ORIGINAL ARTICLE

Quantium Consciousness Index and Quantium Noxious Index in Ketamine Subdose Administration Compared with Fentanyl and Midazolam in Postoperative ICU Patients: A Prospective, Observational Study

Alegra R Masharto[1], Andriamuri P Lubis[2], Chrismas G Bangun[3], Arlinda S Wahyuni[4]

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Abstract

Aims and background: In postoperative patients in the intensive care units (ICUs), not only analgesics are needed but also sedation so that the patient can remain calm during treatment, especially patients with mechanical ventilation. By using the measurement parameters of the quantum consciousness index (qCON) and quantum noxious index (qNOX) in measuring the depth of sedation and adequacy of analgesics, the use of subdose ketamine instead of fentanyl and midazolam as sedative, analgesic agents can be performed as a new alternative to nociceptive monitoring methods with more objective results. This study aims to obtain results of comparing qCON and qNOX in postoperative patients by administering subdose ketamine compared with a combination of fentanyl and midazolam in RSUP Haji Adam Malik Medan.

Materials and methods: A randomized clinical trial with a double-blind approach has been used in this study. A total of 44 experimental samples were gathered and randomly split into two groups after meeting the criteria for inclusion. Group A administered a ketamine subdose, whereas Group B administered a mixture of fentanyl and midazolam. The research data obtained were tested using Statistical Product and Science Service (SPSS).

Results: There were differences in the median, minimum, and maximum values of qCON and qNOX in the groups given subdose ketamine and fentanyl and midazolam, but these were not statistically significant ($p > 0.05$) at T0, T1, and T2.

Conclusion: Administering a subdose of ketamine can provide sedation and analgesia comparable to fentanyl and midazolam.

Keywords: Fentanyl, Intensive care units, Ketamine, Midazolam, Postoperative, qCON, qNOX, Subdose.

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Highlights

This study uses primary data, which is homogeneous based on the normality test, so it is considered appropriate to represent the population and reduce research bias. It was considered not to have much influence on hemodynamics. It was proven that there appeared to be no significant difference between the two groups.

Introduction

Postoperative patients often experience various problems, one of which is pain, with nearly 5 million postoperative patients being treated in intensive care units (ICUs) annually, and it estimated that 71% of these patients stated that they experienced pain while in treatment.[1,2] It is important to note that, leading to increased patient morbidity and mortality, improper pain management in critical patients can increase respiratory, metabolic, and infectious complications, while, on the other hand, adequate pain management is linked to a relatively short duration of mechanical breathing, decreased nosocomial infection rates, and increased patient satisfaction with pain control.[3,4]

In a recent study, the use of the following tool is considered to be more objective because it shows a number/index, while the previous assessment of pain and sedation was carried out by subjective physical examination, where it was stated that the measurement of quantum consciousness index (qCON) and quantum noxious index (qNOX) is considered to be similar to Critical Care Pain Observation Tool or Ramsay Agitation Sedation Scale as a measure of sedation depth and analgesic adequacy. Conox is using electroencephalography (EEG) data as a new alternative to nociceptive monitoring methods, where the first parameter is qNOX to provide information about the depth of analgesia, and the

[1–3]Department of Anesthesiology and Intensive Care, Faculty Medicine, Universitas Sumatera Utara, Medan, Indonesia

[4]Department of Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Corresponding Author: Andriamuri P Lubis, Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, Phone: +62 8126078194, e-mail: andriamuri@usu.ac.id

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second parameter is qCON to determine the depth of anesthesia which is similar to the bispectal index or entropy score.[5,6]

A common method for controlling postoperative pain is the use of either bolus opioids or patient controlled analgesia (PCA) for postoperative pain control. Fentanyl was the most common analgesic agent used followed by Tramadol and Paracetamol.[7,8] However, as we know, the side effects of opioids are very large and have an impact on the length of treatment and patient recovery, so recent research using subdose ketamine shows that this drug can be a substitute for opioids with fewer side effects and is more cost-effective than opioids which are more difficult to access at the regional hospital.[9]

Therefore, based on the explanation above, we hope this study can assess qCON and qNOX in postoperative patients with subdose ketamine administration compared with patients with a combination of fentanyl and in the ICU of RSUP HAM. It is hoped that in this study, the authors can provide new sources and fresh air for further research and monitor future progress in providing analgesic sedation especially in postoperative patients in the ICU.

Materials and Methods

This is an analytic experimental study with a double-blind, randomized prospective cohort study method (double-blind randomized) with primary data sources obtained directly from examining patients in the ICU of RSUP HAM.

Research data were collected in the ICU room of H Adam Malik General Hospital from January to March 2023 in postoperative patients who had been intubated and met the inclusion criteria, implementing successive sampling until the number of study subjects was met. Randomization was carried out by volunteers using the randomization method. By splitting 44 people into two groups of 22 individuals each, a total of 44 samples were recorded. This study used the primary data followed, where Group A was given a subdose of ketamine and Group B was given a combination of fentanyl and midazolam.

The independent variable in this study was the administration of subdose ketamine with a combination of fentanyl and midazolam. At the same time, the dependent variable is the value of qCON and qNOX. Characteristics of the subjects in this study included age, sex, height, weight, body mass index (BMI), length of operation, and Physical Status-American Society of Anesthesiologist (PS-ASA).

For demographic data, descriptive statistical analysis using the Kolmogorov–Smirnov test was employed. Chi-square statistical analysis was performed for categorical data, while the *t*-test or Mann–Whitney *U*-test was executed for numerical data. An ANOVA test was then undertaken between the variables. The research data were statistically evaluated using the Windows Statistical Product and Science Service (SPSS) version 22.0. At $p < 0.05$, differences were considered statistically significant.

Results

Based on 44 respondents, there were 11 neurosurgery patients in the subdose ketamine group, 5 ob-gyn patients, 3 digestive surgery patients, 1 plastic surgery patient, 1 thoracic surgery patient, and 1 orthopedic surgery patient. Whereas in the fentanyl–midazolam group, there were 11 neurosurgery patients, 5 digestive surgery patients, 4 ob-gyn patients, 1 orthopedic surgery patient, and 1 urological surgery patient with a transfer range from completion of surgery to arrival at the ICU of 5–30 minutes.

Normal distribution numeric data are shown in mean ± SD. Numerical data with non-normal distribution are displayed in the median with minimum and maximum values. In this study, the characteristics of the research subjects were based on age with a *p*-value of 0.445, based on gender with a *p*-value of 0.750, based on height with a *p*-value of 0.145, based on weight with a *p*-value of 0.110, based on BMI with a *p*-value of 0.183, based on length of action with *p*-value = 0.887, and based on PS-ASA with *p*-value of 1.000. Showing that the subdose ketamine group and the fentanyl–midazolam group are homogeneous, so they are worth comparing (Table 1), it was found, based on the normality test of the above, that there were no significant differences in the two groups in terms of age, sex, height, weight, BMI, duration of action, and PS-ASA.

Systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), heart rate, respiratory rate, and oxygen saturation have all been measured in this study. T0 is when both groups are 0 hours after drug administration, T1 is when both groups are 12 hours after drug administration, and T2 is when both groups are 24 hours after drug administration. In both treatment groups, from the baseline value (T0) of the hemodynamic variables it can be seen that there is no significant difference (Table 2).

Table 1: Characteristics of research subjects

	Ketamine subdose	*Fentanyl–Midazolam*	
Subject	*N = 22*	*N = 22*	*p-value*
Age			
Mean ± SD	50.9 ± 13	46 ± 16.9	0.445*
Median	51	49	
Range (min.–max.)	23.00–65.00	20.00–65.00	
Gender			
Man	7	8	0.750*
Woman	15	14	
Height (cm)			
Mean ± SD	162 ± 7.5	159 ± 6	0.145*
Median	162	160	
Range (min.–max.)	150–173	150–172	
Weight (kg)			
Mean ± SD	65.5 ± 9.89	59.1 ± 6.9	0.110*
Median	65	60	
Range (min.–max.)	44–90	40–70	
BMI			
Mean ± SD	24.7 ± 2.96	23.4 ± 2.5	0.183*
Median	24.35	23.5	
Range (min.–max.)	19.00–33.00	17.3–26.6	
Action time (minutes)			
Mean ± SD	218.6 ± 155.8	241 ± 177	0.887*
Median	150	180	
Range (min.–max.)	60–720	60–600	
PS-ASA			
III	22	22	1,000*

*Independent *t*-test. BMI, body mass index; PS-ASA: Physical Status-American Society of Anesthesiologist

Table 2: Hemodynamic change status table

Hemodynamic parameters	*Ketamine subdose N = 22*	*Fentanyl + Midazolam N = 22*	*p.s*
Systolic (mm Hg)			
0 hours after drug administration	129.1 ± 21.5	127.8 ± 22.2	0.843*
12 hours postoperatively	127.1 ± 19.0	124.0 ± 21.5	0.611*
24 hours postoperation	125.5 ± 17.3	120.0 ± 17.5	0.323*
Diastolic (mm Hg)			
0 hours after drug administration	72.8 ± 11.3	81.5 ± 15.0	0.037*
12 hours postoperatively	75.0 ± 9.4	77.7 ± 16.9	0.513*
24 hours postoperation	76.5 ± 10.2	73.2 ± 12.4	0.335*
MAPs (mm Hg)			
0 hours after drug administration	90.0 ± 15.9	94.2 ± 15.7	0.381*
12 hours postoperatively	92.5 ± 11.7	91.1 ± 17.8	0.751*
24 hours postoperation	92.5 ± 11.2	87.5 ± 12.5	0.168*
Pulse rate (x/min)			
0 hours after drug administration	97 ± 14.1	92.5 ± 21.1	0.403*
12 hours postoperatively	95.5 (61–126)	98 (60–149)	0.549**
24 hours postoperation	91.2 ± 15.2	96.4 ± 21.0	0.355*

*Independent *t*-test

Table 3: Types of sedation given – analgesics to qCON and qNOX values

Sedation parameters – analgesics	*T0*	*T1*	*T2*
Ketamine subdose			
qCON	63.5 (39–80)	68 (40–79)	72 (41–79)
qNOX	68 (40–78)	70 (42–78)	72 (44–80)
Fentanyl–midazolam			
qCON	57.5 (30–78)	68 (40–80)	72 (40–80)
qNOX	60 (40–75)	68 (45–79)	70 (42–80)

qCON, quantum consciousness index; qNOX, quantum noxious index; T0, 0 hours after drug administration; T1, 12 hours after drug administration; T2, 24 hours after drug administration

Table 4: Comparison of changes in qCON and qNOX values between groups

Sedation parameters	*Ketamine subdose N = 22*	*Fentanyl – Midazolam N = 22*	*p.s*
qCON			
0 hours after drug administration	63.5 (39–80)	57.5 (30–78)	0.052*
12 hours postoperatively	68 (40–79)	68 (40–80)	0.472*
24 hours postoperation	72 (41–79)	72 (40–80)	1,000*
qNOX			
0 hours after drug administration	68 (40–78)	60 (40–75)	0.094*
12 hours postoperatively	70 (42–78)	68 (45–79)	0.539*
24 hours postoperation	72 (44–80)	70 (42–80)	0.287*

*Mann–Whitney test. qCON, quantum consciousness index; qNOX, quantum noxious index

Researchers then measured the sedation parameter variables, which included qCON and qNOX in the two treatment groups at T0, T1, and T2 after drug administration. The two groups, both given subdose ketamine, and fentanyl–midazolam, had mean qCON and qNOX values that were not much different, and changes in their values also had a trend of increasing that was not much different in the two groups, as shown in Table 3.

The researcher then compared, with the Mann–Whitney *U*-test test, the differences in sedation parameter variables which included qCON and qNOX in both groups. The qCON value on subdose ketamine administration has a median value of 0 hours after administration of the drug 63.5 while in the group fentanyl–midazolam 57.5. As for the value of qNOX on, giving sub dose ketamine has a median value of 0 hours after drug administration 68 while in the group fentanyl–midazolam 60. In both treatment groups, from the baseline value (T0) of the hemodynamic variables, it can be seen that there is no significant difference. The same thing was also found at 12 hours postoperatively (T1) and 24 hours postoperatively (T2) with intravenous analgesic sedation drugs. It appears that there is no significant difference in the values of qCON and qNOX in the two groups on postmedication T0, T1, and T2 measurements ($p > 0.05$).

Side effects reported in this study, such as postoperative nausea-vomiting (PONV), nausea, vomiting, and emergence reactions, and that were mainly related to the sub dose of ketamine and the use of opioids, were also not found. Using a rescue dose of the analgesic Paracetamol drips 1000 mg was also not used because all respondents did not reach qNOX >80 (Table 4).

Discussion

Following the research of Masharto et al. that the overall postsurgery in the ICU was 18%, with 23% being patients related to nerves, based on 44 respondents in both groups, the majority were 22 neurosurgery patients, 9 ob-gyn patients, and 8 digestive surgery patients, and the rest were plastic surgery, thoracic surgery, orthopedic surgery and urological surgery patients with a transfer range from completion of surgery to arrival at the ICU ranging from 5 to 30 minutes.[10]

Another study by Harsha et al. showed that of all postoperative patients in the ICU, the majority were neurosurgical 27.58%, followed by gastrosurgical and peripheral surgery patients each 18.39%, ENT surgery 12.64%, thoracic surgery 5.74%, urological surgery 4.59%, and gynecological surgery 2.29%.[6]

Hemodynamic responses in both groups in this study were in balanced hemodynamic conditions. Hemodynamics can be more stable due to using the CONOX monitor, which, because it uses applied mathematics as a diagnostic and analytical too, measures qCON and qNOX values for objective monitoring of pain and sympathetic responses.[11] In line with the study of Jehosua et al., incidents of blood pressure and pulse that exceeded or decreased by 20% from baseline were half as rare as the control group, with the two treatment groups having a mean value of the hemodynamic component that was not much different.[5]

In most cases, hypotension arises during induction, whereas elevations in blood pressure or heart rate emerge after intubation or extubation. In patients in the ICU, hemodynamic responses can experience turmoil during routine care, installation of life-support devices such as intubation and ventilators, use of NGT, or urine tubes, pain responses due to comorbidities and postsurgery, anxiety, and agitation, which have an impact on direct complications in the form of increased oxygen consumption, lengthening the treatment period, length of recovery, and weaning from the ventilator to post-traumatic stress disorder.[6] In general practice, opioid overdose can cause death or disability, while overuse of these drugs can also cause drowsiness, sedation, respiratory distress, urine retention, nausea/vomiting, ileus, or pruritis are all possible outcomes. Early opiate symptoms of withdrawal, such as anxiety, nervousness, lacrimation, nasal congestion, diaphoresis, sleeplessness, frequent yawning, and muscular pains, are also common and may be experienced by patients after discontinuation of a drug overdose. Opioid drug use can increase patients' risk of addiction and substance use disorders. Late opioid withdrawal symptoms involve diarrhea, stomach cramps, piloerection, nausea, and vomiting, as well as tachycardia, hypertension, pupil dilatation, and impaired vision.[5]

From the measurement of sedation parameter variables which include qCON and qNOX in the two treatment groups at T0, T1, and T2 after drug administration. The two groups that were given sub dose ketamine and fentanyl–midazolam had mean values of qCON and qNOX that were not much different and changes in their values also had a tendency to increase that was also not much different in the two groups. This shows that both groups' qCON and qNOX values are at an adequate level for postoperative sedation – analgesia in the ICU, which ranges from 75 to 60, classified as adequate sedation, and being fully responsive to pain stimuli. In fact, according to the Peripheral Arterial Disease Guidelines from AHA/ACC 2016, it is stated that maintaining an adequate dose of light sedation can reduce the time to wean from the ventilator, extubation, and length of ICU stay.[12] The qCON and qNOX measurements can detect movement in response to noxious stimuli, while qNOX detects more movement than qCON. This is possible since an increase in qNOX is a straightforward EEG response to noxious stimuli in the form of pain, but a rise in qCON is a subsequent result of stimulation. In a study of 140 patients under general anesthesia who were scheduled to take propofol, the qCON index was found to be better at predicting a loss of consciousness, such as loss of verbal commands and eyelash reflex, than the qNOX index, whereas the qNOX index was found to be better at predicting responses to noxious stimuli. Furthermore, supporting the theory that reaction to stimuli recovers faster than awareness recovery, the qNOX index increased more rapidly at the conclusion of the surgery.[13]

This study did not show a significant difference in the values of qCON and qNOX in the two groups at the time of measurement 0 hours after drug administration (T0), when both groups were 12 hours after drug administration (T1), and when both groups were 24 hours after drug administration (T2). Both qCON and qNOX are considered to be effective at measuring levels of sedation and pain in intubated patients in the ICU as a way of central nervous system monitoring, which very well predicts noxious stimuli, however, as has been demonstrated with various EEG monitors, this can be influenced by the use of muscle relaxants.[6,14]

Likewise, the known side effects of ketamine, such as hallucinations, delirium, depression, nightmares, and PONV, did not appear in this study. Following the study by Ali et al., it is even more beneficial in patients who are opioid-dependent and opioid-tolerant but does not rule out the possibility that these psychomimetic side effects increase with stress responses such as acute psychosis, patients with cardiovascular disease, pregnant women with delayed gastric emptying, impaired liver function, increased intracranial pressure, and increased intraocular pressure.[15,16]

Likewise, in the research of Wang et al., Gelmanas et al. and Samuel et al., however, in our current study, it was proven that the sedation and analgesic effects that resulted from subdose ketamine and fentanyl–midazolam administration did not, without side effects, differ much. This can be a breath of fresh air in the future, bearing in mind that the use of opioids is expected to decrease; in fact, it is still not new to science outside of anesthesiology and intensive care therapy, so the cost of using opioids can be reduced, even replaced, by ketamine which is also more easily found in type C hospitals in remote areas.[16–19]

In a study by Jehosua et al., it was found that in the group that did not use a CONOX-type EEG monitoring tool, there were more side effects of anesthesia, such as higher intraoperative hemodynamic turmoil, postoperative cognitive disorder, intraoperative awakening, PONV, to moderate to severe pain while in the recovery room.[5] Ren et al.'s study showed that the anxiety score (HAD-A) and depression score (HAD-D) in the postoperative group with colorectal cancer who were given subdose ketamine 5 minutes before a single bolus operation also had a higher Quality of Recovery-40 (QoR-40) level, as well as levels of anxiety and depression and IL-6, IL-8, and TNF-α, being lower.[20] In other studies, it was also found that postoperative fatigue syndrome (POFS) as measured by the identity consequence fatigue scale, namely complaints such as fatigue, lack of enthusiasm, lack of appetite, sleep disturbances, depressed mood, laziness to move in patients with subdose ketamine seems to improve and so patients recover faster.[21]

Our research aims to measure pain objectively with a tool that shows the level of pain and awareness based on the appropriate numerical value so that, in addition to using drugs that are more efficient and effective, patients are also expected to recover faster, and the side effects of drugs are more minimal. If not recovered, these patients will resultingly have a longer rehabilitation time, weakening the patient's ability to work, with even difficulty extubating in intubated patients, reducing the quality of life, and increasing patient care costs, especially in patients who are tolerant to opioids and reducing the risk of chronic postoperative pain. In Aribawa et al.'s study, the application of ketamine administration can also be done using the PCA method so that patients can provide analgesics according to the subjective complaints they feel.[22,23]

Based on the discussion above, this study uses primary data, which is homogeneous based on the normality test, so it is considered appropriate to represent the population and reduce

research bias. It was considered not to have much influence on hemodynamics, as most respondents were postoperative neurosurgery patients with a transfer period from the operating room to the ICU ranging from 5 to 30 minutes. Side effects were not found in intubated postoperative patients in the ICU, where, according to the results of statistical tests, it was proven that there appeared to be no significant difference between the two groups. This meant that the use of subdose ketamine was considered equivalent or could replace the fentanyl–midazolam combination. Likewise, in qCON and qNOX measurements at T0, T1, and T2, there were not many significant differences with values ranging from 60 to 75, which means that the patient is still in adequate sedation and has a full pain response. Hopefully, for future research, this scientific work can be a reference for comparing different types of drugs with a larger number of respondents so that there will be more significant comparisons between the two groups, especially in the group given the sedative analgesic drug fentanyl–midazolam compared with subdose ketamine. While there is no controversy so far, although the use of ketamine in patients with intracranial disorders still require more supporting research, which is certainly very much needed, starting from when is the right time to use CONOX, the therapeutic dose that can be used for each patient, and the criteria according to the type of surgery and the patient's condition.

Conclusion

Administering a subdose of ketamine can provide sedation and analgesia comparable to fentanyl and midazolam.

Clinical Significance

The strength of this research is that it is the first time it has been held at Faculty of Medicine Universitas Sumatera Utara; then the assessment of the CONOX tool is objective so that it is very applicable as an assessment of pain and level of consciousness, and the drugs used are also easy to get anywhere. The limitation is that the CONOX device is not yet considered a mandatory assessment for pain and awareness, so the equipment and probes/electrodes must be purchased first.

Authors Contributors

Alegra R Masharto: Conceptualization, Methodology, and Software.
Andriamuri P Lubis: Data curation, Writing – Original draft preparation, and Supervision.
Chrismas G Bangun: Visualization and Investigation.
Arlinda S Wahyuni: Validation, Writing – Reviewing and Editing.

Orcid

Alegra R Masharto https://orcid.org/0000-0002-6596-5263
Andriamuri P Lubis https://orcid.org/0000-0002-1962-3799
Chrismas G Bangun https://orcid.org/0009-0009-5236-8898
Arlinda S Wahyuni https://orcid.org/0000-0002-5265-4685

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