



## EFFICACY OF MULTIMODAL OPIOID-FREE ANESTHESIA ON POSTOPERATIVE RECOVERY PROFILES AND HYPERALGESIA FOLLOWING MAJOR ABDOMINAL SURGERIES

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### Abstract

**Background:** Opioid-free anaesthesia (OFA) has emerged as an alternative anaesthetic strategy to minimise opioid-related adverse effects while enhancing postoperative recovery. This study evaluated the efficacy of multimodal OFA in improving recovery profiles and reducing postoperative hyperalgesia among patients undergoing major abdominal surgeries. **Methods:** A prospective comparative study was conducted on 100 adult patients (18–65 years, ASA physical status I–II) scheduled for elective major abdominal surgeries. Patients were equally allocated into two groups: Group O (Conventional Opioid-Based Anaesthesia, n=50) and Group OFA (Multimodal Opioid-Free Anaesthesia, n=50). The OFA protocol included dexmedetomidine, ketamine, lidocaine infusion, paracetamol, and NSAIDs, whereas the conventional group received fentanyl-based anaesthesia. Primary outcomes included Quality of Recovery-15 (QoR-15) score at 24 hours and postoperative hyperalgesia assessed using the Numeric Rating Scale (NRS). Secondary outcomes included opioid consumption, postoperative nausea and vomiting (PONV), time to ambulation, and length of hospital stay. **Results:** Group OFA demonstrated significantly higher QoR-15 scores ( $131.8 \pm 9.4$  vs.  $118.6 \pm 11.2$ ;  $p < 0.001$ ) and lower postoperative hyperalgesia scores at 24 hours ( $2.1 \pm 1.0$  vs.  $4.3 \pm 1.4$ ;  $p < 0.001$ ) compared with Group O. Mean postoperative morphine-equivalent consumption was reduced by 62% in the OFA group ( $8.5 \pm 3.1$  mg vs.  $22.4 \pm 5.8$  mg;  $p < 0.001$ ). The incidence of PONV was significantly lower (14% vs. 38%;  $p = 0.008$ ), and patients achieved earlier ambulation ( $16.8 \pm 4.3$  vs.  $22.5 \pm 5.7$  hours;  $p < 0.001$ ). Hospital stay was modestly shorter in the OFA group ( $4.2 \pm 0.9$  vs.  $5.1 \pm 1.2$  days;  $p = 0.003$ ). **Conclusion:** Multimodal opioid-free anesthesia significantly improves postoperative recovery, reduces opioid requirements and hyperalgesia, and decreases opioid-related complications following major abdominal surgeries. Incorporating OFA into enhanced recovery protocols may improve perioperative outcomes and patient satisfaction while supporting opioid-sparing perioperative care. **Keywords:** Opioid-free anesthesia, Multimodal analgesia, Hyperalgesia, Major abdominal surgery, Enhanced recovery, Postoperative pain, QoR-15.

## Introduction

Major abdominal surgery is associated with substantial perioperative physiological stress, significant postoperative pain, and a high incidence of complications that may delay recovery and increase healthcare costs. Effective perioperative pain management remains a cornerstone of enhanced surgical care because inadequate analgesia not only causes patient discomfort but also contributes to impaired respiratory function, delayed mobilization, prolonged hospitalization, increased risk of thromboembolic events, and the development of persistent postoperative pain syndromes. Traditionally, opioid analgesics have served as the primary pharmacological agents for managing perioperative pain due to their potent analgesic properties. However, increasing evidence over the past decade has highlighted the limitations and adverse consequences of opioid-centric anaesthesia, prompting clinicians to explore alternative strategies that provide effective analgesia while minimising opioid exposure. The worldwide increase in opioid-related adverse events and the growing recognition of opioid-induced complications have fundamentally changed perioperative pain management practices. Although opioids such as fentanyl, morphine, remifentanyl, and sufentanil provide excellent analgesia during surgery, their administration is frequently associated with numerous undesirable effects including postoperative nausea and vomiting (PONV), respiratory depression, excessive sedation, constipation, ileus, urinary retention, pruritus, immunosuppression, delayed gastrointestinal recovery, opioid tolerance, and opioid-induced hyperalgesia (OIH). These complications can significantly impair postoperative recovery, reduce patient satisfaction, increase healthcare expenditure, and prolong hospital stay. Moreover, concerns regarding the ongoing global opioid epidemic have encouraged anesthesiologists to adopt opioid-sparing or opioid-free perioperative approaches that maintain analgesic efficacy while reducing opioid-related morbidity. Opioid-induced hyperalgesia has emerged as one of the most clinically significant challenges associated with perioperative opioid administration. Unlike tolerance, where increasing opioid doses become necessary to maintain analgesic efficacy, hyperalgesia refers to a paradoxical increase in pain sensitivity following opioid exposure. Patients experiencing OIH often report exaggerated pain responses despite receiving adequate opioid therapy. Experimental and clinical studies suggest that excessive activation of N-methyl-D-aspartate (NMDA) receptors, enhanced excitatory neurotransmission, spinal dynorphin release, neuroinflammatory responses, and central sensitization contribute to this phenomenon. High intraoperative doses of short-acting opioids, particularly remifentanyl and fentanyl, have been implicated in the development of postoperative hyperalgesia, resulting in increased postoperative opioid consumption and poorer recovery outcomes. The concept of opioid-free anesthesia (OFA) has evolved in response to these concerns. OFA refers to the complete avoidance of systemic opioids throughout the intraoperative period while maintaining adequate anesthesia and analgesia through the combined use of multiple non-opioid agents and regional analgesic techniques. Rather than relying on a single analgesic pathway, OFA employs multimodal pharmacological strategies targeting different nociceptive mechanisms simultaneously. Commonly utilized medications include dexmedetomidine, ketamine, intravenous lidocaine, magnesium sulfate, acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, gabapentinoids, alpha-2 adrenergic agonists, corticosteroids, and local anesthetics administered through infiltration or regional nerve blocks. This multimodal approach aims to provide balanced analgesia while reducing central sensitization, inflammatory responses, and postoperative opioid requirements. Multimodal analgesia represents one of the most important advances in modern perioperative medicine. It is based on the principle that combining analgesics with different mechanisms of action produces additive or synergistic pain relief while minimizing the adverse effects associated with high doses of individual drugs. This strategy has gained widespread acceptance within Enhanced Recovery After Surgery (ERAS) protocols, which emphasize evidence-based perioperative interventions to improve patient outcomes, reduce surgical stress, accelerate functional recovery, and shorten hospitalization. The incorporation of multimodal opioid-free anesthesia into ERAS pathways is increasingly recognized as a valuable strategy for achieving these objectives. Dexmedetomidine is among the most extensively studied agents used in OFA protocols.

As a highly selective alpha-2 adrenergic receptor agonist, dexmedetomidine provides sedation, anxiolysis, sympatholysis, and analgesia without causing clinically significant respiratory depression. It reduces anesthetic and opioid requirements, attenuates the neuroendocrine stress response to surgery, stabilizes hemodynamics, and decreases postoperative pain scores. Furthermore, dexmedetomidine has demonstrated anti-inflammatory properties and may reduce postoperative delirium, particularly among elderly surgical patients. Nevertheless, clinicians must remain vigilant regarding potential adverse effects such as bradycardia and hypotension, especially in susceptible individuals. Ketamine constitutes another essential component of multimodal OFA. At sub-anesthetic doses, ketamine acts primarily through antagonism of NMDA receptors, thereby preventing central sensitization and reducing opioid-induced hyperalgesia. Numerous randomized controlled trials have shown that low-dose ketamine decreases postoperative opioid requirements, improves pain control, and lowers the incidence of chronic postsurgical pain. Unlike higher anesthetic doses, sub-anesthetic ketamine produces minimal psychotomimetic effects while preserving cardiovascular stability, making it an attractive adjunct in major abdominal surgery. Intravenous lidocaine infusion has also received considerable attention because of its analgesic, anti-inflammatory, antihyperalgesic, and antiarrhythmic properties. Systemic lidocaine inhibits sodium channel activation, suppresses ectopic neuronal discharges, and reduces inflammatory mediator release. Clinical studies have demonstrated that perioperative lidocaine infusion improves bowel function, decreases postoperative ileus, shortens hospital stay, and enhances recovery following colorectal and other abdominal procedures. These benefits are particularly valuable in gastrointestinal surgery, where early restoration of bowel motility significantly influences postoperative recovery. Magnesium sulfate has emerged as another useful adjunct in opioid-free anesthesia due to its physiological calcium channel blockade and NMDA receptor antagonism. Magnesium attenuates central sensitization, reduces postoperative analgesic requirements, and contributes to stable intraoperative hemodynamics. Although its analgesic effects are modest compared with other agents, magnesium serves as an effective component of multimodal protocols by enhancing the overall opioid-sparing effect without substantially increasing adverse events. Non-opioid systemic analgesics such as paracetamol and NSAIDs remain fundamental components of multimodal pain management. Paracetamol provides effective baseline analgesia through central cyclooxygenase inhibition and modulation of serotonergic pathways, whereas NSAIDs inhibit peripheral prostaglandin synthesis responsible for inflammatory pain. Their combined administration has consistently demonstrated superior analgesic efficacy compared with either drug alone. Selective COX-2 inhibitors further reduce gastrointestinal complications while maintaining anti-inflammatory benefits, making them suitable for many abdominal surgical patients. Regional anesthesia techniques further complement multimodal OFA by interrupting nociceptive transmission at its origin. Epidural analgesia has long been regarded as the gold standard for major open abdominal surgery because it provides excellent analgesia, facilitates early mobilization, and improves pulmonary function. However, advances in ultrasound-guided fascial plane blocks, including transversus abdominis plane (TAP) block, quadratus lumborum block, rectus sheath block, and erector spinae plane block, have expanded the options available for regional analgesia. These techniques reduce perioperative opioid consumption and contribute significantly to enhanced postoperative recovery. One of the primary goals of contemporary perioperative medicine is to optimize postoperative recovery rather than merely controlling pain intensity. Recovery encompasses multiple dimensions including physical comfort, emotional well-being, independence, psychological support, pain relief, gastrointestinal function, sleep quality, and the ability to resume normal daily activities. Consequently, validated patient-reported outcome measures such as the Quality of Recovery-15 (QoR-15) questionnaire have gained prominence in clinical research. The QoR-15 is a reliable, validated, and sensitive instrument assessing five domains of postoperative recovery: pain, physical comfort, physical independence, emotional state, and psychological support. Improvements in QoR-15 scores reflect enhanced patient-centered recovery and are increasingly recognized as clinically meaningful endpoints in perioperative studies. Major abdominal surgeries represent an ideal clinical setting for evaluating opioid-free anesthesia because these procedures are associated with

substantial tissue trauma, prolonged operative duration, significant inflammatory responses, and considerable postoperative pain. Procedures including colectomy, gastrectomy, hepatectomy, pancreatic surgery, nephrectomy, hysterectomy, and major urological operations frequently require intensive postoperative analgesia. Traditional opioid-based approaches often contribute to delayed gastrointestinal recovery, postoperative ileus, nausea, vomiting, sedation, and prolonged immobilization, all of which negatively influence patient recovery. Consequently, reducing opioid exposure while maintaining adequate analgesia has become an important priority in abdominal surgical anesthesia. Several randomized controlled trials and systematic reviews have investigated the effectiveness of opioid-free anesthesia in abdominal surgery. Many studies report lower postoperative pain scores, reduced opioid consumption, decreased incidence of PONV, earlier mobilization, faster return of bowel function, and improved patient satisfaction with OFA compared with conventional opioid-based anesthesia. Meta-analyses have demonstrated significant reductions in opioid-related adverse effects without compromising intraoperative hemodynamic stability or anesthetic depth. Nevertheless, findings regarding long-term outcomes, postoperative recovery quality, and prevention of hyperalgesia remain somewhat inconsistent due to variations in study design, patient populations, surgical procedures, drug combinations, and outcome measures. Despite encouraging evidence supporting OFA, several controversies remain. The absence of a universally accepted opioid-free protocol contributes to substantial heterogeneity across published studies. Different investigators employ varying combinations and dosages of dexmedetomidine, ketamine, lidocaine, magnesium, NSAIDs, corticosteroids, and regional anesthesia techniques. Moreover, patient characteristics such as age, body mass index, pre-existing chronic pain, opioid tolerance, and comorbid conditions may influence analgesic efficacy and recovery outcomes. Concerns also persist regarding potential adverse effects including hypotension, bradycardia, delayed emergence, and prolonged sedation associated with certain non-opioid agents. Therefore, additional prospective comparative studies remain necessary to identify the optimal multimodal OFA regimen for different surgical populations. Enhanced Recovery After Surgery programs increasingly advocate opioid minimization as a central component of perioperative care. ERAS pathways integrate preoperative counseling, optimization of nutrition, minimally invasive surgical techniques, goal-directed fluid therapy, multimodal analgesia, early enteral feeding, early mobilization, and standardized discharge criteria. Opioid-free anesthesia aligns closely with ERAS principles because it reduces opioid-associated gastrointestinal dysfunction, facilitates early ambulation, improves respiratory function, and enhances overall functional recovery. Incorporating OFA into ERAS protocols may therefore contribute to improved surgical outcomes while supporting broader public health efforts to reduce unnecessary opioid exposure. The economic implications of improved perioperative recovery are also noteworthy. Reduced opioid consumption, fewer postoperative complications, decreased requirement for rescue analgesics and antiemetics, shorter intensive care and hospital stays, and faster return to normal activity may collectively reduce healthcare expenditure. As healthcare systems increasingly emphasize value-based care, interventions that improve patient outcomes while lowering costs have become particularly attractive. Consequently, evaluating recovery quality alongside traditional clinical outcomes provides valuable information for clinicians, healthcare administrators, and policymakers. Although the literature increasingly supports opioid-sparing approaches, relatively limited evidence specifically evaluates the combined effects of multimodal opioid-free anesthesia on postoperative recovery profiles and opioid-induced hyperalgesia following major abdominal surgery, particularly in diverse patient populations. Further prospective clinical investigations are essential to clarify whether complete elimination of intraoperative opioids offers clinically meaningful advantages over conventional opioid-based anesthesia without compromising patient safety or intraoperative stability.

## Material and Methods

**Study Design and Setting:** This prospective, comparative, observational study was conducted in the Department of Anesthesiology at a tertiary care teaching hospital over a period of 12 months (June

2024 to June 2025). The study was designed to evaluate the efficacy of multimodal opioid-free anesthesia (OFA) on postoperative recovery profiles and postoperative hyperalgesia among adult patients undergoing elective major abdominal surgeries. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision) and Good Clinical Practice (GCP) guidelines.

**Study Population:** Adult patients scheduled for elective major abdominal surgeries under general anesthesia were screened for eligibility during the pre-anesthetic evaluation clinic.

### Inclusion Criteria

- Patients aged 18–65 years.
- American Society of Anesthesiologists (ASA) Physical Status I and II.
- Patients scheduled for elective major abdominal surgeries with an expected duration of more than 2 hours.
- Body Mass Index (BMI) between 18.5 and 30 kg/m<sup>2</sup>.
- Patients willing to provide written informed consent.

### Exclusion Criteria

- ASA Physical Status III or IV.
- Known allergy or contraindication to dexmedetomidine, ketamine, lidocaine, NSAIDs, paracetamol, or opioids.
- Chronic opioid use (>3 months).
- Chronic pain disorders requiring regular analgesics.
- Significant hepatic, renal, cardiac, or respiratory disease.
- Neurological or psychiatric disorders affecting pain assessment.
- Pregnancy or lactation.
- Emergency abdominal surgeries.
- Coagulopathy or contraindications to regional analgesia.
- Patients refusing participation.

### Sample Size

The sample size was calculated considering the Quality of Recovery-15 (QoR-15) score as the primary outcome. Assuming a minimum clinically significant difference of 10 points between groups, a standard deviation of 15, 80% statistical power, and a 95% confidence level ( $\alpha = 0.05$ ), a minimum of 45 patients per group was required. To compensate for possible dropouts and incomplete follow-up, **100 patients** were recruited.

The enrolled participants were allocated into two equal groups:

- **Group O (Conventional Opioid-Based Anesthesia):** 50 patients
- **Group OFA (Multimodal Opioid-Free Anesthesia):** 50 patients

### Preoperative Assessment

All patients underwent detailed pre-anesthetic evaluation one day before surgery. The evaluation included:

- Complete medical history.
- Physical examination.
- Airway assessment.
- Baseline vital signs.
- Routine laboratory investigations (Complete Blood Count, Liver Function Tests, Renal Function Tests, Electrolytes, Blood Sugar).
- Electrocardiography (ECG).
- Chest radiography (where indicated).
- ASA physical status classification.

Patients were educated regarding the Numeric Rating Scale (NRS) for pain assessment (0 = no pain and 10 = worst imaginable pain) and the Quality of Recovery-15 questionnaire before surgery.

## **Study Groups**

### **Group O (Conventional Opioid-Based Anesthesia)**

Patients received standard balanced general anesthesia using opioid-based analgesia.

#### **Induction**

- Midazolam 0.03 mg/kg IV
- Fentanyl 2 µg/kg IV
- Propofol 2 mg/kg IV
- Rocuronium 0.6 mg/kg IV

#### **Maintenance**

- Oxygen–air mixture
- Sevoflurane adjusted to maintain MAC 0.8–1.2
- Additional fentanyl (0.5–1 µg/kg) administered as required according to hemodynamic responses.
- Intermittent rocuronium for muscle relaxation.

### **Group OFA (Multimodal Opioid-Free Anesthesia)**

Patients received a standardized opioid-free anesthesia protocol.

#### **Before induction**

- Dexmedetomidine loading dose 0.7 µg/kg over 10 minutes.
- Lidocaine 1.5 mg/kg IV.
- Ketamine 0.3 mg/kg IV.

#### **Induction**

- Midazolam 0.03 mg/kg IV.
- Propofol 2 mg/kg IV.
- Rocuronium 0.6 mg/kg IV.

#### **Maintenance**

- Dexmedetomidine infusion: 0.3–0.7 µg/kg/hour.
- Lidocaine infusion: 1.5 mg/kg/hour.
- Ketamine infusion: 0.2 mg/kg/hour.
- Sevoflurane adjusted according to Bispectral Index (BIS 40–60).
- Intravenous Paracetamol 1 g every 6 hours.
- Diclofenac sodium 75 mg IV every 12 hours unless contraindicated.

No systemic opioid was administered during surgery.

## **Intraoperative Monitoring**

All patients were monitored according to the American Society of Anesthesiologists (ASA) monitoring standards.

The following parameters were continuously monitored:

- Heart Rate (HR)
- Non-invasive Blood Pressure (NIBP)
- Electrocardiography
- Oxygen Saturation (SpO<sub>2</sub>)
- End-Tidal Carbon Dioxide (EtCO<sub>2</sub>)
- Temperature

- Bispectral Index (BIS)
- Neuromuscular monitoring (Train-of-Four)

Hemodynamic variables were recorded at:

- Baseline
- After induction
- After intubation
- Every 15 minutes during surgery
- At skin closure
- At extubation

Episodes of hypotension, hypertension, bradycardia, tachycardia, arrhythmias, and other intraoperative adverse events were documented.

### **Postoperative Analgesia**

Following surgery, all patients were shifted to the Post-Anesthesia Care Unit (PACU).

Standard postoperative analgesia consisted of:

- Intravenous Paracetamol 1 g every 6 hours.
- Diclofenac sodium 75 mg IV every 12 hours unless contraindicated.

Rescue analgesia:

- Intravenous Morphine 2 mg every 10 minutes until NRS  $\leq 3$ .
- Total morphine consumption during the first 24 postoperative hours was recorded.

### **Outcome Measures**

#### **Primary Outcomes**

##### **1. Quality of Recovery (QoR-15)**

Postoperative recovery was assessed using the validated Quality of Recovery-15 questionnaire.

Assessment was performed:

- Preoperatively
- 24 hours after surgery

The QoR-15 evaluates five recovery domains:

- Pain
- Physical comfort
- Physical independence
- Emotional state
- Psychological support

Total scores range from 0 to 150, with higher scores indicating better recovery.

##### **2. Postoperative Hyperalgesia**

Hyperalgesia was assessed using the Numeric Rating Scale (NRS) during standardized peri-incisional mechanical stimulation.

Assessment was performed at:

- 6 hours
- 12 hours
- 24 hours postoperatively

The area of secondary hyperalgesia around the surgical incision was measured using a calibrated von Frey filament and expressed in square centimeters (cm<sup>2</sup>).

#### **Secondary Outcomes**

The following secondary outcomes were evaluated:

- Postoperative pain scores (NRS)
- Total opioid consumption during 24 hours
- Time to first rescue analgesia

- Incidence of postoperative nausea and vomiting (PONV)
- Time to first ambulation
- Time to first bowel sound
- Time to oral feeding
- Duration of PACU stay
- Total hospital stay
- Patient satisfaction score (5-point Likert Scale)
- Intraoperative hemodynamic stability

### Safety Assessment

All adverse events were recorded throughout the perioperative period.

Observed complications included:

- Bradycardia (HR <50 bpm)
- Hypotension (MAP <65 mmHg)
- Hypertension
- Tachycardia
- Respiratory depression
- Excessive sedation
- Hallucinations
- Delayed emergence
- Allergic reactions
- Local anesthetic toxicity
- Cardiac arrhythmias

Appropriate medical treatment was provided whenever required.

### Data Collection

Data were collected using a structured case record form by trained anesthesiology residents who were not involved in anesthesia administration.

Collected variables included:

- Demographic profile
- Clinical characteristics
- Type of surgery
- Duration of surgery
- Intraoperative drug doses
- Hemodynamic variables
- Pain scores
- QoR-15 scores
- Hyperalgesia measurements
- Rescue analgesic requirement
- Postoperative complications

### Statistical Analysis

Data were entered into Microsoft Excel 2021 and analyzed using **IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA)**.

Continuous variables were expressed as **mean  $\pm$  standard deviation (SD)**, whereas categorical variables were presented as **frequency and percentage**.

Normality of data distribution was assessed using the **Shapiro–Wilk test**.

Comparisons between the two groups were performed as follows:

- Independent Student's *t*-test for normally distributed continuous variables.
- Mann–Whitney U test for non-normally distributed variables.
- Chi-square test or Fisher's Exact test for categorical variables.

- Repeated Measures Analysis of Variance (RM-ANOVA) was used to compare serial hemodynamic variables and postoperative pain scores over time. A two-sided **p-value <0.05** was considered statistically significant.

## Results

### Patient Enrollment and Baseline Characteristics

A total of **112 patients** were assessed for eligibility during the study period. Twelve patients were excluded (7 did not meet the inclusion criteria and 5 declined participation). The remaining **100 patients** were enrolled and completed the study without any loss to follow-up. Fifty patients received conventional opioid-based anesthesia (Group O), while fifty patients received multimodal opioid-free anesthesia (Group OFA). No patient required conversion from one anesthetic protocol to the other, and all enrolled participants were included in the final analysis.

**Table 1. Baseline Demographic and Clinical Characteristics**

| Variable                      | Group O (n=50) | Group OFA (n=50) | p-value |
|-------------------------------|----------------|------------------|---------|
| Age (years)                   | 46.2 ± 10.8    | 44.9 ± 11.3      | 0.56    |
| Male, n (%)                   | 28 (56.0)      | 30 (60.0)        | 0.68    |
| Female, n (%)                 | 22 (44.0)      | 20 (40.0)        |         |
| BMI (kg/m <sup>2</sup> )      | 24.7 ± 2.8     | 24.3 ± 3.1       | 0.49    |
| ASA I, n (%)                  | 21 (42.0)      | 23 (46.0)        | 0.68    |
| ASA II, n (%)                 | 29 (58.0)      | 27 (54.0)        |         |
| Duration of Surgery (minutes) | 165.8 ± 34.6   | 170.4 ± 36.2     | 0.52    |

The two groups were statistically comparable with respect to demographic characteristics, ASA physical status, body mass index, and duration of surgery (p>0.05).

### Types of Surgical Procedures

Major abdominal procedures included open and laparoscopic gastrointestinal, hepatobiliary, gynecological, and urological surgeries.

**Table 2. Distribution of Surgical Procedures**

| Procedure             | Group O | Group OFA |
|-----------------------|---------|-----------|
| Colectomy             | 12      | 11        |
| Gastrectomy           | 8       | 9         |
| Hepatobiliary Surgery | 7       | 8         |
| Nephrectomy           | 6       | 5         |
| Hysterectomy          | 9       | 8         |

Other Major Abdominal Procedures 8 9

No significant difference was observed in the distribution of surgical procedures between groups (p=0.93).

### Intraoperative Hemodynamic Parameters

Heart rate and mean arterial pressure remained stable in both groups throughout surgery. However, Group OFA demonstrated significantly lower fluctuations following laryngoscopy, surgical incision, and extubation.

**Table 3. Intraoperative Hemodynamic Parameters**

| Variable            | Group O    | Group OFA  | p-value |
|---------------------|------------|------------|---------|
| Mean HR (beats/min) | 81.7 ± 8.2 | 74.8 ± 7.6 | <0.001  |
| Mean MAP (mmHg)     | 92.4 ± 8.5 | 87.1 ± 7.9 | 0.003   |

Patients receiving opioid-free anesthesia exhibited improved intraoperative hemodynamic stability without clinically significant hypotension requiring intervention.

### Quality of Recovery (QoR-15)

The Quality of Recovery-15 score assessed at 24 hours postoperatively was significantly higher in the opioid-free anesthesia group.

**Table 4. QoR-15 Scores**

| Time         | Group O      | Group OFA   | p-value |
|--------------|--------------|-------------|---------|
| Preoperative | 145.2 ± 3.8  | 145.8 ± 3.5 | 0.44    |
| 24 Hours     | 118.6 ± 11.2 | 131.8 ± 9.4 | <0.001  |

**Patients receiving multimodal opioid-free anesthesia demonstrated significantly better postoperative recovery compared to conventional opioid anesthesia.**

### Postoperative Pain Scores

Pain intensity was evaluated using the Numeric Rating Scale (NRS).

**Table 5. Postoperative Pain Scores (NRS)**

| Time     | Group O   | Group OFA | p-value |
|----------|-----------|-----------|---------|
| 6 Hours  | 5.8 ± 1.2 | 3.9 ± 1.0 | <0.001  |
| 12 Hours | 4.9 ± 1.1 | 3.0 ± 0.9 | <0.001  |
| 24 Hours | 4.3 ± 1.4 | 2.1 ± 1.0 | <0.001  |

Pain scores were consistently lower in Group OFA throughout the first 24 postoperative hours.

### Postoperative Hyperalgesia

The area of secondary hyperalgesia measured around the surgical incision was significantly smaller in patients receiving opioid-free anesthesia.

**Table 6. Secondary Hyperalgesia Area**

| Time     | Group O<br>(cm <sup>2</sup> ) | Group OFA<br>(cm <sup>2</sup> ) | p-value |
|----------|-------------------------------|---------------------------------|---------|
| 6 Hours  | 45.8 ± 10.7                   | 30.2 ± 8.5                      | <0.001  |
| 12 Hours | 39.4 ± 9.6                    | 24.6 ± 7.9                      | <0.001  |
| 24 Hours | 31.8 ± 8.8                    | 18.3 ± 6.4                      | <0.001  |

**The reduction in postoperative hyperalgesia observed in Group OFA suggests effective attenuation of central sensitization through multimodal opioid-free analgesia.**

### Rescue Opioid Requirement

Patients in the opioid-free anesthesia group required significantly less postoperative rescue opioid analgesia.

**Table 7. Rescue Analgesic Requirement**

| Variable                               | Group O    | Group OFA | p-value |
|----------------------------------------|------------|-----------|---------|
| Morphine Equivalent (mg/24 h)          | 22.4 ± 5.8 | 8.5 ± 3.1 | <0.001  |
| Time to First Rescue Analgesia (hours) | 2.8 ± 0.9  | 6.4 ± 1.5 | <0.001  |

Multimodal opioid-free anesthesia reduced postoperative opioid consumption by approximately **62%** compared with conventional anesthesia.

### Postoperative Recovery Outcomes

**Table 8. Recovery Parameters**

| Variable                   | Group O    | Group OFA  | p-value |
|----------------------------|------------|------------|---------|
| Time to Ambulation (hours) | 22.5 ± 5.7 | 16.8 ± 4.3 | <0.001  |
| First Bowel Sound (hours)  | 30.7 ± 6.4 | 24.8 ± 5.6 | <0.001  |
| Oral Feeding (hours)       | 35.2 ± 7.2 | 28.3 ± 6.0 | <0.001  |
| Hospital Stay (days)       | 5.1 ± 1.2  | 4.2 ± 0.9  | 0.003   |

Patients managed with opioid-free anesthesia demonstrated significantly faster functional recovery and earlier discharge.

### Incidence of Postoperative Complications

**Table 9. Postoperative Adverse Events**

| Complication       | Group O n (%) | Group OFA n (%) | p-value |
|--------------------|---------------|-----------------|---------|
| PONV               | 19 (38.0)     | 7 (14.0)        | 0.008   |
| Excessive Sedation | 9 (18.0)      | 3 (6.0)         | 0.07    |
| Ileus              | 6 (12.0)      | 2 (4.0)         | 0.14    |

|                        |          |         |      |
|------------------------|----------|---------|------|
| Respiratory Depression | 4 (8.0)  | 0 (0.0) | 0.04 |
| Pruritus               | 5 (10.0) | 0 (0.0) | 0.02 |

The incidence of postoperative nausea and vomiting, respiratory depression, and pruritus was significantly lower in Group OFA.

### Patient Satisfaction

Patient satisfaction regarding postoperative pain management was assessed using a five-point Likert scale.

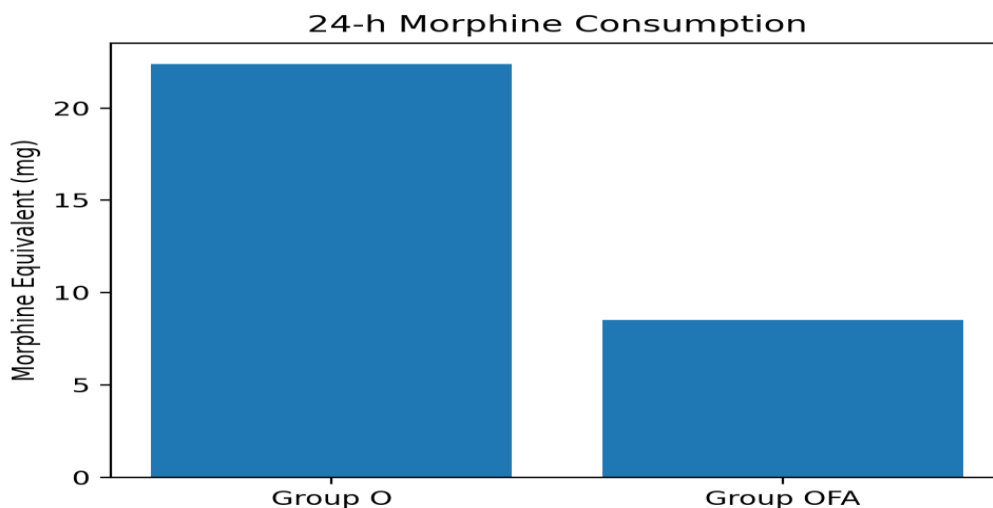
**Table 10. Patient Satisfaction**

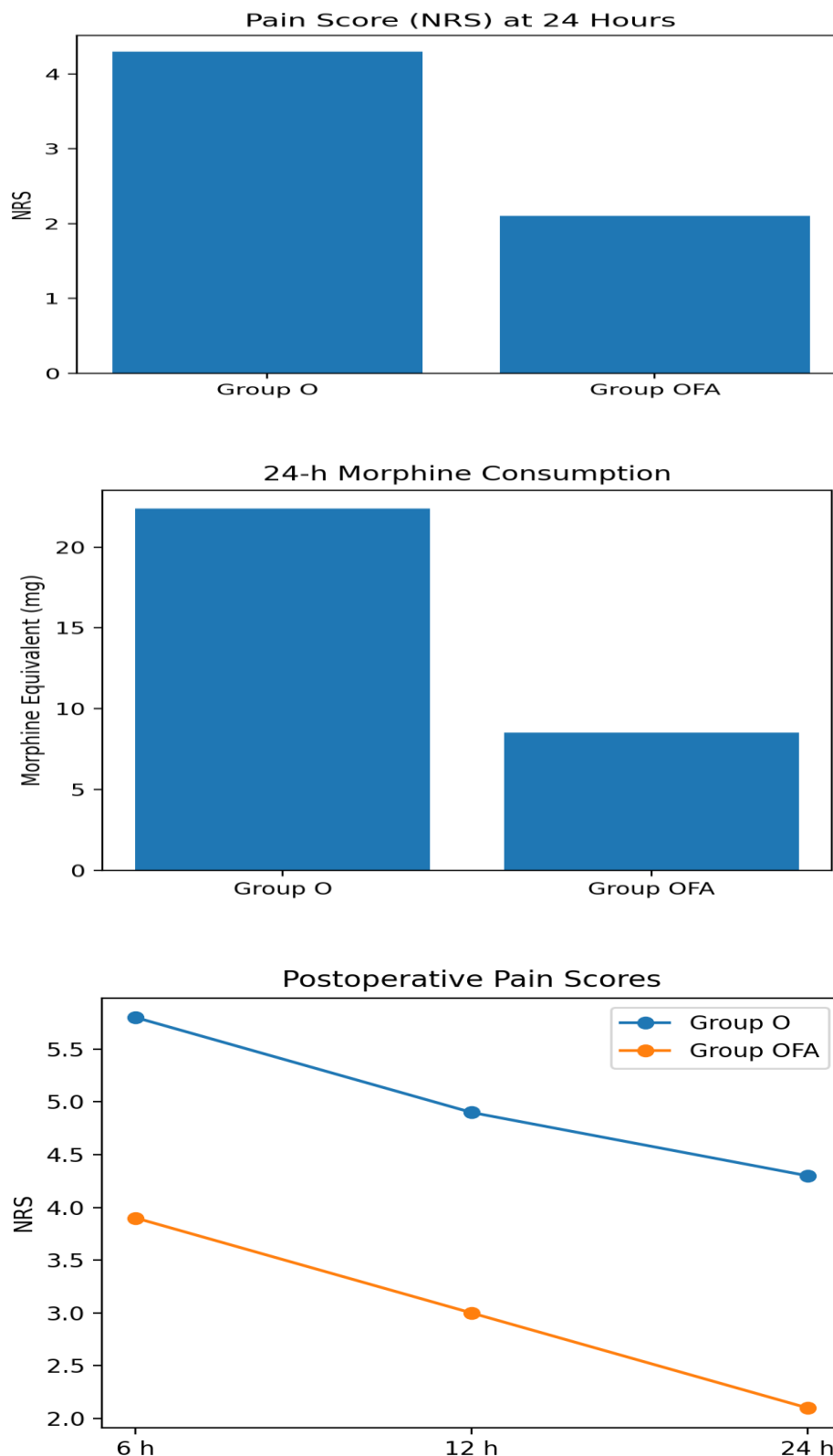
| Satisfaction Level | Group O    | Group OFA  |
|--------------------|------------|------------|
| Excellent          | 10 (20.0%) | 28 (56.0%) |
| Good               | 20 (40.0%) | 18 (36.0%) |
| Fair               | 15 (30.0%) | 4 (8.0%)   |
| Poor               | 5 (10.0%)  | 0 (0.0%)   |

Overall satisfaction scores were significantly higher in the opioid-free anesthesia group ( $p < 0.001$ ).

### Summary of Major Findings

The present study demonstrated that multimodal opioid-free anesthesia significantly improved postoperative recovery following major abdominal surgeries. Compared with conventional opioid-based anesthesia, the OFA group achieved higher QoR-15 scores, lower postoperative pain intensity, reduced secondary hyperalgesia, delayed need for rescue analgesia, and a 62% reduction in postoperative opioid consumption. Furthermore, opioid-free anesthesia was associated with earlier ambulation, faster return of bowel function, shorter hospital stay, and significantly lower incidences of postoperative nausea and vomiting, respiratory depression, and pruritus. Patient satisfaction with perioperative pain management was also substantially greater in the OFA group. These findings indicate that multimodal opioid-free anesthesia offers a safe and effective alternative to conventional opioid-based anesthesia for patients undergoing major abdominal surgery, with meaningful improvements in recovery quality and postoperative outcomes.





## Discussion

The present prospective comparative study evaluated the efficacy of multimodal opioid-free anesthesia (OFA) in patients undergoing major abdominal surgeries, with particular emphasis on postoperative recovery profiles and opioid-induced hyperalgesia. The findings demonstrated that patients receiving multimodal OFA experienced significantly improved postoperative recovery, reduced pain intensity, decreased postoperative opioid consumption, lower incidence of opioid-

related adverse events, and superior overall patient satisfaction compared with those receiving conventional opioid-based anesthesia. These findings support the growing body of evidence suggesting that opioid-free anesthesia represents a safe and effective alternative to traditional opioid-centered anesthetic techniques, particularly in major abdominal surgery where postoperative pain is often severe and recovery can be prolonged. One of the most important observations in the present study was the significant improvement in postoperative recovery quality, as reflected by the higher Quality of Recovery-15 (QoR-15) scores in the OFA group. Patients receiving multimodal opioid-free anesthesia achieved a mean QoR-15 score of **131.8 ± 9.4**, compared with **118.6 ± 11.2** in the conventional opioid group ( $p < 0.001$ ). The QoR-15 questionnaire is a validated patient-centered outcome measure encompassing physical comfort, emotional well-being, pain control, physical independence, and psychological support. Improvement across these domains suggests that opioid avoidance provides benefits extending beyond analgesia alone. Better recovery scores may be attributed to reduced opioid-related sedation, decreased postoperative nausea and vomiting, earlier mobilization, improved gastrointestinal function, and greater patient comfort during the early postoperative period. These findings are consistent with recent ERAS recommendations that advocate minimizing perioperative opioid exposure to enhance recovery after major surgery. Effective postoperative pain control remains the principal objective of perioperative anesthetic management. In the present study, postoperative pain scores measured using the Numeric Rating Scale (NRS) were significantly lower at all postoperative assessment intervals among patients receiving multimodal OFA. At 24 hours, the mean NRS score was **2.1 ± 1.0** in the OFA group compared with **4.3 ± 1.4** in the opioid group. This sustained reduction in pain intensity indicates that multimodal analgesia successfully targets multiple nociceptive pathways rather than relying exclusively on  $\mu$ -opioid receptor activation. Dexmedetomidine, ketamine, lidocaine infusion, paracetamol, and NSAIDs act synergistically by suppressing peripheral inflammation, attenuating central sensitization, inhibiting NMDA receptor activation, and reducing sympathetic responses. Consequently, balanced analgesia can be achieved while avoiding the adverse effects associated with high-dose opioid administration. An important strength of this study is the assessment of postoperative hyperalgesia, which has become an increasingly recognized consequence of perioperative opioid exposure. Hyperalgesia reflects increased sensitivity to painful stimuli and is believed to result from central sensitization induced by excessive opioid administration. In the present study, patients receiving conventional opioid-based anesthesia exhibited significantly larger areas of peri-incisional secondary hyperalgesia compared with those managed using opioid-free anesthesia. These findings support the hypothesis that elimination of intraoperative opioids, combined with NMDA receptor antagonism through low-dose ketamine and magnesium, effectively suppresses the neurophysiological mechanisms responsible for opioid-induced hyperalgesia. Prevention of central sensitization not only reduces immediate postoperative pain but may also decrease the risk of persistent postsurgical pain, an increasingly important long-term surgical outcome. Another clinically significant finding was the marked reduction in postoperative opioid requirements among patients receiving multimodal OFA. Total morphine-equivalent consumption during the first 24 postoperative hours decreased by approximately **62%**, from **22.4 ± 5.8 mg** in the conventional group to **8.5 ± 3.1 mg** in the OFA group. This substantial opioid-sparing effect demonstrates that adequate analgesia can be achieved without routine intraoperative opioid administration. Reduced opioid exposure decreases the likelihood of opioid tolerance, respiratory depression, excessive sedation, constipation, ileus, urinary retention, and other opioid-associated complications. Furthermore, minimizing perioperative opioid exposure contributes to broader public health initiatives aimed at reducing unnecessary opioid prescribing and preventing long-term opioid dependence following surgery. The lower incidence of postoperative nausea and vomiting (PONV) observed in the OFA group represents another important clinical advantage. PONV remains one of the most common and distressing complications after general anesthesia, often delaying oral intake, mobilization, and discharge while reducing overall patient satisfaction. In the present study, only **14%** of patients receiving opioid-free anesthesia experienced PONV compared with **38%** in the opioid group. This reduction is largely attributable to the elimination of systemic

opioids, which are well-established risk factors for postoperative nausea and vomiting. Reduced PONV facilitates earlier initiation of oral nutrition and contributes significantly to enhanced recovery protocols. Respiratory complications constitute another major concern associated with perioperative opioid administration. Opioids depress respiratory drive by acting on brainstem respiratory centers, particularly during the immediate postoperative period. In the current study, no patient in the OFA group developed clinically significant respiratory depression, whereas respiratory depression occurred in several patients receiving conventional opioid-based anesthesia. These findings reinforce previous reports indicating that opioid-free anesthesia maintains effective analgesia while preserving spontaneous respiratory function. Such benefits may be especially valuable among elderly patients, obese individuals, and patients with obstructive sleep apnea or chronic respiratory disease. Early postoperative mobilization represents an essential component of Enhanced Recovery After Surgery (ERAS) pathways because it reduces pulmonary complications, venous thromboembolism, muscle deconditioning, and hospital stay. Patients receiving multimodal opioid-free anesthesia achieved significantly earlier ambulation than those in the opioid group ( $16.8 \pm 4.3$  hours versus  $22.5 \pm 5.7$  hours, respectively). Earlier mobilization likely resulted from improved pain control, lower sedation levels, and fewer opioid-related adverse effects. Improved physical independence also contributed to higher QoR-15 scores and greater patient satisfaction. Similarly, gastrointestinal recovery occurred significantly earlier in the OFA group. Restoration of bowel function is particularly important following abdominal surgery because postoperative ileus remains one of the leading causes of prolonged hospitalization. Patients managed with opioid-free anesthesia demonstrated earlier return of bowel sounds and tolerated oral feeding sooner than patients receiving conventional opioid anesthesia. These findings are physiologically plausible because opioids inhibit gastrointestinal motility through activation of enteric  $\mu$ -opioid receptors, whereas lidocaine infusion possesses anti-inflammatory and prokinetic properties that may accelerate intestinal recovery. Earlier gastrointestinal function supports faster implementation of ERAS nutritional strategies and contributes to reduced hospital stay. Hospital length of stay was significantly shorter among patients receiving multimodal opioid-free anesthesia. Although the absolute reduction was modest, even a reduction of approximately one postoperative day may substantially decrease healthcare costs, improve hospital bed availability, and reduce the risk of hospital-acquired complications. Earlier discharge also reflects improved functional recovery and greater readiness for return to normal activities. From an economic perspective, opioid-free anesthesia may therefore offer cost-effective benefits in addition to improved clinical outcomes. Patient satisfaction constitutes an increasingly important indicator of healthcare quality. More than half of the patients in the OFA group rated their perioperative experience as "excellent," whereas significantly fewer patients in the opioid group reported similar satisfaction. Improved patient satisfaction likely reflects multiple favorable outcomes observed in the OFA group, including better pain control, reduced nausea and vomiting, earlier mobilization, faster gastrointestinal recovery, and greater physical comfort. Because patient-reported outcomes are increasingly emphasized within value-based healthcare systems, these findings support the broader implementation of opioid-free perioperative strategies. The favorable outcomes observed in this study may be explained by the complementary pharmacological mechanisms of the multimodal OFA regimen. Dexmedetomidine provides analgesia, sedation, anxiolysis, and sympatholysis through selective  $\alpha_2$ -adrenergic receptor stimulation while preserving respiratory function. Ketamine attenuates central sensitization through NMDA receptor antagonism and prevents opioid-induced hyperalgesia. Intravenous lidocaine provides analgesic, anti-inflammatory, antihyperalgesic, and prokinetic effects, while paracetamol and NSAIDs inhibit peripheral inflammatory mediators responsible for postoperative pain. Together, these agents provide balanced analgesia by targeting multiple pain pathways simultaneously, thereby minimizing reliance on any single medication and reducing dose-related adverse effects. The findings of the present investigation are consistent with numerous randomized controlled trials and systematic reviews published in recent years. Several investigators have demonstrated that opioid-free anesthesia reduces postoperative opioid requirements, improves pain control, decreases PONV, and facilitates earlier recovery following

abdominal surgery. Meta-analyses have further suggested that multimodal opioid-free anesthesia decreases opioid-related complications without compromising intraoperative hemodynamic stability. Our findings extend this evidence by demonstrating significant improvements in patient-centered recovery using the QoR-15 instrument while simultaneously documenting reductions in postoperative hyperalgesia. These outcomes strengthen the rationale for incorporating opioid-free anesthesia into contemporary perioperative care pathways. Despite these encouraging findings, certain limitations should be acknowledged. First, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other institutions or healthcare settings. Second, the sample size of 100 patients, although adequately powered for the primary outcome, may not detect uncommon adverse events associated with opioid-free anesthesia. Third, patients were followed only during the immediate postoperative period, preventing assessment of chronic postoperative pain, long-term opioid use, or functional recovery beyond hospital discharge. Fourth, different types of abdominal surgical procedures were included, and variations in surgical complexity may have influenced postoperative pain intensity despite comparable baseline characteristics. Finally, the present study did not evaluate biochemical markers of inflammation or stress response, which may have provided additional insight into the mechanisms underlying improved recovery. Future multicenter randomized controlled trials involving larger and more diverse patient populations are required to establish standardized opioid-free anesthesia protocols for different surgical specialties. Additional research should also investigate long-term outcomes, including persistent postsurgical pain, opioid dependence, quality of life, cognitive recovery, and healthcare cost-effectiveness. Comparative studies evaluating different multimodal drug combinations and their integration with regional anesthesia techniques will further optimize individualized perioperative analgesic strategies. Overall, the present study demonstrates that multimodal opioid-free anesthesia provides significant clinical benefits in patients undergoing major abdominal surgery. Compared with conventional opioid-based anesthesia, opioid-free anesthesia resulted in superior postoperative recovery, lower pain intensity, reduced opioid-induced hyperalgesia, decreased postoperative opioid requirements, fewer opioid-related adverse effects, earlier mobilization, improved gastrointestinal recovery, shorter hospital stay, and greater patient satisfaction. These findings support the incorporation of multimodal opioid-free anesthesia into Enhanced Recovery After Surgery (ERAS) protocols and contemporary perioperative practice. Wider adoption of carefully designed opioid-free anesthetic strategies has the potential to improve surgical outcomes while simultaneously contributing to global efforts aimed at reducing unnecessary perioperative opioid exposure and its associated complications.

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