
Duration Surgery (minutes)	57 ± 3	58 ± 2	59 ± 1.5

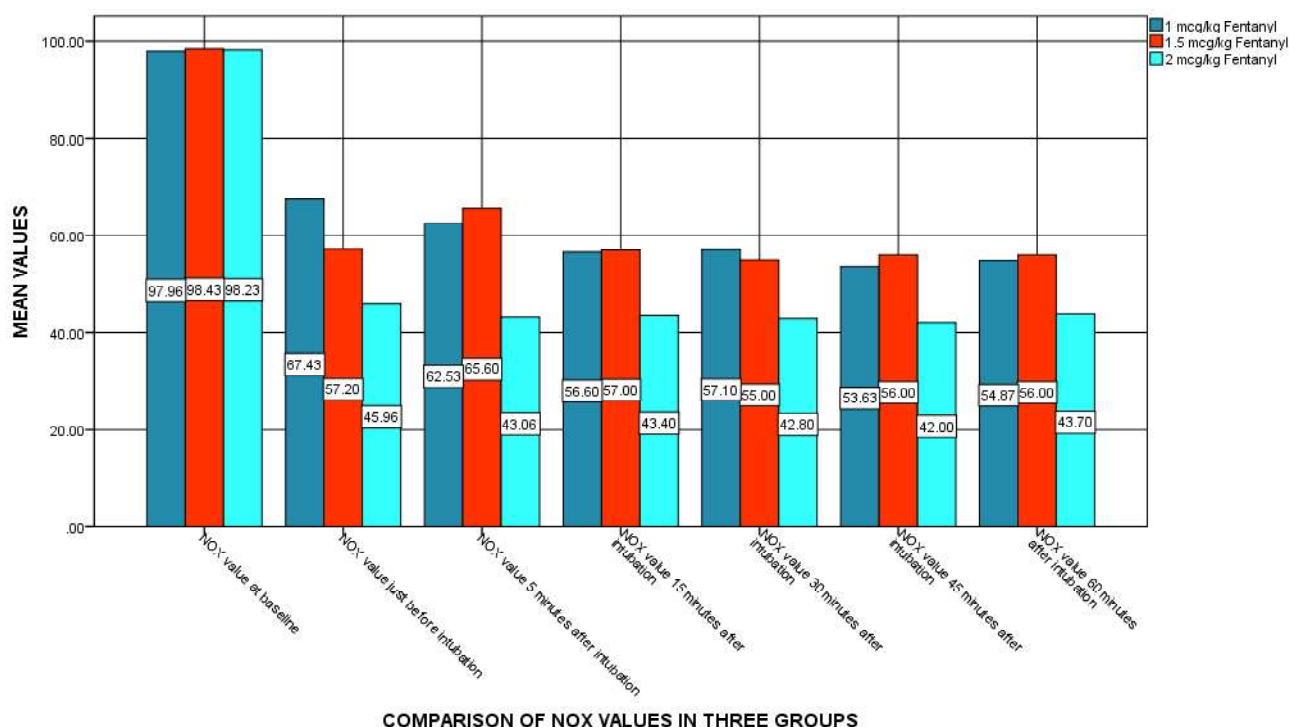


Figure 1: Depicts the Mean qNOX Values in the Three Groups Intraoperatively

demographic characteristics as depicted in *Table 1*.

On inter group comparison between group I & II the NOX value after administration of fentanyl was significant just before intubation and at 5 mins and thereafter remained insignificant. Inter group comparison between group II & III showed significant difference in qNOX values all through the study period ($p < 0.05$). Inter group comparison between group I & III also showed significant difference in NOX values all through the study period ($p < 0.05$) (*Figure 1*) (*Table 2*).

Out of 30 patients in group I, 22 required injection paracetamol whereas in group III only one patient

required the same for intraoperative analgesia. The number of patients who required Inj. paracetamol was highest in patients who received fentanyl in the dose of 1mcg/kg and lowest in patients who were administered fentanyl in the dose of 2mcg/kg. The results were statistically significant ($p < 0.05$) (*Table 3*).

Table 4 shows the mean extubation time in all the three groups. Inter group comparison between the mean extubation time between group I & II, II & III came out to be non-significant (p values 0.0503 and 0.0570 respectively) whereas the intergroup comparison between group I and III came out to be significant ($p = 0.0001$).

Table 2: Mean qNOX Values (Intergroup Comparison)

Time	Group I vs Group II (p values)	Group II vs Group III (p values)	Group I vs Group III (p values)
At baseline	0.06	0.103699	0.1
Just before intubation	0.0001	0.0001	0.0001
5 minutes after intubation	0.0001	0.0001	0.0001
15 minutes after intubation	0.942	0.0001	0.0001
30 minutes after intubation	0.070	0.0001	0.0001
45 minutes after intubation	0.162	0.0001	0.0001
60 minutes after intubation	0.416	0.0001	0.0001

Table 3: Patients Requiring Inj. Paracetamol Intraoperatively

	1µg/kg Fentanyl	1.5µg/kg Fentanyl	2 µg/kg Fentanyl
Yes	22	9	1
No	8	21	29

Table 4: Mean Extubation Time

Extubation Time	1µg/kg Fentanyl	1.5 µg/kg Fentanyl	2 µg/kg Fentanyl
Mean ± SD (minutes)	2.95 ± 0.65	3.56 ± 1.54	4.12 ± 0.35

Discussion

International association for the study of pain has defined nociception as the neural process of encoding noxious stimuli, causing autonomic and/or behavioural responses such as elevation of blood pressure or motor withdrawal reflexes; noxious stimuli are actually or potentially tissue damaging events that occur during surgery (4).

Inadequate intraoperative analgesia can lead to unexpected movements during surgery, release of stress hormones and increases the incidence of postoperative complications like haemorrhage and wound healing (5), whereas excessive intraoperative analgesia can result in prolonged sedation and respiratory insufficiency (6). Thus, monitoring nociception remains an important goal of modern anaesthesia practice and needs to be quantified to prevent over or under dosing of analgesics (7). Ideal dosing of intraoperative opioids is essential because of the growing understanding of their potentially significant non analgesic side effects, such as immunosuppression (8).

The most frequently utilised response to surgical stress is an increase in sympathetic activity or corresponding decrease in parasympathetic tone which forms the basis of most of the available nociception monitors. These monitors measure increase in heart rate, peripheral vasoconstriction, pupillary dilatation and an increase in galvanic skin conductance in response to sympathetic

stimulation. In addition to this, stress may also influence heart rate variability, electroencephalographic and electromyographic patterns and the threshold of peripheral reflexes (1).

The qCON and qNOX scores in the conox monitor measures depth of anaesthesia and analgesia respectively. qNOX is a dimensionless score based on EEG and EMG data. The mathematical model used for the development of qNOX is an adaptive neuro fuzzy inference system which generates the output on a 0-99 scale (9). It differs from other nociception monitoring in that it does not rely on sympathetic activity and there are less chances of the score being affected by cardiovascular medications and comorbidities (8).

Fentanyl being a short acting and a potent opioid is being used in the management of acute perioperative and post operative pain. On literature search, we have not found any study using various doses of fentanyl for maintaining NOX values between 40-60. However, there are a lot of studies for decreasing awareness during perioperative period using propofol alone or in combinations with opioids (10).

We found that the NOX values were highest in Group I and lowest in Group III. On inter group comparison between the three groups (for NOX values) significant difference between Group I and III and Group II and III was observed. The findings of our study show that



although dose of 1.5 mcg/kg brings NOX value between 40-60, but it does not persist for more than a few minutes after intubation. Whereas, dose of 2 mcg/kg maintains the NOX value at the desired level throughout the perioperative period.

Melia *et al.* (11) studied the qNOX and qCON index for the assessment of unconsciousness level and noxious stimulation response during surgery. The results of their study showed that the qCON has a predictive value of loss of consciousness such as loss of verbal command and eyelash reflex while the qNOX has a predictive value of response to noxious stimulation such as LMA insertion. They like our study also found that the qNOX values correlated well with the level of analgesia and qNOX is able to quickly detect a change between unresponsive and responsive states compared with the qCON and it might avoid situations of pain during loss and recovery of consciousness.

Jensen *et al.* (12) did a study to validate the monitoring of hypnotic effect and nociception with two EEG derived indices, CON and NOX during general anaesthesia. They stated that although qCON was able to reliably detect loss of consciousness during general anaesthesia with propofol and remifentanyl, the qNOX showed significant overlap between movers and non movers, but it was able to predict whether or not the patient would move as a response to noxious stimulation, although the anaesthetic concentrations were similar. They also pointed out that the qNOX is not totally independent from the depth of anaesthesia parameter qCON and that the score may be significantly influenced by deep levels of anaesthesia. Study by Ledowski *et al.* (13) found that qNOX score was not useful in predicting pain scores in the immediate postoperative period.

The results of our study showed that number of patients requiring injection paracetamol was lowest in Group III and highest in Group I. Patients receiving fentanyl in the dose of 2 microgram per kg had intraoperative rarely achieved qNOX values more than 60 and required less paracetamol whereas the patients receiving 1 and 1.5 micrograms per kg required more paracetamol intraoperatively. Meijer *et al.* (2) in their systematic review found that out of 12 randomised controlled trials, seven found a reduced opioid consumption when intraoperative nociception monitoring was done and four trials did not find a significant difference in opioid consumption.

Regarding extubation time, in our study, patients in group I could be extubated early as compared to group II

and III. Although statistically the difference in extubation was only significant between group I and III but clinically patients in group I could be extubated earliest at an average of 2.95 ± 0.65 min and those in group III could be extubated at 4.12 ± 0.35 min. Jakuscheit *et al.* (6) in their study found that extubation time was delayed when analgesia was monitored intraoperatively using nociceptive reflexes. We did not encounter any side effect related to the study drug in our study.

Limitation of our study is that although fentanyl is a short acting opioid, we used single bolus dose irrespective of the type and duration of surgery and doses higher than 2 micrograms can also be studied. Further we did not study the effect of duration of surgery on the extubation time.

Conclusion

The desired value of qNOX (40-60) was achieved in almost all through the perioperative period in the group of patients who received fentanyl in the dose of 2 microgram per kg. Also, this group of patients did not require additional doses of injection paracetamol for maintaining nox values between 40-60. Thus, fentanyl in the dose of 2 micrograms per kg provided desired levels of nox score intraoperatively and with no serious side effects.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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