Archives of Anesthesiology and Critical Care (In Press); x(x): xx-xx.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison of Opioid-Free and Opioid-Based Anesthesia Techniques on qNOX Index in Abdominal Surgery under General Anesthesia

Muhammad Rahman E. Nasution[1], Andriamuri Primaputra Lubis[2]*, Muhammad Arshad[2], Putri Eyanoer[3]

[1]*Study Program of Anesthesiology and Intensive Care, Faculty of Medicine, Adam Malik Hospital, Universitas Sumatera Utara, Medan, Indonesia.*

[2]*Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara, Adam Malik Hospital, Medan, Indonesia.*

[3]*Department of Community and Preventive Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.*

ARTICLE INFO

Article history:
Received 29 December 2025
Revised 21 January 2026
Accepted 05 February 2026

Keywords:
Opioid-free anesthesia;
Opioid-based anesthesia;
qNOX;
Abdominal surgery

ABSTRACT

Background: Opioid-Free Anesthesia (OFA) is a multimodal approach designed to avoid intraoperative opioid use, aiming to reduce side effects such as respiratory depression, nausea, vomiting, and postoperative dependency. This study aimed to compare the effectiveness of OFA and Opioid-Based Anesthesia (OBA) on the qNOX index during abdominal surgery under general anesthesia.
Methods: This randomized double-blind controlled trial involved 42 adult patients undergoing elective abdominal surgery under general anesthesia in three hospitals in Medan. Subjects were assigned to two groups: OFA (ketamine, lidocaine, and dexmedetomidine combination) and OBA (fentanyl-based). The qNOX index was measured using the CONOX® monitor at five time points: before induction, during intubation, before incision, during incision, and one hour after incision. Data were analyzed using an independent t-test and a chi-square test.
Results: No significant difference in qNOX values was observed between groups at any time point ($p>0.05$). Both groups maintained comparable intraoperative hemodynamic stability.
Conclusion: Opioid-free anesthesia provides comparable nociceptive control and hemodynamic stability to opioid-based anesthesia. OFA represents a safe and effective alternative for abdominal surgery under general anesthesia.

Introduction

Abdominal surgery is one of the most commonly performed major procedures worldwide, including cholecystectomy and appendectomy, and is associated with significant risks such as infection, bleeding, and multiorgan failure, especially in patients with comorbidities [1].

The World Health Organization (WHO) reports approximately 230 million surgeries annually, with 32.5 million involving abdominal procedures. Appendectomy alone has an incidence of 233 per 100,000 population per year and a lifetime risk of 6.7–8.6% [2]. In Indonesia, abdominal surgery represents a major component of surgical services, with 60% performed electively and 38% as emergency procedures [3].

General anesthesia (GA) remains the standard technique for abdominal surgery, as it provides controlled unconsciousness, analgesia, muscle relaxation, and effective management of airway and ventilation. Approximately 60% of procedures in the United States

The authors declare no conflicts of interest.
*Corresponding author.
E-mail address: andriamuri@usu.ac.id
DOI:

use GA, with similar trends in Indonesia. Opioid-based anesthesia (OBA) has traditionally been used to ensure intraoperative analgesia and blunting of hemodynamic responses [4]. However, opioids may cause respiratory depression, postoperative nausea and vomiting (PONV), constipation, urinary retention, excessive sedation, and opioid-induced hyperalgesia [5].

Opioid-free anesthesia (OFA) has emerged to minimize these adverse effects by utilizing multimodal analgesia with non-opioid agents such as lidocaine, dexmedetomidine, ketamine, and magnesium sulfate. Evidence indicates that OFA can reduce perioperative opioid requirements, improve recovery quality, and decrease the incidence of PONV, particularly in abdominal surgery [6].

Objective monitoring of nociception is essential when comparing analgesic techniques. The CONOX® monitor provides the qNOX index (0–99), which estimates the likelihood of patient response to painful stimuli, with 30–50 indicating adequate analgesia. Studies have shown that qNOX effectively assesses analgesic depth and can reduce intraoperative opioid use compared with bispectral index-guided anesthesia [7-8].

International studies have compared OFA and OBA, showing reduced opioid consumption and PONV in OFA [6]. Additional studies report better pain control with OFA techniques [9].

Research integrating CONOX monitoring in abdominal surgery remains limited due to device availability and cost constraints [7]. Therefore, this randomized controlled trial aims to compare OFA and OBA in abdominal surgery using qNOX for objective intraoperative analgesic assessment.

Methods

This randomized, double-blind clinical trial was conducted at three tertiary hospitals in Medan, Indonesia (Adam Malik Hospital, Pirngadi General Hospital, and Haji General Hospital). The study compared opioid-free anesthesia (OFA) with opioid-based anesthesia (OBA) in adult patients undergoing elective abdominal surgery under general anesthesia. Ethical approval was granted by the Health Research Ethics Committee of Universitas Sumatera Utara (973/KEPK/USU/2025), and institutional permissions were obtained before recruitment.

Eligible participants were adults aged 18–65 years, ASA I–II, scheduled for elective abdominal surgery lasting less than 4 hours with endotracheal intubation. Exclusion criteria included neurological or severe psychiatric disorders, arrhythmias or pacemaker use, elevated intracranial pressure, chronic opioid therapy, hemodynamic instability, drug allergies, advanced hepatic or renal disease, pregnancy, or breastfeeding.

A total sample of 42 participants (21 per group) was determined using G*Power. Patients were consecutively enrolled and randomized into OFA or OBA groups using computer-generated allocation. Double-blinding was maintained using identical gabapentin/placebo capsules and placebo infusions mimicking OFA medications in the OBA group.

Two hours before surgery, participants received either gabapentin (300 mg for body weight ≤60 kg or 600 mg for >60 kg) or a placebo. Upon arrival in the operating room, CONOX® electrodes were applied, and baseline hemodynamic parameters and qNOX values were recorded. All patients received standardized premedication (ondansetron 8 mg IV, ranitidine 50 mg IV, and midazolam 0.1 mg/kg IV).

The OFA group received magnesium sulfate 40 mg/kg IV, ketamine 0.5 mg/kg IV, dexmedetomidine 0.5 µg/kg IV, and lidocaine 3 mg/kg IV. The OBA group received fentanyl 3 µg/kg IV and corresponding placebo infusions. Anesthesia induction in both groups consisted of propofol 2 mg/kg and rocuronium 1 mg/kg, followed by endotracheal intubation.

Maintenance included sevoflurane 2 vol% and rocuronium. The OFA group also received continuous ketamine, dexmedetomidine, and lidocaine infusions, while the OBA group received fentanyl infusions; both groups were given paracetamol and ketorolac.

Hemodynamic parameters and qNOX were recorded before induction, during intubation, before incision, at incision, and one hour afterward.

Rescue therapy followed predefined criteria: ephedrine for MAP reduction >25%, atropine for HR <50 bpm, and fentanyl 0.5 µg/kg when qNOX >60 with HR increase >20%.

Data were analyzed using SPSS version 26.0. Shapiro–Wilk was used to assess normality, and comparisons between groups were performed using independent t-tests or Mann–Whitney U tests as appropriate. Statistical significance was defined as $p < 0.05$.

Results

A total of 42 patients were included in the study, with 21 patients assigned to the OFA group and 21 to the OBA group. The baseline characteristics of both groups were comparable. The majority of patients in each group were within the 46–59-year age range.

The distribution of sex was similar between groups, with a slightly higher proportion of females in the OFA group and males in the OBA group. Both groups predominantly underwent midline incisions (66.7%), followed by Kocher incisions (33.3%). All patients in both groups had an ASA physical status of II. A detailed summary of baseline characteristics is presented in (Table 1).

qNOX values were assessed at five intraoperative time points to compare nociceptive responses between OFA and OBA groups. Baseline qNOX values before induction were comparable between groups (96.10 ± 2.18 vs. 95.81 ± 3.57; p = 0.75), indicating similar pre-anesthetic nociceptive states.

During intubation, qNOX values decreased in both groups; however, the OBA group demonstrated significantly lower values compared with OFA (37.43 ± 4.23 vs. 41.24 ± 3.14; p = 0.002), suggesting superior nociceptive suppression with opioid use during this stimulus-intensive phase.

At subsequent time points before incision, during incision, and one hour after incision, no significant differences were observed between groups. qNOX values remained comparable before incision (p = 0.30), at incision (p = 0.35), and one hour post-incision (p = 0.70), indicating that overall intraoperative nociceptive control was effectively maintained in both groups throughout the surgical course. A detailed summary of comparison of qNOX Values presented in (Table 2).

Overall, aside from the intubation phase, where OBA demonstrated greater suppression, both anesthetic techniques provided similar qNOX stability intraoperatively.

The investigation also tracked several hemodynamic metrics, including heart rate, respiratory rate, oxygen saturation, and systolic, diastolic and mean arterial pressures across five distinct intraoperative stages. Baseline values before induction were comparable across all parameters, with no significant differences between groups.

During the intubation phase, a notable statistical variation occurred in systolic blood pressure (SBP), which was significantly lower in the OBA group (p < 0.001), indicating a more attenuated hemodynamic response to laryngoscopy with opioid-based anesthesia. Other parameters at this phase, including DBP, MAP, HR, RR, and SpO_2, remained similar between groups.

Additionally, just prior to the initial incision, the diastolic blood pressure (DBP) was found to be marginally higher in the OBA cohort (p = 0.04).

At the moment of incision, all hemodynamic parameters were comparable, reflecting similar sympathetic control in both anesthetic techniques. One patient in the OFA group experienced a transient HR increase above 100 bpm at incision, which responded appropriately to rescue fentanyl administration. By the one-hour post-incision mark, all physiological parameters had returned to a state of comparable stability, with no significant differences identified between the OFA and OBA protocols (p > 0.05). A detailed summary of comparison of hemodynamic parameters presented in (Table 3).

Overall, hemodynamic stability was comparable between OFA and OBA throughout the intraoperative period, with significant differences observed only in SBP during intubation and DBP before incision, favoring slightly greater suppression of sympathetic responses in the OBA group.

Table 1- Demographic Characteristics of Study

Variable	Opioid-Free Anesthesia (OFA) (n = 21)	Opioid-Based Anesthesia (OBA) (n = 21)
Age (Year)		
18 - 35	3 (14.3%)	2 (9.5%)
36 - 45	5 (23.8%)	6 (28.6%)
46 - 59	10 (47.6%	13 (61.9%)
≥ 60	3 (14.3%)	0
Gender		
Man	8 (38.1%)	10 (47.6%)
Female	13 (61.9%)	11 (52.4%)
Incision		
Midline	14 (66.7%)	14 (66.7%)
Kocher	7 (33.3%)	7 (33.3%)
ASA Physical Status		
ASA 1	0 (0)	0 (0)
ASA 2	21 (100%)	21 (100%)

Table 2- Comparison of qNOX Values in OFA and OBA Groups

Variable	OFA Group Mean ± SD	OBA Group Mean ± SD	P value
Before Induction	96.10 ± 2.18	95.81 ± 3.57	0.75
During Intubation	41.24 ± 3.14	37.43 ± 4.23	0.002
Before Incision	35.05 ± 2.78	34.14 ± 2.83	0.30
During Incision	38.52 ± 3.44	37.62 ± 2.80	0.35

One Hour After Incision	33.38 ± 2.39	33.00 ± 3.89	0.70

OFA: Opioid-Free Anesthesia; OBA: Opioid-Based Anesthesia. *Independent T-Test

Table 3- Comparison of Hemodynamic Parameters in OFA and OBA Groups

Variable	OFA Group Mean ± SD	OBA Group Mean ± SD	P value
Before Induction			
SBP	3.00 ± 0.00	2.90 ± 0.30	0.16
DBP	2.81 ± 0.40	2.86 ± 0.35	0.68
MAP	2.52 ± 0.51	2.62 ± 0.59	0.54
HR	2.00 ± 0.00	2.00 ± 0.00	NA
RR	2.29 ± 0.46	2.10 ± 0.30	0.12
SpO2	2.00 ± 0.00	2.05 ± 0.21	0.32
During Intubation			
SBP	2.43 ± 0.50	2.00 ± 0.00	<0.001
DBP	2.00 ± 0.63	1.81 ± 0.40	0.25
MAP	2.00 ± 0.00	1.95 ± 0.21	0.32
HR	2.00 ± 0.00	2.00 ± 0.00	NA
RR	2.00 ± 0.00	2.05 ± 0.21	0.32
SpO2	2.00 ± 0.00	2.00 ± 0.00	NA
Before Incision			
SBP	2.00 ± 0.00	2.10 ± 0.30	0.16
DBP	1.48 ± 0.51	1.81 ± 0.51	0.04
MAP	2.00 ± 0.00	2.00 ± 0.00	NA
HR	1.95 ± 0.21	2.00 ± 0.00	0.32
RR	2.00 ± 0.00	2.05 ± 0.21	0.32
SpO2	2.00 ± 0.00	2.00 ± 0.00	NA
During Incision			
SBP	2.00 ± 0.00	2.05 ± 0.21	0.32
DBP	1.81 ± 0.40	1.86 ± 0.47	0.72
MAP	2.00 ± 0.00	2.00 ± 0.00	NA
HR	2.00 ± 0.00	2.00 ± 0.00	NA
RR	2.00 ± 0.00	2.05 ± 0.21	0.32
SpO2	2.00 ± 0.00	2.00 ± 0.00	NA
One Hour After Incision			
SBP	2.10 ± 0.30	2.00 ± 0.00	0.16
DBP	1.76 ± 0.43	1.76 ± 0.43	1.00
MAP	2.00 ± 0.00	2.00 ± 0.00	NA
HR	1.86 ± 0.35	2.00 ± 0.00	0.08
RR	2.00 ± 0.00	2.05 ± 0.21	0.32
SpO2	2.00 ± 0.00	2.00 ± 0.00	NA

OFA: Opioid-Free Anesthesia; OBA: Opioid-Based Anesthesia; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; HR: Heart Rate; RR: Respiratory Rate; SpO2: Oxygen Saturation. *Independent T-Test

Discussion

This study evaluated intraoperative nociceptive control, hemodynamic stability, and PONV in patients undergoing abdominal surgery using either OFA or OBA. The qNOX index, derived from EEG and EMG processing, provides a real-time estimate of nociceptive responsiveness and is useful for guiding intraoperative analgesia [10]. Consistent with previous observations, qNOX values across all measurement points showed no significant differences between groups, indicating comparable nociceptive suppression under both anesthetic strategies. The equivalence aligns with prior findings that OFA regimens combining ketamine, lidocaine, and dexmedetomidine maintain qNOX values within the adequate analgesia range during surgery [11-12]. The pharmacologic rationale supports these findings. OFA agents suppress nociceptive pathways through NMDA antagonism, sodium channel inhibition, and α2-agonism, whereas OBA exerts antinociception primarily

through μ-opioid receptor activation. When titrated appropriately, both pathways converge to similar reductions in nociceptive probability as detected by qNOX [13]. Dexmedetomidine further contributes to analgesia and sedation with favorable safety characteristics, as reported in prior clinical trials [14].

Hemodynamic comparisons demonstrated overall equivalence between OFA and OBA, except for higher systolic blood pressure during intubation and slightly lower diastolic pressure before incision in the OFA group. These differences reflect expected pharmacodynamic effects: opioids blunt sympathetic tone, while ketamine may preserve or increase it. Prior cohort analyses and meta-analyses similarly report no clinically meaningful differences in heart rate or mean arterial pressure between OFA and OBA. The transient systolic elevation during intubation corresponds with ketamine's sympathomimetic action, whereas dexmedetomidine's sympatholytic effect explains the minor diastolic reduction before incision [15-17]. Subsequently, hemodynamics were comparable across groups, consistent with effective nociceptive control [9].

This study has several limitations that warrant consideration. First, assessments were restricted to intraoperative responses and early postoperative outcomes within six hours after extubation, preventing evaluation of longer-term postoperative pain, opioid requirements, or functional recovery, which may differ between opioid-free and opioid-based anesthesia. Second, analgesic depth was measured solely using the CONOX monitor, which, despite its utility, may not fully capture the complex and multidimensional nature of nociception. Minor variations in anesthetic technique, drug titration, or operator experience across centers may also have introduced uncontrolled confounding. Additionally, external factors such as preoperative anxiety, comorbidities, and heterogeneity in surgical procedures were not analyzed, although these variables may influence qNOX patterns and the risk of postoperative nausea and vomiting. Given these limitations, the findings should be interpreted cautiously. Larger studies with extended follow-up and more rigorous control of confounding factors are needed to confirm these results and improve their generalizability.

Conclusion

Opioid-free anesthesia demonstrated nociceptive control comparable to opioid-based anesthesia, as reflected by similar intraoperative qNOX indices across all measurement points. Hemodynamic parameters remained stable in both groups, with only minor differences that were clinically acceptable and consistent with the pharmacologic profiles of the agents used. These findings suggest opioid-free anesthesia represents a safe, effective, and clinically valuable alternative to opioid-based techniques for abdominal surgery under general anesthesia, offering equivalent intraoperative stability while reducing postoperative adverse effects.

References

[1] Liljendahl MS, Gögenur I, Thygesen LC. Emergency laparotomy in Denmark: a nationwide descriptive study. World J Surg. 2020; 44(9):2976-81.

[2] Zhang J, Wang J, Han X, Fan J, Huang C, Dong Y, et al. Global burden and future trends of inguinal, femoral, and abdominal hernia in older adults: A systematic analysis from the Global Burden of Disease Study 2021. PLoS One. 2025; 20(6):e0323790.

[3] Jadoon SK, Khan RM, Khan TA, Akhtar N, Qayyum Y, Kumar K, et al. Comparative study of wound infection between elective and emergency abdominal surgeries: A retrospective cohort study. Ann Med Surg (Lond). 2023; 85(5):1490-5.

[4] Zhao L, Sun Z, Shen W, Zeng Y. Clinical application of dexmedetomidine combined with dezocine in local anesthesia for endoscopic dacryocystorhinostomy. Ear Nose Throat J. 2025; 104(4):NP210-5.

[5] Accurso G, Rampulla D, Cusenza M, Candela G, Savatteri P, Vetrugno L, et al. A blended opioid-free anesthesia protocol and regional parietal blocks in laparoscopic abdominal surgery-a randomized controlled trial. Sci Rep. 2025; 15(1):14097.

[6] da Silveira CA, Rasador AC, Medeiros HJ, Slawka E, Gesteira L, Pereira LC, et al. Opioid-free anesthesia for minimally invasive abdominal surgery: a systematic review, meta-analysis, and trial sequential analysis. Can J Anaesth. 2024; 71(11):1466-85.

[7] Kang J, Fang C, Li Y, Yuan Y, Niu K, Zheng Y, et al. Effects of qCON and qNOX-guided general anaesthesia management on patient opioid use and prognosis: a study protocol. BMJ Open. 2023; 13(5):e069134.

[8] Masharto AR, Lubis AP, Bangun CG, Wahyuni AS. Quantium Consciousness Index and Quantium Noxious Index in Ketamine Subdose Administration Compared with Fentanyl and Midazolam in Postoperative ICU Patients: A Prospective, Observational Study. Indian J Crit Care Med. 2024; 28(6):581-6.

[9] K R V, Singh K, Sahay N, Sinha C, Kumar A, Kumar N. Opioid-free anesthesia using a combination of ketamine and dexmedetomidine in patients undergoing laparoscopic cholecystectomy: a randomized controlled trial. Anesth Pain Med (Seoul). 2024; 19(2):109-16.

[10] Linassi F, Vide S, Ferreira A, Schneider G, Gambús P, Kreuzer M. Relationships between the qNOX, qCON, burst suppression ratio, and muscle activity index of the CONOX monitor during total

intravenous anesthesia: a pilot study. J Clin Monit Comput. 2024; 38(6):1281-90.

[11] Kong H, Ma DD, Ma JH, Zhang YX, Zhang H, Wang DX, et al. Qnox index for quantification of intraoperative nociception and analgesia: a prospective single-centre validation study. Br J Anaesth. 2025; 134(3):736-45.

[12] Walujo AM, Dewi DAMS, Pradhana FXAP. Opioid-Free Anesthesia (OFA) as a Safe Anesthetic Choice for Epilepsy Patient. Bioscientia Med. 2023; 7(12):3846-50.

[13] Sakan S, Turudić Ž, Peremin S, Šribar A, Sojčić N, Čučković M, et al. OPIOID FREE GENERAL ANESTHESIA IN CLINICAL PRACTICE - A REVIEW ARTICLE. Acta Clin Croat. 2023; 62(2):362-7.

[14] Nair VA, Gladston DV, Krishna KM J, Koshy RC. Effects of intravenous dexmedetomidine on perioperative haemodynamics and quality of emergence in patients undergoing head and neck surgery following general anaesthesia—a comparative randomized, double-blind placebo-controlled study. Ain-Shams J Anesthesiol. 2022; 14(1):28.

[15] Puentes Garcia JA, Tocancipa DR, Medina E, Díaz JJ, Pisso, Gil VJ, et al. Effectiveness and Safety of Opioid-Free Anaesthesia and Analgesia in pain control and postoperative recovery of patients undergoing gynaecologic oncologic surgery: a retrospective cohort study. BMC Anesthesiol. 2025; 25(1):75.

[16] Tripodi VF, Sardo S, Ippolito M, Cortegiani A. Effectiveness and safety of opioid-free anesthesia compared to opioid-based anesthesia: a systematic review and network meta-analysis. J Anesth Analg Crit Care. 2025; 5(1):53.

[17] Liebe T, Li S, Lord A, Colic L, Krause AL, Batra A, et al. Factors Influencing the Cardiovascular Response to Subanesthetic Ketamine: A Randomized, Placebo-Controlled Trial. Int J Neuropsychopharmacol. 2017; 20(11):909-18.