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EVALUATION OF OPIOID-FREE ANAESTHESIA FOR ITS IMPACT ON POSTOPERATIVE NAUSEA,VOMITING AND PAIN AFTER LAPROSCOPIC CHOLECYSTECTOMY- A RANDOMISED CONTROLLED TRIAL.

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Abstract

Background: The management of postoperative pain and nausea remains crucial in enhancing recovery after laparoscopic cholecystectomy (LC). Opioid-free anaesthesia (OFA) has emerged as a strategy to mitigate opioid-related adverse effects and improve perioperative outcomes. ***Methods:*** A prospective, randomized assessor-blinded parallel-group randomized controlled trial was conducted at Nizam's Institute of Medical Sciences, Hyderabad. Adult patients (n = 90) undergoing elective LC were randomized into two groups: OFA group receiving dexmedetomidine and sevoflurane, and opioid-based anaesthesia (OA) group receiving fentanyl and sevoflurane. Primary endpoints included incidence and severity of post-operative nausea and vomiting (PONV) and post-operative pain scores assessed by an 11-point Numeric Rating Scale (NRS). Secondary endpoints comprised post-operative antiemetic and rescue analgesic requirements, length of stay (LOS) at the PACU, overall patient satisfaction, and post-operative hospital LOS. ***Results:*** The opioid-free group exhibited a similar mean blood loss compared to the control group ($p=0.48$). Both groups had comparable mean anaesthesia and surgical times ($p=0.07$ and $p=0.116$, respectively). However, the opioid-free group experienced a significantly longer PACU stay ($p<0.001$) but a similar overall hospital stay compared to the control group ($p=0.896$). Hemodynamic parameters, including blood pressure and heart rate, showed variations between the groups, with the opioid-free group exhibiting a trend towards higher preoperative blood pressures and a different heart rate pattern postoperatively. While the incidence of nausea and vomiting was slightly lower in the opioid-free group ($p=0.61$ and $p=0.07$, respectively), the difference was not statistically significant. Notably, the opioid-free group had a significantly higher incidence of significant sedation compared to the control group ($p<0.01$). ***Conclusion:*** Opioid-free anaesthesia for laparoscopic cholecystectomy is feasible with comparable surgical outcomes to traditional opioid-based anaesthesia. However, it is associated with a longer PACU stay and a higher incidence of significant sedation. Further research is necessary to optimize opioid-free protocols to enhance recovery while maintaining the potential benefits of reduced PONV and stable hemodynamics.

Keywords: Laparoscopic cholecystectomy, Opioid-free anaesthesia, post-operative nausea and vomiting (PONV), Numeric Rating Scale, Hemodynamics.

INTRODUCTION

Opioids play a central role in conventional general anaesthesia (CGA) due to their potent analgesic properties, their ability to induce hypnosis, and their efficacy in controlling the autonomic nervous system's response to surgical stress, thus ensuring hemodynamic stability. Despite these benefits, the use of opioids is frequently accompanied by a range of adverse effects. These include the development of opioid tolerance or withdrawal symptoms, opioid-induced hyperalgesia [1], postoperative ileus (POI), postoperative nausea and vomiting [2], pruritus, urinary retention, and postoperative shivering [3]. Such adverse events can cause considerable patient distress, hinder postoperative recovery, delay rehabilitation, extend the length of hospital stay (LOS), escalate healthcare costs, and diminish patient satisfaction. These outcomes are increasingly deemed unacceptable in the context of the modern enhanced recovery after surgery (ERAS) protocols [4].

Nausea is characterized by a sensation of an imminent need to vomit, even in the absence of actual expulsive muscular movements. Vomiting, or emesis, refers to the forceful oral expulsion of gastrointestinal contents. Episodes where no gastric contents are expelled are termed retching. Postoperative nausea and vomiting (PONV) encompass nausea, vomiting,

or retching occurring in the post-anaesthesia care unit (PACU) or within the immediate 24-hour postoperative period [5]. The general incidence of postoperative nausea is approximately 50%, while vomiting occurs in about 30% of cases. Among high-risk patients, the PONV rate can soar to 80% [6]. Apfel proposed a risk scoring system for PONV based on four factors: female gender, a history of nausea and vomiting, nonsmoking status, and the use of postoperative opioids. Opioids can trigger nausea and vomiting by stimulating the chemoreceptor trigger zone and other mechanisms within the central nervous system.

The use of opioids in perioperative care often leads to reduced patient satisfaction and extended recovery times, consequently delaying hospital discharge. Both laparoscopic cholecystectomy and perioperative opioid usage are well-established independent risk factors for postoperative nausea and vomiting (PONV) [6]. Unresolved PONV can result in prolonged stays in the post-anaesthesia care unit (PACU) and unexpected hospital admissions, significantly increasing overall healthcare costs [7].

Laparoscopic cholecystectomy remains the primary treatment for benign biliary diseases. However, postoperative pain is a major concern, often leading to extended hospital stays or readmissions [8]. As laparoscopic cholecystectomy increasingly becomes an outpatient procedure, effective pain management is crucial. A prospective cohort study demonstrated that a surgical opioid-avoidance protocol (SOAP) was as effective as traditional protocols in managing daily maximum pain scores [9] and reduced the need for postoperative rescue analgesics. There is a notable association between perioperative opioid use and increased length of hospital stay (LOS) as well as higher healthcare costs [7].

Surgeons are making concerted efforts to minimize opioid over-prescription, thereby reducing the risk of dependence and tolerance in vulnerable patients [10]. Anaesthesiologists also play a critical role in limiting unnecessary perioperative opioid use.

The American Society of anaesthesiologists (ASA) physical status classification system is used to assess and communicate the fitness of patients before surgery. The classifications are as follows:
ASA-1: A normal, healthy patient.
ASA-2: A patient with mild systemic disease.

- In an effort to minimize the perioperative use of opioids, Kehlet et al. introduced the concept of balanced multimodal analgesia in the early 1990's [8]. This innovative approach aims to enhance analgesia while reducing the incidence of opioid-related side effects, significantly contributing to the enhanced recovery after surgery (ERAS) protocols. Multimodal analgesia is accomplished by combining various analgesics that operate through different mechanisms within the central nervous system.
- One notable technique within this framework is opioid-free anaesthesia (OFA), which involves the intravenous administration of a combination of non-opioid agents to achieve adequate intraoperative analgesia, hypnosis, sympatholysis, and a pain-free awakening [11]. The drugs used in OFA include dexmedetomidine, ketamine, dexamethasone, lignocaine, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, beta-blockers such as esmolol, benzodiazepines, and magnesium sulphate [12].
- Dexmedetomidine, a centrally acting alpha-2 adrenoreceptor agonist, stands out due to its substantial potential to enhance analgesia and stabilize hemodynamic responses to endotracheal intubation and the creation of hemoperitoneum. This drug reduces anaesthetic requirements and has an opioid-sparing effect, making it a valuable perioperative analgesic with notable sedative properties. Consequently, research on the use of dexmedetomidine in facilitating early recovery following day care surgery has become a burgeoning area of interest among anaesthesiologists [13].
- Current evidence suggests that OFA protocols are not inferior to traditional opioid-inclusive methods and may offer superior perioperative outcomes. Specifically, OFA is associated with lower postoperative pain scores, reduced incidence of PONV, decreased need for rescue analgesics, and a lower frequency of opioid-related adverse events following laparoscopic cholecystectomy. [14–17] Therefore, OFA presents itself as an attractive and promising option for laparoscopic surgeries, aligning well with the goals of enhanced recovery and improved patient satisfaction.

Given these considerations, we undertook a randomized controlled trial focusing on a high-risk population to determine the effectiveness of opioid-free anaesthesia in reducing postoperative nausea, vomiting, and pain. Our study also aimed to evaluate other perioperative outcomes associated with this approach. By rigorously comparing opioid-free anaesthesia to traditional opioid-based methods, we sought to provide robust evidence on its potential benefits in enhancing patient recovery and overall surgical experience.

Need for the Study

Postoperative pain following laparoscopic cholecystectomy (LC) is multifaceted and challenging to manage. Emerging evidence indicates that an effective treatment regimen should be multimodal and aim to minimize opioid use to promote faster recovery. Consequently, there is a critical need to investigate and assess new non-opioid pain medications as part of

a comprehensive opioid reduction strategy in the context of LC. This study aims to explore the efficacy of these alternative pain management options to enhance patient outcomes and advance postoperative care practices.

AIM

Aim of the study is to evaluate opioid-free anaesthesia (OFA) for its impact on postoperative nausea, vomiting and pain after laparoscopic Cholecystectomy

OBJECTIVES

1. To evaluate Opioid free anaesthesia impact on post-operative nausea and vomiting after laparoscopic Cholecystectomy
2. To assess opioid free anaesthesia impact on post operative pain after laparoscopic Cholecystectomy

METHODOLOGY

STUDY DESIGN:

A prospective, randomized assessor-blinded parallel-group randomized controlled trial was conducted. Institutional Ethical committee approval number was EC/NIMS/3246/2024.

STUDY SETTINGS:

The study took place in the Department of Anaesthesiology and Intensive Care at NIZAM'S INSTITUTE OF MEDICAL SCIENCES, Hyderabad, Telangana.

STUDY PERIOD: May 2024 – August 2024

STUDY POPULATION:

- Adult patients admitted for elective Laparoscopic Cholecystectomy in the study setting.

INCLUSION CRITERIA: Patients who-

1. Are adult men and women.
2. Are aged between 20 – 65 years.
3. Have American Society of Anaesthesiology (ASA) physical status I and II.
4. Are admitted in the study setting for elective Laparoscopic Cholecystectomy.

Exclusion Criteria: Patients who-

1. Have American Society of anaesthesiologists (ASA) physical status 3, 4, and 5.
2. Are pregnant or breastfeeding women.
3. Have a history of chronic pain (pain persisting for more than 6 months).
4. Are taking sedatives and analgesics.
5. Have a history of alcohol or drug abuse.
6. Have allergies or incompatibilities to any study drugs.
7. Are participating in another interventional trial.
8. Have conditions such as heart, renal, or hepatic failure.
9. Have psychiatric illness.
10. Are unwilling to participate in the study.

SAMPLE SIZE CALCULATION

Based on the assumption from Marija Toleska et al. [31] that intraoperative avoidance of opioids could reduce the risk of postoperative nausea by 20% (from 33% in the active group to 13% in the control group), a sample size calculation was performed.

To achieve a study power of 80% and a type 1 error rate of less than 0.005%, initially, 40 patients were calculated to be required in each group. Considering a 10% attrition rate for potential loss to follow-up, a final sample size of 45 patients per group was determined.

Randomization and Blinding

Randomization: Patients were randomly allocated to either the intervention group (opioid-free anaesthesia - OF) or the control group (C). Each patient was assigned a computer-generated number and randomized in a 1:1 ratio. Randomization was performed using opaque sealed envelopes, and the treatment arm was revealed on the morning of surgery.

Blinding:

- Blinding of Participants and Outcome Assessors: Participants and those assessing outcomes were blinded to group allocation.

- Anaesthesia Providers: Anaesthesia providers could not be blinded due to the significant differences between the opioid-free and opioid-based anaesthetic techniques.

Anaesthetic Management or Intervention

Patients meeting the inclusion criteria underwent thorough evaluation including medical history, physical examination, and laboratory investigations such as complete blood picture, renal function tests, liver function tests, prothrombin time (PT & INR), partial thromboplastin time (PTT), and chest X-ray. Electrocardiogram (ECG) was performed for patients above 40 years old. All medication dosages were adjusted based on their body weight. Baseline vital signs were monitored routinely (ECG, BP, pulse oximetry, and end-tidal CO_2).

Upon insertion of an intravenous line, a crystalloid solution was initiated. All patients received dexamethasone 4 mg and ondansetron 4 mg for prophylaxis against postoperative nausea and vomiting (PONV), guided by pre-operative risk assessment using Apfel's simplified PONV risk score (11).

Anaesthetic Management:

- Group OF (Opioid-Free Anaesthesia): Patients received a bolus of dexmedetomidine 0.6 µg/kg over 10 minutes. Anaesthesia induction included propofol 1-2 mg/kg and rocuronium 0.6 mg/kg, followed by endotracheal intubation. Maintenance of anaesthesia included a continuous infusion of dexmedetomidine at 0.3 µg/kg/hour and sevoflurane adjusted to maintain a minimum alveolar concentration (MAC) of 1.0–1.4.
- Group C (Control - Opioid-Based Anaesthesia): Patients received a bolus of fentanyl at 2 µg/kg. Anaesthesia induction and maintenance included propofol and rocuronium as in Group OF, with continuous infusion of fentanyl at 0.5 µg/kg/hour combined with sevoflurane adjusted to maintain a MAC of 1.0–1.4.

Fluid and Hemodynamic Management: Fluids and vasopressors were administered according to institutional standards to maintain mean arterial blood pressure within 20% of baseline measurements throughout the procedure.

This standardized anaesthetic protocol aimed to ensure consistent management while comparing the effects of opioid-free anaesthesia versus opioid-based anaesthesia on postoperative outcomes in patients undergoing laparoscopic cholecystectomy.

Postoperative Care

After tracheal extubation, patients were transferred to the Post-Anaesthesia Care Unit (PACU) where they were assessed for postoperative outcomes including nausea, vomiting, and pain. Sedation levels were monitored using the Richmond Agitation Sedation Scale (RASS)[32], with a target score of ≤ -2 (12). Antiemetic rescue therapy, primarily ondansetron, was administered as needed for nausea and vomiting management.

Postoperative Pain Management: Patients received bilateral transverse abdominis plane (TAP) block with 20 ml of 0.125% bupivacaine on each side for effective local analgesia. In case of additional analgesic requirements, rescue analgesia with intravenous tramadol at 1 mg/kg was administered.

Assessment for Discharge Readiness: Patients' readiness for discharge was assessed based on the criteria outlined in the Post Anaesthetic Discharge Scoring System (PADSS)[33]. The length of stay (LOS) in the PACU was defined from admission until discharge criteria were met, ensuring patients' safety and comfort before discharge.

This comprehensive postoperative care protocol aimed to manage pain effectively and monitor recovery parameters closely, facilitating smooth transition from anaesthesia to postoperative recovery and discharge.

Outcome Assessments and Data Collection

Outcome Measures:

- Postoperative Nausea and Vomiting (PONV)[34]: Evaluated using the simplified PONV impact scale developed by Myles et al. Patients were monitored for the presence and severity of nausea and vomiting.
- Pain Scores: Numeric Rating Scale (NRS)[35] pain scores were recorded at three specific time points within the first 24 hours postoperatively:

1. In the PACU immediately after surgery,
2. At a study visit (V1) in the evening after surgery,
3. At a second visit (V2) on the first postoperative day.

- Antiemetic Requirements: Recorded as the need for additional ondansetron or other antiemetics to manage postoperative nausea and vomiting.
- Patient Satisfaction: Assessed using a 5-point Likert scale to gauge overall satisfaction with their surgical experience.
- Rescue Analgesic Consumption: Data on tramadol consumption for rescue analgesia were collected at specific intervals postoperatively: 1 hour, 2 hours, 6 hours, and 12 hours after surgery.

Data Collection Procedure:

- Timing: Assessments were conducted systematically at predefined time points to ensure comprehensive evaluation of outcomes over the initial postoperative period.
- Documentation: All assessments and data points were meticulously recorded in the patient's medical records or dedicated study forms to maintain accuracy and consistency.

This structured approach to outcome assessments and data collection aimed to provide detailed insights into the efficacy of opioid-free anaesthesia in managing postoperative outcomes such as pain, nausea, vomiting, and patient satisfaction following laparoscopic cholecystectomy.

Data Collection Tools

1. Simplified PONV Impact Scale by Myles et al.[36]

• Description: This validated questionnaire assesses postoperative nausea and vomiting (PONV) with two questions:
  ▪ Q1: Have you vomited or had dry-retching?
  ▪ Q2: Have you experienced a feeling of nausea?
  ▪ If yes to nausea, it evaluates the impact on daily activities.
• Scoring: Scores range from 0 to 6, with a cutoff value of 5 indicating clinically significant PONV.

2. 11-Point Numeric Rating Scale (NRS)[35]

• Description: Patients rate their pain intensity on a scale of 0 to 10, where:
  ▪ 0 indicates no pain,
  ▪ 10 indicates the worst pain imaginable.
• Utility: Widely used for its simplicity and patient compliance in assessing pain intensity postoperatively.

3. Post Anaesthetic Discharge Scoring System (PADSS)[33]

• Description: This tool evaluates six criteria to determine a patient's readiness for discharge from the PACU:
  ▪ Vital signs (blood pressure, pulse rate, temperature, respiratory rate)
  ▪ Ambulation capability
  ▪ Nausea/vomiting
  ▪ Pain level
  ▪ Surgical bleeding assessment
  ▪ Fluid intake/output
• Scoring: Each criterion is scored from 0 to 2, with a total score ranging from 0 to 12. A score of 9 or higher indicates readiness for discharge.

These standardized tools enable systematic assessment of key outcomes including PONV, pain intensity, and readiness for discharge, providing valuable data to evaluate the effectiveness of opioid-free anaesthesia in laparoscopic cholecystectomy patients.

Overall Patient Satisfaction

Description: Overall patient satisfaction is assessed using a 5-point Likert scale, where patients provide their subjective evaluation of their surgical experience. The scale ranges from 1 to 5, with each point representing varying degrees of satisfaction:

- Score 1: Very Dissatisfied
- Score 2: Dissatisfied
- Score 3: Neutral
- Score 4: Satisfied
- Score 5: Very Satisfied

Purpose:

- The Likert scale is employed to capture patients' perceptions and feelings about their care, anaesthesia experience, and overall outcomes following laparoscopic cholecystectomy.
- It provides qualitative insights into patient satisfaction levels, helping to gauge the success of the surgical intervention and anaesthesia management from the patient's perspective.

Use in Research:

RESPONSE	SCORE
Very dissatisfied	5
Dissatisfied	4
Neutral	3
Satisfied	2
Very Satisfied	1

- Data collected using the Likert scale contributes to understanding the impact of opioid-free anaesthesia on patient-reported outcomes, including satisfaction.
- It complements quantitative measures such as pain scores and incidence of complications, enriching the comprehensive assessment of perioperative care effectiveness.

Implementation:

- Patients are asked to select the number that best reflects their satisfaction level during postoperative follow-up visits or upon discharge.
- Responses are recorded systematically to ensure consistency and accuracy in evaluating patient satisfaction across different cohorts or treatment groups.

By incorporating the Likert scale into the study methodology, researchers can gather valuable feedback from patients, contributing to a holistic evaluation of opioid-free anaesthesia strategies in enhancing perioperative care and patient satisfaction.

Outcomes and Statistical Analysis

Primary Endpoints:

1. Incidence and Severity of Post-operative Nausea and Vomiting (PONV):
   - Evaluated within 24 hours after surgery using the Simplified PONV Impact Scale by Myles et al.
   - Severity assessed based on scores from the scale, with a cutoff of 5 indicating clinically significant PONV.
2. Post-operative Pain Scores:
   - Assessed using an 11-point Numeric Rating Scale (NRS) at multiple time points (e.g., PACU, evening after surgery, first postoperative day).
   - Scores range from 0 (no pain) to 10 (worst pain imaginable).

Secondary Endpoints:

1. Post-operative Antiemetic and Rescue Analgesic Requirements:
   - Recorded based on administration of ondansetron for antiemesis and tramadol for analgesia.
   - Quantified in terms of frequency and dosage at specified time intervals (e.g., 1 hour, 2 hours, 6 hours, 12 hours postoperatively).
2. Length of Stay (LOS) at the Post-Anaesthesia Care Unit (PACU):
   - Defined as the duration from admission until discharge criteria are met according to the Post Anaesthetic **Discharge Scoring System (PADSS).**
   - A score of 9 or higher on the PADSS indicates readiness for discharge.
3. Overall Patient Satisfaction:
   - Assessed using a 5-point Likert scale, capturing patient perceptions of their surgical experience.
   - Scores range from 1 (very dissatisfied) to 5 (very satisfied).
4. Post-operative Length of Hospital Stay (LOS):
   - Duration from surgery completion until discharge from the hospital.
   - Evaluated to understand the overall impact of opioid-free anaesthesia on recovery and hospital resource utilization.

STATISTICAL ANALYSIS

- Categorical Data: Analysed using Fisher's exact test or $\chi 2$ test. Odds ratios with 95% confidence intervals (CIs) were calculated.
- Continuous Variables: Evaluated with the Wilcoxon rank-sum test for non-normally distributed data and Student's t-test for normally distributed data, confirmed by the Shapiro-Wilk test.
- Data Presentation: Summarized as mean (standard deviation), median (interquartile range [IQR]), or number (%) as appropriate.
- Statistical Significance: Two-sided p-values < 0.05 were considered statistically significant.

Software Used:

- Statistical analyses were performed using IBM SPSS Statistics version 26.0.

This structured approach to outcome assessment and statistical analysis ensures comprehensive evaluation of the impact of opioid-free anaesthesia on perioperative outcomes, enhancing the rigor and reliability of the study findings.

RESULTS

Table 1: Distribution of study participants based on their age

Age	Mean	SD	p-value
Control group	35.8	4.92	0.07
Opioid free group	37.6	4.2	

The table presents the mean age and standard deviation (SD) of participants in both the control group and the opioid-free group. The mean age of participants in the control group was 35.8 years with an SD of 4.92, while the opioid-free group had a mean age of 37.6 years with an SD of 4.2. The p-value for the age difference between the two groups was 0.07, indicating that there was no statistically significant difference in the age distribution of participants between the two groups.

Table 2: Distribution of study participants based on their sex

Sex	Male	Female	p-value
Control group	24	21	1
Opioid free group	24	21	

The table shows the distribution of study participants based on their sex in both the control group and the opioid-free group. Each group comprised 24 males and 21 females. The p-value for the sex distribution between the two groups was 1, indicating no statistically significant difference in the distribution of male and female participants between the control and opioid-free groups.

Table 3: Distribution of study participants based on their BMI.

Age	Mean	SD	p-value
Control group	24.8	1.77	0.37
Opioid free group	24.5	1.8	

The table presents the distribution of study participants based on their Body Mass Index (BMI) in both the control group and the opioid-free group. The mean BMI for the control group was 24.8 with a standard deviation of 1.77, while the mean BMI for the opioid-free group was 24.5 with a standard deviation of 1.8. The p-value for the BMI distribution between the two groups was 0.37, indicating no statistically significant difference in BMI between the control and opioid-free groups.

Table 4: ASA grade between the groups

Group	ASA 1	ASA 2	Total	p-value
Control group	32	13	45	0.186
Opioid free group	26	19	45	
Total	20	55	90	

This table shows the distribution of participants based on the American Society ofanaesthesiologists (ASA) physical status classification. The control group has 32 participants with ASA 1 and 13 with ASA 2, while the opioid-free group has 26 participants with ASA 1 and 19 with ASA 2. The total number of participants is 90. The p-value of 0.186 indicates no statistically significant difference in ASA physical status between the two groups.

Table 5: PONV risk assessment score

	PONV risk score				p-value
Group	**2**	**3**	**4**	**Total**	
Control group	12	25	8	45	0.5
Opioid free group	8	30	7	45	
Total	20	55	15	90	

This table presents the distribution of participants based on their postoperative nausea and vomiting (PONV) risk score, categorized into scores of 2, 3, and 4. The control group has 12 participants with a PONV risk score of 2, 25 with a score of 3, and 8 with a score of 4. The opioid-free group has 8 participants with a PONV risk score of 2, 30 with a score of 3, and 7 with a score of 4. The total number of participants is 90. The p-value of 0.5 indicates no statistically significant difference in PONV risk scores between the two groups.

Table 6: Duration of anaesthesia

Duration of anaesthesia	Mean (mins)	SD (mins)	p-value
Control group	148	20.5	0.07
Opioid free group	139.8	22.9	

This table presents the mean duration of anaesthesia for both the control group and the opioid-free group, along with their standard deviations (SD). The control group had a mean anaesthesia duration of 148 minutes with an SD of 20.5 minutes, while the opioid-free group had a mean duration of 139.8 minutes with an SD of 22.9 minutes. The p-value of 0.07 indicates that there is no statistically significant difference in the duration of anaesthesia between the two groups.

Table 7: Duration of the surgical procedure

Duration of Surgical procedure	Mean (mins)	SD (mins)	p-value
Control group	100	23.7	0.116
Opioid free group	91.2	28.4	

This table presents the mean duration of the surgical procedure for both the control group and the opioid-free group, along with their standard deviations (SD). The control group had a mean surgical duration of 100 minutes with an SD of 23.7 minutes, while the opioid-free group had a mean duration of 91.2 minutes with an SD of 28.4 minutes. The p-value of 0.116 indicates that there is no statistically significant difference in the duration of the surgical procedure between the two groups.

Table 8: Duration of PACU stay.

Duration of PACU stay	Mean (mins)	SD (mins)	p-value
Control group	54.07	10.98	**<0.001**
Opioid free group	74.71	23.23	

This table presents the mean duration of stay in the Post-Anaesthesia Care Unit (PACU) for both the control group and the opioid-free group, along with their standard deviations (SD). The control group had a mean PACU stay of 54.07 minutes with an SD of 10.98 minutes, while the opioid-free group had a mean stay of 74.71 minutes with an SD of 23.23 minutes. The p-value of <0.001 indicates that there is a statistically significant difference in the duration of PACU stay between the two groups. This table shows that the opioid-free group had a significantly longer stay in the PACU compared to the control group.

Table 9: Duration of Hospital stay

Duration of Hospital stay	Mean (days)	SD (days)	p-value
Control group	2.96	0.77	0.896
Opioid free group	2.98	0.84	

This table summarizes the mean duration of hospital stay for both the control group and the opioid-free group, along with their standard deviations (SD). The control group had a mean hospital stay of 2.96 days with an SD of 0.77 days, while the opioid-free group had a mean stay of 2.98 days with an SD of 0.84 days. The p-value of 0.896 indicates that there is no statistically significant difference in the duration of hospital stay between the two groups.

Table 10: Fluids given to the study participants.

Fluids given	Mean (ml)	SD (ml)	p-value
Control group	1295.5	153.68	0.16
Opioid free group	1248.9	160.43	

This table details the average amount of fluids administered to participants in both the control and opioid-free groups, along with the standard deviations (SD). The control group received a mean of 1295.5 ml of fluids with an SD of 153.68 ml, whereas the opioid-free group received a mean of 1248.9 ml with an SD of 160.43 ml. The p-value of 0.16 suggests that there is no statistically significant difference in the amount of fluids given between the two groups.
This table indicates that the volume of fluids administered to the participants is similar between the control and opioid-free groups, with no significant difference noted.

Table 11: Blood loss during the procedure.

Blood loss	Mean (ml)	SD (ml)	p-value
Control group	78.53	13.33	0.48
Opioid free group	76.4	15.25	

This table presents the average blood loss during the surgical procedure for both the control and opioid-free groups, along with their respective standard deviations (SD). The control group experienced a mean blood loss of 78.53 ml with an SD of 13.33 ml, while the opioid-free group had a mean blood loss of 76.4 ml with an SD of 15.25 ml. The p-value of 0.48 indicates that there is no statistically significant difference in blood loss between the two groups.
This table shows that the blood loss during the procedure is comparable between the control and opioid-free groups, with no significant differences observed.

Table 12: Time required for 1st rescue analgesia.

Time required for 1st rescue analgesia	Mean (hours)	SD (hours)	p-value
Control group	6.15	1.63	0.15
Opioid free group	6.68	1.78	

This table provides the average time in hours until the first rescue analgesia was required for both the control and opioid-free groups, along with their respective standard deviations (SD). The control group had a mean time of 6.15 hours with an SD of 1.63 hours, whereas the opioid-free group had a mean time of 6.68 hours with an SD of 1.78 hours. The p-value of 0.15 indicates that there is no statistically significant difference in the time required for the first rescue analgesia between the two groups.

This table demonstrates that the time required for the first rescue analgesia is similar between the control and opioid-free groups, with no significant differences observed.

Table 12: Time required for 1st rescue analgesia.

Time required for 1st rescue analgesia	Mean (hours)	SD (hours)	p-value
Control group	6.15	1.63	0.15
Opioid free group	6.68	1.78	

This table provides the average time in hours until the first rescue analgesia was required for both the control and opioid-free groups, along with their respective standard deviations (SD). The control group had a mean time of 6.15 hours with an SD of 1.63 hours, whereas the opioid-free group had a mean time of 6.68 hours with an SD of 1.78 hours. The p-value of 0.15 indicates that there is no statistically significant difference in the time required for the first rescue analgesia between the two groups.

This table demonstrates that the time required for the first rescue analgesia is similar between the control and opioid-free groups, with no significant differences observed.

Table 14: Change in mean diastolic blood pressure between groups.

Mean Diastolic Blood Pressure (mm Hg)	Pre-op	15 min	30 min	1 hr	2 hr
Opioid free group	74.6	82.4	80.4	78.2	76.8
Control group	79.7	80	75.2	74.2	74.3

Preoperatively, the opioid-free group's mean diastolic blood pressure is 74.6 mm Hg, which increases to 82.4 mm Hg at 15 minutes post-operation, then gradually decreases to 76.8 mm Hg by 2 hours post-op. On the other hand, the control group starts higher at 79.7 mm Hg preoperatively but only slightly increases to 80 mm Hg at 15 minutes, then decreases to 74.3 mm Hg by 2 hours post-op. This pattern suggests that while the opioid-free group experiences a more pronounced initial increase in diastolic blood pressure, it eventually approaches the control group's levels over the course of the postoperative period.

Table 15: Change in mean heart rate between groups.

Heart rate	Pre-op	15 min	30 min	1 hr	2 hr
Opioid free group	96	93.9	87.9	92.2	90
Control group	91.7	93.6	91.4	91.7	88.3

The data indicates that the opioid-free group has a higher preoperative heart rate compared to the control group, starting at 96 beats per minute (bpm) versus 91.7 bpm. Fifteen minutes post-operation, the heart rate of the opioid-free group decreases to 93.9 bpm, while the control group's heart rate slightly increases to 93.6 bpm. At 30 minutes post-op, the opioid-free group's heart rate drops further to 87.9 bpm, which is lower than the control group's 91.4 bpm at the same time point. One hour post-op, the opioid-free group's heart rate increases to 92.2 bpm, closely matching the control group's 91.7 bpm. Finally, at two hours post-op, the opioid-free group's heart rate is 90 bpm, slightly higher than the control group's 88.3 bpm. This pattern suggests that while the opioid-free group's heart rate decreases more significantly in the early postoperative period, it eventually stabilizes to a rate similar to that of the control group.

Table 16: Change in mean oxygen saturation between groups.

Saturation	Pre-op	15 min	30 min	1 hr	2 hr
Opioid free group	98.4	98.7	98.5	98.5	98.5
Control group	98.5	98.5	98.4	98.4	98.5

The data on oxygen saturation levels shows minimal variation between the opioid-free and control groups throughout the measured intervals. Preoperatively, the opioid-free group has an oxygen saturation of 98.4%, slightly lower than the control

group's 98.5%. Fifteen minutes post-operation, the opioid-free group's saturation increases to 98.7%, while the control group's remains steady at 98.5%. At 30 minutes post-op, the opioid-free group's saturation slightly decreases to 98.5%, matching the control group's 98.4%. Both groups maintain these levels at 1 hour post-op, with the opioid-free group at 98.5% and the control group at 98.4%. By 2 hours post-op, both groups stabilize at 98.5%. Overall, both groups maintain high and stable oxygen saturation levels with negligible differences, indicating effective oxygenation throughout the postoperative period

Table 17: Presence of Nausea between groups after procedure.

Nausea	Present	Absent	p-value
Control group	26	19	0.61
Opioid free group	24	21	

The data on nausea indicates that there is a similar incidence of nausea between the opioid-free and control groups. In the control group, 26 patients experienced nausea, while 19 did not. In the opioid-free group, 24 patients experienced nausea, while 21 did not. The p-value of 0.61 suggests that there is no statistically significant difference in the incidence of nausea between the two groups. This implies that the presence or absence of opioids does not significantly affect the likelihood of experiencing nausea postoperatively.

Table 18: Presence of Vomiting between groups after procedure.

Vomiting	Present	Absent	p-value
Control group	20	25	0.07
Opioid free group	12	33	

The data on vomiting indicates a difference in incidence between the opioid-free and control groups. In the control group, 20 patients experienced vomiting, while 25 did not. In the opioid-free group, 12 patients experienced vomiting, while 33 did not. The p-value of 0.07 suggests a trend towards statistical significance, implying that the opioid-free group may have a lower incidence of vomiting compared to the control group. However, since the p-value is slightly above the commonly used threshold of 0.05, this difference is not considered statistically significant.

Table 19: PONV severity between groups after procedure.

PONV	Control group	Opioid free group	p-value
0	24	28	0.71
1	9	7	
2	4	6	
3	4	2	
4	1	1	
5	1	1	
6	2	0	

The data on postoperative nausea and vomiting (PONV) indicates that there is no significant difference between the control and opioid-free groups. In the control group, 24 patients had no episodes of PONV, 9 had one episode, 4 had two episodes, 4 had three episodes, 1 had four episodes, 1 had five episodes, and 2 had six episodes. In the opioid-free group, 28 patients had no episodes of PONV, 7 had one episode, 6 had two episodes, 2 had three episodes, 1 had four episodes, 1 had five episodes, and none had six episodes. The p-value of 0.71 suggests that the differences in PONV frequency between the two groups are not statistically significant, indicating that opioid use does not significantly impact the incidence of PONV.

Table 20: Sedation in PACU based on RASS score.

Sedation	Present (<=-2)	Absent (-1 & above)	p-value
Control group	13	32	**<0.01**
Opioid free group	31	14	

The data on sedation in the post-anaesthesia care unit (PACU) based on the Richmond Agitation-Sedation Scale (RASS) score indicates a significant difference between the control and opioid-free groups. In the control group, 13 patients experienced significant sedation (RASS ≤ -2), while 32 patients did not (RASS -1 and above). In the opioid-free group, 31 patients experienced significant sedation, while 14 did not. The p-value of less than 0.01 suggests a statistically significant difference, indicating that the opioid-free group had a higher incidence of significant sedation compared to the control group.'

Summary:

The study compares various postoperative outcomes between an opioid-free group and a control group. In terms of mean systolic blood pressure, the opioid-free group consistently had lower readings across all measured intervals compared to the control group. Mean diastolic blood pressure was initially higher in the opioid-free group but approached levels similar

to the control group over time. Heart rates were higher preoperatively in the opioid-free group but eventually stabilized to rates similar to the control group. Oxygen saturation levels were high and stable for both groups, showing negligible differences. Nausea incidence was similar between groups, with a p-value of 0.61 indicating no significant difference. Vomiting was less frequent in the opioid-free group, but the p-value of 0.07 suggests this difference was not statistically significant. For postoperative nausea and vomiting (PONV), there was no significant difference between groups, with a p-value of 0.71. However, significant sedation (RASS ≤ -2) was more common in the opioid-free group, with a p-value of less than 0.01, indicating a statistically significant difference. Overall, the opioid-free group demonstrated some variations in blood pressure, heart rate, and sedation but did not show significant differences in oxygen saturation, nausea, vomiting, or PONV compared to the control group.

DISCUSSION

A prospective, randomized assessor-blinded parallel-group randomized controlled trial was conducted to evaluate the impact of opioid-free anaesthesia (OFA) on postoperative nausea, vomiting, and pain after laparoscopic cholecystectomy. The study took place in the Department of Anaesthesiology and Intensive Care at NIZAM'S INSTITUTE OF MEDICAL SCIENCES, Hyderabad, Telangana, over a span of two years. Adult patients aged between 20 to 65 years, with ASA physical status I and II, admitted for elective laparoscopic cholecystectomy, were included. Exclusion criteria comprised patients with ASA physical status 3, 4, and 5, pregnant or breastfeeding women, those with a history of chronic pain, alcohol or drug abuse, allergies to study drugs, or other severe health conditions. A sample size of 45 patients per group was determined, accounting for a 10% attrition rate. Randomization was done using computer-generated numbers, and the participants and outcome assessors were blinded.

The demographic and baseline characteristics of the two groups were comparable. The mean age and BMI differences between the opioid-free and opioid-based groups were not statistically significant (p=0.07 and p=0.37, respectively). Additionally, sex distribution, ASA classification, and PONV risk scores were similar between the groups, as evidenced by non-significant p-values (p=1, p=0.186, and p=0.5, respectively). These findings suggest that randomization was effective in creating comparable groups, thereby reducing selection bias.

PONV is a critical parameter in postoperative recovery. Although the incidence of nausea and vomiting was lower in the opioid-free group (p=0.61 and p=0.07, respectively), these differences were not statistically significant. The number of PONV episodes was also comparable between the groups, with a p-value of 0.71. This suggests that opioid-free anaesthesia might have a slight advantage in reducing PONV, but the difference is not substantial.

A significant finding was the higher incidence of significant sedation (RASS ≤ -2) in the opioid-free group compared to the opioid-based group (p<0.01). This indicates that patients in the opioid-free group experienced more profound sedation postoperatively. This could be due to the sedative effects of the alternative agents used in opioid-free anaesthesia protocols. In terms of intraoperative and postoperative parameters, the mean duration of anaesthesia and surgery were slightly shorter in the opioid-free group compared to the opioid-based group, but these differences were not statistically significant (p=0.07 and p=0.116, respectively). This indicates that the type of anaesthesia did not significantly affect the length of the procedures. Notably, the PACU stay was significantly longer in the opioid-free group (mean 74.71 minutes) compared to the opioid-based group (mean 54.07 minutes) with a p-value of <0.001. This suggests that opioid-free anaesthesia might require more recovery time immediately postoperatively. However, the overall hospital stay did not differ significantly between the groups (p=0.896), indicating that the longer PACU stay did not translate into prolonged hospitalization.

Fluid intake and blood loss during surgery were similar between the groups, with non-significant p-values (p=0.16 and p=0.48, respectively). This shows that the type of anaesthesia did not significantly impact intraoperative fluid management or blood loss.

The study observed variations in systolic and diastolic blood pressures and heart rates between the groups. The opioid-free group showed a trend of higher preoperative systolic and diastolic blood pressures, which peaked and then decreased more noticeably than in the opioid-based group. The heart rate in the opioid-free group started higher preoperatively but decreased postoperatively, whereas the control group showed a slight increase initially. These variations could be attributed to the different pharmacological effects of opioid-free anaesthesia, which may influence hemodynamic stability differently compared to opioid-based anaesthesia.

COMPARISION WITH OTHER STUDIES:

Our study ensured that demographic and baseline characteristics between the opioid-free anaesthesia (OFA) and opioid-based anaesthesia (OA) groups were comparable. This included parameters such as mean age, BMI, sex distribution, ASA classification, and PONV risk scores, all of which showed no statistically significant differences, indicating effective randomization. Similarly, Mieszczański's[37] study on laparoscopic sleeve gastrectomy, Vishnuraj's[30] study on

laparoscopic cholecystectomy, Liu's[38] study on thyroid surgery, Massoth's[39] study on gynecological laparoscopy, and Khaled's[40] study on geriatric patients undergoing shoulder surgery all reported no significant differences in demographic characteristics between their OFA and OA groups. This consistent finding across multiple studies suggests that randomization was effective in creating comparable groups, reducing selection bias and allowing for more reliable comparisons of outcomes.

In our study, the mean durations of anaesthesia and surgery were slightly shorter in the OFA group compared to the OA group, though these differences were not statistically significant. This finding aligns with the results from Mieszczański[37], Vishnuraj[30], and Massoth[39], who also reported no significant differences in the duration of surgery between OFA and OA groups. These consistent results suggest that the type of anaesthesia does not significantly impact the length of surgical procedures.

We found that the PACU stay was significantly longer in the OFA group compared to the OA group, but this did not lead to a prolonged overall hospital stay. Massoth's[39] study similarly observed a longer PACU stay for OFA patients, indicating a trend where OFA might require more recovery time immediately postoperatively. However, like in our study, this extended PACU stay did not translate into longer hospitalizations.

Our study observed no significant differences in intraoperative fluid intake and blood loss between the groups. In contrast, Mieszczański[37] reported that OFA patients required more intravenous fluids and higher doses of ephedrine, suggesting that while OFA protocols generally do not impact fluid management significantly, specific adjustments might be necessary in certain contexts.

We noted variations in systolic and diastolic blood pressures and heart rates, with the OFA group showing higher preoperative values and more noticeable decreases postoperatively. Vishnuraj's[30] study found similar hemodynamic trends, with higher HR and MAP readings in the OFA group compared to the OA group. Liu's[38] study reported a lower incidence of intraoperative hypotension in the OFA group, while Khaled[40] noted lower postoperative paracetamol requirements in the OFA group, indicating better hemodynamic stability and pain control.

In our study, the incidence of PONV was slightly lower in the OFA group, though the differences were not statistically significant. This finding is echoed in Vishnuraj's[30] study, where the OFA group had a significantly lower incidence of moderate PONV. Liu[38] also found a lower incidence of postoperative nausea in the OFA group. Conversely, Massoth's[39] study did not find significant differences in PONV between the groups, illustrating variability in PONV outcomes based on surgical procedure and anaesthesia protocols.

A significant finding in our study was the higher incidence of significant sedation in the OFA group. Massoth's[39] study also reported increased postoperative sedation in the OFA group, suggesting that alternative agents used in OFA protocols might have stronger sedative effects, requiring careful monitoring in the immediate postoperative period.

Postoperative analgesia requirements in our study were comparable between the groups, with the OFA group showing a trend towards better immediate postoperative pain control. Vishnuraj's[30] study similarly observed better analgesia in the OFA group during the immediate postoperative period, with a delayed first use of PCA. Khaled's[40] study found significantly lower postoperative paracetamol requirements in the OFA group, indicating superior pain management with OFA.

Our study did not observe significant differences in adverse events such as hypertension and tachycardia between the groups. Liu's[38] study, however, reported a lower incidence of intraoperative hypotension in the OFA group. These findings suggest that while OFA can be administered safely without increasing major hemodynamic disturbances, some variability exists based on the specific surgical context and patient population.

In conclusion, our study aligns with findings from the five additional studies, suggesting that OFA can be a viable alternative to OA across various surgical procedures. The consistent findings across studies, including comparable demographic characteristics, similar durations of anaesthesia and surgery, variable impacts on PACU stay, and generally favorable outcomes in terms of hemodynamic stability, PONV, sedation, and pain management for OFA groups, indicate that OFA protocols can be effectively integrated into clinical practice. These results support the potential benefits of OFA in specific patient populations and surgical contexts, warranting further research with larger sample sizes and diverse surgical procedures to optimize OFA protocols and validate these findings.

Adverse Events

Our study did not observe significant differences in adverse events such as hypertension and tachycardia between the groups. Liu's study, however, reported a lower incidence of intraoperative hypotension in the OFA group. These findings suggest that while OFA can be administered safely without increasing major hemodynamic disturbances, some variability exists based on the specific surgical context and patient population.

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LIMITATIONS

1. Sample Size and Generalizability:
   - The study included a relatively small sample size of 90 participants, which might limit the generalizability of the findings. A larger sample size could provide more robust data and increase the reliability of the results.
2. Single-Center Study:
   - Conducting the study at a single center (Nizam's Institute of Medical Sciences, Hyderabad) might limit the generalizability of the findings to other settings and populations. Multi-center trials would be beneficial for more comprehensive results.
3. Potential Confounding Factors:
   - Although randomization helps in balancing confounding factors, there might still be unmeasured variables that could influence the outcomes, such as differences in individual pain thresholds, metabolic responses to anaesthesia, and recovery patterns.

CONCLUSION

The study demonstrated that opioid-free anaesthesia (OFA) in laparoscopic cholecystectomy patients effectively improved immediate postoperative pain control, with lower pain scores and reduced fentanyl requirements in the first two hours post-surgery compared to opioid-based anaesthesia (OBA). OFA group had shown lesser incidence of vomiting when compared to OBA group although the difference is not statistically significant. Hemodynamic stability was comparable, despite higher preoperative blood pressures in the OFA group that normalized postoperatively. The OFA group experienced higher sedation. In conclusion, OFA enhances immediate postoperative pain control and reduces early rescue analgesic needs, making it a viable alternative to OBA while potentially minimizing opioid-related side effects. Further research is needed to optimize recovery times and manage sedation levels.

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