Research Article ISSN 2639-846X

Anesthesia & Pain Research

Assessment of Depth of Anesthesia Using Three Different Doses of Fentanyl: Validation of qCON

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Received: 21 Jan 2025; **Accepted:** 21 Mar 2025; **Published:** 28 March 2025

Citation: Mehta Nandita, Kour Alisha, Agha Aqib Ali. Assessment of Depth of Anesthesia Using Three Different Doses of Fentanyl: Validation of qCON. Anesth Pain Res. 2025; 9(1): 1-5.

Keywords

Depth of Anesthesia, Fentanyl, qCON.

Introduction

Ensuring effective pain relief and preventing awareness are crucial elements of balanced anesthesia. Various techniques have been employed to monitor both pain perception and awareness during general anesthesia. In the context of anesthesia literature, "awareness" refers to a situation where, despite undergoing intended general anesthesia, the brain remains responsive to stimuli, leading to memories that can be consciously recalled later. Patients who experience such awareness during surgery are likely to remember these experiences after the procedure [1]. Many patients experience anxiety, including feelings of helplessness, panic, and fears of impending disaster. Some may develop post-traumatic stress disorder, which can manifest as nightmares, disturbing dreams, sleep disturbances, daytime anxiety, intrusive thoughts, irritability, avoidance of medical care, and fear of future anesthesia and long-term psychological issues. Intraoperative awareness can have significant and lasting effects, including potential legal consequences [2]. The most frequent cause of awareness is insufficient anesthesia, which may result from inadequate anesthetic medication, individual variations in anesthesia needs, or problems with the anesthesia machine [1]. For monitoring of intraoperative awareness, a range of techniques have been developed over the years. These include methods that measure responses to auditory stimuli, as well as those that analyze spontaneous Electroencephalography and electromyographic activity. Notable systems in this category are Danmeter, Cerebral State Monitor, SNAP Index, Patient State Analyzer, Entropy, Narcotrend, Bispectral Index (BIS), and CONOX.

The CONOX monitor (Q Con 2000 Plus, Quantum Medical, Barcelona, Spain) is used to gauge the depth of anesthesia. It assesses NOX, which reflects the likelihood that a patient will respond to noxious stimuli, and CON, which represents the patient's level of consciousness. The monitor provides both primary and secondary indices derived from the patient's EEG. The primary qCON index is a dimensionless scale ranging from 0 to 99, used to estimate the patient's consciousness level. Lower values on this index indicate a deeper level of anesthesia and a progressive loss of consciousness.

In balanced anesthesia, we utilize propofol and inhalational anesthetics, along with multimodal analgesia, which includes opioids, NSAIDs, and acetaminophen, to reduce awareness. Opioids administered parenterally are also part of this approach to ensure adequate depth of anesthesia and pain relief. Fentanyl, favoured for its relatively short duration of action and fewer side effects, is the opioid most commonly used to manage intraoperative analgesia and reduce awareness. Because fentanyl dosages for intraoperative analgesia and awareness can range widely, from 1 mcg/kg to 5 mcg/kg, this study aimed to compare and assess the effects of three different minimum doses of fentanyl (1 mcg/kg, 1.5 mcg/kg, and 2 mcg/kg) on the CON value as measured by the CONOX monitor.

Materials and Methodology

The research was undertaken at Acharya Shri Chander College of Medical Sciences and Hospital, Jammu in the Department of Anaesthesia and Critical Care. The study involved 90 patients. Before the procedure, the study respondents gave their written, informed consent. Participants were randomly assigned into three groups, each consisting of 30 patients, based on a computer-generated randomization table.

Group I- was given fentanyl at a dose of 1 µg/kg.
Group II- was given fentanyl at 1.5 µg/kg.
Group III- was given fentanyl at 2 µg/kg.

American Society of Anaesthesiologists (ASA) grade I and II patients, of any gender, between the ages of 18 and 65 years, who were scheduled for procedures under general anaesthesia, met the study's inclusion requirements. Patients with psychiatric or neurological disorders, those taking medications that affect the central nervous system, drug or alcohol abusers, those with known hypersensitivity or intolerance to fentanyl and other opioid analgesics, patients with head injuries or elevated intracranial pressure, and patients classified as ASA grade III and grade IV were all excluded. Furthermore, procedures that lasted longer than two hours were not included in the study.

Pre-anaesthetic check-up was conducted one day prior to surgery, which comprised of a detailed medical history, a systematic physical examination, and routine tests. On the night before surgery all the patients received 0.25 mg of alprazolam and 40 mg of pantoprazole. The patients were kept nil per oral six hours before the procedure. Upon arrival in the operation theatre, all the routine monitors (Electrocardiography, Non-Invasive Blood Pressure, Pulse oximetry) were attached in addition to the CONOX monitor.

Depending on the assigned group, fentanyl at 1 µg/kg, 1.5 µg/kg, or 2 µg/kg was used to induce anaesthesia. Propofol at 2.5 mg/kg was then administered intravenously. In order to facilitate tracheal intubation and laryngoscopy, 0.6 mg/kg of rocuronium was given. qCON values were noted prior to laryngoscopy, five minutes after intubation, and then every fifteen minutes until the procedure was concluded. Following induction, all patients received 75 mg of diclofenac via intravenous infusion. Isoflurane at an inspired concentration of 1–1.5%, together with 66% N_2O and 33% O_2, and intermittent rocuronium dosages, were used to maintain anaesthesia. Instances where CON values were greater than 60 for more than 5 minutes, the plane of anaesthesia was deepened by increasing the concentration of Isoflurane. Observations of all the participants requiring this measure was made. All the participants were administered intravenous ondansetron at a dose of 0.1 mg/kg, 10-15 minutes prior to the conclusion of the surgery, to help prevent postoperative nausea and vomiting. Inhaled anaesthetics were stopped once the skin closure was complete. To reverse any remaining neuromuscular block, neostigmine at 50 µg/kg and glycopyrrolate at 10 µg/kg were administered.

Intraoperatively, the frequency of patients needing an increase in isoflurane concentration was monitored, particularly when the qCON values stayed above 60. Additionally, the time required for extubation was recorded as the duration from the closure of skin to the extubation of the trachea. Furthermore, any adverse effects associated with the study drug, including skeletal or thoracic muscle rigidity, were carefully documented. Post-anesthesia care unit (PACU) discharge readiness was also assessed using the Modified Aldrete Scoring system.

Statistical Analysis

The data were collected and statistically examined at the end of the study. The Student's t-test was used to compare the mean values between the two groups, and chi-square test was used to evaluate percentage comparisons. The ANOVA test was used for comparing more than two variables. A p-value of less than 0.05 was deemed statistically significant.

Results

The baseline demographic characteristics of 90 patients across the three groups were comparable, as illustrated in Table 1.

Table 1: Demographic Characteristics.

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

Comparing Fentanyl 1mcg/kg versus Fentanyl 1.5mcg/kg groups, there was a significant difference in CON values after fentanyl administration, specifically just before intubation, as well as at 5 minutes and 15 minutes ($p<0.05$). A comparison between Fentanyl 1.5mcg/kg and Fentanyl 2mcg/kg groups revealed significant differences in CON values throughout the entire study period ($p<0.05$). Similarly, Fentanyl 1mcg/kg versus Fentanyl 2mcg/kg groups also showed significant differences in CON values throughout the study period ($p<0.05$) (See Figure 1 and Table 2).

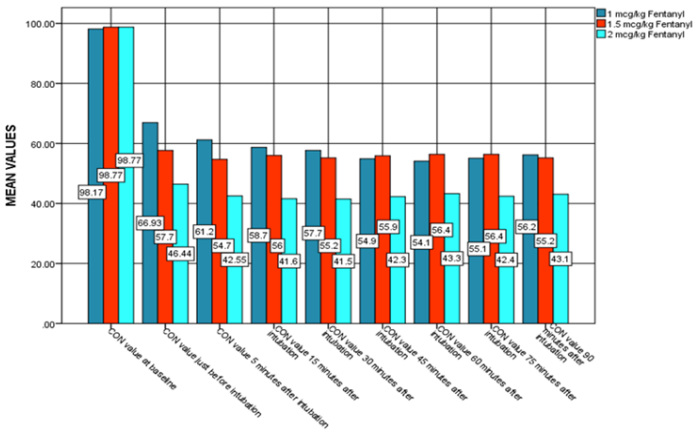

Figure 1: Comparison of Mean qCON Values among three Groups.

Table 2: Intergroup comparison of mean qCON values.

Observation Time	Fentanyl 1 µg/kg vs Fentanyl 1.5 µg/kg	Fentanyl 1.5 µg/kg vs Fentanyl 2 µg/kg	Fentanyl 1 µg/kg vs Fentanyl 2 µg/kg
Baseline	0.0	1.00	0.08
Just before intubation	0.0001	0.0001	0.0001
5 mins after intubation	0.0001	0.0001	0.0001
15 minutes after intubation	0.028	0.0001	0.0001
30 minutes after intubation	0.68	0.0001	0.0001
45 minutes after intubation	0.55	0.0001	0.0001
60 minutes after intubation	0.11	0.0001	0.0001

Among 30 patients who were given 1 µg/kg fentanyl, 23 patients required an increase in Isoflurane concentration to deepen the plane of anaesthesia whereas no patient in the 2 µg/kg Fentanyl group required the same. Patients who received Fentanyl at a dose of 1 µg/kg had the highest need for isoflurane to deepen the plane of anaesthesia, whereas no patients required it when administered Fentanyl at a dose of 2 µg/kg. This finding was statistically significant ($p < 0.05$).

Table 3: Comparison of three groups according to increased Isoflurane requirement.

Increased Isoflurane Requirement	1 µg/kg Fentanyl	1.5 µg/kg Fentanyl	2 µg/kg Fentanyl	p-value
Yes	23	10	0	0.00**
No	7	20	30	

The average extubation time for patients who received fentanyl at doses of 1 µg/kg, 1.5 µg/kg, and 2 µg/kg was 2.73, 4.23, and 6.96 minutes, respectively (see Table 4). This indicates that the extubation time was shortest for those given 1 µg/kg of fentanyl and longest for those given 2 µg/kg. The differences observed were statistically significant ($p < 0.05$). Regarding post anaesthesia discharge, the average time to PACU discharge readiness, as assessed by the Modified Aldrete Scoring system for patients receiving fentanyl at doses of 1 µg/kg, 1.5 µg/kg, and 2 µg/kg was 5.56, 7.46, and 15 minutes, respectively (see Table 5). This shows that patients who received 1 µg/kg of fentanyl were ready for discharge from the PACU the earliest, while those who received 2 µg/kg had the longest discharge readiness time. These differences were statistically significant ($p < 0.05$).

Table 4: Comparison of three groups according to Extubation time.

	1 µg/kg Fentanyl (Mean ± SD)	1.5 µg/kg Fentanyl (Mean ± SD)	2 µg/kg Fentanyl (Mean ± SD)	ANOVA (p-value)
Extubation time (in mins)	2.73 ± 0.58	4.23 ± 1.79	6.96 ± 0.08	0.005*

Table 5: Comparison of three groups according to PACU discharge readiness.

	1 µg/kg Fentanyl (Mean ± SD)	1.5 µg/kg Fentanyl (Mean ± SD)	2 µg/kg Fentanyl (Mean ± SD)	ANOVA (p-value)
PACU discharge readiness (in mins)	5.56 ± 2.53	7.46 ± 3.57	15	0.020*

Discussion

Awareness is defined as a patient's ability to remember, either with or without assistance, any events that took place during anesthesia. A patient experiencing intraoperative awareness may remember conversations among the surgical team, various images, and dream-like experiences. They might also report sensations of weakness, paralysis, or immobility, as well as hearing noises (such as instrument sounds) or voices (like the surgeon's voice).

Clinical and conventional monitoring techniques are being used to assess awareness during anaesthesia. Clinical techniques include checking for movement, response to commands, eyelash reflex, pupillary responses, respiratory pattern, perspiration and tearing. Conventional monitoring systems include ECG, blood pressure, heart rate, end tidal anesthetic analyser and capnography. Though clinical parameters like patient's cardiac and respiratory rhythm, blood pressure, production of tears and sweat, pupil size have been used for assessing the depth of anaesthesia but they are all surrogate markers and cannot reliably tell about analgesia and awareness [3].

The CONOX monitor, introduced in 2019, offered the capability to measure both CON (level of consciousness) and NOX (level of analgesia). The CONOX monitor uses qCON and qNOX scores to assess the depth of anesthesia and analgesia, respectively. qCON is a dimensionless score derived from EEG and EMG data, and its calculation is based on an adaptive neuro-fuzzy inference system that produces results on a 0-99 scale [4].

In comparison to the BIS monitor, the CONOX monitor offers several advantages, especially in terms of cost-effectiveness and financial viability. The CONOX monitor is generally more affordable, making it a more accessible option for many healthcare facilities without compromising on the quality of data. This financial benefit is particularly important in settings where budget constraints are a significant concern. The BIS monitor has notable drawbacks, primarily its reliance on EEG data alone, which may not fully capture individual patient responses or complex anesthetic interactions. It also lacks a dedicated measure of analgesia, necessitating additional tools or subjective assessments for comprehensive pain management, which can complicate and increase the cost of anesthesia monitoring. Furthermore, BIS monitors are often criticized for their high cost, which can be prohibitive for resource-limited settings, and their accuracy may be affected by muscle relaxants and EEG signal artifacts, leading to potential inconsistencies in depth-of-anesthesia readings. Fentanyl,

introduced by Janssen Pharmaceutica in the 1960s, quickly became a widely used potent analgesic for intraoperative pain management due to its relatively few side effects. In smaller to moderate doses (1-5 µg/kg), it is typically used alongside other intravenous agents to achieve balanced anesthesia. In contrast, larger doses (up to 100 µg/kg) are employed to both induce and maintain anesthesia in critically ill patients and those undergoing cardiopulmonary bypass procedures. Fentanyl offers several benefits, including the ability to reduce the required doses of volatile and hypnotic anesthetic agents, which lowers the risk of side effects and promotes quicker recovery [5]. Therefore, a study was carried out to determine the optimal fentanyl dose for achieving the appropriate depth of anesthesia using the CONOX monitor. The research involved 90 patients classified as ASA I and II, aged 18 to 65 years, who were scheduled for surgery under general anesthesia. In our study, the goal was to keep the qCON value within the range of 40 to 60 throughout the perioperative period.

In our study, a significant difference in CON values was noted among the three groups, specifically between Fentanyl 1 µg/kg and Fentanyl 1.5 µg/kg groups, Fentanyl 1 µg/kg and Fentanyl 2 µg/kg groups and Fentanyl 1.5 µg/kg and Fentanyl 2 µg/kg groups. The results indicate that while a dose of 1.5 µg/kg achieves a CON value between 40 and 60, this effect is short-lived, lasting only a few minutes after intubation. In contrast, a dose of 2 µg/kg effectively maintains the CON value at the desired level throughout the entire perioperative period. The findings of our study are in accordance with a study conducted by Pineda et al. [6], who monitored the hypnotic effects during general anesthesia using qCON. The results indicated that qCON was a reliable indicator for detecting loss of consciousness. During anesthesia, qCON values decreased within the 40 to 60 range. If the value of CON exceeded 60 and remained so for more than 5 minutes, we increased the concentration of Isoflurane to decrease the value of CON to 40-60. The number of patients requiring Isoflurane was highest in the group that received 1 µg/kg Fentanyl and none of the patients in the group that received Fentanyl 2 µg/kg required an increase in Isoflurane concentration.

As far as extubation time (the time from the closure of skin to the removal of the endotracheal tube) is concerned patients who were administered Fentanyl 1 µg/kg could be extubated earlier (2.73 minutes) as compared to those who were administered Fentanyl 2 µg/kg (6.96 minutes). Although the extubation time in the 2 µg/kg Fentanyl group (6.96 minutes) was statistically significant as compared to Fentanyl 1 µg/kg group (2.73 minutes) and Fentanyl 1.5 µg/kg group (4.23 minutes) but clinically this increase in extubation time is not so significant given the haemodynamic stability with 2 µg/kg Fentanyl. Additionally, a 6.96-minute extubation time, while longer, is not considered a significant delay in practical terms.

In a 2015 randomized controlled trial by Shi et al. [7], fentanyl at 2 µg/kg was compared to a placebo in children undergoing sevoflurane anesthesia. The study found that fentanyl administration reduced the incidence of emergence agitation and postoperative pain but also slightly increased the extubation time, emergence time, and time spent in the PACU compared to the placebo. These findings align with our study, where the extubation and PACU discharge times were only slightly longer with a 2 µg/kg dose compared to a 1 µg/kg dose. Regarding post-anesthesia discharge, the average time to reach PACU discharge readiness, as evaluated by the Modified Aldrete Scoring system, varied for patients administered fentanyl at doses of 1 µg/kg, 1.5 µg/kg, and 2 µg/kg. The times recorded were 5.56 minutes, 7.46 minutes, and 15 minutes, respectively. This indicates that patients who received 1 µg/kg of fentanyl were ready for PACU discharge the earliest, whereas those given 2 µg/kg had the longest readiness time. These differences were statistically significant.

Arora et al. [8] aimed to compare the postoperative recovery characteristics of fentanyl and butorphanol in 100 patients undergoing open cholecystectomy under general anesthesia. Their findings indicated that patients administered fentanyl at a dose of 2 mcg/kg were discharged earlier compared to those who received butorphanol. This aligns with our observation that patients receiving lower doses of fentanyl (1 µg/kg) were ready for PACU discharge sooner, whereas higher doses of fentanyl (2 µg/kg) resulted in longer discharge times. The prolonged discharge readiness with higher fentanyl doses may be attributed to its extended effects, though it was still quicker than butorphanol, which is known to cause postoperative respiratory depression and prolonged sedation. This underscores the impact of opioid choice and dosage on recovery time and highlights the need to balance efficacy and side effects in postoperative pain management [9].

Our study has the following limitation: Although fentanyl is classified as a short-acting opioid, it was administered as a single bolus dose irrespective of the duration of the surgical procedure. This approach may not fully account for variations in opioid requirements based on the length and intensity of the surgery. This limitation suggests that further research with a dosing regimen tailored to the length of the surgical procedure could provide more accurate insights into the relationship between fentanyl dosage and extubation times.

Conclusion

In patients who received fentanyl at a dose of 2 µg/kg, the desired qCON range of 40-60 was effectively maintained throughout the perioperative period. This dosage also eliminated the need for additional increases in isoflurane concentration to sustain qCON values within the target range. Consequently, fentanyl at 2 µg/kg was successful in achieving the appropriate depth of anesthesia during surgery and was associated with no significant side effects. Furthermore, the CONOX monitor demonstrated its efficacy as a reliable tool for measuring consciousness levels perioperatively.

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